

Ninth
Edition

GHAI

Essential

Pediatrics

Editors

Vinod K Paul
Arvind Bagga



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radiographs, graphic illustrations and
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GHAI

Essential Pediatrics

Ninth Edition

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Medical knowledge is constantly changing. As new information becomes available, changes in treatment, procedures, equipment and the use of drugs become necessary. The contributors, editors and the publishers, as far as possible, have taken care to ensure that the information given in this text is accurate and up-to-date. However, the readers are strongly advised to confirm that the information, especially with regard to drug usage, complies with the latest legislation and standards of practice.

Notice

Research in treatment and drug therapy is continually in progress throughout the world. Recommendations and contraindications in dosage schedules require constant updating and change, both from year-to-year and country-to-country. Different drugs may have a similar name in other countries or the same drugs may be packed in different strengths. It is, therefore, advisable to consult the product information sheet provided with each drug, particularly in the case of new, foreign or rarely used drugs, to ensure that changes have not been made in the recommended dosages.

to

*Our parents for providing us the opportunity to learn and serve
Our teachers and mentors for imparting knowledge and inculcating values
Our colleagues for their affection and inspiration
Our families for their patience and unstinted support*

— Editors



Prof. Om Prakash Ghai

Prof. Om Prakash Ghai had a distinguished academic tenure at the All India Institute of Medical Sciences, New Delhi. He started the Department of Pediatrics in 1959 with six beds for children. Under his leadership, the department evolved into a multispecialty centre of international repute. After his retirement as Dean of the Institute and Professor and Head of the Department of Pediatrics, he chaired the Department of Pediatrics at the University College of Medical Sciences, Delhi, where he served until 1991.

Prof. Ghai was President of the Indian Academy of Pediatrics in 1978 and President of the International College of Pediatrics from 1987 to 1990. The International Pediatric Association presented him the prestigious 'Insignia of Merit Medallion' (1977) for his outstanding contributions to child welfare. The Indian Council of Medical Research awarded him the Dr Kamla Menon Prize (1983) and Amrut Mody Prize (1985). The Medical Council of India bestowed on him the Dr BC Roy Memorial Award for 'Eminent Medical Teacher' (1987). He was awarded honorary fellowships of the American Academy of Pediatrics, the National Academy of Medical Sciences and the Indian Academy of Pediatrics.

Prof. Ghai served as a short-term consultant to the World Health Organization and Asian Development Bank. He was a member of the Technical Advisory Group of the Control of Diarrheal Diseases Program of the World Health Organization (1987-89). He was member of the National Children's Board and several expert groups of the Government of India, UNICEF and Indian Council of Child Welfare. He was the editor of *Indian Pediatrics* and member of the editorial advisory boards of multiple journals.

Prof. Ghai was a teacher par excellence, an inspiring leader and a true visionary. His name shall always remain etched in the annals of pediatrics of our country.



Preface to the Ninth Edition

As we present the ninth edition of *Essential Pediatrics*, we are humbled by the role this textbook has played in imparting knowledge in child health to generations of doctors. Four decades ago, late Prof. OP Ghai foresaw the need for a textbook of pediatrics for medical students of the country and South Asia. Thereafter, each new edition has attempted to present updated knowledge to an expanding group of undergraduate and postgraduate students.

For India, the next three decades offer a never-before window of opportunity to accelerate its economic growth and emerge as a nation that would banish poverty forever, and attain heights of prosperity and well-being. We are transitioning through a demographic phase characterized by an exceptionally high young population constituting a workforce that is available for economic activity and nation-building. This demographic dividend can be realized only if children and adolescents are healthy, strong and intelligent. Pediatrics, the science and art of child healthcare, has thus acquired a new meaning and relevance in the context of new India.

With Ayushman Bharat, the nation has committed itself to a comprehensive primary health system and to ensure financial protection for the vulnerable families in accessing care for children and adults alike. Preventive and promotive health and nutrition will gain further ground, and the agenda of health loss due to pneumonia, diarrhea, other infections, complications of preterm birth and vaccine preventable diseases would receive even more attention. Adolescent health and development will be increasingly important in the coming years. We are already witnessing an upsurge in demand for healthcare for chronic systemic diseases, developmental disorders, disabilities and childhood origins of adult diseases. The realization that children have the right to secondary and tertiary health care has stimulated the development of pediatric superspecialty programs.

The present edition of *Essential Pediatrics* continues to respond to these developments. The book maintains its focus on undergraduate medical students. While we ensure that the 'must know' contents are thoroughly covered, we provide a glimpse of the 'should know' curriculum. We have ensured that the size of the book enables it to be readable and handy enough for the classroom and the bedside—as Prof. Ghai always reminded us. Given the emphasis on updated management of common childhood illnesses, primary care physicians and pediatricians would find the book useful. As before, there are strong sections on core areas that continue to serve the needs of postgraduate students.

A number of changes have been incorporated in this edition. We welcome new authors for chapters on disorders of development, central nervous system, micronutrients, otorhinolaryngology, poisoning and accidents, and integrated management of childhood illnesses. Most other chapters, especially on growth, nutrition, immunization, malignancies, genetics, inborn errors of metabolism and infections, have been revised. The CBSiCentral App featuring illustrations, clinical photographs, tables and algorithms shall serve as a useful educational resource. The editors are grateful to all the contributing authors for their scholarly inputs and ensuring that the chapters continue to provide succinct and updated information, meeting the learning needs of students.

We thank our undergraduate and postgraduate students for their suggestions on content. Dr Priyanka Khandelwal has helped during multiple stages of preparation, ensuring consistent style across chapters. Dr Aditi Sinha, Dr Biswaroop Chakrabarty and Dr Jitendra Meena read through several sections and made useful suggestions.

We thank our colleagues at CBSP&D, Mr YN Arjuna and Ms Ritu Chawla, for ensuring the quality of publication of previous and the present editions. We gratefully acknowledge our colleagues at the AIIMS and other centers for contributing illustrations and the support of our secretaries, Mr Anil Bhutani and Mr Akhilesh Sharma.

We whole-heartedly thank our readers for the trust, support and suggestions.

Vinod K Paul
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Introduction to Pediatrics

Vinod K Paul

The branch of medicine that deals with the care of children and adolescents is *pediatrics*. This term has roots in the Greek word *pedo pais* (a child) and *iatros* (healer). Pediatrics covers the age group less than 18 years of age. The goal of the specialty is to enable a child to survive, remain healthy, and attain the highest possible potential of growth, development and intellectual achievement. Child health encompasses approaches, interventions and strategies that preserve, protect, promote and restore health of children at individual and population level. A physician who specializes in the healthcare of children and adolescents is a *pediatrician*.

Children under 15 years of age comprise about 30% of India's population. Childhood is the state when the human being is growing and developing. It is the age to acquire good habits, values and lifestyles that would make children fit, responsible and productive adults and citizens. The family, society and nation are duty-bound to make children feel secure, cared for, and protected from exploitation, violence and societal ills. Female children face gender bias in access to healthcare and nutrition. A civilized society nurtures all its children, girls and boys alike, with love, generosity and benevolence.

Child is not a miniature adult. The principles of adult medicine cannot be directly adapted to children. Pediatric biology is unique and risk factors of disease are distinct. Clinical manifestations of childhood diseases may be different from adults. Indeed, many disorders are unique to children—these do not occur in adults. Drug dosages in children are specific and not a mathematical derivation of adult dosages. Wholesome nutrition is even more important for children not only to sustain life, but also to ensure their growth and development.

PEDIATRICS AS A SPECIALITY

Pediatrics is a fascinating speciality. It encompasses care of premature neonates on the one hand, and adolescents, on the other. The discipline of pediatrics has branched into well-developed superspecialities (such as neonatology,

nephrology, pulmonology, infectious disease, critical care, neurology, hemato-oncology, endocrinology and cardiology). Pediatrics encompasses intensive care of neonates and children using the most sophisticated technology, on the one hand, and, providing home care to newborns and children, on the other. Child health is thus a state-of-the-art clinical science as well as a rich public health discipline.

Medical students should possess competencies for the care of healthy and sick children. The agenda of high child mortality due to pneumonia, neonatal infections, preterm birth complications, diarrhea, birth asphyxia and vaccine preventable diseases is still unfinished. The benefits of advancing pediatric speciality care must reach all children. Besides, an increasing body of knowledge on pediatric origins of non-communicable diseases of the adult is set to change the paradigm of child health. Primary prevention and early detection of adult disorders is an important goal of pediatrics. Adolescence offers second chance in life to shape good lifestyles and prepare for adulthood.

HISTORICAL PERSPECTIVE

Medical care of children finds place in the ancient Indian, Greek and Chinese systems of health. But as a formal discipline, pediatrics took root in Europe and the US in the 19th century when some of the famous children hospitals were established. BJ Hospital for Children, Mumbai was the first child hospital to be established in India in 1928. Postgraduate diploma in pediatrics was started there in 1944; postgraduate degree programs began in the fifties. Pediatrics became an independent subject in MBBS course in mid-nineties. The first DM program in neonatology started in 1989 at PGIMER, Chandigarh, followed by one in pediatric neurology at AIIMS in 2004. Half a dozen institutions in the country now run DM programs in various pediatric specialities that include nephrology, pulmonology, critical care, hematology-oncology, oncology, cardiology and endocrinology.

CHALLENGE OF HIGH CHILD MORTALITY

India has the highest number of child births as well as child deaths for any single nation in the world. Each year, as many as 26 million babies are born in India. This comprises 18% of the global birth cohort. Of the 5.95 million under 5 child deaths in the world in 2015, 1.20 million (20%) occurred in our country. Table 1.1 provides the most recent figures on the key child mortality indices.

At 39 per 1000 live births (2016), under 5 mortality in the country is unacceptably high given our stature as an economic, scientific and strategic power. Under 5 mortality rate (U5MR) in Japan (3), UK (4), USA (7), Sri Lanka (10), China (11) and Brazil (16) is worth comparing with that of India. Great nations not only have negligible child mortality, but also ensure good health, nutrition, education and opportunities to their children. Almost 60% of under 5 deaths occur in the neonatal period (<28 days

Table 1.1: Child mortality indices in India in 2016

Indices	Rate
Under 5 mortality rate (U5MR)	39 per 1000 live births
Infant mortality rate (IMR)	34 per 1000 live births
Neonatal mortality rate (NMR)	24 per 1000 live births
Early neonatal mortality rate (ENMR)	18 per 1000 live births
Late neonatal mortality rate (LNMR)	06 per 1000 live births

U5MR: Number of deaths under the age of 5 years per 1000 live births
 IMR: Number of deaths under the age of 1 year per 1000 live births
 NMR: Number of deaths under the age of 28 days per 1000 live births
 ENMR: Number of deaths under the age of 7 days per 1000 live births
 LNMR: Number of deaths after completing 7 days of age but before 28 days per 1000 live births

of life), and the neonatal mortality (NMR) accounts for 70% infant deaths.

There has been a steady decline in child deaths. U5MR has declined by almost two-thirds between 1990 and 2015 from 126 to 43 per 1000 live births. The country missed the Millennium Development Goal 4 of achieving U5MR of 42 by 2015 by just one number. Between 2000 and 2016, IMR declined by 50%, while NMR decreased by 45% (Fig. 1.1). The early neonatal mortality (deaths under 7 days of life) has been less amenable to change.

In 2016, there were 9.8 lakh under-5 deaths and 5.7 lakh neonatal deaths in the country.

National programs focus generally on child deaths under the age of 5 years (under-5 mortality). The U5MR, IMR and NMR targets enshrined in the National Health Policy 2017 are depicted in Table 1.2.

Why do Children Die?

The eight important causes of under 5 mortality in children in India (with % contribution) are: (i) complications of prematurity (24%), (ii) pneumonia (13%), (iii) neonatal infections (12%), (iv) diarrhea (11%), (v) birth asphyxia (11%), (vi) congenital malformations (4%), (vii) measles (3%), and (viii) injuries (3%) (Fig. 1.2). The above causes are the proximate conditions that lead to death. Poverty, illiteracy, low caste, rural habitat, harmful cultural practices, and poor access to safe water and sanitation are important determinants of child health. Undernutrition is a critical underlying intermediate risk factor of child mortality, associated with about 45% of under 5 child deaths. Undernutrition causes stunting and wasting, predisposes to infections and is associated with adult disorders and low economic productivity.

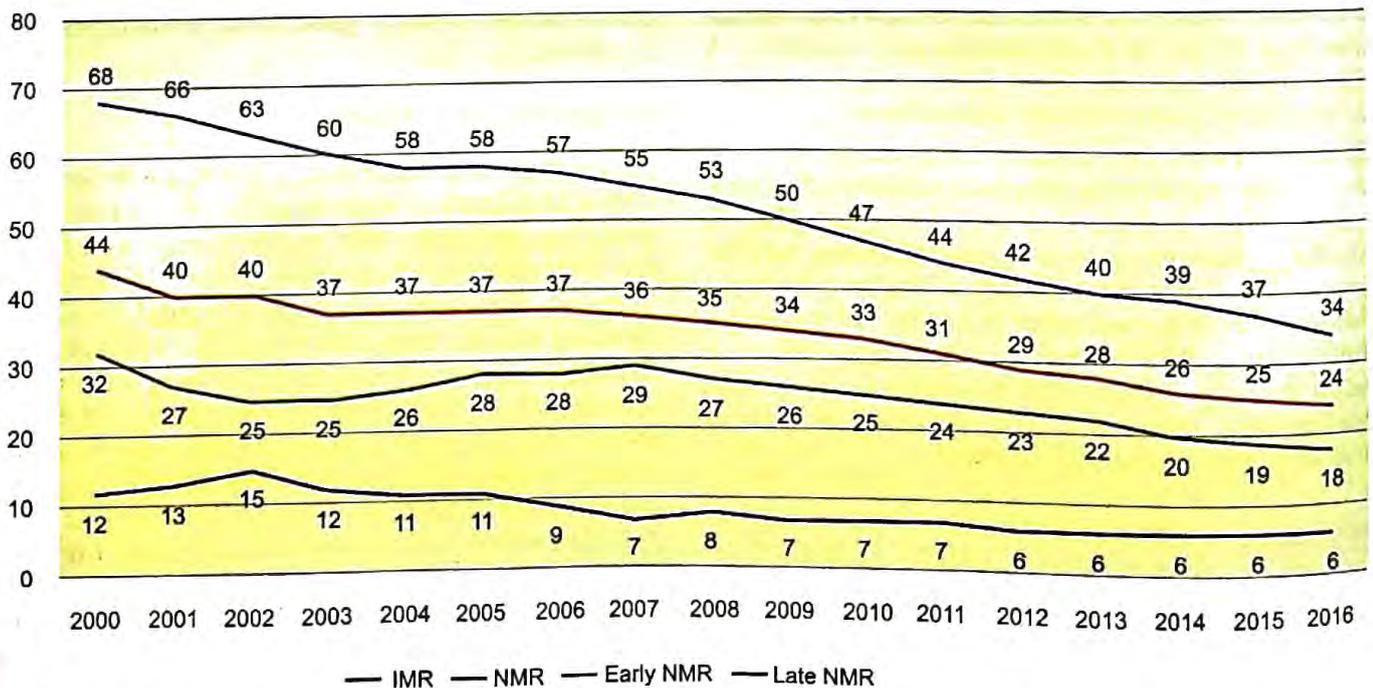


Fig. 1.1: Trends in neonatal and infant mortality, sample registration system. IMR infant mortality rate; NMR neonatal mortality rate

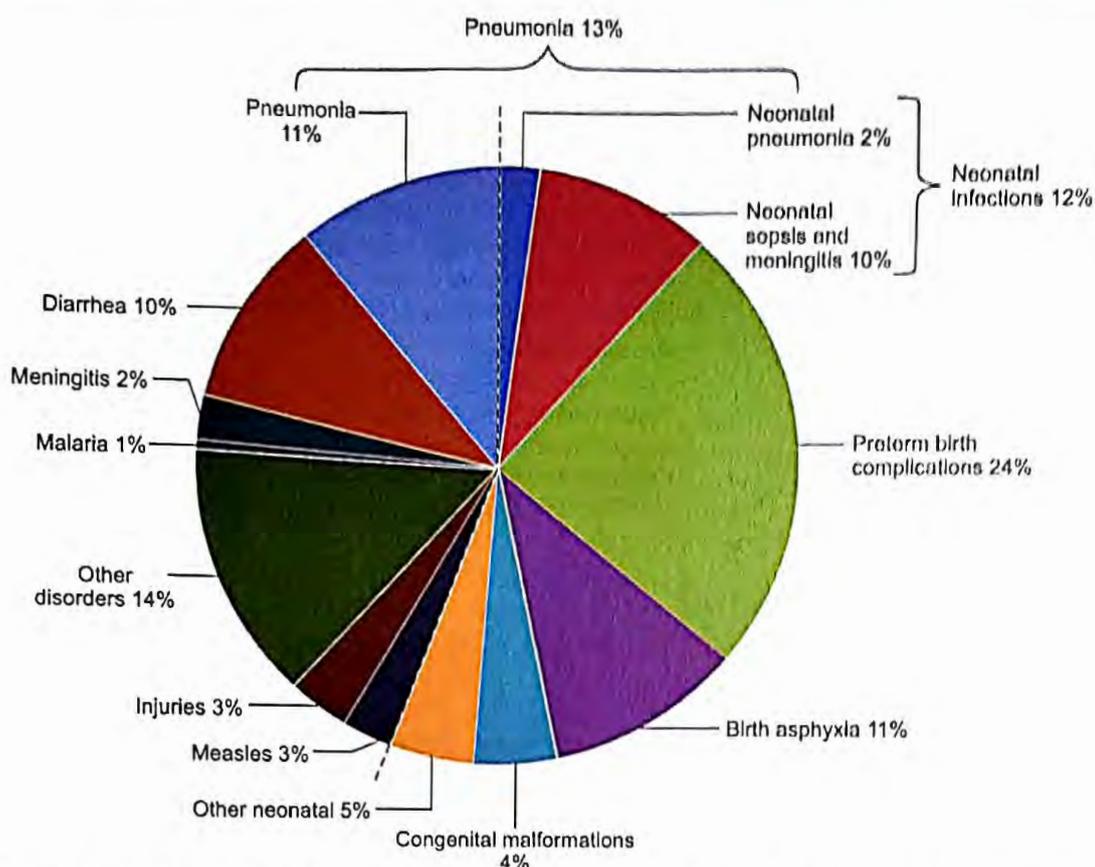


Fig. 1.2: Causes of under-5 child deaths. The area to the right of the dotted line indicates neonatal conditions

Table 1.2: Child mortality targets in the National Health Policy 2017

Reduce Under Five Mortality Rate (U5MR) to 23 per 1000 live births by 2025

Reduce Infant Mortality Rate (IMR) to 28 per 1000 live births by 2019.

Reduce Neonatal Mortality Rate (NMR) to 16 per 1000 live births by 2025

NATIONAL PROGRAMS ON CHILD HEALTH

Child health has been at the core of our health policy. The Universal Immunization Program launched in 1985 focused on immunization against six diseases (tuberculosis, poliomyelitis, diphtheria, pertussis, tetanus and measles). The Diarrhoeal Disease Control Programme was initiated in 1981 and Acute Respiratory Infections Control Programme in 1990. In 1992, India launched the Child Survival and Safe Motherhood (CSSM) program by combining interventions for child survival (immunization, control of diarrheal disease, respiratory infections, vitamin A supplementation, essential newborn care) and maternal health (antenatal care, deliveries in institutions, emergency obstetric care). In 1997, the program for family planning and the CSSM program were merged to create the Reproductive and Child Health Programme. In phase 2 of the RCH program (2005), adolescent health component was added.

The government launched the National Rural Health Mission (NRHM) in 2005. This mission included investment in public health, improvements in health systems, focus on communities, decentralisation and demand-side interventions to improve effectiveness of the programs. The RCH program was integrated into the NRHM, with prime focus on child and maternal health. Strategies include deployment of more than 900 000 ASHAs; an increase in ANMs, nurses and doctors; setting up of village health and sanitation; strengthened primary health care infrastructure; strengthened program management capacity, establishment of patient-welfare committees at facilities, and creation of emergency transport networks.

In 2013, the government reviewed maternal and child health program under NRHM and launched a Strategic Approach to Reproductive, Maternal, Newborn, Child and Adolescent Health (RMNCH+A) under the XII Plan. The intervention packages under the RMNCH+A strategy and details are shown in Table 1.3.

With the advent of the National Urban Health Mission, the NRHM is now called as National Health Mission (NHM). The roles of ASHA, AWW and ANM in maternal, newborn and child health in national programs are shown in Table 1.4.

In 2014, the country launched India Newborn Action Plan (INAP) which commits the country to single digit

Table 1.3: Summary of maternal, newborn and child health services under NHM

<i>Pregnancy, childbirth and immediate newborn care</i> Skilled obstetric care and essential newborn care including resuscitation	Interventions Package Facility deliveries by skilled birth attendants Neonatal resuscitation (Navjat Shishu Suraksha Karyakram that aims to train nurses and doctors in neonatal resuscitation)
Emergency Obstetric and Newborn care (EmONC)	Essential newborn care (warmth, hygienic care, breastfeeding, extra care of small babies, sickness detection) Linkages to Facility-based Newborn Care for sick neonates Program drivers
Postpartum care for mother and baby	Janani Suraksha Yojana (JSY) that provides cash incentive to the woman (and to the ASHA) for delivery in the facility Janani Shishu Suraksha Karyakram (JSSK) that entitles the mother and infants to free delivery, medicines / blood, diet, pickup and drop in government facilities
<i>Newborn and child care</i>	
Home based newborn care	Home visits by ASHAs (six for facility born babies, on days 3, 7, 14, 21, 28 and 42; an extra visit on day 1 for home births) Interventions for infants Examination; counsel for warmth; breastfeeding; hygiene; extra care of low birth weight babies; detection of sickness, referral Interventions for mother Postpartum care and counselling for family planning Program driver ASHA paid incentive for home care, birth weight record, birth registration and immunization (BCG, first dose OPV and pentavalent)
Facility based newborn care	Special Newborn Care Units (SNCUs) These specialized newborn units at district hospitals with specialised equipments including radiant warmers. These units have 12–16 beds with a staff of 3 physicians, 10 nurses and 4 support staff to provide round the clock services for newborn requiring special care, such as those with very low birth weight, neonatal sepsis/pneumonia & common complications. Newborn Stabilization Units (NBSUs) These are step down units providing facilities for neonates from the periphery where babies can be stabilized through effective care. These are set up in CHCs and provide services, including resuscitation, provision of warmth, initiation of breastfeeding, prevention of infection and cord care, supportive care: oxygen, IV fluids, provision for monitoring of vital signs and referral. Newborn Care Corners (NBCCs) These are special corners within the labor room at all facilities (PHC, CHC, DH) where deliveries occur. Services include resuscitation, provision of warmth, prevention of infections and early initiation of breastfeeding. Program driver Janani Shishu Suraksha Karyakram (JSSK) that entitles the mother and infants to free delivery, medicines/blood, diet, pickup and drop in government facilities
Integrated management of common childhood illnesses	Integrated Management of Neonatal and Childhood Illness (IMNCI) by ANMs and at first level facility (PHC) Facility-IMNCI at first referral level (e.g. CHC). Focuses on providing inpatient management of major causes of childhood mortality such as asphyxia, sepsis, low birth weight and pneumonia, diarrhea, malaria, meningitis and severe malnutrition Program driver Janani Shishu Suraksha Karyakram (JSSK) that entitles the infants to free delivery, medicines/blood, diet, pickup and drop in government facilities

Contd...

Table 1.3: Summary of maternal, newborn and child health services under NHM (Contd...)**Newborn and child care****Immunization**

Universal Immunization Programme now includes 7 vaccine preventable diseases (BCG, polio, diphtheria, pertussis, tetanus, measles and hepatitis B) for all children given push by Mission Indradhanush to ensure no one is left behind
 Pentavalent (DPT, hepatitis B and hemophilus Influenza B) vaccine
 OPV supplementary doses administered on National Immunization Days
 Injectable polio vaccine (IPV)
 MR (measles and rubella) vaccine
 Rotavirus vaccine in selected states
 Pneumococcal vaccine initiated in selected states
 Japanese encephalitis B vaccine in endemic districts; combined with routine immunization

Child health screening and early intervention services (Rashtriya Bal Swasthya Karyakram; RBSK)

Launched January 2013; child health screening and early intervention services through mobile health teams at block level.

Screening of all children (0–6 years' old) enrolled at least twice a year for 30 disorders (4Ds).

Defects (neural tube defect, Down syndrome, cleft lip/palate, club foot, dysplasia hip, congenital cataract or deafness, congenital heart diseases and retinopathy of prematurity)

Deficiencies (anemia, vitamin A deficiency, vitamin D deficiency, severe acute malnutrition and goiter)

Diseases (skin conditions, otitis media, rheumatic heart disease, reactive airway disease, dental caries and convulsions)

Developmental delays and disabilities (vision or hearing impairment, neuromotor impairment, motor delay, cognitive delay, language delay, behaviour disorder, learning disorders, attention deficit hyperactivity disorder)

Optional (congenital hypothyroidism, sickle cell anemia, beta thalassemia)

Free management of these children at district early intervention centres or identified tertiary level institutions

CHC: Community health centre; PHC: Primary health centre; DH: District hospital; Further reading; State of India's Newborns 2014

Table 1.4: Roles of grassroots team in child health

<i>Provider</i>	<i>Role in maternal, newborn and child health</i>
ASHA Accredited Social Health Activist	Mobilizing pregnant mother for antenatal check and care Accompanying pregnant mother to facility for delivery Home care of the newborn and post-partum mothers Facilitating immunization Promoting complementary feeding Primary care in diarrhea and pneumonia Health education
AWW Anganwari Worker	Providing nutrition supplement to pregnant mother and children Facilitating antenatal checks and immunization Promoting infant and young child feeding Growth monitoring of children Supplementary nutrition to children Managing malnourished children Non-formal pre-school education
ANM Auxiliary Nurse Midwife	Facilitating antenatal checks and care of pregnant mothers Immunization Supervising ASHA and AWW in newborn and child care Providing IMNCI services for neonates and children Antenatal checks Health education

The government has also revamped the adolescent health programme, namely, the Rashtriya Kishore Swasthya Karyakram with focus on nutrition, sexual and reproductive health, mental health, prevention of injuries and violence and prevention of substance misuse and addressing non-communicable disease.

NMR and stillbirth rate by 2030 and lays down strategies to achieve these targets.

Mission Indradhanush, launched in 2014, is a national immunization drive to attain 90% coverage of 7 vaccines (BCG, polio, diphtheria, pertussis, tetanus, measles and hepatitis B) by 2020.

Since 2014, the government also observes the Intensified Diarrhea Control Fortnight (IDCF) in June/July to intensify efforts to reduce child deaths due to diarrhoea. Through this initiative, mass awareness about prevention and treatment of diarrhea with a combination of Oral Rehydration Salt (ORS) solution and zinc tablets is created.

A new program, namely Home-based Care of Young Child (HBYC), will be introduced in 2018. This encompasses 3 monthly home visits by ASHA workers from 3 months to 15 months of age. The program aims to ensure introduction of complementary feed at 6 months of age with adequate nutritional intake with increasing age, continuing breast feeding; counselling for immunization, and early care seeking in diarrhea and pneumonia; growth monitoring and care of undernourished child; early childhood development; and to ensure hygiene and sanitation.

All these efforts coupled with overall socio-economic development are paying good dividends. India has attained institutional delivery rate of over 80%, a remarkable jump from just 39% a decade ago. In 2015-16, full immunization coverage (BCG, OPV, DPT, measles) was 62% and use ORS for diarrhea reached 51% (compared to 44% and 26% in 2005-06, respectively).

FUTURE OF CHILD HEALTH

The Nation is addressing child health challenges with greater dynamism than ever before. Investments are being made for health programs and health system strengthening. Likewise, complete conditional cash transfers and entitlements are enshrined to stimulate demand for maternal, newborn and child healthcare. The country is surging ahead with stronger economy and accelerated development. Child health and survival is at the core of the National Health Policy 2017 as well as country's commitments for the Sustainable Development Goals (SDGs). Ayushman Bharat initiative of the government announced in 2018 encompasses strengthening of primary health care by developing 150,000 health and wellness centres, and by providing financial protection for hospitalizations for 100 million families (500 million persons). The latter will enable families cashless access to in-patient care for pediatric and neonatal illnesses. Swachh Bharat mission will help reduce ill health. India is poised to attain low child mortality rate, and improve remarkably the health and nutrition status of her children in near future.

Suggested Reading

- You D, Hug L, Ejdemyr S et al. Global, regional, and national levels and trends in under-5 mortality between 1990 and 2015, with scenario-based projections to 2030: systematic analysis by the UN inter-agency group for child mortality estimates. *The Lancet* 2015; 386: 2275-86.
- Registrar General of India (2016). Sample Registration System (SRS) statistical report 2016. New Delhi: Registrar General of India.
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Growth

Ramesh Agarwal • Naveen Sankhyan • Vandana Jain

Growth is an essential feature that distinguishes a child from an adult. The process of growth starts from the time of conception and continues until the child grows into a fully mature adult. The terms 'growth' and 'development' are often used together, but are not interchangeable because they represent two different facets of the dynamics of change, i.e. those of quantity and quality.

The term *growth* denotes a net increase in the size or mass of tissues. It is largely attributed to multiplication of cells and increase in the intracellular substance. Hypertrophy or expansion of cell size contributes to a lesser extent to the process of growth.

Development specifies maturation of functions. It is related to the maturation and myelination of the nervous system and indicates acquisition of a variety of skills for optimal functioning of the individual.

Growth and development usually proceed concurrently. While they are discussed separately, both growth and development are closely related; hence, factors affecting one also tend to have an impact on the other. During early embryonic period of life, an exponential increase in the number of cells occurs. At the early embryonic stage, fetal cells divide and differentiate to form tissues and organs. In the latter half of pregnancy and early childhood, there is also an increase in cell size. This manifests as an increase in the protein to DNA ratio. The cell size continues to enlarge until about 10 years of age. The body cells remain in a state of dynamic equilibrium; hence aging cells are continuously replaced by new cells. The rate of turnover of cells in different tissues is variable.

FACTORS AFFECTING GROWTH

Fetal Growth

Fetal growth is influenced primarily by fetal, placental and maternal factors. In humans, 40% of variation in the birth-weight is due to genetic factors while the rest is due to environmental factors. The fetus has an inherent growth potential, and under normal circumstances, grows into a healthy appropriate sized newborn. The maternal-

placental-fetal unit acts in harmony to provide the needs of the fetus.

Genetic potential: Parental traits are usually transmitted to the offspring. Thus, tall parents have tall children; the size of the head is more closely related to that of parents than are the size and shape of hands and feet. Similarly, the structure of the chest and fatty tissue has better genetic association than other somatic characteristics.

Sex: Boys are generally taller and heavier than girls at the time of birth.

Fetal hormones: Human fetus secretes thyroxine from the 12th week of gestation. Thyroxine and insulin have an important role in regulating tissue accretion and differentiation in the fetus. Both hormones are required for normal growth and development, particularly during late gestation. Glucocorticoids also play an important role, primarily towards the end of gestation and influence the prepartum maturation of organs such as liver, lungs and gastrointestinal tract. Growth hormone, though present in high levels in fetus, is not known to influence fetal growth.

Fetal growth factors: A large number of growth factors are synthesized locally in fetal tissues, and act principally by autocrine and paracrine mechanisms. Their prime effect is on cell division, though they also influence other aspects of tissue growth. These factors can be both growth promoting or inhibitory. The insulin like growth factor (IGF)-I and IGF-II are among the most extensively studied fetal growth factors.

Placental factors: As in most species, fetal weight directly correlates with placental weight at term. Fetal growth is highly dependent on the structural and functional integrity of the placenta. With advancing gestation, the weight of the placenta increases to cater to the increased needs of the baby. There are important functional and structural changes in the placenta that make this adaptation more efficient. The total villous surface area increases, the diffusion distance decreases, the fetal capillaries dilate and the resistance in fetoplacental vasculature falls. This positive remodeling facilitates nutrient transport across the placenta.

Maternal factors: The mother's own fetal and childhood growth and her nutrient intake and body composition at the time of conception and during pregnancy, play an important role in determining fetal size. Teenage or advanced age, recent pregnancy, high parity and anemia negatively influence fetal size and health. Maternal intake of tobacco (smoked or chewed) and drug or alcohol abuse also retard fetal growth. Obstetric complications such as pregnancy-induced hypertension, pre-eclampsia and multiple pregnancies produce fetal growth restriction. Pre-existing chronic systemic disease (chronic renal failure, congestive heart failure) and acquired infections (rubella, syphilis, hepatitis B, HIV, CMV, toxoplasmosis) may influence fetal growth.

Postnatal Period

The growth of the child during postnatal life is determined by genetic potential as well as internal and external influences.

Genetic factors: Both chromosomal disorders and mutations in specific genes can affect growth. Chromosomal defects like Turner syndrome and Down syndrome manifest as growth retardation. Mutation of single genes may result in inherited retardation of growth, e.g. Prader-Willi syndrome and Noonan syndrome. While most disorders lead to short stature, some genetic defects can also result in tall stature, e.g. Klinefelter syndrome and Sotos syndrome.

Intrauterine growth restriction (IUGR): IUGR resulting in low birth weight (LBW) constitutes an important risk factor for postnatal malnutrition and poor growth. LBW increases the odds of underweight, stunting and wasting in the first 5 years of life by 3 to 5 times. At 6 months of age, approximately one-third each of underweight (28%), stunting (28%) and wasting (22%) are attributable to LBW. At ages between 1 and 5 years, LBW accounts for 16–21% of wasting, 8–16% of stunting and 16–19% of underweight. Almost one-third and one-fifth of infants have wasting and stunting, respectively, even at birth (Fig. 2.1).

During early infancy, exclusive breastfeeding provides adequate nutrition, prevents infections and protects the infants from further undernourishment. However, at 3–5 months, the common practice of supplementing the infants with animal milk increases morbidity due to infections leading to underweight and stunting. Subsequently, faulty complementary feeding practices (starting too late, using too little and very less calorie dense foods) along with poor hygiene lead to a further rise in rates of underweight and stunting.

Hormonal influence: Normal growth cannot proceed without the right milieu of hormones in the body throughout childhood and adolescence. Absence of growth hormone or thyroxine results in dwarfism, underscoring the importance of these factors in promoting growth. During adolescence, androgens and estrogens have an important influence on the growth spurt and final adult height.

Sex: The pubertal growth spurt occurs earlier in girls. However, their mean height and weight in girls are usually less than those in boys of corresponding ages at the time of full maturity.

Nutrition: Growth of children suffering from protein-energy malnutrition, anemia and vitamin deficiency states is retarded. Calcium, iron, zinc, iodine and vitamins A and D are closely related to disorders of growth and development. On the other hand, overeating and obesity accelerate somatic growth.

Infections: In low resource settings, one of the commonest contributors to poor childhood growth is infections. Persistent or recurrent diarrhea and respiratory tract infections are common causes of growth impairment. Systemic infections and parasitic infestations may also retard the velocity of growth. The risk of stunting at 2 years of age is shown to increase with each episode of diarrhea and with each day of diarrhea before 2 years of age. It was also shown that the attributable risk for stunting for 5 or more episodes of diarrhea before 24 months of age was 25%.

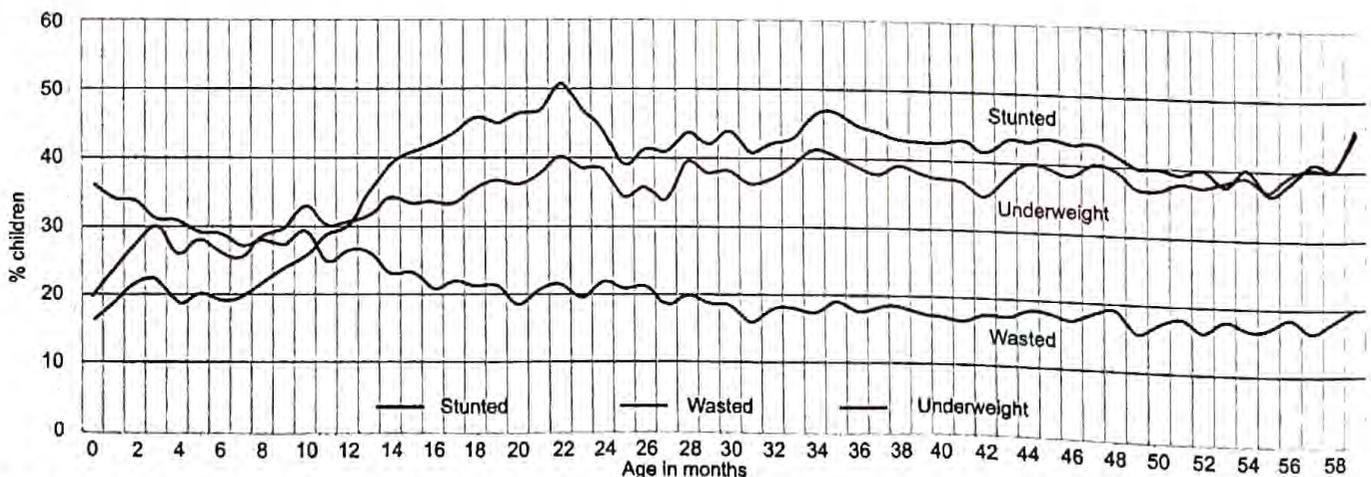


Fig. 2.1: Proportion of children with stunting, underweight and wasting from birth to 5 years. Reproduced with permission from Paul, et al. *Lancet* 2011;377:332–49

Chemical agents: Administration of androgenic hormones initially accelerates the skeletal growth. However, androgens cause the epiphyses of bones to close prematurely, leading to early cessation of bone growth.

Trauma: A fracture at the end of a bone may damage the growing epiphysis, and thus hamper skeletal growth.

Social Factors

Socioeconomic level: Children from families with high socioeconomic level usually have better nutritional state. They suffer from fewer infections because of better nutrition and hygienic living conditions.

Poverty: Hunger, undernutrition and infections, often associated with poverty, cause poor growth.

Natural resources: Plentiful natural resources encourage industrial and agricultural enterprise in the country. Improved nutrition of children in the community is facilitated when there is a climb in gross national product and per capita income is high.

Climate: The velocity of growth may alter in different seasons and is usually higher in spring and low in summer months. Infections and infestations are common in hot and humid climate. Weather also has a pivotal effect on agricultural productivity, ready availability of food and capacity for strenuous labor by the population.

Emotional factors: Children from broken homes and orphanages do not grow and develop at an optimal rate. Anxiety, insecurity and lack of emotional support and love from the family prejudice the neurochemical regulation of growth hormone release. Parents who had happy childhood and carry a cheerful personality are more likely to have children with similar countenance.

Cultural factors: Methods of child rearing and infant feeding in the community are determined by cultural habits and conventions. There may be religious taboos against consumption of particular types of food. These affect the nutritional state and growth performance of children.

Parental education: Mothers with more education are more likely to adopt appropriate health promoting behaviors, which have direct and indirect influences on growth and development.

Consequences of Impaired Growth

Maternal and child undernutrition is the underlying cause of 3–5 million deaths annually and accounts for 35% of the disease burden in children younger than 5 years. It is estimated that India has more than 61 million stunted children, that amounts to 34% of the global total.

Several major disorders of later life, including coronary heart disease, hypertension and type 2 diabetes, originate from impaired intrauterine growth and development. These diseases may be consequences of 'programming', whereby a stimulus or insult at a critical, sensitive period

of early life has permanent effects on structure, physiology and metabolism. The "Developmental Origins of Health and Diseases; DOHaD; Barker hypothesis" proposes that alterations in fetal nutrition and endocrine status result in developmental adaptations that permanently change structure, physiology and metabolism, thereby predisposing individuals to cardiovascular, metabolic and endocrine disease in adult life. As a result, infants born with low birth weight have increased risk of diabetes, hypertension, coronary artery disease and hyperlipidemia in adult life.

Laws of Growth

Growth and development of children is a continuous and orderly process: There are specific periods in a child's life when the rate of growth is steady, accelerates or decelerates (Table 2.1). The fetus grows fast in the first half of gestation. Thereafter, the rate of growth is slowed down until the baby is born. In the early postnatal period, the velocity of growth is high, especially in the first a few months. Thereafter, there is slower but steady rate of growth during mid-childhood. A second phase of accelerated growth occurs at puberty. Growth decelerates thereafter for some time and then ceases altogether. The general body growth is rapid during the fetal life, first one or two years of postnatal life and also during puberty (Fig. 2.2). In the intervening years of mid-childhood, the somatic growth velocity is relatively slowed down.

Growth pattern of every individual is unique: Order of growth is cephalocaudal and distal to proximal. During fetal life, growth of head occurs before that of neck, and arms grow before legs. Distal parts of the body such as hands increase in size before upper arms. In the postnatal life, growth of head slows down but limbs continue to grow rapidly.

Table 2.1: Periods of growth

Prenatal period	
Ovum	0 to 2 weeks
Embryo	3 to 8 weeks
Fetus	9 weeks to birth
Perinatal period	22 weeks to 7 days after birth
Postnatal period	
Newborn	First 4 weeks after birth
Infant	Birth to <12 months (neonate: Birth to 28 days; post-neonate: 29 days to <1 year)
Toddler	1 year to 36 months
Preschool child	37–72 months
School age child	73 months–12 years
Adolescence	
Early	10–13 years
Middle	14–16 years
Late	17–20 years

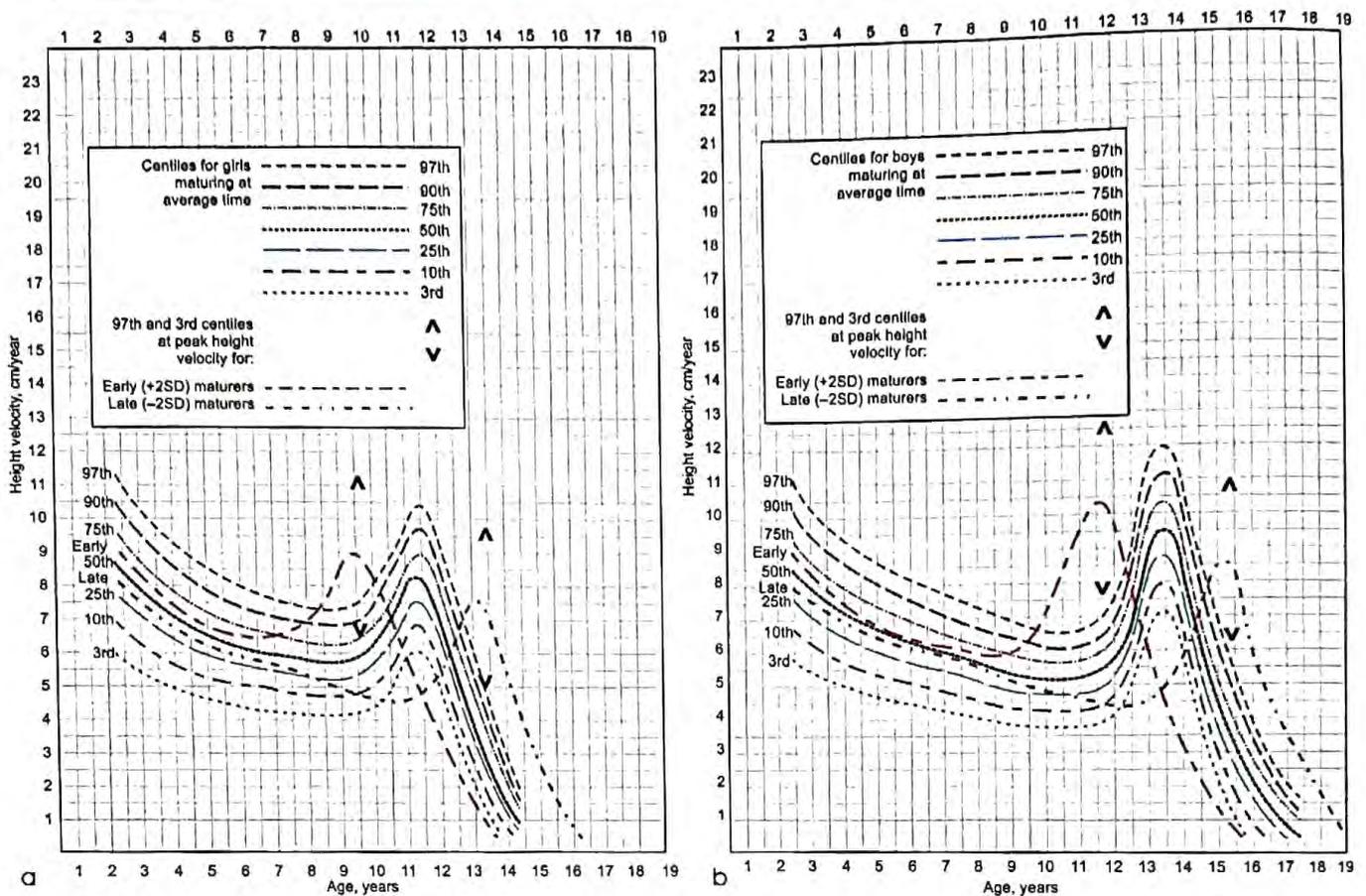


Fig. 2.2: Normal height velocity (a) girls and (b) boys according to age. Curves for height velocity at 50th centile for early and late maturers are also depicted. The open arrow heads indicate the 3rd and 97th centile for peak height velocity for these individuals. Reprinted from *J Pediatr* 1985;107:317-29; with permission from Elsevier

Different tissues grow at different rates (Fig. 2.3)

Brain growth: The brain enlarges rapidly during the latter months of fetal life and early months of postnatal life. At birth, the head size is about 65-70% of the expected head size in adults. It reaches 90% of the adult head size by the age of 2 years. Thus, the fetal phase and the first two years are crucial periods for brain development. Later periods are also important for acquiring neuromotor functions and cognitive ability.

Growth of gonads: Gonadal growth is dormant during childhood and becomes conspicuous during pubescence.

Lymphoid growth: The growth of lymphoid tissue is most notable during mid-childhood. During this period, the lymphoid tissue is overgrown and its mass may appear to be larger than that of the fully mature adult. A sign of accelerated lymphoid growth is the frequent finding of large tonsils and palpable lymph nodes in normal children between 4 and 8 years.

Growth of body fat and muscle mass: Body tissues can be divided into fat and fat-free components. The lean body mass includes muscle tissue, internal organs and skeleton and contains only a small amount of fat. The growth in lean body mass is primarily due to increase in muscle mass.

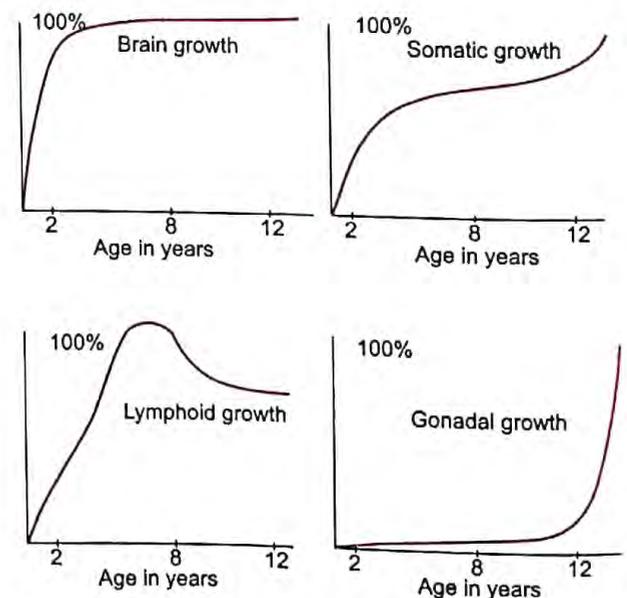


Fig. 2.3: Rates of growth of different tissues and organs

Lean body mass correlates closely with stature. Taller children have greater lean body mass than shorter children of the same age. After the pubertal growth spurt, boys have greater lean body mass compared to girls. Body fat is the

storehouse of energy. It is primarily deposited in the subcutaneous adipose tissue. Girls have more subcutaneous adipose tissue than boys. Moreover, the sites and quantity of adipose tissue differs in girls and boys. Girls tend to add adipose tissue to breasts, buttocks, thighs and back of arms during adolescence.

SOMATIC GROWTH

Skeletal Growth

Skeletal growth is a continuous process occurring during the whole of childhood and adolescence. It is steady until the pubertal growth spurt when it accelerates and subsequently slows considerably. The skeleton is mature once the epiphysis or growth plates at the end of long bones fuse to the shaft or diaphysis. This occurs by about 18 years in girls and 20–22 years in boys. The degree of skeletal maturation closely correlates with the degree of sexual maturation. A child who has advanced sexual maturity will also have earlier skeletal maturation.

Skeletal maturation is assessed by noting the appearance and fusion of epiphysis at the ends of long bones. Apart from this, bone mineral density can be ascertained by dual energy X-ray absorptiometry [DXA]. This method allows assessment of bone mineral content and density at different ages.

Bone Age Estimation

Assessment of bone age postnatally is based on (i) number, shape and size of epiphyseal centers and (ii) size, shape and density of the ends of bones. Tanner and Whitehouse described 8 to 9 stages of development of ossification centers and gave them 'maturity scoring'. Fifty percent of the score was given for carpal bones, 20% for radius, ulna and 30% for phalanges. Twenty ossification centers are generally used for determining the bone age. These include: (i) carpal bones, (ii) metacarpals, (iii) patella, (iv) distal and

proximal toes in both sexes; and (v) distal and middle phalanges in boys and distal and proximal phalanges in girls. To determine the skeletal age in infants between 3 and 9 months, a radiograph of shoulder is most helpful. A single film of hands and wrists is adequate in children between the ages of 1 and 13 years. For children between 12 and 14 years, radiographs of elbow and hip give helpful clues.

Eruption of Teeth

Primary teeth: The teeth in the upper jaw erupt earlier than those in the lower jaw, except for lower central incisors and second molar (Table 2.2).

Permanent teeth: The order of eruption is shown in Table 2.2. The first molars are the first to erupt.

ASSESSMENT OF PHYSICAL GROWTH

Weight: The weight of the child in the nude or minimal light clothing is recorded accurately on a lever or electronic type of weighing scale (Fig. 2.4). Spring balances are less accurate. It is important that child be placed in the middle of weighing pan. The weighing scale should be corrected

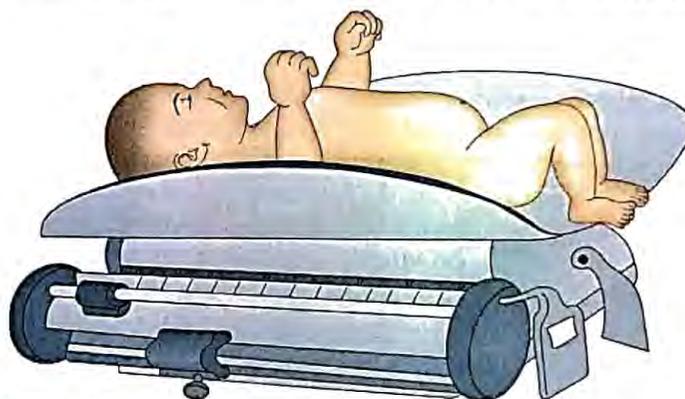


Fig. 2.4: Beam scale for accurate measurement of weight. The child should be nude or in minimal clothing

Table 2.2: Timing of dentition

Primary dentition	Time of eruption, months		Time of fall, years	
	Upper	Lower	Upper	Lower
Central incisors	8–12	6–10	6–7	6–7
Lateral incisors	9–13	10–16	7–8	7–8
First molar	13–19	14–18	9–11	9–11
Canine	16–22	17–23	10–12	9–12
Second molar	25–33	23–31	10–12	10–12

Permanent teeth	Time of eruption, years			
	Upper	Lower	Upper	Lower
First molar	6–7	6–7	First premolar	10–11
Central incisors	7–8	6–7	Second premolar	10–12
Lateral incisors	8–9	7–8	Second molar	12–13
Canine	11–12	10–12	Third molar	17–21

for any zero error before measurement. Serial measurement should be done on the same weighing scale. The weight of a small baby can also be recorded with the mother/caregiver using a tared weighing scale (Panel 1).

2

Panel 1: Steps in weighing a baby using a digital scale with taring facility (Fig. 2.5)

1. Use the tared weighing method to weigh children who cannot stand on the weighing scale
2. Place the weighing scale on a flat, hard, and even surface.
3. Babies should be weighed naked or with minimal clothing.
4. Ask the mother/caregiver to stand in the middle of the scale (without footwear), feet slightly apart and to remain still.
5. With the mother/caregiver still standing on the scale, press the *tare* button.
6. The scale is tared when the display shows the number zero (while mother/caregiver is still standing on the scale).
7. Handover the baby to the mother
8. Record the baby's weight that appears on the display.

Note: If the mother is very heavy (e.g. 100 kg), then a lighter person should hold the baby on the tared scale.

Reference: World Health Organization. Training Course on Child Growth Assessment. Geneva, WHO, 2008.

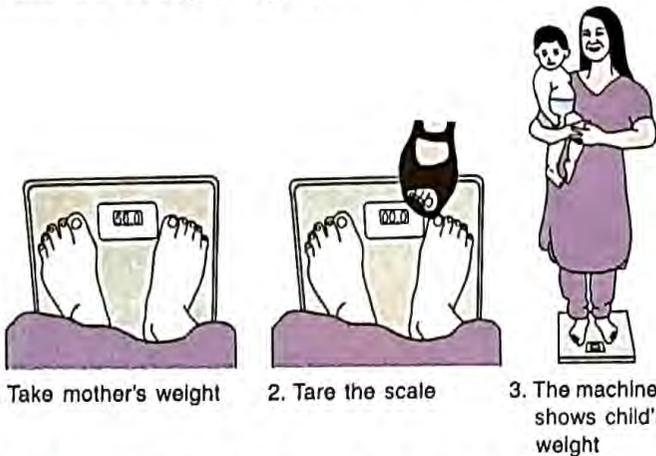


Fig. 2.5: Weighing a small child with mother on a weighing scale with taring facility

Length: Length is recorded for children under 2 years of age. Hairpins are removed and braids undone. Bulky diapers should be removed. The child is placed supine on a rigid measuring table or an infantometer. The head is held firmly in position against a fixed upright headboard by one person. Legs are straightened, keeping feet at right angles to legs, with toes pointing upward. The free footboard is brought into firm contact with the child's heels (Fig. 2.6). Length of the baby is measured from a scale, which is set in the measuring table. Measurement of length of a child lying on a mattress and/or using cloth tapes, is inaccurate and not recommended (Panel 2).

Panel 2: Steps in measuring length (Fig. 2.6)

1. Place the child on his back on a clean length board (use a clean cloth to make the board comfortable)
2. Ensure that the head is in firm contact with the headboard

3. Position the head such that the child is looking straight up (the line joining the external auditory meatus and the lower border of the eyeball is perpendicular to the board)
 4. The shoulders and the spine should be in touch with the board and the knees should be gently straightened.
 5. The footboard should be moved to ensure that the feet are firmly against it.
 6. Measure the length in this position.
- Note:* Be very gentle with newborns, their knees may not straighten fully. If it is not possible to position both knees, then measure with one leg in position.

Reference: World Health Organization. Training Course on Child Growth Assessment. Geneva, WHO, 2008.



Fig. 2.6: Measurement of length on an infantometer. Note how the knees are gently straightened while the head and feet are aligned

Standing height: For the standing height, the child stands upright. Heels are slightly separated and the weight is borne evenly on both feet. Heels, buttocks, shoulder blades and back of head are brought in contact with a vertical surface such as wall, height measuring rod or a stadiometer. The head is so positioned that the child looks directly forwards with Frankfort plane (the line joining the root of external auditory meatus to the lower margin of orbit) and the biauricular plane being horizontal. The head piece is kept firmly over the head to compress the hair (Fig. 2.7 and Panel 3).

Panel 3: Steps in measuring standing height (Fig. 2.7)

1. The child's footwear and any hair tie-up should be removed.
2. The child should stand on the height board with the back of the head, shoulders, buttocks, calves, and heels touching the vertical board.
3. Position the head such that the child is looking straight ahead (the line joining the external auditory meatus and the lower border of the eyeball should be parallel to the floor)
4. With the child still in this position, the headboard is gently pulled down to rest firmly on the head.
5. Measure the length in this position.

Reference: World Health Organization. Training Course on Child Growth Assessment. Geneva, WHO, 2008.

Head circumference: Hair ornaments are removed and braids undone. Using a nonstretchable tape, the maximum circumference of the head from the occipital protuberance to the supraorbital ridges on the forehead is recorded (Fig. 2.8).

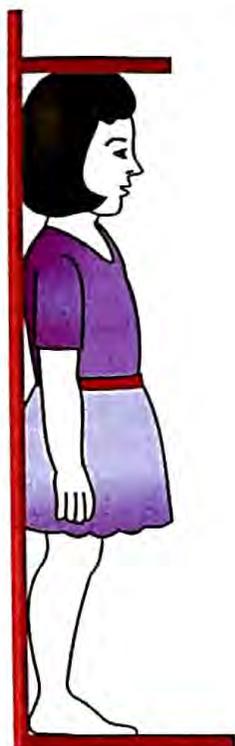


Fig. 2.7: Method of recording height. Note the erect posture and the bare feet placed flat on the ground. The back of heels, buttocks, shoulders and occiput are touching the wall



Fig. 2.8: Method of recording head circumference

Chest circumference: The chest circumference is measured at the level of the nipples, midway between inspiration and expiration (Fig. 2.9).

Mid-upper arm circumference: To measuring the mid-upper arm circumference, first mark a point midway between the tip of acromian process of scapula and the olecranon of ulna, while the child holds the left arm by his side (Fig. 2.10). It should be ensured that the tape is just tight enough to avoid any gap as well as avoid compression of soft tissues.

Normal Growth

It is difficult to precisely define the normal pattern of growth. Generally, it implies an average of readings obtained in a group of healthy individuals, along with a permissible range of variation, i.e. between the third and ninety-seventh percentiles. Most healthy children maintain their growth percentile on the growth charts as the years pass by. Significant deviation in a child's plotted position on the growth chart can be due to a recent illness or over- or



Fig. 2.9: Method of measurement of chest circumference at the level of nipples

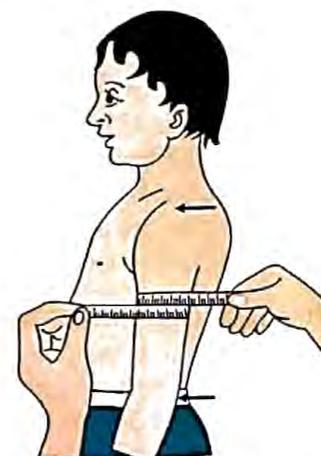


Fig. 2.10: Measurement of mid-upper arm circumference. Note how the anatomical landmarks are first located (arrows) to accurately measure the circumference

undernutrition. It is also important to take into account the gestational age of infants born prematurely. The duration of prematurity is subtracted from the infant's chronological age. This correction, however, is not required after 2 years of age.

Weight: The average birth weight of neonates is about 3 kg. During the first a few days after birth, the newborn loses extracellular fluid equivalent to about 10% of the body weight. Most infants regain their birth weight by the age of 10 days. Subsequently, they gain weight at a rate of approximately 20–40 g per day for the first 3 months of life. Thereafter, they gain about 400 g weight every month for the remaining part of the first year. An infant usually doubles his birth weight by the age of 5 months. The birth weight triples at 1 year and is four times at 2 years of age. Thus, the weight at 5 months, 1 year and 2 years is approximately 6, 9 and 12 kg, respectively. The weight of a child at the age of 3 years is approximately five times that of the birth weight. At 5 years, the expected weight can be calculated by multiplying the birth weight by 6, at 7 years by 7 and at 10 years by 10. It follows that the expected weight at 3, 5, 7 and 10 years is approximately 15, 18, 21 and 30 kg, respectively. On an average, a child gains about 2 kg every year between the ages of 3 and 7 years, and 3 kg per year after that till the pubertal growth spurt begins (Table 2.3).

Table 2.3: Approximate anthropometric values by age

Age	Weight (kg)	Length or height (cm)	Head circumference (cm)
Birth	3	50	34
6 months	6 (doubles)	65	43
1 year	9 (triples)	75	46
2 years	12 (quadruples)	90	48
3 years	15	95	49
4 years	16	100	50

2 **Length or height:** The infant measures approximately 50 cm at birth, 60 cm at 3 months, 65 cm at 6 months 70 cm at 9 months, 75 cm at 1 year and 90 cm at 2 years. A normal Indian child is 100 cm tall at the age of 4 years. Thereafter, the child gains about 6 cm in height every year, until the age of 12 years. After this, increments in height vary according to the age at the onset of puberty. There is a marked acceleration of the growth during puberty.

Head circumference (HC): Head growth is rapid, especially in the first half of infancy. It reflects the brain growth during this period. The head growth slows considerably thereafter. Beginning at 34 cm at birth, the head circumference increases approximately 2 cm per month for first 3 months, 1 cm per month between 3 and 6 months and 0.5 cm per month for the rest of the first year of life. The head circumference is approximately 40 cm at 3 months, 43 cm at 6 months, 46–47 cm at 1 year, 48 cm at 2 years. By 12 years, it is 52 cm.

Chest circumference: The circumference of chest is about 3 cm less than the head circumference at birth. The circumference of head and chest are almost equal by the age of 1 year. Thereafter, the chest circumference exceeds the head circumference.

Body mass index (BMI): The formula to calculate BMI is weight (kg)/height (meter)². BMI is primarily used to assess obesity.

Growth Charts

If the growth measurements are recorded in a child over a period of time and are plotted on a graph, the deviation in the growth profile of the child from the normal pattern of growth for that age can be easily interpreted. This is a satisfactory tool to diagnose deviation of growth from normal. Allowed normal range of variation in observations is conventionally taken as values between 3rd and 97th percentile curves. Percentile curves represent frequency distribution curves. For example, 25th percentile for height in a population would mean that height of 75% of individuals is above and 24% are below this value. One standard deviation (SD) above the mean coincides with 84th percentile curve. Likewise 16th percentile curve represents one SD below the mean. Values between third and 97th percentile curve correspond to mean ± 2 SD.

Z-scores: In a population with observations in a typical Gaussian (normal) distribution, any individual value can be expressed as how many SDs it lies above or below the mean. This is the Z-score for that observation. Thus, if a child's weight is at 2 SD below the mean, it is equivalent to $-2 Z$. If the value lies above the mean, Z-score is positive, otherwise it is negative. The formula for calculating the Z-score is:

$$\text{Z-score} = \frac{\text{Observed value} - \text{mean value}}{\text{Standard deviation}}$$

Z-score allows comparison of different observations between individuals. For example, one can compare the height and weight of two individuals by obtaining the respective Z-scores.

Growth Standards

Growth standards represent norms of growth and can be presented in tabular or graphical manner. These are obtained by either cross-sectional or longitudinal studies in large populations. Based on data obtained from US children, the National Center for Health Statistics (NCHS) developed growth charts in 1977. In the year 2000, revised growth charts provided by CDC offered an improved tool to assess child health. However, these charts were based on data obtained from US children who were formula fed.

Sensing the need for more internationally applicable growth standards, the WHO conducted the 'Multicentre Growth Reference Study' (MGRS) and published new growth charts for infants and children up to 5 years of age in 2006. The MGRS was a community-based, multi-country project conducted in Brazil, Ghana, India, Norway, Oman and the United States. The children included in the study were raised in environment that minimized constraints to growth such as poor nutrition and infection. In addition, their mothers followed healthy practices such as breastfeeding their children and did not smoke during and after pregnancy. These WHO child growth standards are unique on several counts. They provide data on 'how children should grow', and go beyond the traditional descriptive references. The new standards make breastfeeding the biological norm and establishes the breastfed infant as the normative growth model. The pooled sample from the six participating countries makes it a truly international standard and reiterates the fact that child populations grow similarly across the world's major regions when their needs for health and care are met. These standards also include new growth indicators beyond height and weight that are particularly useful for monitoring the increasing epidemic of childhood obesity, such as skinfold thickness. The study's longitudinal nature further allows the development of growth velocity standards, enabling the early identification of under or over-nourishment. Figures 2.11 to 2.20 provide percentile curves for weight, length or height, weight for height and head circumference for girls and boys up to 5 years of age based on WHO MGRS standards. Tables 2.4 to 2.8 summarize the data on length, weight and head circumference for these children.

Growth standards are not available for children older than 5 years. The Indian Academy of Pediatrics (IAP) has provided updated growth charts for children 5 to 18 years, based on data from 33148 children (Table 2.9 and 2.10). The charts can also be downloaded from <http://iapindia.org/Revised-IAP-Growth-Charts-2015.php>.



Fig. 2.11: Weight-for-age (girls) from birth to 5 years (percentiles)

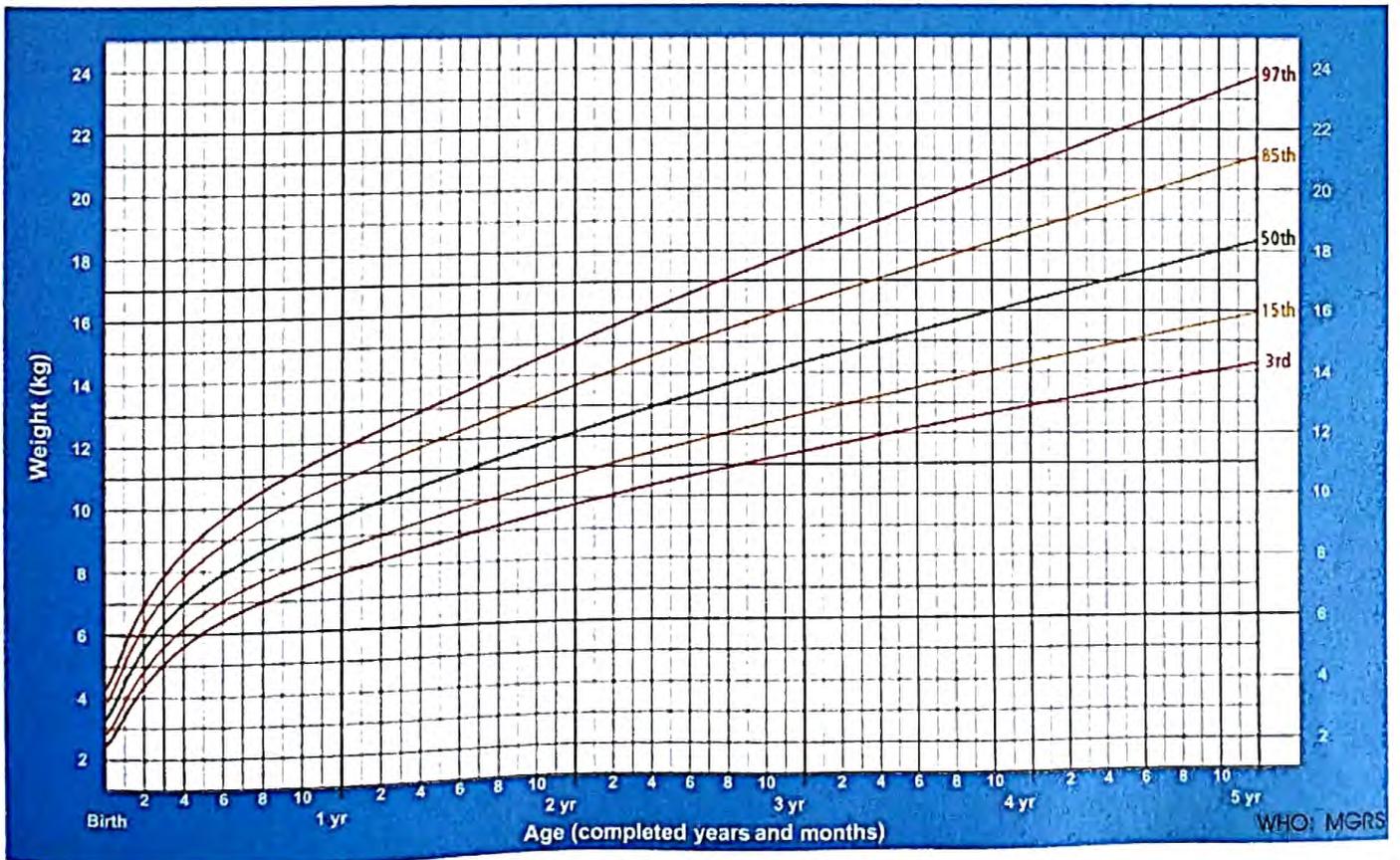


Fig. 2.12: Weight-for-age (boys) from birth to 5 years (percentiles)

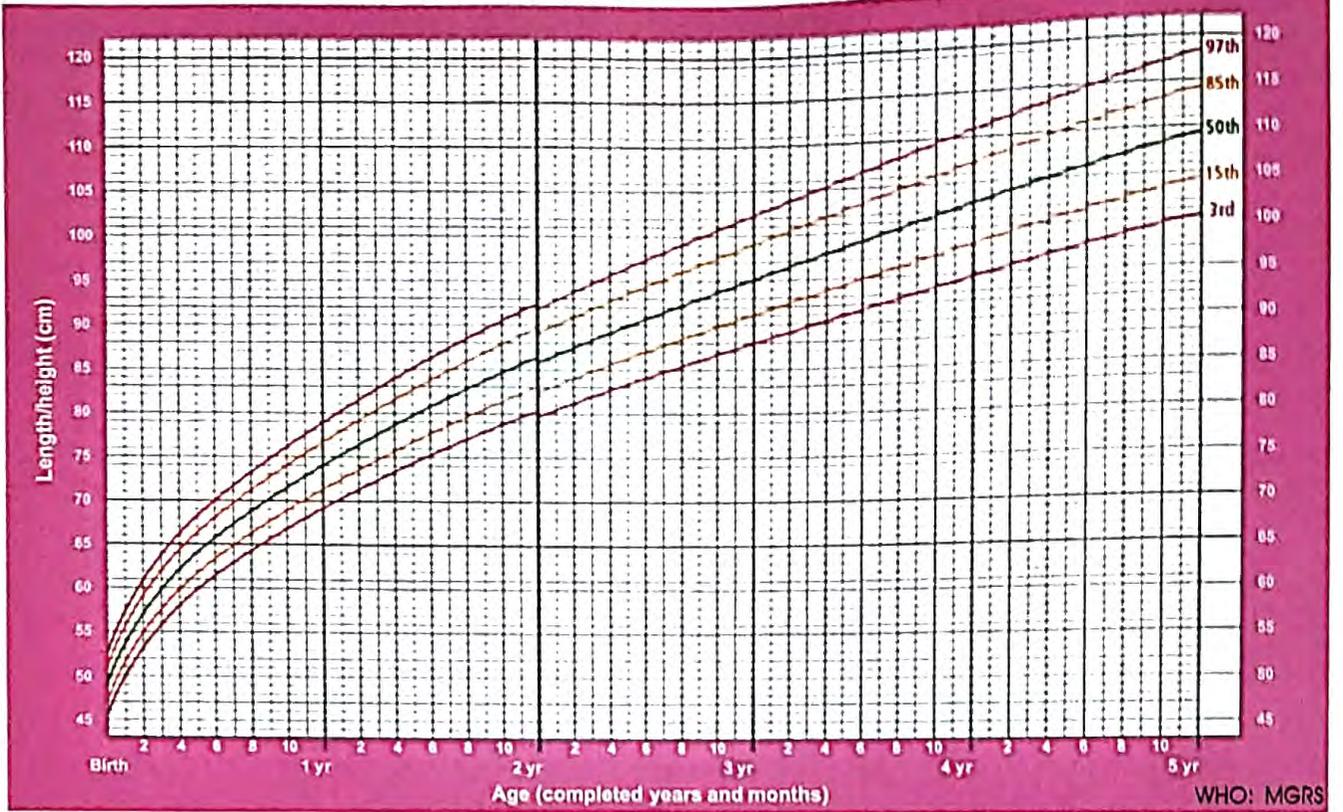


Fig. 2.13: Height-for-age (girls) from birth to 5 years (percentiles)

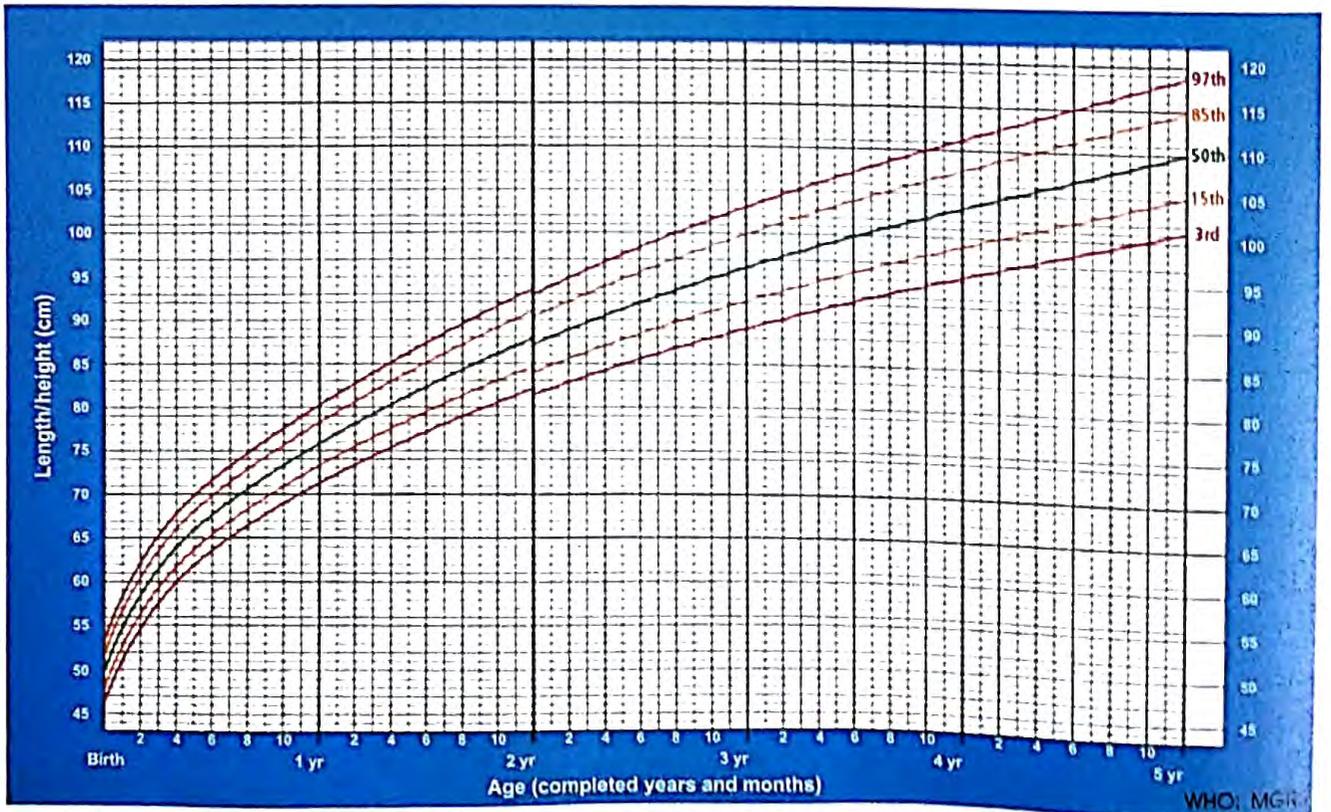


Fig. 2.14: Height-for-age (boys) from birth to 5 years (percentiles)

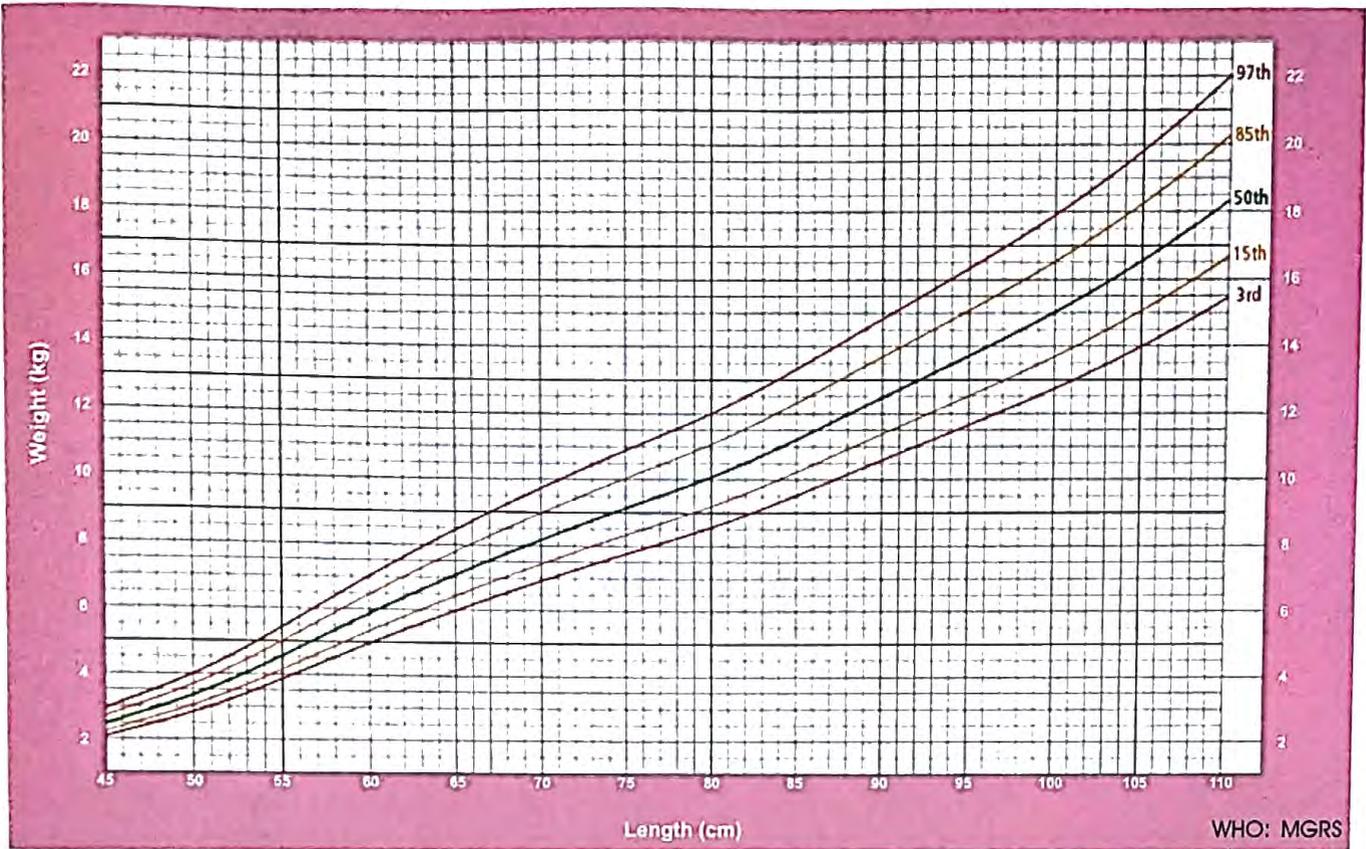


Fig. 2.15: Weight-for-length (girls) from birth to 2 years (percentiles)

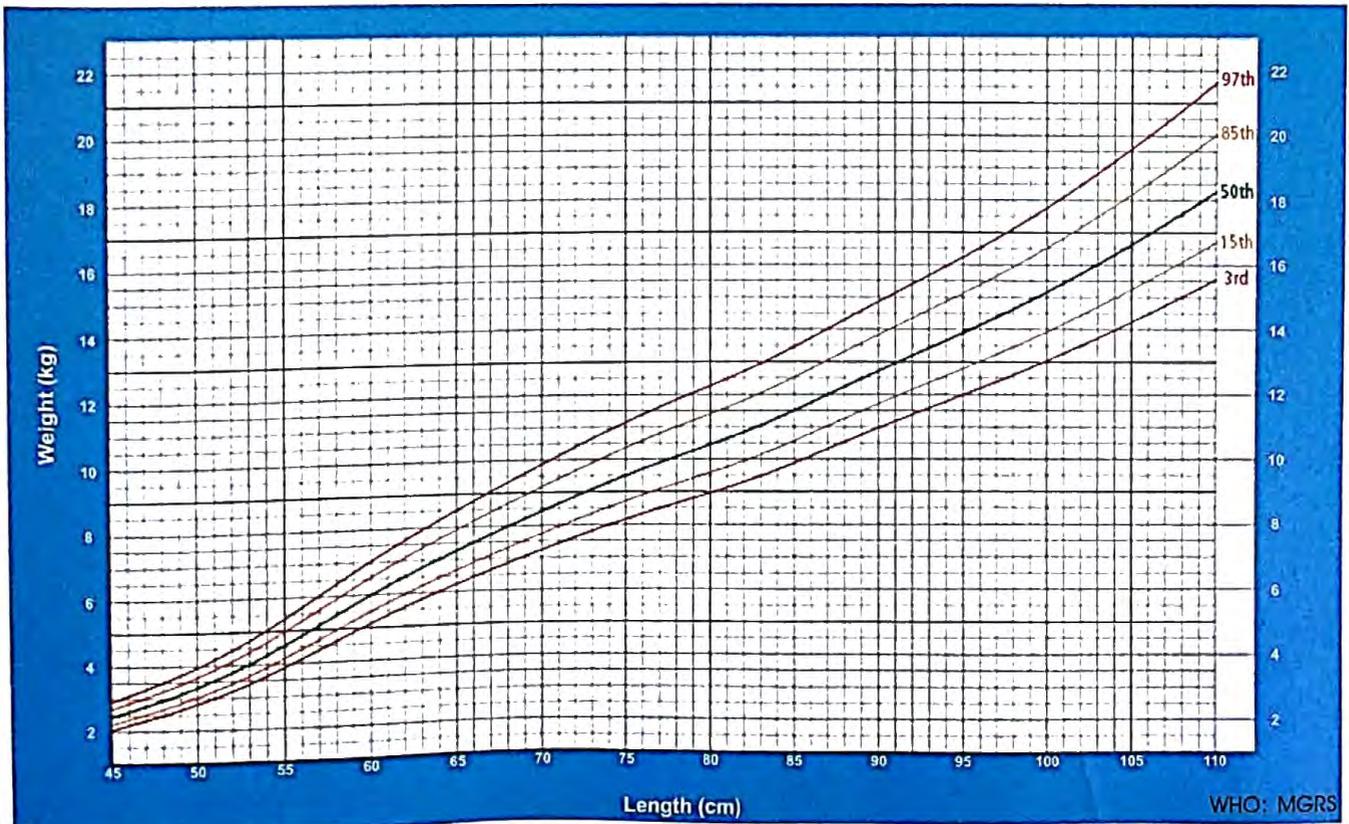


Fig. 2.16: Weight-for-length (boys) from birth to 2 years (percentiles)

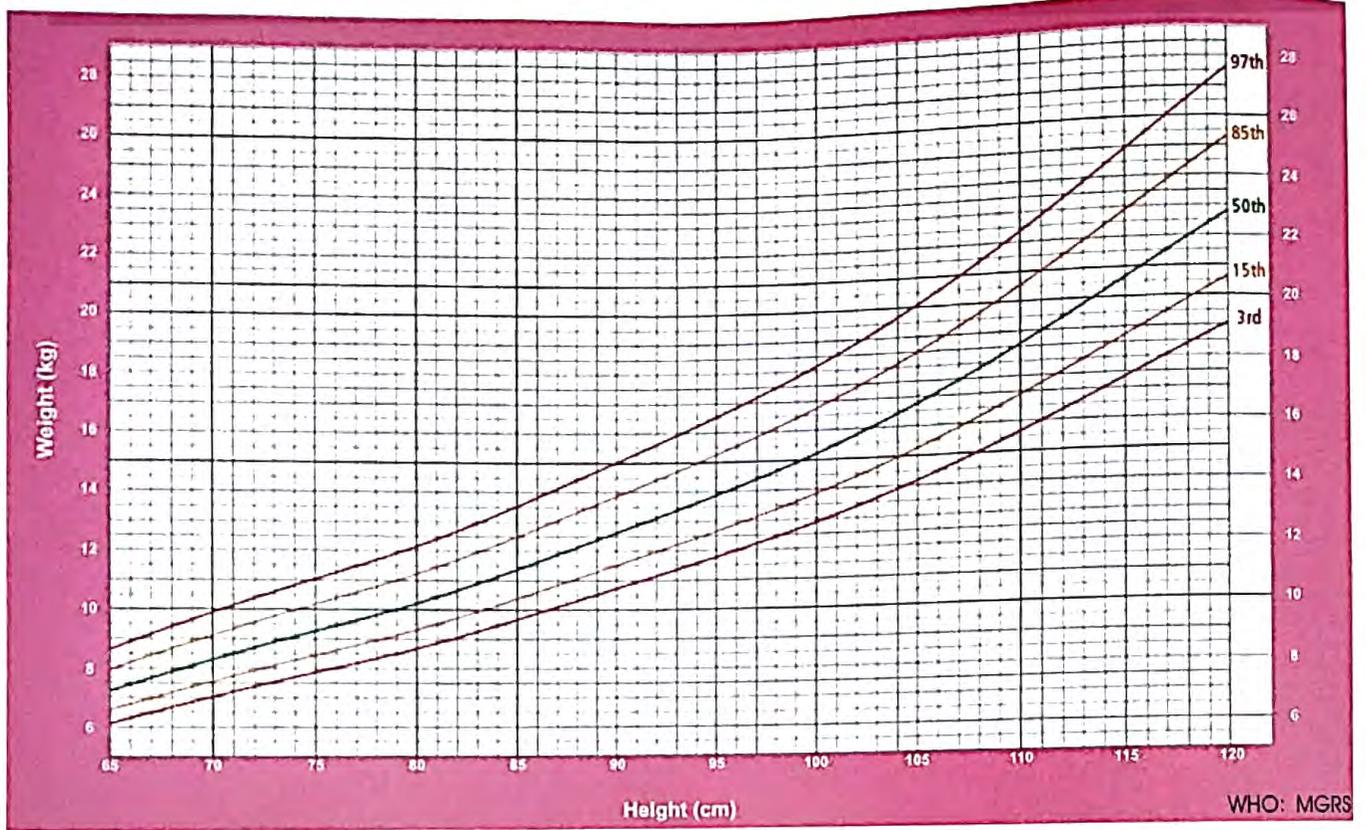


Fig. 2.17: Weight-for-height (girls) from 2 to 5 years (percentiles)

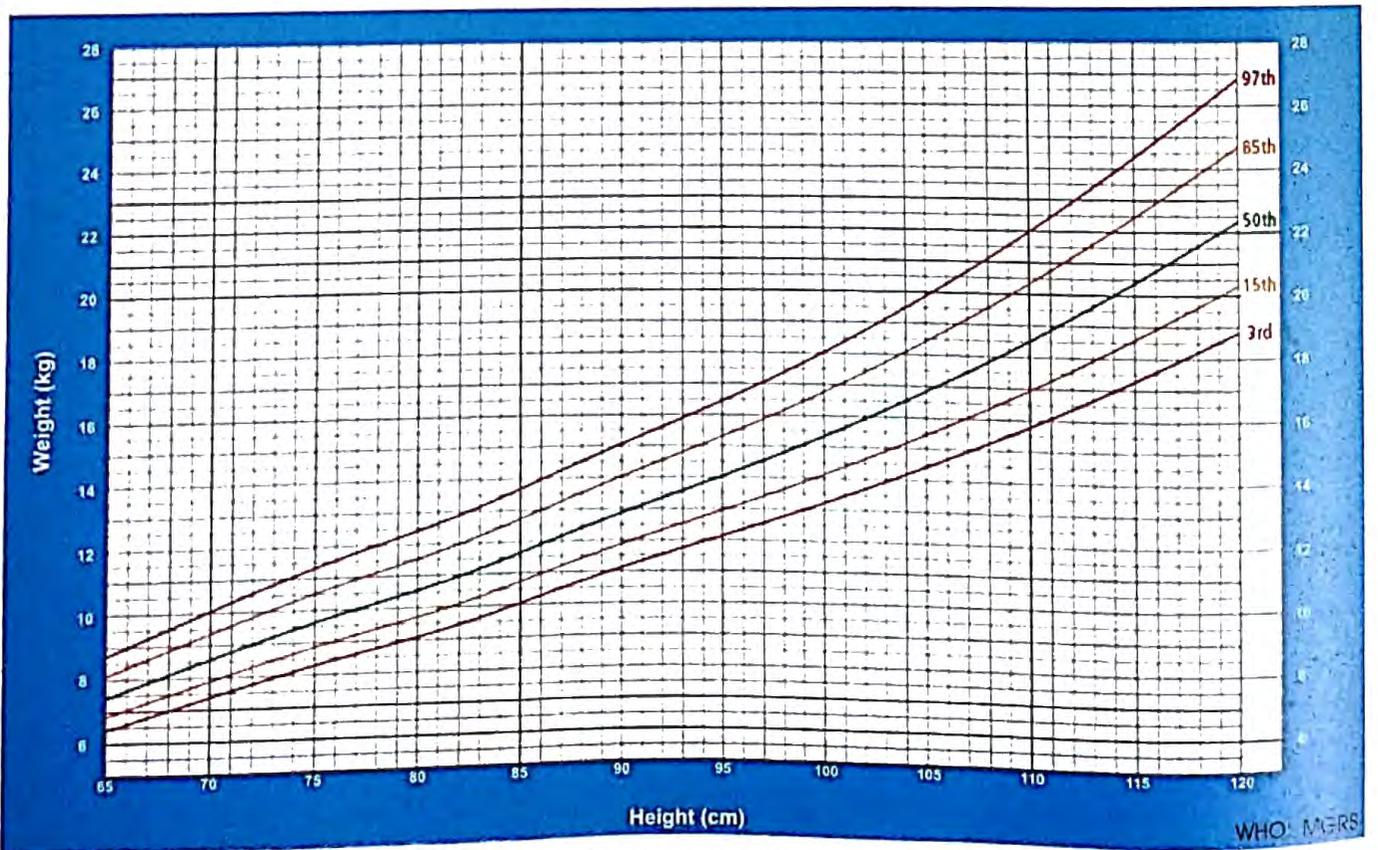


Fig. 2.18: Weight-for-height (boys) from 2 to 5 years (percentiles)

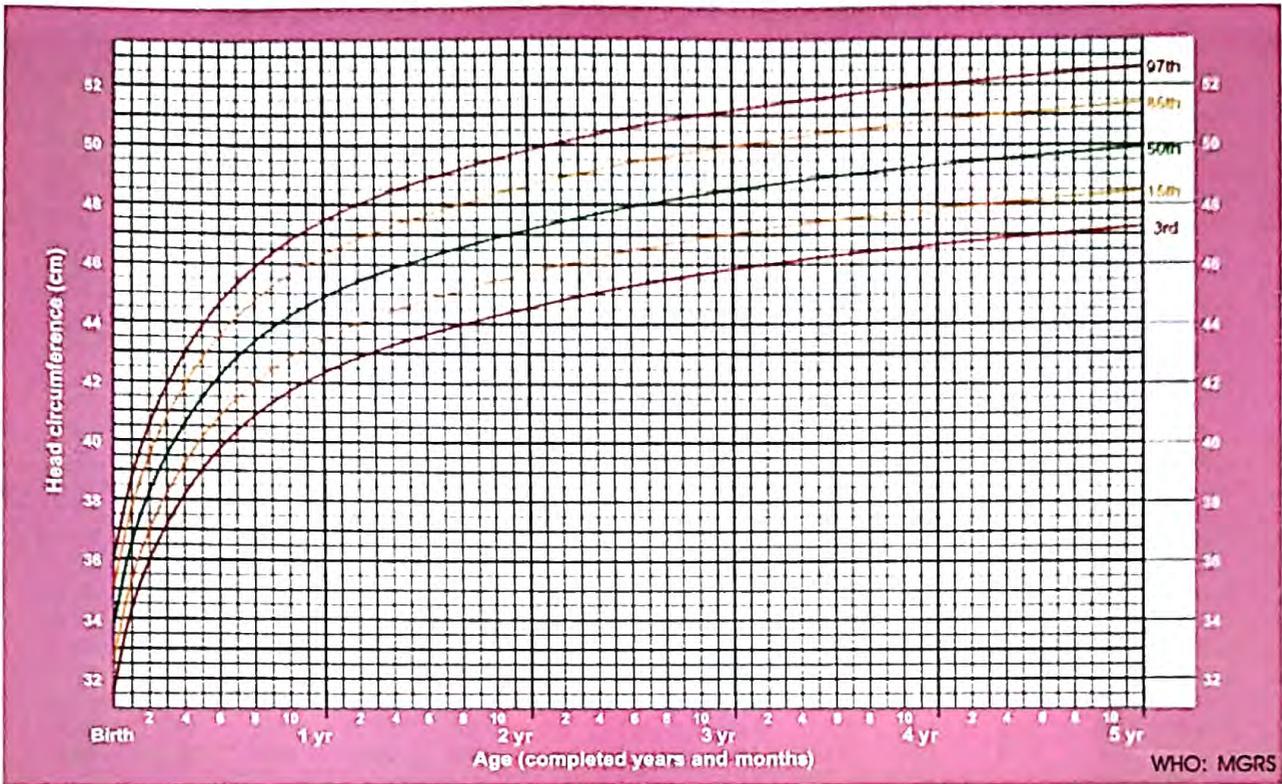


Fig. 2.19: Head circumference (girls) from birth to 5 years (percentiles)

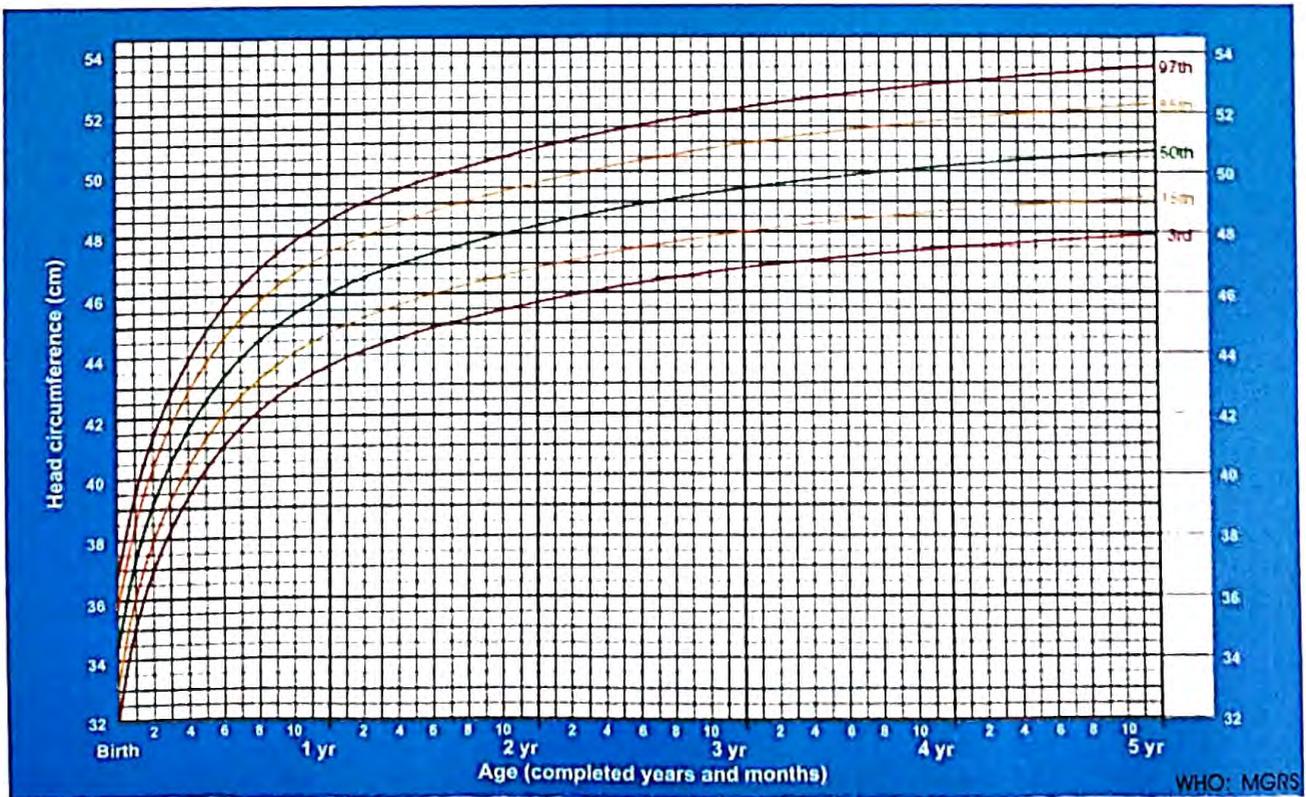


Fig. 2.20: Head circumference (boys) from birth to 5 years (percentiles)

Table 2.4: Weight-for-age and length/height-for-age in girls 0–5 years of age

Months	Weight-for-age, kg							Length-for-age, cm						
	-3 SD	-2 SD	-1 SD	Median	1 SD	2 SD	3 SD	-3 SD	-2 SD	-1 SD	Median	1 SD	2 SD	3 SD
0	2.0	2.4	2.8	3.2	3.7	4.2	4.8	43.6	45.4	47.3	49.1	51.0	52.9	54.7
1	2.7	3.2	3.6	4.2	4.8	5.5	6.2	47.8	49.8	51.7	53.7	55.6	57.6	59.5
2	3.4	3.9	4.5	5.1	5.8	6.6	7.5	51.0	53.0	55.0	57.1	59.1	61.1	63.2
3	4.0	4.5	5.2	5.8	6.6	7.5	8.5	53.5	55.6	57.7	59.8	61.9	64.0	66.1
4	4.4	5.0	5.7	6.4	7.3	8.2	9.3	55.6	57.8	59.9	62.1	64.3	66.4	68.6
5	4.8	5.4	6.1	6.9	7.8	8.8	10.0	57.4	59.6	61.8	64.0	66.2	68.5	70.7
6	5.1	5.7	6.5	7.3	8.2	9.3	10.6	58.9	61.2	63.5	65.7	68.0	70.3	72.5
7	5.3	6.0	6.8	7.6	8.6	9.8	11.1	60.3	62.7	65.0	67.3	69.6	71.9	74.2
8	5.6	6.3	7.0	7.9	9.0	10.2	11.6	61.7	64.0	66.4	68.7	71.1	73.5	75.8
9	5.8	6.5	7.3	8.2	9.3	10.5	12.0	62.9	65.3	67.7	70.1	72.6	75.0	77.4
10	5.9	6.7	7.5	8.5	9.6	10.9	12.4	64.1	66.5	69.0	71.5	73.9	76.4	78.9
11	6.1	6.9	7.7	8.7	9.9	11.2	12.8	65.2	67.7	70.3	72.8	75.3	77.8	80.3
12	6.3	7.0	7.9	8.9	10.1	11.5	13.1	66.3	68.9	71.4	74.0	76.6	79.2	81.7
13	6.4	7.2	8.1	9.2	10.4	11.8	13.5	67.3	70.0	72.6	75.2	77.8	80.5	83.1
14	6.6	7.4	8.3	9.4	10.6	12.1	13.8	68.3	71.0	73.7	76.4	79.1	81.7	84.4
15	6.7	7.6	8.5	9.6	10.9	12.4	14.1	69.3	72.0	74.8	77.5	80.2	83.0	85.7
16	6.9	7.7	8.7	9.8	11.1	12.6	14.5	70.2	73.0	75.8	78.6	81.4	84.2	87.0
17	7.0	7.9	8.9	10.0	11.4	12.9	14.8	71.1	74.0	76.8	79.7	82.5	85.4	88.2
18	7.2	8.1	9.1	10.2	11.6	13.2	15.1	72.0	74.9	77.8	80.7	83.6	86.5	89.4
19	7.3	8.2	9.2	10.4	11.8	13.5	15.4	72.8	75.8	78.8	81.7	84.7	87.6	90.6
20	7.5	8.4	9.4	10.6	12.1	13.7	15.7	73.7	76.7	79.7	82.7	85.7	88.7	91.7
21	7.6	8.6	9.6	10.9	12.3	14.0	16.0	74.5	77.5	80.6	83.7	86.7	89.8	92.9
22	7.8	8.7	9.8	11.1	12.5	14.3	16.4	75.2	78.4	81.5	84.6	87.7	90.8	94.0
23	7.9	8.9	10.0	11.3	12.8	14.6	16.7	76.0	79.2	82.3	85.5	88.7	91.9	95.0
24	8.1	9.0	10.2	11.5	13.0	14.8	17.0	76.7	80.0	83.2	86.4	89.6	92.9	96.1
	Weight-for-age, kg							Height-for-age, cm						
24								76.0	79.3	82.5	85.7	88.9	92.2	95.4
25	8.2	9.2	10.3	11.7	13.3	15.1	17.3	76.8	80.0	83.3	86.6	89.9	93.1	96.4
26	8.4	9.4	10.5	11.9	13.5	15.4	17.7	77.5	80.8	84.1	87.4	90.8	94.1	97.4
27	8.5	9.5	10.7	12.1	13.7	15.7	18.0	78.1	81.5	84.9	88.3	91.7	95.0	98.4
28	8.6	9.7	10.9	12.3	14.0	16.0	18.3	78.8	82.2	85.7	89.1	92.5	96.0	99.4
29	8.8	9.8	11.1	12.5	14.2	16.2	18.7	79.5	82.9	86.4	89.9	93.4	96.9	100.3
30	8.9	10.0	11.2	12.7	14.4	16.5	19.0	80.1	83.6	87.1	90.7	94.2	97.7	101.3
31	9.0	10.1	11.4	12.9	14.7	16.8	19.3	80.7	84.3	87.9	91.4	95.0	98.6	102.2
32	9.1	10.3	11.6	13.1	14.9	17.1	19.6	81.3	84.9	88.6	92.2	95.8	99.4	103.1
33	9.3	10.4	11.7	13.3	15.1	17.3	20.0	81.9	85.6	89.3	92.9	96.6	100.3	103.9
34	9.4	10.5	11.9	13.5	15.4	17.6	20.3	82.5	86.2	89.9	93.6	97.4	101.1	104.8
35	9.5	10.7	12.0	13.7	15.6	17.9	20.6	83.1	86.8	90.6	94.4	98.1	101.9	105.6
36	9.6	10.8	12.2	13.9	15.8	18.1	20.9	83.6	87.4	91.2	95.1	98.9	102.7	106.5
37	9.7	10.9	12.4	14.0	16.0	18.4	21.3	84.2	88.0	91.9	95.7	99.6	103.4	107.3
38	9.8	11.1	12.5	14.2	16.3	18.7	21.6	84.7	88.6	92.5	96.4	100.3	104.2	108.1
39	9.9	11.2	12.7	14.4	16.5	19.0	22.0	85.3	89.2	93.1	97.1	101.0	105.0	108.9
40	10.1	11.3	12.8	14.6	16.7	19.2	22.3	85.8	89.8	93.8	97.7	101.7	105.7	109.7
41	10.2	11.5	13.0	14.8	16.9	19.5	22.7	86.3	90.4	94.4	98.4	102.4	106.4	110.5
42	10.3	11.6	13.1	15.0	17.2	19.8	23.0	86.8	90.9	95.0	99.0	103.1	107.2	111.2
43	10.4	11.7	13.3	15.2	17.4	20.1	23.4	87.4	91.5	95.6	99.7	103.8	107.9	112.0
44	10.5	11.8	13.4	15.3	17.6	20.4	23.7	87.9	92.0	96.2	100.3	104.5	108.8	112.7
45	10.6	12.0	13.6	15.5	17.8	20.7	24.1	88.4	92.5	96.7	100.9	105.1	109.3	113.5
46	10.7	12.1	13.7	15.7	18.1	20.9	24.5	88.9	93.1	97.3	101.5	105.8	110.0	114.2
47	10.8	12.2	13.9	15.9	18.3	21.2	24.8	89.3	93.6	97.9	102.1	106.4	110.7	114.9
48	10.9	12.3	14.0	16.1	18.5	21.5	25.2	89.8	94.1	98.4	102.7	107.0	111.3	115.7
49	11.0	12.4	14.2	16.3	18.8	21.8	25.5	90.3	94.6	99.0	103.3	107.7	112.0	116.4
50	11.1	12.6	14.3	16.4	19.0	22.1	25.9	90.7	95.1	99.5	103.9	108.3	112.7	117.1
51	11.2	12.7	14.5	16.6	19.2	22.4	26.3	91.2	95.6	100.1	104.5	108.9	113.3	117.7
52	11.3	12.8	14.6	16.8	19.4	22.6	26.6	91.7	96.1	100.6	105.0	109.5	114.0	118.4
53	11.4	12.9	14.8	17.0	19.7	22.9	27.0	92.1	96.6	101.1	105.6	110.1	114.8	119.1
54	11.5	13.0	14.9	17.2	19.9	23.2	27.4	92.6	97.1	101.6	106.2	110.7	115.2	119.8
55	11.6	13.2	15.1	17.3	20.1	23.5	27.7	93.0	97.6	102.2	106.7	111.3	115.9	120.4
56	11.7	13.3	15.2	17.5	20.3	23.8	28.1	93.4	98.1	102.7	107.3	111.9	116.5	121.1
57	11.8	13.4	15.3	17.7	20.6	24.1	28.5	93.9	98.5	103.2	107.8	112.5	117.1	121.8
58	11.9	13.5	15.5	17.9	20.8	24.4	28.8	94.3	99.0	103.7	108.4	113.0	117.7	122.4
59	12.0	13.6	15.6	18.0	21.0	24.6	29.2	94.7	99.5	104.2	108.9	113.6	118.3	123.1
60	12.1	13.7	15.8	18.2	21.2	24.9	29.5	95.2	99.9	104.7	109.4	114.2	118.9	123.7

Table 2.5: Weight-for-age and length/height-for-age in boys 0-5 years of age

Months	Weight-for-age, kg							Length-for-age, cm						
	-3 SD	-2 SD	-1 SD	Median	1 SD	2 SD	3 SD	-3 SD	-2 SD	-1 SD	Median	1 SD	2 SD	3 SD
0	2.1	2.5	2.9	3.3	3.9	4.4	5.0	44.2	46.1	48.0	49.9	51.8	53.7	55.6
1	2.9	3.4	3.9	4.5	5.1	5.8	6.6	48.9	50.8	52.8	54.7	56.7	58.6	60.6
2	3.8	4.3	4.9	5.6	6.3	7.1	8.0	52.4	54.4	56.4	58.4	60.4	62.4	64.4
3	4.4	5.0	5.7	6.4	7.2	8.0	9.0	55.3	57.3	59.4	61.4	63.5	65.5	67.6
4	4.9	5.6	6.2	7.0	7.8	8.7	9.7	57.6	59.7	61.8	63.9	66.0	68.0	70.1
5	5.3	6.0	6.7	7.5	8.4	9.3	10.4	59.6	61.7	63.8	65.9	68.0	70.1	72.2
6	5.7	6.4	7.1	7.9	8.8	9.8	10.9	61.2	63.3	65.5	67.6	69.8	71.9	74.0
7	5.9	6.7	7.4	8.3	9.2	10.3	11.4	62.7	64.8	67.0	69.2	71.3	73.5	75.7
8	6.2	6.9	7.7	8.6	9.6	10.7	11.9	64.0	66.2	68.4	70.6	72.8	75.0	77.2
9	6.4	7.1	8.0	8.9	9.9	11.0	12.3	65.2	67.5	69.7	72.0	74.2	76.5	78.7
10	6.6	7.4	8.2	9.2	10.2	11.4	12.7	66.4	68.7	71.0	73.3	75.6	77.9	80.1
11	6.8	7.6	8.4	9.4	10.5	11.7	13.0	67.6	69.9	72.2	74.5	76.9	79.2	81.5
12	6.9	7.7	8.6	9.6	10.8	12.0	13.3	68.6	71.0	73.4	75.7	78.1	80.5	82.9
13	7.1	7.9	8.8	9.9	11.0	12.3	13.7	69.6	72.1	74.5	76.9	79.3	81.8	84.2
14	7.2	8.1	9.0	10.1	11.3	12.6	14.0	70.6	73.1	75.6	78.0	80.5	83.0	85.5
15	7.4	8.3	9.2	10.3	11.5	12.8	14.3	71.6	74.1	76.6	79.1	81.7	84.2	86.7
16	7.5	8.4	9.4	10.5	11.7	13.1	14.6	72.5	75.0	77.6	80.2	82.8	85.4	88.0
17	7.7	8.6	9.6	10.7	12.0	13.4	14.9	73.3	76.0	78.6	81.2	83.9	86.5	89.2
18	7.8	8.8	9.8	10.9	12.2	13.7	15.3	74.2	76.9	79.6	82.3	85.0	87.7	90.4
19	8.0	8.9	10.0	11.1	12.5	13.9	15.6	75.0	77.7	80.5	83.2	86.0	88.8	91.5
20	8.1	9.1	10.1	11.3	12.7	14.2	15.9	75.8	78.6	81.4	84.2	87.0	89.8	92.6
21	8.2	9.2	10.3	11.5	12.9	14.5	16.2	76.5	79.4	82.3	85.1	88.0	90.9	93.8
22	8.4	9.4	10.5	11.8	13.2	14.7	16.5	77.2	80.2	83.1	86.0	89.0	91.9	94.9
23	8.5	9.5	10.7	12.0	13.4	15.0	16.8	78.0	81.0	83.9	86.9	89.9	92.9	95.9
24	8.6	9.7	10.8	12.2	13.6	15.3	17.1	78.7	81.7	84.8	87.8	90.9	93.9	97.0
	Weight-for-age, kg							Height-for-age, cm						
24								78.0	81.0	84.1	87.1	90.2	93.2	96.3
25	8.8	9.8	11.0	12.4	13.9	15.5	17.5	78.6	81.7	84.9	88.0	91.1	94.2	97.3
26	8.9	10.0	11.2	12.5	14.1	15.8	17.8	79.3	82.5	85.6	88.8	92.0	95.2	98.3
27	9.0	10.1	11.3	12.7	14.3	16.1	18.1	79.9	83.1	86.4	89.6	92.9	96.1	99.3
28	9.1	10.2	11.5	12.9	14.5	16.3	18.4	80.5	83.8	87.1	90.4	93.7	97.0	100.3
29	9.2	10.4	11.7	13.1	14.8	16.6	18.7	81.1	84.5	87.8	91.2	94.5	97.9	101.2
30	9.4	10.5	11.8	13.3	15.0	16.9	19.0	81.7	85.1	88.5	91.9	95.3	98.7	102.1
31	9.5	10.7	12.0	13.5	15.2	17.1	19.3	82.3	85.7	89.2	92.7	96.1	99.6	103.0
32	9.6	10.8	12.1	13.7	15.4	17.4	19.6	82.8	86.4	89.9	93.4	96.9	100.4	103.9
33	9.7	10.9	12.3	13.8	15.6	17.6	19.9	83.4	86.9	90.5	94.1	97.6	101.2	104.8
34	9.8	11.0	12.4	14.0	15.8	17.8	20.2	83.9	87.5	91.1	94.8	98.4	102.0	105.6
35	9.9	11.2	12.6	14.2	16.0	18.1	20.4	84.4	88.1	91.8	95.4	99.1	102.7	106.4
36	10.0	11.3	12.7	14.3	16.2	18.3	20.7	85.0	88.7	92.4	96.1	99.8	103.5	107.2
37	10.1	11.4	12.9	14.5	16.4	18.6	21.0	85.5	89.2	93.0	96.7	100.5	104.2	108.0
38	10.2	11.5	13.0	14.7	16.6	18.8	21.3	86.0	89.8	93.6	97.4	101.2	105.0	108.8
39	10.3	11.6	13.1	14.8	16.8	19.0	21.6	86.5	90.3	94.2	98.0	101.8	105.7	109.5
40	10.4	11.8	13.3	15.0	17.0	19.3	21.9	87.0	90.9	94.7	98.6	102.5	106.4	110.3
41	10.5	11.9	13.4	15.2	17.2	19.5	22.1	87.5	91.4	95.3	99.2	103.2	107.1	111.0
42	10.6	12.0	13.6	15.3	17.4	19.7	22.4	88.0	91.9	95.9	99.9	103.8	107.8	111.7
43	10.7	12.1	13.7	15.5	17.6	20.0	22.7	88.4	92.4	96.4	100.4	104.5	108.5	112.5
44	10.8	12.2	13.8	15.7	17.8	20.2	23.0	88.9	93.0	97.0	101.0	105.1	109.1	113.2
45	10.9	12.4	14.0	15.8	18.0	20.5	23.3	89.4	93.5	97.5	101.6	105.7	109.8	113.9
46	11.0	12.5	14.1	16.0	18.2	20.7	23.6	89.8	94.0	98.1	102.2	106.3	110.4	114.6
47	11.1	12.6	14.3	16.2	18.4	20.9	23.9	90.3	94.4	98.6	102.8	106.9	111.1	115.2
48	11.2	12.7	14.4	16.3	18.6	21.2	24.2	90.7	94.9	99.1	103.3	107.5	111.7	115.9
49	11.3	12.8	14.5	16.5	18.8	21.4	24.5	91.2	95.4	99.7	103.9	108.1	112.4	116.6
50	11.4	12.9	14.7	16.7	19.0	21.7	24.8	91.6	95.9	100.2	104.4	108.7	113.0	117.3
51	11.5	13.1	14.8	16.8	19.2	21.9	25.1	92.1	96.4	100.7	105.0	109.3	113.6	117.9
52	11.6	13.2	15.0	17.0	19.4	22.2	25.4	92.5	96.9	101.2	105.6	109.9	114.2	118.6
53	11.7	13.3	15.1	17.2	19.6	22.4	25.7	93.0	97.4	101.7	106.1	110.5	114.9	119.2
54	11.8	13.4	15.2	17.3	19.8	22.7	26.0	93.4	97.8	102.3	106.7	111.1	115.5	119.9
55	11.9	13.5	15.4	17.5	20.0	22.9	26.3	93.9	98.3	102.8	107.2	111.7	116.1	120.6
56	12.0	13.6	15.5	17.7	20.2	23.2	26.6	94.3	98.8	103.3	107.8	112.3	116.7	121.2
57	12.1	13.7	15.6	17.8	20.4	23.4	26.9	94.7	99.3	103.8	108.3	112.8	117.4	121.9
58	12.2	13.8	15.8	18.0	20.6	23.7	27.2	95.2	99.7	104.3	108.9	113.4	118.0	122.6
59	12.3	14.0	15.9	18.2	20.8	23.9	27.6	95.6	100.2	104.8	109.4	114.0	118.6	123.2
60	12.4	14.1	16.0	18.3	21.0	24.2	27.9	96.1	100.7	105.3	110.0	114.6	119.2	123.9

Table 2.6A: Weight-for-length/height (kg) in girls and boys 0–5 years of age

Length (cm)	Weight (kg) Girls							Length (cm)	Weight (kg) Boys						
	-3 SD	-2 SD	-1 SD	Median	1 SD	2 SD	3 SD		-3 SD	-2 SD	-1 SD	Median	1 SD	2 SD	3 SD
45.0	1.9	2.1	2.3	2.5	2.7	3.0	3.3	45.0	1.9	2.0	2.2	2.4	2.7	3.0	3.3
45.5	2.0	2.1	2.3	2.5	2.8	3.1	3.4	45.5	1.9	2.1	2.3	2.5	2.8	3.1	3.4
46.0	2.0	2.2	2.4	2.6	2.9	3.2	3.5	46.0	2.0	2.2	2.4	2.6	2.9	3.1	3.5
46.5	2.1	2.3	2.5	2.7	3.0	3.3	3.6	46.5	2.1	2.3	2.5	2.7	3.0	3.2	3.6
47.0	2.2	2.4	2.6	2.8	3.1	3.4	3.7	47.0	2.1	2.3	2.5	2.8	3.0	3.3	3.7
47.5	2.2	2.4	2.6	2.9	3.2	3.5	3.8	47.5	2.2	2.4	2.6	2.9	3.1	3.4	3.8
48.0	2.3	2.5	2.7	3.0	3.3	3.6	4.0	48.0	2.3	2.5	2.7	2.9	3.2	3.6	3.9
48.5	2.4	2.6	2.8	3.1	3.4	3.7	4.1	48.5	2.3	2.6	2.8	3.0	3.3	3.7	4.0
49.0	2.4	2.6	2.9	3.2	3.5	3.8	4.2	49.0	2.4	2.6	2.9	3.1	3.4	3.8	4.2
49.5	2.5	2.7	3.0	3.3	3.6	3.9	4.3	49.5	2.5	2.7	3.0	3.2	3.5	3.9	4.3
50.0	2.6	2.8	3.1	3.4	3.7	4.0	4.5	50.0	2.6	2.8	3.0	3.3	3.6	4.0	4.4
50.5	2.7	2.9	3.2	3.5	3.8	4.2	4.6	50.5	2.7	2.9	3.1	3.4	3.8	4.1	4.5
51.0	2.8	3.0	3.3	3.6	3.9	4.3	4.8	51.0	2.7	3.0	3.2	3.5	3.9	4.2	4.7
51.5	2.8	3.1	3.4	3.7	4.0	4.4	4.9	51.5	2.8	3.1	3.3	3.6	4.0	4.4	4.8
52.0	2.9	3.2	3.5	3.8	4.2	4.6	5.1	52.0	2.9	3.2	3.5	3.8	4.1	4.5	5.0
52.5	3.0	3.3	3.6	3.9	4.3	4.7	5.2	52.5	3.0	3.3	3.6	3.9	4.2	4.6	5.1
53.0	3.1	3.4	3.7	4.0	4.4	4.9	5.4	53.0	3.1	3.4	3.7	4.0	4.4	4.8	5.3
53.5	3.2	3.5	3.8	4.2	4.6	5.0	5.5	53.5	3.2	3.5	3.8	4.1	4.5	4.9	5.4
54.0	3.3	3.6	3.9	4.3	4.7	5.2	5.7	54.0	3.3	3.6	3.9	4.3	4.7	5.1	5.6
54.5	3.4	3.7	4.0	4.4	4.8	5.3	5.9	54.5	3.4	3.7	4.0	4.4	4.8	5.3	5.8
55.0	3.5	3.8	4.2	4.5	5.0	5.5	6.1	55.0	3.6	3.8	4.2	4.5	5.0	5.4	6.0
55.5	3.6	3.9	4.3	4.7	5.1	5.7	6.3	55.5	3.7	4.0	4.3	4.7	5.1	5.6	6.1
56.0	3.7	4.0	4.4	4.8	5.3	5.8	6.4	56.0	3.8	4.1	4.4	4.8	5.3	5.8	6.3
56.5	3.8	4.1	4.5	5.0	5.4	6.0	6.6	56.5	3.9	4.2	4.6	5.0	5.4	5.9	6.5
57.0	3.9	4.3	4.6	5.1	5.6	6.1	6.8	57.0	4.0	4.3	4.7	5.1	5.6	6.1	6.7
57.5	4.0	4.4	4.8	5.2	5.7	6.3	7.0	57.5	4.1	4.5	4.9	5.3	5.7	6.3	6.9
58.0	4.1	4.5	4.9	5.4	5.9	6.5	7.1	58.0	4.3	4.6	5.0	5.4	5.9	6.4	7.1
58.5	4.2	4.6	5.0	5.5	6.0	6.6	7.3	58.5	4.4	4.7	5.1	5.6	6.1	6.6	7.2
59.0	4.3	4.7	5.1	5.6	6.2	6.8	7.5	59.0	4.5	4.8	5.3	5.7	6.2	6.8	7.4
59.5	4.4	4.8	5.3	5.7	6.3	6.9	7.7	59.5	4.6	5.0	5.4	5.9	6.4	7.0	7.6
60.0	4.5	4.9	5.4	5.9	6.4	7.1	7.8	60.0	4.7	5.1	5.5	6.0	6.5	7.1	7.8
60.5	4.6	5.0	5.5	6.0	6.6	7.3	8.0	60.5	4.8	5.2	5.6	6.1	6.7	7.3	8.0
61.0	4.7	5.1	5.6	6.1	6.7	7.4	8.2	61.0	4.9	5.3	5.8	6.3	6.8	7.4	8.1
61.5	4.8	5.2	5.7	6.3	6.9	7.6	8.4	61.5	5.0	5.4	5.9	6.4	7.0	7.6	8.3
62.0	4.9	5.3	5.8	6.4	7.0	7.7	8.5	62.0	5.1	5.6	6.0	6.5	7.1	7.7	8.5
62.5	5.0	5.4	5.9	6.5	7.1	7.8	8.7	62.5	5.2	5.7	6.1	6.7	7.2	7.9	8.6
63.0	5.1	5.5	6.0	6.6	7.3	8.0	8.8	63.0	5.3	5.8	6.2	6.8	7.4	8.0	8.8
63.5	5.2	5.6	6.2	6.7	7.4	8.1	9.0	63.5	5.4	5.9	6.4	6.9	7.5	8.2	8.9
64.0	5.3	5.7	6.3	6.9	7.5	8.3	9.1	64.0	5.5	6.0	6.5	7.0	7.6	8.3	9.1
64.5	5.4	5.8	6.4	7.0	7.6	8.4	9.3	64.5	5.6	6.1	6.6	7.1	7.8	8.5	9.3
65.0	5.5	5.9	6.5	7.1	7.8	8.6	9.5	65.0	5.7	6.2	6.7	7.3	7.9	8.6	9.4
65.5	5.5	6.0	6.6	7.2	7.9	8.7	9.6	65.5	5.8	6.3	6.8	7.4	8.0	8.7	9.6
66.0	5.6	6.1	6.7	7.3	8.0	8.8	9.8	66.0	5.9	6.4	6.9	7.5	8.2	8.9	9.7
66.5	5.7	6.2	6.8	7.4	8.1	9.0	9.9	66.5	6.0	6.5	7.0	7.6	8.3	9.0	9.9
67.0	5.8	6.3	6.9	7.5	8.3	9.1	10.0	67.0	6.1	6.6	7.1	7.7	8.4	9.2	10.0
67.5	5.9	6.4	7.0	7.6	8.4	9.2	10.2	67.5	6.2	6.7	7.2	7.9	8.5	9.3	10.2
68.0	6.0	6.5	7.1	7.7	8.5	9.4	10.3	68.0	6.3	6.8	7.3	8.0	8.7	9.4	10.3
68.5	6.1	6.6	7.2	7.9	8.6	9.5	10.5	68.5	6.4	6.9	7.5	8.1	8.8	9.6	10.5
69.0	6.1	6.7	7.3	8.0	8.7	9.6	10.6	69.0	6.5	7.0	7.6	8.2	8.9	9.7	10.6
69.5	6.2	6.8	7.4	8.1	8.8	9.7	10.7	69.5	6.6	7.1	7.7	8.3	9.0	9.8	10.8
70.0	6.3	6.9	7.5	8.2	9.0	9.9	10.9	70.0	6.6	7.2	7.8	8.4	9.2	10.0	10.9
70.5	6.4	6.9	7.6	8.3	9.1	10.0	11.0	70.5	6.7	7.3	7.9	8.5	9.3	10.1	11.1
71.0	6.5	7.0	7.7	8.4	9.2	10.1	11.1	71.0	6.8	7.4	8.0	8.6	9.4	10.2	11.2
71.5	6.5	7.1	7.7	8.5	9.3	10.2	11.3	71.5	6.9	7.5	8.1	8.8	9.5	10.4	11.3
72.0	6.6	7.2	7.8	8.6	9.4	10.3	11.4	72.0	7.0	7.6	8.2	8.9	9.6	10.5	11.5
72.5	6.7	7.3	7.9	8.7	9.5	10.5	11.5	72.5	7.1	7.6	8.3	9.0	9.8	10.6	11.6
73.0	6.8	7.4	8.0	8.8	9.6	10.6	11.7	73.0	7.2	7.7	8.4	9.1	9.9	10.8	11.8
73.5	6.9	7.4	8.1	8.9	9.7	10.7	11.8	73.5	7.2	7.8	8.5	9.2	10.0	10.9	11.9
74.0	6.9	7.5	8.2	9.0	9.8	10.8	11.9	74.0	7.3	7.9	8.6	9.3	10.1	11.0	12.1
74.5	7.0	7.6	8.3	9.1	9.9	10.9	12.0	74.5	7.4	8.0	8.7	9.4	10.2	11.2	12.2
75.0	7.1	7.7	8.4	9.1	10.0	11.0	12.2	75.0	7.5	8.1	8.8	9.5	10.3	11.3	12.3
75.5	7.1	7.8	8.5	9.2	10.1	11.1	12.3	75.5	7.6	8.2	8.8	9.6	10.4	11.4	12.5
76.0	7.2	7.8	8.5	9.3	10.2	11.2	12.4	76.0	7.6	8.3	8.9	9.7	10.6	11.5	12.6
76.5	7.3	7.9	8.6	9.4	10.3	11.4	12.5	76.5	7.7	8.3	9.0	9.8	10.7	11.6	12.7
77.0	7.4	8.0	8.7	9.5	10.4	11.5	12.6	77.0	7.8	8.4	9.1	9.9	10.8	11.7	12.8

Contd.

Table 2.6A: Weight-for-length/height (kg) in girls and boys 0–5 years of age (Contd.)

Length (cm)	Weight (kg) Girls							Length (cm)	Weight (kg) Boys						
	-3 SD	-2 SD	-1 SD	Median	1 SD	2 SD	3 SD		-3 SD	-2 SD	-1 SD	Median	1 SD	2 SD	3 SD
77.5	7.4	8.1	8.8	9.6	10.5	11.6	12.8	77.5	7.9	8.5	9.2	10.0	10.9	11.9	13.0
78.0	7.5	8.2	8.9	9.7	10.6	11.7	12.9	78.0	7.9	8.6	9.3	10.1	11.0	12.0	13.1
78.5	7.6	8.2	9.0	9.8	10.7	11.8	13.0	78.5	8.0	8.7	9.4	10.2	11.1	12.1	13.2
79.0	7.7	8.3	9.1	9.9	10.8	11.9	13.1	79.0	8.1	8.7	9.5	10.3	11.2	12.2	13.3
79.5	7.7	8.4	9.1	10.0	10.9	12.0	13.3	79.5	8.2	8.8	9.5	10.4	11.3	12.3	13.4
80.0	7.8	8.5	9.2	10.1	11.0	12.1	13.4	80.0	8.2	8.9	9.6	10.4	11.4	12.4	13.6
80.5	7.9	8.6	9.3	10.2	11.2	12.3	13.5	80.5	8.3	9.0	9.7	10.5	11.5	12.5	13.7
81.0	8.0	8.7	9.4	10.3	11.3	12.4	13.7	81.0	8.4	9.1	9.8	10.6	11.6	12.6	13.8
81.5	8.1	8.8	9.5	10.4	11.4	12.5	13.8	81.5	8.5	9.1	9.9	10.7	11.7	12.7	13.9
82.0	8.1	8.8	9.6	10.5	11.5	12.6	13.9	82.0	8.5	9.2	10.0	10.8	11.8	12.8	14.0
82.5	8.2	8.9	9.7	10.6	11.6	12.8	14.1	82.5	8.6	9.3	10.1	10.9	11.9	13.0	14.2
83.0	8.3	9.0	9.8	10.7	11.8	12.9	14.2	83.0	8.7	9.4	10.2	11.0	12.0	13.1	14.3
83.5	8.4	9.1	9.9	10.9	11.9	13.1	14.4	83.5	8.8	9.5	10.3	11.2	12.1	13.2	14.4
84.0	8.5	9.2	10.1	11.0	12.0	13.2	14.5	84.0	8.9	9.6	10.4	11.3	12.2	13.3	14.6
84.5	8.6	9.3	10.2	11.1	12.1	13.3	14.7	84.5	9.0	9.7	10.5	11.4	12.4	13.5	14.7
85.0	8.7	9.4	10.3	11.2	12.3	13.5	14.9	85.0	9.1	9.8	10.6	11.5	12.5	13.6	14.9
85.5	8.8	9.5	10.4	11.3	12.4	13.6	15.0	85.5	9.2	9.9	10.7	11.6	12.6	13.7	15.0
86.0	8.9	9.7	10.5	11.5	12.6	13.8	15.2	86.0	9.3	10.0	10.8	11.7	12.8	13.9	15.2
86.5	9.0	9.8	10.6	11.6	12.7	13.9	15.4	86.5	9.4	10.1	11.0	11.9	12.9	14.0	15.3
87.0	9.1	9.9	10.7	11.7	12.8	14.1	15.5	87.0	9.5	10.2	11.1	12.0	13.0	14.2	15.5
87.5	9.2	10.0	10.9	11.8	13.0	14.2	15.7	87.5	9.6	10.4	11.2	12.1	13.2	14.3	15.6
88.0	9.3	10.1	11.0	12.0	13.1	14.4	15.9	88.0	9.7	10.5	11.3	12.2	13.3	14.5	15.8
88.5	9.4	10.2	11.1	12.1	13.2	14.5	16.0	88.5	9.8	10.6	11.4	12.4	13.4	14.6	15.9
89.0	9.5	10.3	11.2	12.2	13.4	14.7	16.2	89.0	9.9	10.7	11.5	12.5	13.5	14.7	16.1
89.5	9.6	10.4	11.3	12.3	13.5	14.8	16.4	89.5	10.0	10.8	11.6	12.6	13.7	14.9	16.2
90.0	9.7	10.5	11.4	12.5	13.7	15.0	16.5	90.0	10.1	10.9	11.8	12.7	13.8	15	16.4
90.5	9.8	10.6	11.5	12.6	13.8	15.1	16.7	90.5	10.2	11	11.9	12.8	13.9	15.1	16.5
91.0	9.9	10.7	11.7	12.7	13.9	15.3	16.9	91.0	10.3	11.1	12.0	13.0	14.1	15.3	16.7
91.5	10.0	10.8	11.8	12.8	14.1	15.5	17.0	91.5	10.4	11.2	12.1	13.1	14.2	15.4	16.8
92.0	10.1	10.9	11.9	13.0	14.2	15.6	17.2	92.0	10.5	11.3	12.2	13.2	14.3	15.6	17.0
92.5	10.1	11.0	12.0	13.1	14.3	15.8	17.4	92.5	10.6	11.4	12.3	13.3	14.4	15.7	17.1
93.0	10.2	11.1	12.1	13.2	14.5	15.9	17.5	93.0	10.7	11.5	12.4	13.4	14.6	15.8	17.3
93.5	10.3	11.2	12.2	13.3	14.6	16.1	17.7	93.5	10.7	11.6	12.5	13.5	14.7	16.0	17.4
94.0	10.4	11.3	12.3	13.5	14.7	16.2	17.9	94.0	10.8	11.7	12.6	13.7	14.8	16.1	17.6
94.5	10.5	11.4	12.4	13.6	14.9	16.4	18.0	94.5	10.9	11.8	12.7	13.8	14.9	16.3	17.7
95.0	10.6	11.5	12.6	13.7	15.0	16.5	18.2	95.0	11.0	11.9	12.8	13.9	15.1	16.4	17.9
95.5	10.7	11.6	12.7	13.8	15.2	16.7	18.4	95.5	11.1	12	12.9	14.0	15.2	16.5	18.0
96.0	10.8	11.7	12.8	14.0	15.3	16.8	18.6	96.0	11.2	12.1	13.1	14.1	15.3	16.7	18.2
96.5	10.9	11.8	12.9	14.1	15.4	17.0	18.7	96.5	11.3	12.2	13.2	14.3	15.5	16.8	18.4
97.0	11.0	12.0	13.0	14.2	15.6	17.1	18.9	97.0	11.4	12.3	13.3	14.4	15.6	17.0	18.5
97.5	11.1	12.1	13.1	14.4	15.7	17.3	19.1	97.5	11.5	12.4	13.4	14.5	15.7	17.1	18.7
98.0	11.2	12.2	13.3	14.5	15.9	17.5	19.3	98.0	11.6	12.5	13.5	14.6	15.9	17.3	18.9
98.5	11.3	12.3	13.4	14.6	16.0	17.6	19.5	98.5	11.7	12.6	13.6	14.8	16.0	17.5	19.1
99.0	11.4	12.4	13.5	14.8	16.2	17.8	19.6	99.0	11.8	12.7	13.7	14.9	16.2	17.6	19.2
99.5	11.5	12.5	13.6	14.9	16.3	18.0	19.8	99.5	11.9	12.8	13.9	15.0	16.3	17.8	19.4
100.0	11.6	12.6	13.7	15.0	16.5	18.1	20.0	100.0	12.0	12.9	14.0	15.2	16.5	18.0	19.6
100.5	11.7	12.7	13.9	15.2	16.6	18.3	20.2	100.5	12.1	13	14.1	15.3	16.6	18.1	19.8
101.0	11.8	12.8	14.0	15.3	16.8	18.5	20.4	101.0	12.2	13.2	14.2	15.4	16.8	18.3	20.0
101.5	11.9	13.0	14.1	15.5	17.0	18.7	20.6	101.5	12.3	13.3	14.4	15.6	16.9	18.5	20.2
102.0	12.0	13.1	14.3	15.6	17.1	18.9	20.8	102.0	12.4	13.4	14.5	15.7	17.1	18.7	20.4
102.5	12.1	13.2	14.4	15.8	17.3	19.0	21.0	102.5	12.5	13.5	14.6	15.9	17.3	18.8	20.6
103.0	12.3	13.3	14.5	15.9	17.5	19.2	21.3	103.0	12.6	13.6	14.8	16.0	17.4	19.0	20.8
103.5	12.4	13.5	14.7	16.1	17.6	19.4	21.5	103.5	12.7	13.7	14.9	16.2	17.6	19.2	21.0
104.0	12.5	13.6	14.8	16.2	17.8	19.6	21.7	104.0	12.8	13.9	15.0	16.3	17.8	19.4	21.2
104.5	12.6	13.7	15.0	16.4	18.0	19.8	21.9	104.5	12.9	14.0	15.2	16.5	17.9	19.6	21.5
105.0	12.7	13.8	15.1	16.5	18.2	20.0	22.2	105.0	13.0	14.1	15.3	16.6	18.1	19.8	21.7
105.5	12.8	14.0	15.3	16.7	18.4	20.2	22.4	105.5	13.2	14.2	15.4	16.8	18.3	20.0	21.9
106.0	13.0	14.1	15.4	16.9	18.5	20.5	22.6	106.0	13.3	14.4	15.6	16.9	18.5	20.2	22.1
106.5	13.1	14.3	15.6	17.1	18.7	20.7	22.9	106.5	13.4	14.5	15.7	17.1	18.6	20.4	22.4
107.0	13.2	14.4	15.7	17.2	18.9	20.9	23.1	107.0	13.5	14.6	15.9	17.3	18.8	20.6	22.6
107.5	13.3	14.5	15.9	17.4	19.1	21.1	23.4	107.5	13.6	14.7	16.0	17.4	19.0	20.8	22.8
108.0	13.5	14.7	16.0	17.6	19.3	21.3	23.6	108.0	13.7	14.9	16.2	17.6	19.2	21.0	23.1
108.5	13.6	14.8	16.2	17.8	19.5	21.6	23.9	108.5	13.8	15.0	16.3	17.8	19.4	21.2	23.3
109.0	13.7	15.0	16.4	18.0	19.7	21.8	24.2	109.0	14.0	15.1	16.5	17.9	19.6	21.4	23.6
109.5	13.9	15.1	16.5	18.1	20.0	22.0	24.4	109.5	14.1	15.3	16.6	18.1	19.8	21.7	23.8
110.0	14.0	15.3	16.7	18.3	20.2	22.3	24.7	110.0	14.2	15.4	16.8	18.3	20.0	21.9	24.1

Table 2.6B: Weight-for-height/length (kg) in girls and boys 0-5 years of age

Height (cm)	Weight (kg) Girls							Height (cm)	Weight (kg) Boys						
	-3 SD	-2 SD	-1 SD	Median	1 SD	2 SD	3 SD		-3 SD	-2 SD	-1 SD	Median	1 SD	2 SD	3 SD
65.0	5.6	6.1	6.6	7.2	7.9	8.7	9.7	65	5.9	6.3	6.9	7.4	8.1	8.8	9.6
65.5	5.7	6.2	6.7	7.4	8.1	8.9	9.8	65.5	6.0	6.4	7.0	7.6	8.2	8.9	9.8
66.0	5.8	6.3	6.8	7.5	8.2	9.0	10.0	66	6.1	6.5	7.1	7.7	8.3	9.1	9.9
66.5	5.8	6.4	6.9	7.6	8.3	9.1	10.1	66.5	6.1	6.6	7.2	7.8	8.5	9.2	10.1
67.0	5.9	6.4	7.0	7.7	8.4	9.3	10.2	67	6.2	6.7	7.3	7.9	8.6	9.4	10.2
67.5	6.0	6.5	7.1	7.8	8.5	9.4	10.4	67.5	6.3	6.8	7.4	8.0	8.7	9.5	10.4
68.0	6.1	6.6	7.2	7.9	8.7	9.5	10.5	68	6.4	6.9	7.5	8.1	8.8	9.6	10.5
68.5	6.2	6.7	7.3	8.0	8.8	9.7	10.7	68.5	6.5	7.0	7.6	8.2	9.0	9.8	10.7
69.0	6.3	6.8	7.4	8.1	8.9	9.8	10.8	69	6.6	7.1	7.7	8.4	9.1	9.9	10.8
69.5	6.3	6.9	7.5	8.2	9.0	9.9	10.9	69.5	6.7	7.2	7.8	8.5	9.2	10.0	11.0
70.0	6.4	7.0	7.6	8.3	9.1	10.0	11.1	70	6.8	7.3	7.9	8.6	9.3	10.2	11.1
70.5	6.5	7.1	7.7	8.4	9.2	10.1	11.2	70.5	6.9	7.4	8.0	8.7	9.5	10.3	11.3
71.0	6.6	7.1	7.8	8.5	9.3	10.3	11.3	71	6.9	7.5	8.1	8.8	9.6	10.4	11.4
71.5	6.7	7.2	7.9	8.6	9.4	10.4	11.5	71.5	7.0	7.6	8.2	8.9	9.7	10.6	11.6
72.0	6.7	7.3	8.0	8.7	9.5	10.5	11.6	72	7.1	7.7	8.3	9.0	9.8	10.7	11.7
72.5	6.8	7.4	8.1	8.8	9.7	10.6	11.7	72.5	7.2	7.8	8.4	9.1	9.9	10.8	11.8
73.0	6.9	7.5	8.1	8.9	9.8	10.7	11.8	73	7.3	7.9	8.5	9.2	10.0	11.0	12.0
73.5	7.0	7.6	8.2	9.0	9.9	10.8	12.0	73.5	7.4	7.9	8.6	9.3	10.2	11.1	12.1
74.0	7.0	7.6	8.3	9.1	10.0	11.0	12.1	74	7.4	8.0	8.7	9.4	10.3	11.2	12.2
74.5	7.1	7.7	8.4	9.2	10.1	11.1	12.2	74.5	7.5	8.1	8.8	9.5	10.4	11.3	12.4
75.0	7.2	7.8	8.5	9.3	10.2	11.2	12.3	75	7.6	8.2	8.9	9.6	10.5	11.4	12.5
75.5	7.2	7.9	8.6	9.4	10.3	11.3	12.5	75.5	7.7	8.3	9.0	9.7	10.6	11.6	12.6
76.0	7.3	8.0	8.7	9.5	10.4	11.4	12.6	76	7.7	8.4	9.1	9.8	10.7	11.7	12.8
76.5	7.4	8.0	8.7	9.6	10.5	11.5	12.7	76.5	7.8	8.5	9.2	9.9	10.8	11.8	12.9
77.0	7.5	8.1	8.8	9.6	10.6	11.6	12.8	77	7.9	8.5	9.2	10.0	10.9	11.9	13.0
77.5	7.5	8.2	8.9	9.7	10.7	11.7	12.9	77.5	8.0	8.6	9.3	10.1	11.0	12.0	13.1
78.0	7.6	8.3	9.0	9.8	10.8	11.8	13.1	78	8.0	8.7	9.4	10.2	11.1	12.1	13.3
78.5	7.7	8.4	9.1	9.9	10.9	12.0	13.2	78.5	8.1	8.8	9.5	10.3	11.2	12.2	13.4
79.0	7.8	8.4	9.2	10.0	11.0	12.1	13.3	79	8.2	8.8	9.6	10.4	11.3	12.3	13.5
79.5	7.8	8.5	9.3	10.1	11.1	12.2	13.4	79.5	8.3	8.9	9.7	10.5	11.4	12.4	13.6
80.0	7.9	8.6	9.4	10.2	11.2	12.3	13.6	80	8.3	9.0	9.7	10.6	11.5	12.6	13.7
80.5	8.0	8.7	9.5	10.3	11.3	12.4	13.7	80.5	8.4	9.1	9.8	10.7	11.6	12.7	13.8
81.0	8.1	8.8	9.6	10.4	11.4	12.6	13.9	81	8.5	9.2	9.9	10.8	11.7	12.8	14.0
81.5	8.2	8.9	9.7	10.6	11.6	12.7	14.0	81.5	8.6	9.3	10.0	10.9	11.8	12.9	14.1
82.0	8.3	9.0	9.8	10.7	11.7	12.8	14.1	82	8.7	9.3	10.1	11.0	11.9	13.0	14.2
82.5	8.4	9.1	9.9	10.8	11.8	13.0	14.3	82.5	8.7	9.4	10.2	11.1	12.1	13.1	14.4
83.0	8.5	9.2	10.0	10.9	11.9	13.1	14.5	83	8.8	9.5	10.3	11.2	12.2	13.3	14.5
83.5	8.5	9.3	10.1	11.0	12.1	13.3	14.6	83.5	8.9	9.6	10.4	11.3	12.3	13.4	14.6
84.0	8.6	9.4	10.2	11.1	12.2	13.4	14.8	84	9.0	9.7	10.5	11.4	12.4	13.5	14.8
84.5	8.7	9.5	10.3	11.3	12.3	13.5	14.9	84.5	9.1	9.9	10.7	11.5	12.5	13.7	14.9
85.0	8.8	9.6	10.4	11.4	12.5	13.7	15.1	85	9.2	10.0	10.8	11.7	12.7	13.8	15.1
85.5	8.9	9.7	10.6	11.5	12.6	13.8	15.3	85.5	9.3	10.1	10.9	11.8	12.8	13.9	15.2
86.0	9.0	9.8	10.7	11.6	12.7	14.0	15.4	86	9.4	10.2	11.0	11.9	12.9	14.1	15.4
86.5	9.1	9.9	10.8	11.8	12.9	14.2	15.6	86.5	9.5	10.3	11.1	12.0	13.1	14.2	15.5
87.0	9.2	10.0	10.9	11.9	13.0	14.3	15.8	87	9.6	10.4	11.2	12.2	13.2	14.4	15.7
87.5	9.3	10.1	11.0	12.0	13.2	14.5	15.9	87.5	9.7	10.5	11.3	12.3	13.3	14.5	15.8
88.0	9.4	10.2	11.1	12.1	13.3	14.6	16.1	88	9.8	10.6	11.5	12.4	13.5	14.7	16.0
88.5	9.5	10.3	11.2	12.3	13.4	14.8	16.3	88.5	9.9	10.7	11.6	12.5	13.6	14.8	16.1
89.0	9.6	10.4	11.4	12.4	13.6	14.9	16.4	89	10.0	10.8	11.7	12.6	13.7	14.9	16.3
89.5	9.7	10.5	11.5	12.5	13.7	15.1	16.6	89.5	10.1	10.9	11.8	12.8	13.9	15.1	16.4
90.0	9.8	10.6	11.6	12.6	13.8	15.2	16.8	90	10.2	11.0	11.9	12.9	14.0	15.2	16.6
90.5	9.9	10.7	11.7	12.8	14.0	15.4	16.9	90.5	10.3	11.1	12.0	13.0	14.1	15.3	16.7
91.0	10.0	10.9	11.8	12.9	14.1	15.5	17.1	91	10.4	11.2	12.1	13.1	14.2	15.5	16.9
91.5	10.1	11.0	11.9	13.0	14.3	15.7	17.3	91.5	10.5	11.3	12.2	13.2	14.4	15.6	17.0

Table 2.6B: Weight-for-height/length (kg) in girls and boys 0-5 years of age (Contd.)

Height (cm)	Weight (kg) Girls							Height (cm)	Weight (kg) Boys						
	-3 SD	-2 SD	-1 SD	Median	1 SD	2 SD	3 SD		-3 SD	-2 SD	-1 SD	Median	1 SD	2 SD	3 SD
92.0	10.2	11.1	12.0	13.1	14.4	15.8	17.4	92.0	10.6	11.4	12.3	13.4	14.5	15.8	17.2
92.5	10.3	11.2	12.1	13.3	14.5	16.0	17.6	92.5	10.7	11.5	12.4	13.5	14.6	15.9	17.3
93.0	10.4	11.3	12.3	13.4	14.7	16.1	17.8	93.0	10.8	11.6	12.6	13.6	14.7	16.0	17.5
93.5	10.5	11.4	12.4	13.5	14.8	16.3	17.9	93.5	10.9	11.7	12.7	13.7	14.9	16.2	17.6
94.0	10.6	11.5	12.5	13.6	14.9	16.4	18.1	94.0	11.0	11.8	12.8	13.8	15.0	16.3	17.8
94.5	10.7	11.6	12.6	13.8	15.1	16.6	18.3	94.5	11.1	11.9	12.9	13.9	15.1	16.5	17.9
95.0	10.8	11.7	12.7	13.9	15.2	16.7	18.5	95.0	11.1	12.0	13.0	14.1	15.3	16.6	18.1
95.5	10.8	11.8	12.8	14.0	15.4	16.9	18.6	95.5	11.2	12.1	13.1	14.2	15.4	16.7	18.3
96.0	10.9	11.9	12.9	14.1	15.5	17.0	18.8	96.0	11.3	12.2	13.2	14.3	15.5	16.9	18.4
96.5	11.0	12.0	13.1	14.3	15.6	17.2	19.0	96.5	11.4	12.3	13.3	14.4	15.7	17.0	18.6
97.0	11.1	12.1	13.2	14.4	15.8	17.4	19.2	97.0	11.5	12.4	13.4	14.6	15.8	17.2	18.8
97.5	11.2	12.2	13.3	14.5	15.9	17.5	19.3	97.5	11.6	12.5	13.6	14.7	15.9	17.4	18.9
98.0	11.3	12.3	13.4	14.7	16.1	17.7	19.5	98.0	11.7	12.6	13.7	14.8	16.1	17.5	19.1
98.5	11.4	12.4	13.5	14.8	16.2	17.9	19.7	98.5	11.8	12.8	13.8	14.9	16.2	17.7	19.3
99.0	11.5	12.5	13.7	14.9	16.4	18.0	19.9	99.0	11.9	12.9	13.9	15.1	16.4	17.9	19.5
99.5	11.6	12.7	13.8	15.1	16.5	18.2	20.1	99.5	12.0	13.0	14.0	15.2	16.5	18.0	19.7
100.0	11.7	12.8	13.9	15.2	16.7	18.4	20.3	100.0	12.1	13.1	14.2	15.4	16.7	18.2	19.9
100.5	11.9	12.9	14.1	15.4	16.9	18.6	20.5	100.5	12.2	13.2	14.3	15.5	16.9	18.4	20.1
101.0	12.0	13.0	14.2	15.5	17.0	18.7	20.7	101.0	12.3	13.3	14.4	15.6	17.0	18.5	20.3
101.5	12.1	13.1	14.3	15.7	17.2	18.9	20.9	101.5	12.4	13.4	14.5	15.8	17.2	18.7	20.5
102.0	12.2	13.3	14.5	15.8	17.4	19.1	21.1	102.0	12.5	13.6	14.7	15.9	17.3	18.9	20.7
102.5	12.3	13.4	14.6	16.0	17.5	19.3	21.4	102.5	12.6	13.7	14.8	16.1	17.5	19.1	20.9
103.0	12.4	13.5	14.7	16.1	17.7	19.5	21.6	103.0	12.8	13.8	14.9	16.2	17.7	19.3	21.1
103.5	12.5	13.6	14.9	16.3	17.9	19.7	21.8	103.5	12.9	13.9	15.1	16.4	17.8	19.5	21.3
104.0	12.6	13.8	15.0	16.4	18.1	19.9	22.0	104.0	13.0	14.0	15.2	16.5	18.0	19.7	21.6
104.5	12.8	13.9	15.2	16.6	18.2	20.1	22.3	104.5	13.1	14.2	15.4	16.7	18.2	19.9	21.8
105.0	12.9	14.0	15.3	16.8	18.4	20.3	22.5	105.0	13.2	14.3	15.5	16.8	18.4	20.1	22.0
105.5	13.0	14.2	15.5	16.9	18.6	20.5	22.7	105.5	13.3	14.4	15.6	17.0	18.5	20.3	22.2
106.0	13.1	14.3	15.6	17.1	18.8	20.8	23.0	106.0	13.4	14.5	15.8	17.2	18.7	20.5	22.5
106.5	13.3	14.5	15.8	17.3	19.0	21.0	23.2	106.5	13.5	14.7	15.9	17.3	18.9	20.7	22.7
107.0	13.4	14.6	15.9	17.5	19.2	21.2	23.5	107.0	13.7	14.8	16.1	17.5	19.1	20.9	22.9
107.5	13.5	14.7	16.1	17.7	19.4	21.4	23.7	107.5	13.8	14.9	16.2	17.7	19.3	21.1	23.2
108.0	13.7	14.9	16.3	17.8	19.6	21.7	24.0	108.0	13.9	15.1	16.4	17.8	19.5	21.3	23.4
108.5	13.8	15.0	16.4	18.0	19.8	21.9	24.3	108.5	14.0	15.2	16.5	18.0	19.7	21.5	23.7
109.0	13.9	15.2	16.6	18.2	20.0	22.1	24.5	109.0	14.1	15.3	16.7	18.2	19.8	21.8	23.9
109.5	14.1	15.4	16.8	18.4	20.3	22.4	24.8	109.5	14.3	15.5	16.8	18.3	20.0	22.0	24.2
110.0	14.2	15.5	17.0	18.6	20.5	22.6	25.1	110.0	14.4	15.6	17.0	18.5	20.2	22.2	24.4
110.5	14.4	15.7	17.1	18.8	20.7	22.9	25.4	110.5	14.5	15.8	17.1	18.7	20.4	22.4	24.7
111.0	14.5	15.8	17.3	19.0	20.9	23.1	25.7	111.0	14.6	15.9	17.3	18.9	20.7	22.7	25.0
111.5	14.7	16.0	17.5	19.2	21.2	23.4	26.0	111.5	14.8	16.0	17.5	19.1	20.9	22.9	25.2
112.0	14.8	16.2	17.7	19.4	21.4	23.6	26.2	112.0	14.9	16.2	17.6	19.2	21.1	23.1	25.5
112.5	15.0	16.3	17.9	19.6	21.6	23.9	26.5	112.5	15.0	16.3	17.8	19.4	21.3	23.4	25.8
113.0	15.1	16.5	18.0	19.8	21.8	24.2	26.8	113.0	15.2	16.5	18.0	19.6	21.5	23.6	26.0
113.5	15.3	16.7	18.2	20.0	22.1	24.4	27.1	113.5	15.3	16.6	18.1	19.8	21.7	23.9	26.3
114.0	15.4	16.8	18.4	20.2	22.3	24.7	27.4	114.0	15.4	16.8	18.3	20.0	21.9	24.1	26.6
114.5	15.6	17.0	18.6	20.5	22.6	25.0	27.8	114.5	15.6	16.9	18.5	20.2	22.1	24.4	26.9
115.0	15.7	17.2	18.8	20.7	22.8	25.2	28.1	115.0	15.7	17.1	18.6	20.4	22.4	24.6	27.2
115.5	15.9	17.3	19.0	20.9	23.0	25.5	28.4	115.5	15.8	17.2	18.8	20.6	22.6	24.9	27.5
116.0	16.0	17.5	19.2	21.1	23.3	25.8	28.7	116.0	16.0	17.4	19.0	20.8	22.8	25.1	27.8
116.5	16.2	17.7	19.4	21.3	23.5	26.1	29.0	116.5	16.1	17.5	19.2	21.0	23.0	25.4	28.0
117.0	16.3	17.8	19.6	21.5	23.8	26.3	29.3	117.0	16.2	17.7	19.3	21.2	23.3	25.6	28.3
117.5	16.5	18.0	19.8	21.7	24.0	26.6	29.6	117.5	16.4	17.9	19.5	21.4	23.5	25.9	28.6
118.0	16.6	18.2	19.9	22.0	24.2	26.9	29.9	118.0	16.5	18.0	19.7	21.6	23.7	26.1	28.9
118.5	16.8	18.4	20.1	22.2	24.5	27.2	30.3	118.5	16.7	18.2	19.9	21.8	23.9	26.4	29.2
119.0	16.9	18.5	20.3	22.4	24.7	27.4	30.6	119.0	16.8	18.3	20.0	22.0	24.1	26.6	29.5
119.5	17.1	18.7	20.5	22.6	25.0	27.7	30.9	119.5	16.9	18.5	20.2	22.2	24.4	26.9	29.8
120.0	17.3	18.9	20.7	22.8	25.2	28.0	31.2	120.0	17.1	18.6	20.4	22.4	24.6	27.2	30.1

Table 2.7: Body mass index (BMI) for age in girls and boys 0-5 years

Age (mo)	BMI Girls							BMI Boys						
	-3 SD	-2 SD	-1 SD	Median	1 SD	2 SD	3 SD	-3 SD	-2 SD	-1 SD	Median	1 SD	2 SD	3 SD
0	10.1	11.1	12.2	13.3	14.6	16.1	17.7	10.2	11.1	12.2	13.4	14.8	16.3	18.1
1	10.8	12.0	13.2	14.6	16.0	17.5	19.1	11.3	12.4	13.6	14.9	16.3	17.8	19.4
2	11.8	13.0	14.3	15.8	17.3	19.0	20.7	12.5	13.7	15.0	16.3	17.8	19.4	21.1
3	12.4	13.6	14.9	16.4	17.9	19.7	21.5	13.1	14.3	15.5	16.9	18.4	20.0	21.8
4	12.7	13.9	15.2	16.7	18.3	20.0	22.0	13.4	14.5	15.8	17.2	18.7	20.3	22.1
5	12.9	14.1	15.4	16.8	18.4	20.2	22.2	13.5	14.7	15.9	17.3	18.8	20.5	22.3
6	13.0	14.1	15.5	16.9	18.5	20.3	22.3	13.6	14.7	16.0	17.3	18.8	20.5	22.3
7	13.0	14.2	15.5	16.9	18.5	20.3	22.3	13.7	14.8	16.0	17.3	18.7	20.4	22.2
8	13.0	14.1	15.4	16.8	18.4	20.2	22.2	13.6	14.7	15.8	17.2	18.6	20.3	22.1
9	12.9	14.1	15.3	16.7	18.3	20.1	22.1	13.6	14.7	15.7	17.0	18.5	20.1	22.0
10	12.9	14.0	15.2	16.6	18.2	19.9	21.9	13.5	14.6	15.7	16.9	18.4	20.0	21.8
11	12.8	13.9	15.1	16.5	18.0	19.8	21.8	13.4	14.5	15.6	16.8	18.2	19.8	21.6
12	12.7	13.8	15.0	16.4	17.9	19.6	21.6	13.4	14.4	15.5	16.7	18.1	19.7	21.5
13	12.6	13.7	14.9	16.2	17.7	19.5	21.4	13.3	14.3	15.4	16.6	18.0	19.5	21.3
14	12.6	13.6	14.8	16.1	17.6	19.3	21.3	13.2	14.2	15.3	16.4	17.8	19.4	21.2
15	12.5	13.5	14.7	16.0	17.5	19.2	21.1	13.1	14.1	15.2	16.3	17.7	19.3	21.0
16	12.4	13.5	14.6	15.9	17.4	19.1	21.0	13.1	14.0	15.1	16.2	17.6	19.1	20.9
17	12.4	13.4	14.5	15.8	17.3	18.9	20.9	13.0	13.9	15.0	16.1	17.5	19.0	20.8
18	12.3	13.3	14.4	15.7	17.2	18.8	20.8	12.9	13.9	14.9	16.1	17.4	18.9	20.7
19	12.3	13.3	14.4	15.7	17.1	18.8	20.7	12.9	13.8	14.9	16.1	17.4	18.9	20.7
20	12.2	13.2	14.3	15.6	17.0	18.7	20.6	12.8	13.7	14.8	16.0	17.3	18.8	20.6
21	12.2	13.2	14.3	15.5	17.0	18.6	20.5	12.8	13.7	14.7	15.9	17.2	18.7	20.5
22	12.2	13.1	14.2	15.5	16.9	18.5	20.4	12.7	13.6	14.7	15.8	17.2	18.7	20.4
23	12.2	13.1	14.2	15.4	16.9	18.5	20.4	12.7	13.6	14.6	15.8	17.1	18.6	20.3
24	12.1	13.1	14.2	15.4	16.8	18.4	20.3	12.7	13.6	14.6	15.7	17.0	18.5	20.3

Age (mo)	By height							By height						
	-3 SD	-2 SD	-1 SD	Median	1 SD	2 SD	3 SD	-3 SD	-2 SD	-1 SD	Median	1 SD	2 SD	3 SD
24	12.4	13.3	14.4	15.7	17.1	18.7	20.6	12.9	13.8	14.8	16.0	17.3	18.9	20.6
25	12.4	13.3	14.4	15.7	17.1	18.7	20.6	12.8	13.8	14.8	16.0	17.3	18.8	20.5
26	12.3	13.3	14.4	15.6	17.0	18.7	20.6	12.8	13.7	14.8	15.9	17.3	18.8	20.5
27	12.3	13.3	14.4	15.6	17.0	18.6	20.5	12.7	13.7	14.7	15.9	17.2	18.7	20.4
28	12.3	13.3	14.3	15.6	17.0	18.6	20.5	12.7	13.6	14.7	15.9	17.2	18.7	20.4
29	12.3	13.2	14.3	15.6	17.0	18.6	20.4	12.7	13.6	14.7	15.8	17.1	18.6	20.3
30	12.3	13.2	14.3	15.5	16.9	18.5	20.4	12.6	13.6	14.6	15.8	17.1	18.6	20.2
31	12.2	13.2	14.3	15.5	16.9	18.5	20.4	12.6	13.5	14.6	15.8	17.1	18.5	20.2
32	12.2	13.2	14.3	15.5	16.9	18.5	20.4	12.5	13.5	14.6	15.7	17.0	18.5	20.1
33	12.2	13.1	14.2	15.5	16.9	18.5	20.3	12.5	13.5	14.5	15.7	17.0	18.5	20.1
34	12.2	13.1	14.2	15.4	16.8	18.5	20.3	12.5	13.4	14.5	15.7	17.0	18.4	20.0
35	12.1	13.1	14.2	15.4	16.8	18.4	20.3	12.4	13.4	14.5	15.6	16.9	18.4	20.0
36	12.1	13.1	14.2	15.4	16.8	18.4	20.3	12.4	13.4	14.4	15.6	16.9	18.4	20.0
37	12.1	13.1	14.1	15.4	16.8	18.4	20.3	12.4	13.3	14.4	15.6	16.9	18.3	19.9
38	12.1	13.0	14.1	15.4	16.8	18.4	20.3	12.3	13.3	14.4	15.5	16.8	18.3	19.9
39	12.0	13.0	14.1	15.3	16.8	18.4	20.3	12.3	13.3	14.3	15.5	16.8	18.3	19.9
40	12.0	13.0	14.1	15.3	16.8	18.4	20.3	12.3	13.2	14.3	15.5	16.8	18.2	19.9
41	12.0	13.0	14.1	15.3	16.8	18.4	20.4	12.2	13.2	14.3	15.5	16.8	18.2	19.9
42	12.0	12.9	14.0	15.3	16.8	18.4	20.4	12.2	13.2	14.3	15.4	16.8	18.2	19.8
43	11.9	12.9	14.0	15.3	16.8	18.4	20.4	12.2	13.2	14.2	15.4	16.7	18.2	19.8
44	11.9	12.9	14.0	15.3	16.8	18.5	20.4	12.2	13.1	14.2	15.4	16.7	18.2	19.8
45	11.9	12.9	14.0	15.3	16.8	18.5	20.5	12.2	13.1	14.2	15.4	16.7	18.2	19.8
46	11.9	12.9	14.0	15.3	16.8	18.5	20.5	12.1	13.1	14.2	15.4	16.7	18.2	19.8
47	11.8	12.8	14.0	15.3	16.8	18.5	20.5	12.1	13.1	14.2	15.3	16.7	18.2	19.8
48	11.8	12.8	14.0	15.3	16.8	18.5	20.6	12.1	13.1	14.1	15.3	16.7	18.2	19.9
49	11.8	12.8	13.9	15.3	16.8	18.5	20.6	12.1	13.0	14.1	15.3	16.7	18.2	19.9
50	11.8	12.8	13.9	15.3	16.8	18.6	20.7	12.1	13.0	14.1	15.3	16.7	18.2	19.9
51	11.8	12.8	13.9	15.3	16.8	18.6	20.7	12.1	13.0	14.1	15.3	16.7	18.2	19.9
52	11.7	12.8	13.9	15.2	16.8	18.6	20.7	12.0	13.0	14.1	15.3	16.6	18.2	19.9
53	11.7	12.7	13.9	15.3	16.8	18.6	20.8	12.0	13.0	14.1	15.3	16.6	18.2	19.9
54	11.7	12.7	13.9	15.3	16.8	18.7	20.8	12.0	13.0	14.0	15.3	16.6	18.2	20.0
55	11.7	12.7	13.9	15.3	16.8	18.7	20.9	12.0	13.0	14.0	15.3	16.6	18.2	20.0
56	11.7	12.7	13.9	15.3	16.8	18.7	20.9	12.0	12.9	14.0	15.2	16.6	18.2	20.0
57	11.7	12.7	13.9	15.3	16.9	18.7	21.0	12.0	12.9	14.0	15.2	16.6	18.2	20.1
58	11.7	12.7	13.9	15.3	16.9	18.8	21.0	12.0	12.9	14.0	15.2	16.6	18.2	20.1
59	11.6	12.7	13.9	15.3	16.9	18.8	21.0	12.0	12.9	14.0	15.2	16.6	18.3	20.2

Table 2.8: Head circumference for age (cm) in girls and boys 0–5 years of age

Age (mo)	BMI Girls							BMI Boys						
	-3 SD	-2 SD	-1 SD	Median	1 SD	2 SD	3 SD	-3 SD	-2 SD	-1 SD	Median	1 SD	2 SD	3 SD
0	30.3	31.5	32.7	33.9	35.1	36.2	37.4	30.7	31.9	33.2	34.5	35.7	37.0	38.3
1	33.0	34.2	35.4	36.5	37.7	38.9	40.1	33.8	34.9	36.1	37.3	38.4	39.6	40.8
2	34.6	35.8	37.0	38.3	39.5	40.7	41.9	35.6	36.8	38.0	39.1	40.3	41.5	42.6
3	35.8	37.1	38.3	39.5	40.8	42.0	43.3	37.0	38.1	39.3	40.5	41.7	42.9	44.1
4	36.8	38.1	39.3	40.6	41.8	43.1	44.4	38.0	39.2	40.4	41.6	42.8	44.0	45.2
5	37.6	38.9	40.2	41.5	42.7	44.0	45.3	38.9	40.1	41.4	42.6	43.8	45.0	46.2
6	38.3	39.6	40.9	42.2	43.5	44.8	46.1	39.7	40.9	42.1	43.3	44.6	45.8	47.0
7	38.9	40.2	41.5	42.8	44.1	45.5	46.8	40.3	41.5	42.7	44.0	45.2	46.4	47.7
8	39.4	40.7	42.0	43.4	44.7	46.0	47.4	40.8	42.0	43.3	44.5	45.8	47.0	48.3
9	39.8	41.2	42.5	43.8	45.2	46.5	47.8	41.2	42.5	43.7	45.0	46.3	47.5	48.8
10	40.2	41.5	42.9	44.2	45.6	46.9	48.3	41.6	42.9	44.1	45.4	46.7	47.9	49.2
11	40.5	41.9	43.2	44.6	45.9	47.3	48.6	41.9	43.2	44.5	45.8	47.0	48.3	49.6
12	40.8	42.2	43.5	44.9	46.3	47.6	49.0	42.2	43.5	44.8	46.1	47.4	48.6	49.9
13	41.1	42.4	43.8	45.2	46.5	47.9	49.3	42.5	43.8	45.0	46.3	47.6	48.9	50.2
14	41.3	42.7	44.1	45.4	46.8	48.2	49.5	42.7	44.0	45.3	46.6	47.9	49.2	50.5
15	41.5	42.9	44.3	45.7	47.0	48.4	49.8	42.9	44.2	45.5	46.8	48.1	49.4	50.7
16	41.7	43.1	44.5	45.9	47.2	48.6	50.0	43.1	44.4	45.7	47.0	48.3	49.6	51.0
17	41.9	43.3	44.7	46.1	47.4	48.8	50.2	43.2	44.6	45.9	47.2	48.5	49.8	51.2
18	42.1	43.5	44.9	46.2	47.6	49.0	50.4	43.4	44.7	46.0	47.4	48.7	50.0	51.4
19	42.3	43.6	45.0	46.4	47.8	49.2	50.6	43.5	44.9	46.2	47.5	48.9	50.2	51.5
20	42.4	43.8	45.2	46.6	48.0	49.4	50.7	43.7	45.0	46.4	47.7	49.0	50.4	51.7
21	42.6	44.0	45.3	46.7	48.1	49.5	50.9	43.8	45.2	46.5	47.8	49.2	50.5	51.9
22	42.7	44.1	45.5	46.9	48.3	49.7	51.1	43.9	45.3	46.6	48.0	49.3	50.7	52.0
23	42.9	44.3	45.6	47.0	48.4	49.8	51.2	44.1	45.4	46.8	48.1	49.5	50.8	52.2
24	43.0	44.4	45.8	47.2	48.6	50.0	51.4	44.2	45.5	46.9	48.3	49.6	51.0	52.3
25	43.1	44.5	45.9	47.3	48.7	50.1	51.5	44.3	45.6	47.0	48.4	49.7	51.1	52.5
26	43.3	44.7	46.1	47.5	48.9	50.3	51.7	44.4	45.8	47.1	48.5	49.9	51.2	52.6
27	43.4	44.8	46.2	47.6	49.0	50.4	51.8	44.5	45.9	47.2	48.6	50.0	51.4	52.7
28	43.5	44.9	46.3	47.7	49.1	50.5	51.9	44.6	46.0	47.3	48.7	50.1	51.5	52.9
29	43.6	45.0	46.4	47.8	49.2	50.6	52.0	44.7	46.1	47.4	48.8	50.2	51.6	53.0
30	43.7	45.1	46.5	47.9	49.3	50.7	52.2	44.8	46.1	47.5	48.9	50.3	51.7	53.1
31	43.8	45.2	46.6	48.0	49.4	50.9	52.3	44.8	46.2	47.6	49.0	50.4	51.8	53.2
32	43.9	45.3	46.7	48.1	49.6	51.0	52.4	44.9	46.3	47.7	49.1	50.5	51.9	53.3
33	44.0	45.4	46.8	48.2	49.7	51.1	52.5	45.0	46.4	47.8	49.2	50.6	52.0	53.4
34	44.1	45.5	46.9	48.3	49.7	51.2	52.6	45.1	46.5	47.9	49.3	50.7	52.1	53.5
35	44.2	45.6	47.0	48.4	49.8	51.2	52.7	45.1	46.6	48.0	49.4	50.8	52.2	53.6
36	44.3	45.7	47.1	48.5	49.9	51.3	52.7	45.2	46.6	48.0	49.5	50.9	52.3	53.7
37	44.4	45.8	47.2	48.6	50.0	51.4	52.8	45.3	46.7	48.1	49.5	51.0	52.4	53.8
38	44.4	45.8	47.3	48.7	50.1	51.5	52.9	45.3	46.8	48.2	49.6	51.0	52.5	53.9
39	44.5	45.9	47.3	48.7	50.2	51.6	53.0	45.4	46.8	48.2	49.7	51.1	52.5	54.0
40	44.6	46.0	47.4	48.8	50.2	51.7	53.1	45.4	46.9	48.3	49.7	51.2	52.6	54.1
41	44.6	46.1	47.5	48.9	50.3	51.7	53.1	45.5	46.9	48.4	49.8	51.3	52.7	54.1
42	44.7	46.1	47.5	49.0	50.4	51.8	53.2	45.5	47.0	48.4	49.9	51.3	52.8	54.2
43	44.8	46.2	47.6	49.0	50.4	51.9	53.3	45.6	47.0	48.5	49.9	51.4	52.8	54.3
44	44.8	46.3	47.7	49.1	50.5	51.9	53.3	45.6	47.1	48.5	50.0	51.4	52.9	54.3
45	44.9	46.3	47.7	49.2	50.6	52.0	53.4	45.7	47.1	48.6	50.1	51.5	53.0	54.4
46	45.0	46.4	47.8	49.2	50.6	52.1	53.5	45.7	47.2	48.7	50.1	51.6	53.0	54.5
47	45.0	46.4	47.9	49.3	50.7	52.1	53.5	45.8	47.2	48.7	50.2	51.6	53.1	54.5
48	45.1	46.5	47.9	49.3	50.8	52.2	53.6	45.8	47.3	48.7	50.2	51.7	53.1	54.6
49	45.1	46.5	48.0	49.4	50.8	52.2	53.6	45.9	47.3	48.8	50.3	51.7	53.2	54.7
50	45.2	46.6	48.0	49.4	50.9	52.3	53.7	45.9	47.4	48.8	50.3	51.8	53.2	54.7
51	45.2	46.7	48.1	49.5	50.9	52.3	53.8	45.9	47.4	48.9	50.4	51.8	53.3	54.8
52	45.3	46.7	48.1	49.5	51.0	52.4	53.8	46.0	47.5	48.9	50.4	51.9	53.4	54.8
53	45.3	46.8	48.2	49.6	51.0	52.4	53.9	46.0	47.5	49.0	50.4	51.9	53.4	54.9
54	45.4	46.8	48.2	49.6	51.1	52.5	53.9	46.1	47.5	49.0	50.5	52.0	53.5	54.9
55	45.4	46.9	48.3	49.7	51.1	52.5	54.0	46.1	47.6	49.1	50.5	52.0	53.5	55.0
56	45.5	46.9	48.3	49.7	51.2	52.6	54.0	46.1	47.6	49.1	50.6	52.1	53.5	55.0
57	45.5	46.9	48.4	49.8	51.2	52.6	54.1	46.2	47.6	49.1	50.6	52.1	53.6	55.1
58	45.6	47.0	48.4	49.8	51.3	52.7	54.1	46.2	47.7	49.2	50.7	52.1	53.6	55.1
59	45.6	47.0	48.5	49.9	51.3	52.7	54.1	46.2	47.7	49.2	50.7	52.2	53.7	55.2
60	45.7	47.1	48.5	49.9	51.3	52.8	54.2	46.3	47.7	49.2	50.7	52.2	53.7	55.2

Table 2.9: Boys aged 5 to 18 years old: IAP charts for weight, height, body mass index (percentiles) (reproduced with permission from Indian Pediatr, 2015;52:47–55)

Age (years)	Height (cm)						Weight (kg)						Body mass index						
	3rd	10th	50th	90th	97th	SD	3rd	10th	50th	90th	97th	SD	3th	5th	10th	50th	23rd AE	27th AE	SD
5.0	99.0	102.3	108.9	115.9	119.4	5.7	13.2	14.3	17.1	21.3	24.2	3.2	12.1	12.4	12.8	14.7	15.7	17.5	1.6
5.5	101.6	105.0	111.9	119.0	122.7	5.3	13.8	15.0	18.2	22.9	26.1	2.9	12.2	12.4	12.9	14.8	15.8	17.6	1.5
6.0	104.2	107.7	114.8	122.2	126.0	5.6	14.5	15.8	19.3	24.6	28.3	3.6	12.2	12.5	12.9	14.9	16.0	17.8	1.8
6.5	106.8	110.4	117.8	125.4	129.3	5.5	15.3	16.8	20.7	26.6	30.8	3.8	12.3	12.5	13.0	15.0	16.1	18.0	1.8
7.0	109.3	113.0	120.7	128.6	132.6	5.9	16.0	17.6	21.9	28.6	33.4	4.2	12.3	12.6	13.1	15.1	16.3	18.2	1.9
7.5	111.8	115.7	123.5	131.7	135.9	5.7	16.7	18.5	23.3	30.8	36.2	4.9	12.4	12.7	13.2	15.3	16.5	18.5	2.2
8.0	114.3	118.2	126.4	134.8	139.1	6.3	17.5	19.5	24.8	33.2	39.4	5.7	12.5	12.8	13.3	15.5	16.7	18.8	2.5
8.5	116.7	120.8	129.1	137.8	142.2	6.1	18.3	20.5	26.4	35.7	42.6	6.5	12.6	12.9	13.4	15.7	17.0	19.2	2.8
9.0	119.0	123.2	131.8	140.7	145.3	6.4	19.1	21.5	27.9	38.0	45.5	6.3	12.7	13.0	13.5	15.9	17.3	19.6	2.6
9.5	121.3	125.6	134.5	143.7	148.3	6.4	19.9	22.4	29.4	40.5	48.6	7.0	12.8	13.1	13.7	16.2	17.6	20.1	2.8
10.0	123.6	128.1	137.2	146.6	151.4	6.8	20.7	23.5	31.1	43.0	51.8	7.9	12.9	13.2	13.8	16.4	18.0	20.5	3.1
10.5	125.9	130.5	139.9	149.5	154.4	6.5	21.6	24.6	32.8	45.8	55.2	8.3	13.0	13.3	14.0	16.7	18.3	21.0	3.2
11.0	128.2	133.0	142.7	152.5	157.5	7.6	22.6	25.9	34.7	48.7	58.7	8.9	13.1	13.5	14.1	17.0	18.7	21.5	3.2
11.5	130.7	135.6	145.5	155.6	160.6	7.3	23.8	27.3	36.9	51.8	62.5	9.3	13.2	13.6	14.3	17.3	19.1	22.1	3.3
12.0	133.2	138.3	148.4	158.6	163.7	8.1	24.9	28.7	39.0	54.8	66.1	10.0	13.3	13.8	14.5	17.7	19.5	22.6	3.4
12.5	135.7	141.0	151.4	161.7	166.8	7.9	26.1	30.2	41.2	57.8	69.5	10.6	13.5	13.9	14.6	17.9	19.8	23.0	3.6
13.0	138.3	143.7	154.3	164.7	169.9	9.0	27.5	31.8	43.3	60.7	72.6	11.3	13.6	14.0	14.8	18.2	20.2	23.4	3.5
13.5	140.9	146.4	157.2	167.6	172.7	8.4	29.0	33.6	45.7	63.6	75.6	11.4	13.7	14.2	14.9	18.5	20.5	23.8	3.7
14.0	143.4	149.0	159.9	170.3	175.4	9.0	30.7	35.5	48.2	66.3	78.3	12.1	13.8	14.3	15.1	18.7	20.8	24.2	3.7
14.5	145.8	151.5	162.3	172.7	177.7	7.8	32.6	37.7	50.8	69.1	80.9	11.6	14.0	14.5	15.3	19.0	21.1	24.5	3.5
15.0	148.0	153.7	164.5	174.8	179.7	7.9	34.5	39.8	53.1	71.5	83.1	12.1	14.2	14.7	15.5	19.3	21.4	24.9	3.7
15.5	150.0	155.7	166.5	176.5	181.4	6.6	36.1	41.6	55.2	73.4	84.7	11.2	14.4	14.9	15.8	19.6	21.7	25.2	3.4
16.0	151.8	157.4	168.1	178.0	182.7	7.2	37.5	43.1	56.8	74.8	85.8	12.2	14.6	15.1	16.0	19.9	22.0	25.5	3.7
16.5	153.4	159.1	169.6	179.3	183.8	6.7	38.7	44.4	58.2	76.1	86.8	12.6	14.9	15.4	16.3	20.2	22.4	25.8	3.8
17.0	155.0	160.6	171.0	180.4	184.8	6.9	39.8	45.6	59.5	77.1	87.5	12.3	15.1	15.6	16.6	20.5	22.6	26.0	3.8
17.5	156.6	162.1	172.3	181.5	185.8	6.1	40.8	46.7	60.6	77.8	88.0	12.3	15.4	15.9	16.8	20.8	22.9	26.3	3.6
18.0	158.1	163.6	173.6	182.5	186.7	6.9	41.8	47.7	61.6	78.6	88.4	11.3	15.6	16.2	17.1	21.1	23.2	26.6	3.2

23rd AE: equivalent to BMI of 23 in adults (overweight); 27th AE: equivalent to BMI of 27 in adults (obesity)

Table 2.10: Girls aged 5 to 18 years old: IAP charts for weight, height, body mass index (percentiles) (reproduced with permission from Indian Pediatr 2015;52:47–55)

Age (years)	Height (cm)						Weight (kg)						Body Mass Index						
	3rd	10th	50th	90th	97th	SD	3rd	10th	50th	90th	97th	SD	3rd	5th	10th	50th	23rd AE	27th AE	SD
5.0	97.2	100.5	107.5	115.2	119.3	5.4	12.3	13.4	16.4	21.3	25.0	2.5	11.9	12.1	12.5	14.3	15.5	18.0	1.4
5.5	99.8	103.2	110.5	118.3	122.5	5.7	13.0	14.3	17.6	22.9	27.0	3.5	11.9	12.2	12.6	14.4	15.7	18.3	1.7
6.0	102.3	106.0	113.5	121.5	125.6	5.8	13.7	15.1	18.7	24.6	29.1	3.4	12.0	12.2	12.7	14.5	15.9	18.6	1.7
6.5	104.9	108.7	116.5	124.6	128.7	5.5	14.4	15.9	19.9	26.3	31.2	4.1	12.1	12.3	12.8	14.7	16.1	18.9	2.0
7.0	107.4	111.4	119.4	127.7	131.9	6.1	15.1	16.8	21.2	28.2	33.4	4.4	12.1	12.4	12.8	14.9	16.4	19.3	2.1
7.5	110.0	114.1	122.4	130.8	135.0	6.0	15.9	17.7	22.5	30.1	35.7	4.8	12.2	12.5	12.9	15.1	16.6	19.7	2.2
8.0	112.6	116.8	125.4	133.9	138.1	6.2	16.7	18.7	24.0	32.2	38.1	5.2	12.3	12.6	13.1	15.3	16.9	20.1	2.3
8.5	115.2	119.6	128.4	137.0	141.3	6.8	17.5	19.7	25.5	34.4	40.7	6.4	12.3	12.7	13.2	15.6	17.2	20.5	2.7
9.0	117.8	122.4	131.4	140.2	144.5	6.9	18.5	20.9	27.2	36.7	43.4	6.4	12.4	12.8	13.3	15.8	17.6	21.0	2.7
9.5	120.5	125.2	134.4	143.3	147.6	6.6	19.5	22.1	29.0	39.3	46.3	6.9	12.5	12.9	13.5	16.1	18.0	21.4	2.8
10.0	123.3	128.1	137.4	146.4	150.8	7.8	20.7	23.5	31.0	42.0	49.4	7.7	12.7	13.1	13.7	16.5	18.4	21.9	2.9
10.5	126.1	130.9	140.4	149.5	153.9	7.3	22.0	25.1	33.2	44.8	52.6	8.3	12.8	13.2	13.9	16.8	18.8	22.5	3.1
11.0	128.8	133.7	143.3	152.4	156.8	7.9	23.3	26.7	35.4	47.7	55.9	8.5	13.0	13.4	14.1	17.2	19.3	23.0	3.1
11.5	131.5	136.4	145.9	155.1	159.6	7.1	24.8	28.4	37.6	50.6	59.1	9.1	13.2	13.7	14.4	17.6	19.8	23.6	3.3
12.0	134.0	138.9	148.4	157.5	162.0	7.0	26.2	30.0	39.8	53.4	62.1	9.0	13.4	13.9	14.7	18.0	20.2	24.1	3.2
12.5	136.3	141.1	150.5	159.6	164.1	6.7	27.6	31.6	41.8	55.8	64.8	9.7	13.7	14.2	15.0	18.4	20.7	24.7	3.3
13.0	138.2	142.9	152.2	161.3	165.9	6.9	28.9	33.1	43.6	57.9	67.1	9.4	13.9	14.4	15.2	18.8	21.1	25.2	3.2
13.5	139.9	144.5	153.6	162.7	167.2	6.0	30.2	34.4	45.1	59.7	69.0	9.8	14.1	14.6	15.5	19.1	21.5	25.6	3.5
14.0	141.3	145.8	154.7	163.7	168.2	6.6	31.3	35.6	46.4	61.1	70.4	9.6	14.3	14.9	15.7	19.4	21.8	25.9	3.4
14.5	142.4	146.8	155.5	164.5	169.0	5.9	32.3	36.6	47.5	62.2	71.4	9.4	14.5	15.1	16.0	19.7	22.0	26.2	3.3
15.0	143.3	147.5	156.1	165.0	169.5	6.6	33.1	37.5	48.4	62.9	72.1	9.6	14.7	15.2	16.1	19.9	22.3	26.3	3.4
15.5	144.1	148.1	156.6	165.3	169.8	5.9	34.0	38.3	49.1	63.5	72.5	8.7	14.9	15.4	16.3	20.1	22.4	26.4	3.1
16.0	144.7	148.6	156.9	165.6	170.1	6.1	34.7	39.1	49.7	64.0	72.8	8.7	15.0	15.6	16.5	20.3	22.6	26.5	3.1
16.5	145.2	149.1	157.2	165.7	170.2	6.4	35.5	39.8	50.3	64.4	73.1	9.2	15.2	15.8	16.7	20.4	22.8	26.6	3.2
17.0	145.7	149.5	157.4	165.9	170.4	6.5	36.2	40.5	50.9	64.7	73.3	8.8	15.4	16.0	16.9	20.6	22.9	26.7	3.0
17.5	146.2	149.8	157.6	166.0	170.5	6.7	36.9	41.1	51.5	65.0	73.4	9.5	15.5	16.1	17.1	20.8	23.1	26.7	3.1
18.0	146.6	150.2	157.8	166.1	170.6	6.6	37.6	41.8	52.0	65.3	73.5	10.2	15.7	16.3	17.3	21.0	23.2	26.8	3.6

IAP

23rd AE: equivalent to BMI of 23 in adults (overweight); 27th AE equivalent to BMI of 27 in adults (obesity)

Growth

Velocity of Growth

Plotting a child's height and weight on a growth chart helps to determine if he is within the normal range for his or her age. One time measurement, however, does not indicate, if the rate of growth of the child has been normal in the recent past. The position on the growth chart becomes evidently abnormal only when the factors retarding growth are profound or have persisted for a long time. On the other hand, serial measurements provide rate of growth. Plotting growth velocity is useful tool for early identification of factors affecting growth. Velocity of growth more accurately helps in predicting the ultimate adult height.

Interpretation of growth measurements: Table 2.11 provides details regarding interpretation of growth charts for children 0 to 5 years of age.

Growth Monitoring

The Indian Academy of Pediatrics has given guidelines to monitor growth during childhood (Table 2.12). During

infancy, the monitoring is conveniently done during visits for vaccination. Later it can be integrated into visits for vaccination, minor illnesses or into school health program. During adolescence, sexual maturity rating (SMR) staging should also be monitored.

Software and Apps to Assist Anthropometric Analysis for Clinical and Research Use

The WHO provides software "WHO-Anthro" for anthropometric analysis. The software consists of three modules: Anthropometric calculator, individual assessment, and nutritional survey.

The software is downloadable at <http://www.who.int/childgrowth/software/en/>

The page provides the option to download the software WHO-Anthro for personal computers (PC) and mobile devices. In addition, there are macros for the statistical software packages to facilitate data analysis.

Table 2.11: Interpretation of growth parameters in children 0 to 5 years of age

Growth indicators

Z-score	Length/height-for-age	Weight-for-age	Weight-for-length/height	BMI-for-age
Above 3	See note 1		Obese	Obese
Above 2			Overweight	Overweight
Above 1		See note 2	Possible risk of overweight (see note 3)	Possible risk of overweight (see note 3)
0 (median)				
Below -1				
Below -2	Stunted (see note 4)	Underweight	Wasted	Wasted
Below -3	Severely stunted (see note 4)	Severely underweight (see note 5)	Severely wasted	Severely wasted

Measurements in the grey shaded boxes are in the normal range

Notes:

1. A child in this range is very tall. Tallness is rarely a problem unless it is so excessive that it may indicate an endocrine disorder such as a growth-hormone producing tumor. Refer a child in this range for assessment, if you suspect an endocrine disorder (e.g. if parents of normal height have a child who is excessively tall for his or her age).
2. A child whose weight-for-age falls in this range may have growth problem, but this is better assessed from weight-for-length/height or BMI-for-age.
3. A plotted point above 1 shows possible risk. A trend towards the +2 Z-score line shows definite risk.
4. It is possible for a stunted or severely stunted child to become overweight.
5. This is referred to as very low weight in IMCI training modules

Table 2.12: Suggested growth monitoring in children at different ages

Age	Height/length	Weight	Head circumference	Other
Birth	✓	✓	✓	
1½, 3 ½, 6, 9, 15 months	✓	✓	✓	
18 months–3 years	✓ (6 monthly)	✓ (6 monthly)	✓ (6 monthly)	
3.5–5.5 years	✓ (6 monthly)	✓ (6 monthly)		
6–8 years	✓ (6 monthly)	✓ (6 monthly)		BMI (yearly)
9–18 years	✓ (yearly)	✓ (yearly)		BMI and SMR (yearly)

Adapted from guidelines of Indian Academy of Pediatrics (2006)

BMI: Body mass index, SMR: Sexual maturity rating

Table 2.13: Examples of selected mobile apps to interpret anthropometric data

Name	Operating mobile system	Basis of calculation
AnthroCal	Android	WHO and IAP
Growth percentiles	Android	WHO
Growth chart CDC WHO percentiles	Android	WHO, CDC
IAP growth charts	Android, IOS	WHO
Pediatric growth chart	IOS	WHO
Pediatric growth charts by Boston Children's Hospital	IOS	WHO, CDC
STAT growth charts Lite	IOS	WHO
Child growth chart	Windows	WHO
Ped (Z)	Windows, Android	WHO, CDC

The authors provide this list only as examples; they do not endorse these apps. Many other apps are continually being developed, User discretion is advised.

Mobile Applications (Apps) for Analysis of Anthropometric Data

Several mobile applications (apps) are now available for instant and quick analysis of anthropometric data (Table 2.13). While a few are paid, many of them are free for download. Some use the CDC charts while others use WHO charts for analysis. A few apps allow users to make choice of charts for calculations and interpretation. Many of these apps have additional capabilities and calculators.

Suggested Reading

- Agarwal DK, Agarwal KN, et al. Physical and sexual growth pattern of affluent Indian children from 5–18 years of age. *Indian Pediatrics* 1992;29:1203–82
- Agarwal DK, Agarwal KN, et al. Physical growth assessment in adolescence. *Indian Pediatrics* 2001;38:1217–35
- Graham CB. Assessment of bone maturation—methods and pitfalls. *Radiol Clin North Am* 1972;10:185–202
- World Health Organisation. <http://www.who.int/nut-growthdb/en>. Guidelines on growth monitoring from birth to 18 years

DISORDERS OF GROWTH

Short Stature

Definition and Epidemiology

Short stature is defined as height below third centile or more than 2 standard deviations (SDs) below the median height for age and gender (<-2 SD) according to the population standard. As is evident from the definition, approximately 3% of children in any given populations will be short. Children whose stature is more than 3 SD below the population mean for age and gender (<-3 SD) are more likely to be suffering from pathological short stature, as compared to those with stature between -2 and -3 SD, who are more likely to be affected by physiological, i.e. familial or constitutional short stature.

Etiology

Short stature can be attributed to many causes (Table 2.14). Undernutrition and chronic systemic illness are the

Table 2.14: Causes of short stature

Physiological short stature or normal variant

Familial
Constitutional

Pathological

Undernutrition

Chronic systemic illness

Cerebral palsy
Congenital heart disease, cystic fibrosis, asthma
Malabsorption, e.g. celiac disease, chronic liver disease
Acquired immunodeficiency syndrome, other chronic infections

Endocrine causes

Growth hormone deficiency, insensitivity
Hypothyroidism
Cushing syndrome
Pseudohypoparathyroidism
Precocious or delayed puberty
Psychosocial dwarfism
Children born small for gestational age
Skeletal dysplasias, e.g. achondroplasia, rickets
Genetic syndromes, e.g. Turner, Down syndrome

common etiological factors, followed by growth hormone deficiency (GHD) and hypothyroidism.

Steps In Assessment

Accurate height measurement: For children below 2 years, supine length should be measured using an infantometer with a rigid headboard on one side and a moveable footboard on the other side, while holding the infant straight on the horizontal board (Fig. 2.6). For older children, height should be measured with a stadiometer, as explained in previous section (Fig. 2.7).

Assessment of height velocity: Height velocity is the rate of increase in height over a period of time expressed as cm/year. The average height velocity is 25 cm/yr in the first year, declines to 4–6 cm/yr in prepubertal children between 4 and 9 years of age and increases during puberty

to a peak height velocity of 10–12 cm/yr. If height velocity is lower than expected for age, the child is likely to be suffering from a pathological cause of short stature.

Comparison with population norms: The height should be plotted on appropriate growth charts and expressed in centile or as standard deviation score.

Comparison with child's own genetic potential: Parents' height significantly affects the child's height. Mid-parental height (MPH) gives an approximate estimate of the child's genetically determined potential.

$$\text{MPH for boys} = \frac{\text{Mother} + \text{Father height (cm)}}{2} + 6.5 \text{ cm}$$

$$\text{MPH for girls} = \frac{\text{Mother} + \text{Father height (cm)}}{2} - 6.5 \text{ cm}$$

This value is then plotted on the growth chart at 18–20 years (adult equivalent) of age. This gives an estimate of the target height for the child and the percentile that he/she is likely to follow.

Assessment of body proportion: Short stature can be proportionate or disproportionate. The proportionality is assessed by upper segment (US): lower segment (LS) ratio and comparison of arm span with height. US can be measured by taking the sitting height of the child. Child is made to sit on a square stool placed against the vertical rod of the stadiometer. The headboard is brought down to the vertex similarly as for taking height. The height of the stool is subtracted from the reading obtained to get sitting height. LS can be obtained by subtracting US from height. Alternatively, LS can be measured by taking the length from pubic symphysis to the ground while the child is standing erect. For measuring arm span, child is asked to stand straight with both arms extended outwards parallel to the ground. Length between the tips of the middle finger of the outstretched hands is the arm span.

Normally, US : LS ratio is 1.7 at birth, 1.3 at 3 years, 1.1 by 6 years, 1 by 10 years and 0.9 in adults. Increase in US : LS ratio is seen in rickets, achondroplasia and untreated congenital hypothyroidism. Decrease in US : LS ratio is seen in spondyloepiphyseal dysplasia and vertebral anomalies. Arm span is shorter than length by 2.5 cm at birth, equals height at 11 years and thereafter is slightly (usually, <1 cm) greater than height.

Sexual maturity rating (SMR): SMR stage should be assessed in older children (see Chapter 5). Height spurt is seen in early puberty in girls and mid-puberty in boys. Precocious puberty can lead to early height spurt followed by premature epiphyseal fusion and ultimate short stature. On the other hand, delayed puberty can also present with short stature in adolescents as the height spurt is also delayed.

Differential Diagnosis

Diagnosis is based on a detailed history, examination and laboratory evaluation. Careful history and examination can

unravel many clues to the etiology of short stature (Tables 2.15 and 2.16). The investigative work-up to be done is guided by clues from history and physical examination.

Bone age assessment should be done in all children with short stature. The appearance of various epiphyseal centers and fusion of epiphyses with metaphyses tells about the skeletal maturity of the child. Bone age is conventionally read from radiograph of the left hand and wrist using either Gruelich-Pyle atlas or Tanner-Whitehouse method. It gives an idea as to what proportion of the adult height has been achieved by the child and what is the remaining potential for height gain. Bone age is delayed compared to chronological age in almost all causes of short stature. Exceptions to this are familial short stature, in which bone age equals chronological age, and precocious puberty, in which bone age exceeds chronological age. In case of constitutional delay, undernutrition and systemic illness, bone age is less than chronological age and corresponds to height age. In cases of growth hormone deficiency and

Table 2.15: Clues to etiology of short stature from history

History	Etiology
Low birth weight	Small for gestational age
Polyuria	Chronic renal failure, renal tubular acidosis
Chronic diarrhea, greasy stools	Malabsorption
Neonatal hypoglycemia, jaundice, micropenis	Hypopituitarism
Headache, vomiting, visual problem	Pituitary or hypothalamic space occupying lesion, e.g. craniopharyngioma
Lethargy, constipation, weight gain	Hypothyroidism
Inadequate dietary intake	Undernutrition
Social history	Psychosocial dwarfism
Delayed puberty in parent(s)	Constitutional delay of growth and puberty

Table 2.16: Clues to etiology of short stature from examination

Examination finding	Etiology
Disproportion	Skeletal dysplasia, rickets, hypothyroidism
Dysmorphism	Congenital syndromes
Pallor	Chronic anemia, chronic kidney disease
Hypertension	Chronic kidney disease
Frontal bossing, depressed nasal bridge, crowded teeth, small penis	Hypopituitarism
Goiter, coarse skin	Hypothyroidism
Central obesity, striae	Cushing syndrome

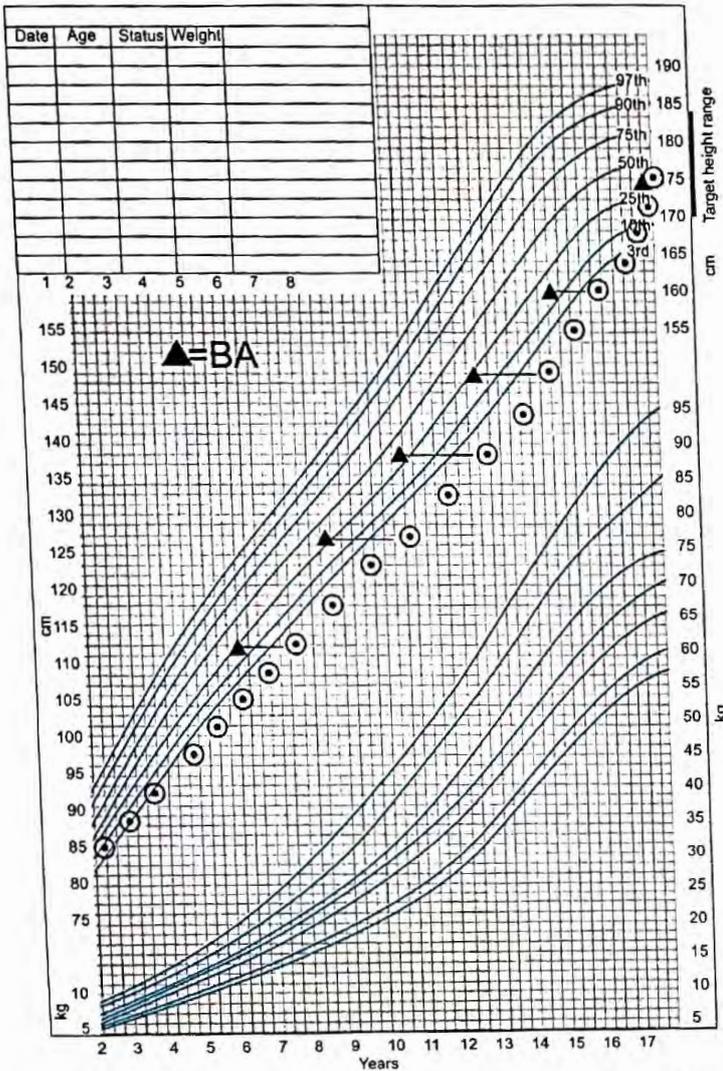


Fig. 2.22: Growth chart of a boy with constitutional delay of growth and puberty. The child falls to a lower centile in early childhood, grows below and parallel to 3rd centile in childhood, with an apparent downward deviation of growth curve during the normal time of pubertal growth, with later acceleration of growth and reaching target height (range indicated by vertical bold bar). Bone age (BA) is lower than chronological age by 2–3 years

Table 2.18: Distinction between constitutional delay in growth and familial short stature

Feature	Constitutional growth delay	Familial short stature
Height	Short	Short
Height velocity	Normal	Normal
Family history	Delayed puberty	Short stature
Bone age	Less than chronological age	Normal
Puberty	Delayed	Normal
Final height	Normal	Low but normal for target height

dysplasias, that are usually associated with abnormal skeletal proportions and severe short stature (except hypochondroplasia, where growth retardation is mild).

Careful elicitation of family history, measurement of body proportions, examination of the limbs and skull and skeletal survey are required for diagnosis.

Genetic syndromes: Turner syndrome, with an incidence of 1:2000 live births, is a common cause of short stature in girls and should not be ruled out even if the typical phenotypic features are absent. Other syndromes associated with short stature are Down, Prader-Willi, Russell-Silver and Seckel syndromes.

Psychosocial dwarfism: This condition, also known as emotional deprivation dwarfism, maternal deprivation dwarfism or hyperphagic short stature, is seen in children in unhappy homes where the emotional needs of the child are totally neglected. It is characterized by functional hypopituitarism indicated by low IGF-1 levels and inadequate response of GH to stimulation. Therapy with GH is, however, not beneficial. Good catch-up growth is seen when the child is placed in a less stressful environment and nurtured with love and affection.

Children born small for gestational age (SGA): Birth weight below the 10th centile for gestational age can be caused by maternal, placental or fetal factors. Most of these infants show catchup growth by 2 years of age. However, an estimated 20–30% of babies born SGA fail to show catchup growth and remain short. Subtle defects in the growth hormone and insulin-like growth factor (GH-IGF) axis are also considered responsible.

Management

The general principles of management for any child who presents with short stature include counseling of parents and dietary advice. Parents should be counseled to highlight the positive aspects in child's personality and not put undue emphasis on stature. Intake of a balanced diet containing the recommended amounts of macro- and micronutrients is recommended. The specific management depends on the underlying cause. For physiological causes, reassurance and annual monitoring of height and weight is sufficient. Dietary rehabilitation for undernutrition and treatment of underlying condition such as renal tubular acidosis or celiac disease are generally associated with satisfactory catch-up growth. With any form of therapy, monitoring with regular and accurate recording of height is mandatory for satisfactory outcome.

For skeletal dysplasias, limb lengthening procedures are offered at a few orthopedic centers. For hypothyroidism, levothyroxine replacement is advised. For growth hormone deficiency, treatment with daily subcutaneous injections of GH is recommended. GH therapy is also approved for several other conditions though the doses required are generally higher and improvement in final height smaller and more variable as compared to GH deficiency. Some of these conditions are Turner syndrome, SGA with inadequate catchup growth and chronic renal failure prior to transplant.

Failure to Thrive

Definition and Epidemiology

Failure to thrive (FTT) is a descriptive term rather than diagnosis and is used for infants and children up to 5 years of age whose physical growth is significantly less than their peers of same age and sex. FTT usually refers to weight below 3rd or 5th centile, failure to gain weight over a period of time or a change in rate of growth that has crossed two major centiles, e.g. 75th to 50th, over a period of time. The prevalence of FTT varies according to the population sampled.

Etiology

Traditionally, FTT is classified as organic, where the child has some known underlying medical condition, and non-organic or psychosocial, where poor growth is the result of inadequate caloric provision and/or emotional deprivation. Organic and nonorganic etiological factors may coexist, e.g. in children with cerebral palsy or multiple congenital anomalies. FTT is nonorganic in up to 80% of cases. The common etiological factors are listed in Table 2.19.

Clinical Features

These children present with poor growth, often associated with poor development and cognitive functioning. The degree of FTT is usually measured by calculating weight, height and weight-for-height as percentage of the median value for age based on appropriate growth charts (Table 2.20).

History, physical examination and observation of parent-child interaction are important. Detailed laboratory investigations are needed, only if history and physical examination suggest that an organic cause is responsible for FTT and to localize the systems involved. For initial evaluation, the following investigations are adequate: (i) complete blood count with ESR; (ii) urine and stool microscopy and culture and (iii) renal and liver function test and serum electrolytes. Weight gain in response to adequate calorie feeding establishes the diagnosis of psychosocial FTT.

ABNORMALITIES OF HEAD SIZE AND SHAPE

Head growth may be affected by abnormal growth of the skull bones or alterations in brain parenchyma, cerebrospinal fluid or bone.

Table 2.19: Causes of failure to thrive

Organic

Gastrointestinal: Gastroesophageal reflux, malabsorption, inflammatory bowel disease, pyloric stenosis

Neurological: Mental retardation, cerebral palsy

Renal: Renal tubular acidosis, chronic kidney disease

Cardiopulmonary: Congenital heart disease, cystic fibrosis, asthma

Endocrine: Hypothyroidism, diabetes mellitus

Infections: Chronic parasitic infections of gastrointestinal tract, tuberculosis, human immunodeficiency virus

Genetic: Inborn errors of metabolism, chromosomal anomalies

Miscellaneous: Lead poisoning, malignancy

Nonorganic

Poverty

Misperceptions or lack of knowledge about diet and feeding

Lack of breastfeeding, feeding diluted formulae

Dysfunctional parent child relationship

Macrocephaly

Macrocephaly is defined as an occipitofrontal circumference greater than two standard deviations (SD) above the mean for age and sex (Table 2.21). Megalencephaly or enlargement of the brain parenchyma may be familial or associated with inherited syndromes or neurometabolic disease. Infants with benign familial megalencephaly have increased head size at birth that persists through infancy along the upper growth curve percentiles, and is associated with normal body size, neurologic examination and development. Children with metabolic causes have normal head circumference at birth; macrocephaly is noted as the child gets older. Diagnosis is suggested by accompanying features and biochemical abnormalities.

Hydrocephalus, characterized by an excessive amount of CSF, may be caused by increased production, decreased absorption or obstruction to CSF flow. Most patients show postnatal rapid increase in head size and are symptomatic due to underlying disease or raised intracranial pressure (nausea, vomiting and irritability). Benign enlargement of the subarachnoid space is relatively common and is characterized by head growth velocity that slows to normal by 6 months of age; development assessment and neurological examination are normal.

Evaluation for macrocephaly is indicated, if the head circumference is above 3 SD of the mean for age and sex, or

Table 2.20: Degree of failure to thrive

Degree	Weight-for-age (% of median)	Length/height-for-age (% of median)	Weight-for-height (% of median)
Mild	75–90	90–95	81–90
Moderate	60–74	85–89	70–80
Severe	<60	<85	<70

Table 2.21: Causes of macrocephaly**Megalencephaly****Benign familial**

Neurocutaneous syndromes: Neurofibromatosis, tuberous sclerosis, Sturge-Weber, Klippel-Trenaunay-Weber, linear sebaceous nevus

Leukodystrophies: Alexander, Canavan diseases; megalencephalic leukoencephalopathy

Lysosomal storage diseases: Tay-Sachs disease, mucopolysaccharidosis, gangliosidosis

Others: Sotos disease, fragile X syndrome

Increased cerebrospinal fluid**Hydrocephalus**

Benign enlargement of subarachnoid space

Hydranencephaly, choroid plexus papilloma

Enlarged vascular compartment

Arteriovenous malformation

Subdural, epidural, subarachnoid or intraventricular hemorrhage

Increase in bony compartment

Bone disease: Achondroplasia, osteogenesis imperfecta, osteopetrosis, hyperphosphatasia, cleidocranial dysostosis

Bone marrow expansion: Thalassemia major

Miscellaneous causes

Intracranial mass lesions: Cyst, abscess or tumor

Raised intracranial pressure: Idiopathic pseudotumor cerebri, lead poisoning, hypervitaminosis A, galactosemia

when serial measurements reveal progressive enlargement, as suggested by an increase by >2 cm per month during first 6 months of life, or the crossing of one or more major percentile lines between routine visits. Measurement of head size in parents is useful in diagnosing familial cases. Majority of patients require cranial imaging, ultrasonography or computed tomography (CT) scan.

Children with asymptomatic familial megalencephaly or benign enlargement of the subarachnoid space do not require treatment. Infants with hydrocephalus may require neurosurgical intervention (e.g. placement of a ventriculoperitoneal shunt).

Microcephaly

Microcephaly is defined as an occipitofrontal circumference more than 3 standard deviations (SD) below the mean for given age, sex and gestation. Defining microcephaly as >3 SD below the mean is more likely to be associated with genetic and non-genetic disorders affecting brain than if defined as >2 SD below the mean, since the latter may include intellectually normal healthy children with head circumference at the lower end of the population distribution. The term *primary* microcephaly is used to describe conditions associated with reduced generation of neurons during neural development and migration. Secondary microcephaly follows injury or insult to a

previously normal brain causing reduction in the number of dendritic processes and synaptic connections. *Microencephaly* (micrencephaly) is the term used for an abnormally small brain, based on findings on neuroimaging or neuropathology. Since head growth is driven by brain growth, microcephaly usually implies microencephaly (except in craniosynostosis in which skull growth is restricted).

Important causes of microcephaly are listed in Table 2.22. Isolated inherited microcephaly, most commonly as an autosomal recessive phenotype, is associated with reduced head circumferences since birth, normal cerebral anatomy and absence of neurologic signs with or without learning difficulties. Other associations include structural brain malformations, inherited syndromes, congenital or acquired infections, hypoxic ischemic insults and rarely, metabolic disorders.

Evaluation for microcephaly should be initiated, if a single head circumference measurement is more than 2-3 SD below the mean or when serial measurements reveal progressive decrease in head size. Careful history and physical examination are necessary, including development assessment and measurement of head size of parents.

Table 2.22: Causes of microcephaly**Isolated microcephaly**

Autosomal recessive, autosomal dominant or X-linked

Syndromic

Trisomies 21, 18, 13

Monosomy 1p36 deletion

Syndromes: William, Cri-du-chat, Seckel, Smith-Lemli-Opitz, Cornelia de Lange, Rubinstein-Taybi, Cockayne, Angelman

Structural diseases

Neural tube defects (anencephaly, hydranencephaly, encephalocele, holoprosencephaly)

Lissencephaly, schizencephaly, polymicrogyria, pachygyria

Metabolic disorders

Phenylketonuria, methylmalonic aciduria, citrullinemia

Neuronal ceroid lipofuscinosis

Maternal: Diabetes mellitus, untreated phenylketonuria

Infections

Congenital: Cytomegalovirus, herpes simplex virus, rubella, varicella, toxoplasmosis, HIV, syphilis, enterovirus

Meningitis

Teratogens

Alcohol, tobacco, marijuana, cocaine, heroin, toluene

Antineoplastic agents, antiepileptic agents

Radiation

Perinatal insult

Hypoxic ischemic encephalopathy, hypoglycemia

Endocrine

Hypothyroidism, hypopituitarism, adrenal insufficiency

Need for neuroimaging is determined by the age at onset, severity of microcephaly, head circumference in parents, history of antenatal insult(s) and associated clinical features. An abnormal head shape and ridges along the suture lines are suggestive of craniosynostosis. The prognosis depends upon the underlying cause, and is worse for secondary than primary microcephaly.

Craniosynostosis

Craniosynostosis is the premature fusion of one or more cranial sutures, either major (e.g. metopic, coronal, sagittal, and lambdoid) or minor (frontonasal, temporosquamosal, and frontosphenoidal) (Fig. 2.23a). Cranial sutures normally fuse during early childhood, starting with the metopic suture (beginning at 2 months), followed by sagittal, coronal and lambdoid sutures (22–26 months), such that the frontonasal and frontozygomatic sutures close last (68–72 months). Premature fusion restricts the growth of the skull perpendicular to the affected suture. Compensatory skull growth occurs parallel to the affected suture in order to accommodate the growing brain. The resulting skull deformity is termed as scaphocephaly, plagiocephaly or trigonocephaly based on the suture involved (Fig. 2.23b to f). Cloverleaf skull deformity is caused by the fusion of multiple sutures and

is associated with hydrocephalus. Patients with tower skull or acrocephaly have combined sagittal, coronal and lambdoid synostosis, often as part of Apert or Crouzon syndrome. Oxycephaly or turricephaly refers to a tall cranium resulting from delayed repair of brachycephaly, and is often syndromic.

Apert syndrome is an autosomal dominant or sporadic disorder caused by defects in the fibroblast growth factor (*FGF*) gene, characterized by bicoronal synostosis and maxillary hypoplasia, associated with recessed forehead, flat midface, protruding eyes, hypertelorism, antimongoloid slant of eyes and low-set ears. Most patients have a high arched palate, malocclusion, cleft palate and complex syndactyly (mitten hand). Other findings are strabismus, conductive hearing loss, airway compromise and severe acne.

Crouzon syndrome is an autosomal dominant disorder caused by mutations in *FGFR2* or *FGFR3*, and characterized by tall, flattened forehead (secondary to bicoronal synostosis), proptosis, beaked nose and midface hypoplasia. Many patients have cervical spine abnormalities. The degree of facial deformity is milder than in Apert syndrome and patients do not show cleft palate, syndactyly and mental retardation. Other conditions associated with craniosynostosis are Carpenter syndrome and Pfeiffer syndrome.

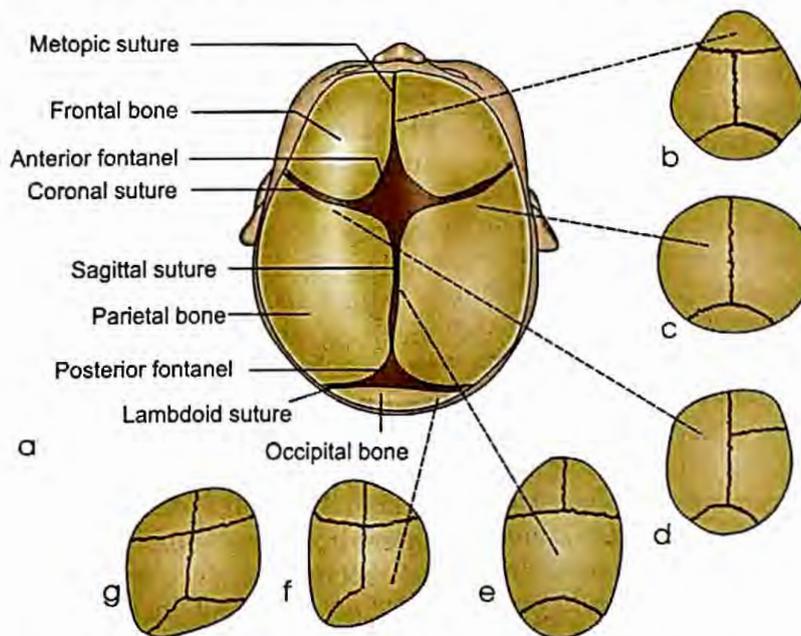


Fig. 2.23: (a) Head of normal neonate showing fontanelles and sutures. The common forms of craniosynostosis (secondary to premature fusion of sutures) include; (b) Trigonocephaly (metopic suture); (c) Brachycephaly (bilateral coronal sutures); (d) Left anterior plagiocephaly (left coronal suture); (e) Scaphocephaly (sagittal suture); (f) Right posterior plagiocephaly (right lambdoid suture). Children with deformation plagiocephaly (g) have positional skull flattening without sutural fusion

Development

Ramesh Agarwal • Naveen Sankhyan

NORMAL DEVELOPMENT

Development refers to maturation of functions and acquisition of various skills for optimal functioning of an individual. The maturation and myelination of the nervous system is reflected in the sequential attainment of developmental milestones. Developmental milestones are important, easily identifiable events during the continuous process of development, e.g. turning over, sitting, reaching for objects, and pointing to objects.

While development is a global process reflected in new motor abilities and language, social and cognitive skills, intelligence pertains to the part of the development dealing with cognitive or adaptive behavior. Different researchers define intelligence variably; an objective measurement is done using multiple criteria in tests of intelligence quotient (IQ).

Rules of Development

To understand the complex process of human development, some basic facts should be understood:

- i. Development is a *continuous process*, starting *in utero* and progressing in an orderly manner until maturity. The child has to go through many *developmental stages* before a milestone is achieved.
- ii. Development *depends on the functional maturation of the nervous system*. Maturity of the central nervous system is essential for a child to learn a particular milestone or skill; no amount of practice can make a child learn new skills in its absence. However, in absence of practice, the child may be unable to learn skills despite neural maturation.
- iii. The *sequence of attainment of milestones is the same in all children*. All infants babble before they speak in words and sit before they stand. Variations may exist in the time and manner of their attainment.
- iv. The *process of development progresses in a cephalocaudal direction*. Head control precedes trunk control, which precedes ability to use lower limbs. The control of limbs proceeds in a proximal to distal manner, such that hand use is learnt before control over fingers.

- v. Certain *primitive reflexes have to be lost* before relevant milestones are attained. *Palmar grasp is lost* before *voluntary grasp is attained* and the *asymmetric tonic neck reflex has to disappear* to allow the child to turnover.
- vi. The initial *disorganized mass activity is gradually replaced by specific actions*. Hence, when shown a bright toy, a 3–4-month-old squeals loudly and excitedly moves all limbs, whereas a 3–4-year-old may just smile and ask for it.

Factors Affecting Development

Development depends on a variety of mutually interactive factors such as hereditary potential, biological integrity, physical and psychosocial environment and emotional stimulation. The brain matures through a dynamic interplay of genetic, biological and psychosocial factors. Infancy and early childhood are the most crucial phases during which development takes place.

Appropriate sensory inputs through hearing and vision, a secure environment and responsive parenting provide the bases for healthy patterns of learning, behavior and health. Poverty is among the most important risk factors associated with poor development. Poverty exposes the child to many other risk factors such as lack of stimulation or excessive stress, malnutrition, exposure to environmental toxins, and concurrent diseases that adversely affect development. The factors that influence child development are listed below.

Prenatal Factors

Genetic factors: Intelligence of parents has direct correlation on the IQ of the child. Moreover, certain developmental patterns are observed to follow parental patterns like speech. There are numerous genetic causes such as chromosomal abnormalities (e.g. Down syndrome), X-linked mental retardation, subtelomeric deletions, single gene disorders causing disorders of brain formation (lissencephaly) and other metabolic disorders (phenylketonuria) for developmental delay and subsequent mental retardation (MR).

Maternal factors: A host of factors which impair growth *in utero* also can potentially affect brain growth, particularly if they are severe and/or sustained:

- I. **Maternal nutrition:** Maternal malnutrition (of macro-nutrient as well as micronutrients) has adverse effect on birth weight and child development. Studies from developing countries suggest that nutrition supplements including multiple micronutrient supplements have positive impact on birth weight as well as child development.
- II. **Exposure to drugs and toxins:** Various drugs and toxins such as maternal drug or alcohol abuse, antiepileptic drugs and environmental toxins can have adverse effect on child development.
- III. **Maternal diseases and infections:** Pregnancy-induced hypertension, hypothyroidism, malnutrition and fetoplacental insufficiency due to any cause. Acquired infections (e.g. syphilis, toxoplasmosis, AIDS, rubella, CMV, herpes) impact fetal physical and brain growth. Exposure to free radicals and oxidants *in utero* (e.g. chorioamnionitis) has been incriminated in the causation of cerebral palsy and developmental impairment.

Neonatal Risk Factors

Intrauterine growth restriction: Intrauterine growth restriction (IUGR) indicates constraints in fetal nutrition during a crucial period for brain development. In developing countries, IUGR is mainly due to poor maternal nutrition and infections. IUGR infants are disadvantaged compared to their normal birth weight counterparts in terms of short-term as well as long-term neurocognitive development.

Prematurity: Babies born before 37 weeks of gestation are more likely to have developmental impairment compared to term counterparts with babies born before 32 weeks gestation being at the highest risk.

Perinatal asphyxia: Significant asphyxia occurs in approximately 2% of total births. Studies have indicated that over 40% of survivors of significant asphyxia suffer from major neurocognitive disabilities.

Postneonatal Factors

Infant and child nutrition: Severe calorie deficiency, as evident by stunting, is associated with apathy, depressed affect, decreased play and activities and insecure attachment. Calorie deficiency is often associated with deficiency of multiple micronutrients and vitamins that contribute to developmental impairment.

Linear growth retardation or stunting occurs in nearly one-third of children aged less than 5 years in low-income and middle-income countries. There is positive association between early height-for-age and cognitive or language ability, rates of school enrolment and grades attained by late adolescence and formal employment at age 20–22 years.

Early growth faltering (<24 months) seems to be more detrimental to childhood development.

Iron deficiency: Iron deficiency has been shown to be associated with electrophysiological evidence of delayed brain maturation, poorer cognitive, motor and social-emotional development in infancy and early childhood.

Iodine deficiency: Iodine is a constituent of thyroid hormones, which affect central nervous system development and regulate many physiological processes. Iodine deficiency can lead to congenital hypothyroidism and irreversible mental retardation, making it the most common preventable cause of mental retardation. Children growing in iodine deficient areas have an IQ 12.5 points lower than those growing in iodine sufficient areas.

Infectious diseases: A variety of infectious morbidities such as diarrhea, malaria, other parasitic infections and HIV are associated with poorer neurodevelopment.

Environmental toxins: Children exposed to environmental toxins (lead, arsenic, pesticides, mercury and polycyclic aromatic hydrocarbons) prenatally through maternal exposure and postnatally through breast milk, food, water, house dust, or soil can have adverse influence on their neurocognitive development.

Acquired insults to brain: Traumatic or infectious insults (meningitis, encephalitis, cerebral malaria) and other factors (near drowning, trauma), particularly during early years of life, can have a permanent adverse effect on brain development.

Associated impairments: Impairments particularly those involving sensory inputs from the eyes or ears can have a significant impact on attainment of milestones. Early detection and management of hearing and visual impairments constitutes an important intervention for promoting child development.

Psychosocial Factors

During the critical period of development and learning, several social factors have an important bearing on not only cognition but also attitudes, social-emotional competence and sensorimotor development.

Parenting: Cognitive stimulation, caregiver's sensitivity and affection (emotional warmth or rejection of child) and responsiveness to the child in the setting of other factors such as poverty, cultural values and practices have an important bearing on child development. Apart from these, parental attitudes, involvement, education and desire for the child also have an impact on the development of the child.

Poverty: This is possibly the *most common underlying factor* for impaired child development worldwide. It acts throughout the lifetime of the individual and also affects the next generation.

Lack of stimulation: Social and emotional deprivation and lack of adequate interaction and stimulation is an important cause of developmental impairment, particularly evident in the setting of poverty.

Violence and abuse: Domestic and community violence are emerging threats to child development. Child abuse, physical and sexual, can have a profound psychological effect on the child. Problems of attention and cognition are more common in children exposed to violence or abuse.

Maternal depression: Low to middle income countries have a high incidence of maternal depressive symptoms, which is negatively associated with early child development and quality of parenting by virtue of unresponsive caregiving.

Institutionalization: Institutional care (e.g. orphanages) during early life increases the risk of poor growth, ill-health, attachment disorders, attention disorders, poor cognitive function, anxiety, and autistic-like behavior.

The interaction of risk factors and protective factors interact to determine the developmental trajectory of a child (Fig. 3.1). In presence of protective factors, children attain their developmental potential. Presence of a variety of risk factors in early life lowers the developmental trajectory of the child. Timely intervention can help children achieve near normal potential.

Protective Factors

Breastfeeding: Breastfeeding has a protective and promotive effect on childhood development.

Maternal education: Maternal education is a protective factor reducing child mortality and promoting early child development. Infant and young children of educated mothers have higher levels of cognitive development.

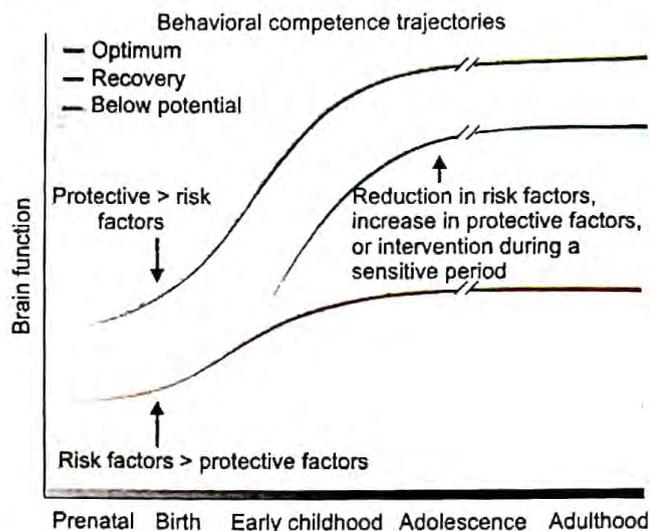


Fig. 3.1: Differing trajectories of brain and behavioral development as a function of exposure to risk and protective factors. Reproduced with permission from Walker, et al. Inequalities in early childhood, *Lancet* 2011;378:1325–38

Domains of Development

Normal development is a complex process and has a multitude of facets. However, it is convenient to understand and assess development under the following domains:

- i. Gross motor development
- ii. Fine motor skill development
- iii. Personal and social development and general understanding
- iv. Language
- v. Vision and hearing

Gross Motor Development

Motor development progresses in an orderly sequence to ultimate attainment of locomotion and more complex motor tasks thereafter. In an infant, it is assessed and observed as follows:

Supine and pull to sit: The infant is observed in supine and then gently pulled to sitting position. Control of head and curvature of the spine is observed. In the newborn period, the head completely lags behind and back is rounded (Fig. 3.2). Starting at 6 weeks, the head control develops and by 12 weeks there is only a slight head lag. The spine curvature also decreases accordingly (Fig. 3.3).



Fig. 3.2: Pull to sit; complete head lag in a newborn



Fig. 3.3: Pull to sit; no head lag at 4 months



Fig. 3.4: Pull to sit; flexes the head onto chest at 5 months

The child has complete neck control by 20 weeks (Fig. 3.4). This can be ascertained by swaying him gently 'side-to-side' when sitting. At this age, the baby loves to play with his feet, and may take his foot to mouth as well. Infant lifts head from the supine position when about to be pulled at 5 months.

Ventral suspension: The child is held in prone position and then lifted from the couch, with the examiner supporting the chest and abdomen of the child with the palm of his hand. Up to 4 weeks of age, the head flops down (Fig. 3.5). At 6 weeks, the child momentarily holds head in the horizontal plane and by 8 weeks, he can maintain this position well (Fig. 3.6). By 12 weeks, he can lift his head above the horizontal plane (Fig. 3.7).

Prone position: At birth or within a few days, the newborn turns the head to one side. At 2 weeks, the baby lies on the bed with high pelvis and knees drawn up (Fig. 3.8). At 4 weeks, the infant lifts the chin up momentarily in the midline. The infant lies with flat pelvis and extended hips at 6 weeks (Fig. 3.9). By 8 weeks, face is lifted up at 45°



Fig. 3.6: Ventral suspension; head in line with the trunk at 8-10 weeks



Fig. 3.7: Ventral suspension; head in line with the trunk at 12 weeks



Fig. 3.8: The infant lies on the bed with high pelvis and knees drawn up at 2 weeks (Photo courtesy: Dr Vijay K Charchi)



Fig. 3.5: Ventral suspension; unable to hold neck in the line with trunk at 4 weeks



Fig. 3.9: The infant lies with flat pelvis and extended hips at 6 weeks (Photo courtesy: Dr Vijay K Charchi)

(Fig. 3.10) and by 12 weeks, the child can bear weight on forearms with chin and shoulder off the couch and face at 45° (Fig. 3.11). At 6 months, he can lift his head and greater part of the chest while supporting weight on the extended arms (Fig. 3.12). Between 4 and 6 months, he learns to roll over, at first from back to side and then from back to stomach. By the age of 8 months, he crawls (with abdomen on the ground) and by 10 months, creeps (abdomen off the ground, with weight on knees and hands) (Fig. 3.13).

Sitting: By the age of 5 months, the child can sit steadily with support of pillows or the examiner's hands (Figs 3.14 and 3.15). At first the back is rounded but gradually it straightens (Figs 3.14 and 3.15). He independently sits with his arms forward for support (tripod or truly 'sitting with



Fig. 3.13: Creep position at 10 months of age (abdomen off ground and weight on hands and knees) (Photo courtesy: Dr Vijay K Charchl)



Fig. 3.10: In prone; face lifted to about 45° at 8 weeks



Fig. 3.11: In prone; face, head and chest off the couch at 3 months



Fig. 3.12: In prone; weight on hands with extended arms at 6 months



Fig. 3.14: Sitting; back rounded but able to hold head at 8 weeks

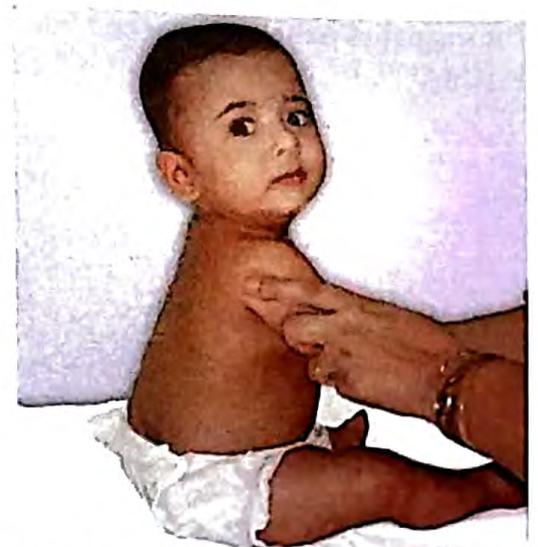


Fig. 3.15: Sitting; back much straighter at 4 months

support) by the age of 6–7 months (Fig. 3.16). Steady sitting without any support generally develops at around 8 months (Fig. 3.17). By 10–11 months, he can pivot in sitting position to play around with toys (Fig. 3.18).



Fig. 3.16: Sitting with support of hands at 6 months



Fig. 3.17: Sitting without support at 8 months



Fig. 3.18: Pivoting; turns around to pick up an object at 11 months

Standing and walking: By 6 months, the child can bear almost all his weight when made to stand (Fig. 3.19). At 9 months, the child begins to stand holding onto furniture and pulls himself to standing position. By 10 and 11 months, the child starts cruising around furniture (Fig. 3.20). At about 12–13 months, the child can stand independently (Fig. 3.21) and can walk with one hand held (Fig. 3.22). Between the ages of 13 and 15 months, the child starts walking independently. He runs by 18 months, and at this age he can crawl up or down stairs and pulls a doll or wheeled toy along the floor. By 2 years, the child can also walk backwards. He climbs upstairs with both feet on one step at 2 years. By 3 years he can climb upstairs with one foot per step and by 4 years he can move down the stairs in the same fashion (Fig. 3.23). He can ride a tricycle at 3 years. He can hop at 4 years and skip at 5 years (Table 3.1).



Fig. 3.19: Bears almost entire weight at 6 months



Fig. 3.20: Cruising around furniture at 10 to 11 months of age (Photo courtesy: Dr Vijay K Charchi)

Table 3.1: Key gross motor developmental milestones

Age	Milestone
3 months	Neck holding
5 months	Rolls over
6 months	Sits in tripod fashion (sitting with own support)
8 months	Sitting without support
9 months	Stands holding on (with support)
12 months	Creeps well; walks but falls; stands without support
15 months	Walks alone; creeps upstairs
18 months	Runs; explores drawers
2 years	Walks up and downstairs (2 feet/step); jumps
3 years	Rides tricycle; alternate feet going upstairs
4 years	Hops on one foot; alternate feet going downstairs



Fig. 3.21: Stands independently at 12 months



Fig. 3.22: Child walking with one hand-held at 12–13 months



Fig. 3.23: The child is able to walk upstairs and downstairs one foot per step at 4 years

Fine Motor Skill Development

This primarily involves the development of fine manipulation skills and coordination with age.

Hand eye coordination: Between 12 and 20 weeks, the child observes his own hands very intently, this is called hand regard (Fig. 3.24). Its persistence after 20 weeks is considered abnormal. At 3 to 4 months, hands of the child come together in midline as he plays (Fig. 3.25). If a red ring is dangled in front of him, he fixes his attention on it and then tries to reach for it (Fig. 3.26). Initially, he may overshoot but eventually he gets it and brings it to his mouth.

Grasp is best assessed by offering a red cube to the child. A 6-month-old infant reaches and holds the cube (larger object) in a crude manner using the ulnar aspect of his hand (Fig. 3.27). He can transfer objects from one hand to other by 6–7 months. The child is able to grasp from the radial side of hand at 8–9 months (Fig. 3.28). By the age of 1 year, mature grasp (index finger and thumb) is evident (Fig. 3.29).

By offering pellets (smaller object), finer hand skills are assessed. By 9–10 months, the child approaches the pellet



Fig. 3.24: Hand regard (between 12 and 20 weeks)



Fig. 3.25: The child brings hands in midline as he plays at 3 to 4 months of age

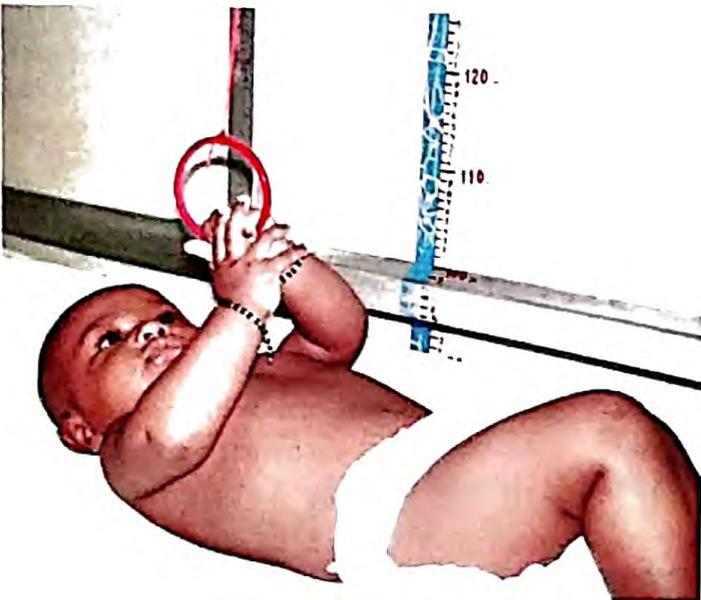


Fig. 3.26: Bidextrous grasp approach to a dangling ring at 4 months

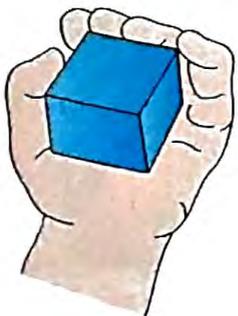


Fig. 3.27: Immature grasp at 6 months (palmar grasp)



Fig. 3.28: Intermediate grasp at 8 months, beginning to use radial aspect of the hand



Fig. 3.29: Mature grasp at 1 year of age, note the use of thumb and index finger

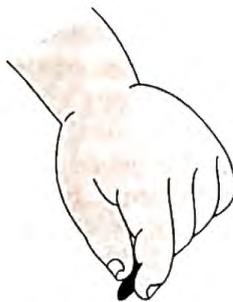


Fig. 3.30: Pincer grasp approach to small objects (index finger and thumb)

by an index finger and lifts it using finger thumb apposition, termed 'pincer' grasp (Fig. 3.30).

Hand-to-mouth coordination: At 6 months, as the ability to chew develops, the child can take a biscuit to his mouth and chew. At this age, he tends to mouth all objects offered to him (Fig. 3.31). This tendency abates by around 1 year of age (Fig. 3.32). By this age, he tries to feed self from a cup but spills some of the contents. By 15 months, the child can pick up a cup and drink from it without much spilling. By 18 months, he can feed himself well using a spoon.



Fig. 3.31: A child mouthing an object at 6 months of age



Fig. 3.32: Feeding from a cup at 12 months of age

Advanced hand skills: With advancing age, the child can use hands to perform finer activities. Much of the advanced skills depend partly on the opportunity given by the caretakers to the child. At around 15 months, he turns 2–3 pages of a book at a time and scribbles on a paper, if given a pencil (Fig. 3.33). By 18 months, he can build a tower of 2–3 cubes and draw a stroke with pencil. By 2 years, he can unscrew lids and turn doorknobs and his block skills also advance (Table 3.2, Fig. 3.34). He now draws a circular stroke. He now can turn pages of a book, one at a time.

Drawing and block skills at various ages are shown in Figs 3.35 and 3.36, respectively. In general, copying of the skill comes 6 months after imitating the skills (doing it while seeing).

Dressing: Between 18 and 30 months of age, children are very eager to learn dressing skills. Undressing being easier, is learned before dressing. At 1 year, the child starts to pull off mittens, caps and socks. At around 18 months, he can unzip, but fumbles with buttons. By 2 years, he can put on shoes or socks and can undress completely. By 3 years, he can dress and undress fully, if helped with buttons. By 5 years, he can tie his shoelaces as well.



Fig. 3.33: Scribbles spontaneously at 15 months

Table 3.2: Key fine motor milestones

Age	Milestone
4 months	Bidextrous reach (reaching out for objects with both hands)
6 months	Unidextrous reach (reaching out for objects with one hand); transfers objects
9 months	Immature pincer grasp; probes with forefinger
12 months	Pincer grasp mature
15 months	Imitates scribbling; tower of 2 blocks
18 months	Scribbles; tower of 3 blocks
2 years	Tower of 6 blocks; vertical and circular stroke
3 years	Tower of 9 blocks; copies circle
4 years	Copies cross; bridge with blocks
5 years	Copies triangle; gate with blocks



Fig. 3.34: A child makes tower of 5–6 cubes at 2 years of age

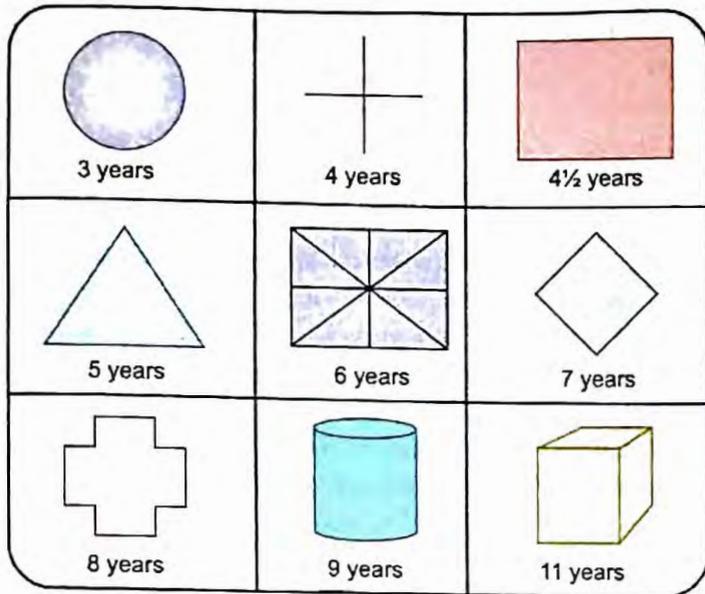


Fig. 3.35: Drawing skills at various ages

Personal and Social Development and General Understanding

Much of the cognitive development and understanding is reflected by the attainment of important milestones in this sphere. Beginning at around 1 month, the child intently watches his mother when she talks to him (Fig. 3.37). He starts smiling back (social smile) when anyone talks to him or smiles at him by 6–8 weeks of age (Fig. 3.38). It is important to differentiate social smile from spontaneous smile (smile without any social interaction), which is present even in neonates. By 3 months, he enjoys looking around and recognizes his mother. By 6 months, he vocalizes and smiles at his mirror image (Fig. 3.39), and imitates acts such as cough or tongue protrusion.

The child becomes anxious on meeting strangers (stranger anxiety) by 6–7 months of age. At this age, he inhibits to “no”. At 9 months, he waves “bye-bye” and also repeats any performance that evokes an appreciative response from the observers. By 1 year, he can understand

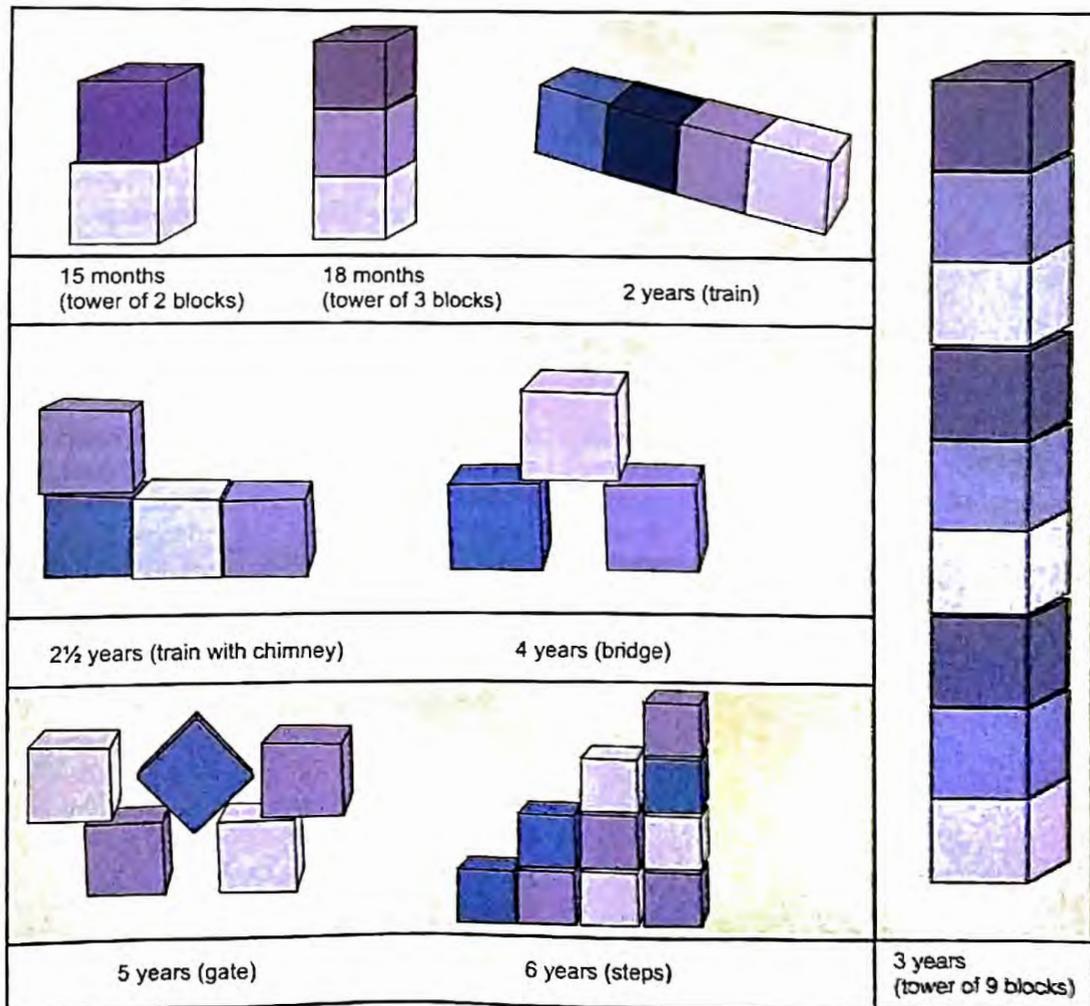


Fig. 3.36: Block skills at various ages

Table 3.3: Key social and adaptive milestones

Age	Milestone
2 months	Social smile (smile after being talked to)
3 months	Recognizes mother; anticipates feeds
6 months	Recognizes strangers, stranger anxiety
9 months	Waves "bye bye"
12 months	Comes when called; plays simple ball game
15 months	Jargon
18 months	Copies parents in task (e.g. sweeping)
2 years	Asks for food, drink, toilet; pulls people to show toys
3 years	Shares toys; knows full name and gender
4 years	Plays cooperatively in a group; goes to toilet alone
5 years	Helps in household tasks, dresses and undresses

simple questions, such as "where is papa", "where is your ball", etc. By 15 months, he points to objects in which he is interested. By 18 months, he follows simple orders and indulges in domestic mimicry (imitates mother sweeping or cleaning). At 2 years, when asked he can point to 5-6 familiar objects, name at least 2-3 objects and point to 3-4 body parts. He begins to count, identify 1-2 colors and sing simple rhymes by age of 3 years. Much of these milestones depend on the caretaker's interaction and opportunities provided to the child. The left and right discrimination develops by 4 years. By this age, play activities are also very imaginative. By 5 years of age, children can follow 3 step commands, identify four colors and repeat four digits (Table 3.3).

Language

Throughout the development of language it is the *receptive ability and understanding, which precedes expressive abilities*. Soon after appearance of social smile at around 6 to 8 weeks, the child begins to vocalize with vowel sounds such as 'ah, uh'. At 3-4 months, he squeals with delight and laughs loud. He begins to say 'ah-goo', 'gaga' by 5 months of age. By 6 months, he uses monosyllables (ba, da, pa). Later, he joins consonants to form bisyllables (mama, baba, dada).

Before developing true meaningful speech, at around 9-10 months, the child learns to imitate sounds derived from his native language. At his first birthday, he can usually say 1-2 words with meaning. At 18 months, he has a vocabulary of 8-10 words. Thereafter, the vocabulary increases rapidly to around 100 words by 2 years, at which time 2-3 words are joined to form simple sentences. By 3 years, the toddler continually asks questions and knows his full name. He can give a coherent account of recent experiences and events by the age of 4 years (Table 3.4).



Fig. 3.37: At 1 month, the baby showing intent regard of his mother's face as she talks to him



Fig. 3.38: Social smile



Fig. 3.39: A child smiles at himself in the mirror at 6 months of age

Table 3.4: Key language milestones

Age	Milestone
1 month	Alerts to sound
3 months	Coos (musical vowel sounds)
4 months	Laugh loud
6 months	Monosyllables (ba, da, pa), ah-goo sounds
9 months	Bisyllables (mama, baba, dada)
12 months	1–2 words with meaning
18 months	8–10 word vocabulary
2 years	2–3 word sentences, uses pronouns "I", "me", "you"
3 years	Asks questions; knows full name and gender
4 years	Says song or poem; tells stories
5 years	Asks meaning of words

Vision and Hearing

Adequate sensory inputs are essential for development. Both normal vision and hearing are of paramount importance for child development. The ability to see and hear is apparent even in the newborn. Thereafter maturation of visual and hearing pathways are reflected by specific visual and auditory behaviors.

Vision: The best stimulus to check visual behavior is the primary caretaker's face. At birth, a baby can fixate and follow a moving person or dangling ring held 8–10 inches away up to a range of 45°. This increases to 90° by 4 weeks and 180° by 12 weeks. At around 1 month, the baby can fixate on his mother as she talks to her (Fig. 3.40).

At about 3–4 months, the child fixates intently on an object shown to him ('grasping with the eye') as if the child wants to reach for the object (Fig. 3.41). Binocular vision begins at around 6 weeks and is well established by 4 months. By 6 months, the child adjusts his position to follow objects of interest, can follow rapidly moving objects by 1 year. Later the child displays more maturity in vision by not only identifying smaller objects but also being able to recognize them.



Fig. 3.40: Infant fixates on her mother as she talks to her at 1 month



Fig. 3.41: Grasping 'with the eye' at 3 months



Fig. 3.42: Diagonal localization of the source of sound at 10 months

Hearing: Newborns respond to sounds by startle, blink, cry, quieting or change in ongoing activity. By 3 to 4 months, the child turns his head towards the source of sound. Hearing, may be checked by producing sound 1½ feet away from the ear (out of field of vision), and a pattern of evolving maturity of hearing can be observed. At 5 to 6 months, the child turns the head to one side and then downwards, if a sound is made below the level of ears. One month later, he is able to localize sounds made above the level of ears. By the age of 10 months, the child directly looks at the source of sound diagonally (Fig. 3.42).

Developmental Assessment

Developmental delay is estimated to be present in about 10% of children. It is possible to recognize severe developmental disorders early in infancy. Speech impairment, hyperactivity and emotional disturbances are often not detected until the child is 3–4-year-old. Learning disabilities are not picked up until the child starts schooling.

Prerequisites

The development assessment should be assessed in a place, which is free from distractions. It is important that the child should not be hungry, tired, ill or irritated at time of development assessment. It would be desirable to assess him when he is in a playful mood with mother being around. Adequate time should be spent in making the child and family comfortable. Observation for alertness, concentration and skills of the child is an integral part of assessment. The assessors must carry a development kit (Box 3.1).

Steps

History: A detailed history is the starting point for any development assessment. Observations by parents are very informative. Hence, a well-taken history will help in (i) determining the details of probable risk factors affecting development, (ii) evaluation of rate of acquisition of skills and differentiating between delay and regression, and (iii) forming a gross impression about the development age of the child. This helps to choose the appropriate tools for further evaluation and confirmation.

Examination: This should be done to (i) assess physical growth and head circumference, (ii) do a physical assessment particularly for presence of dysmorphic features, stigmata of intrauterine infections and signs of hypothyroidism, (iii) assess vision and hearing, and (iv) conduct neurological examination and examine for primitive reflexes (if required).

Adequate time should be spent in observing the baby especially social responsiveness, alertness, concentration, interest and distractibility. It would be appropriate to assess vision and hearing at the outset so that further observations are not confounded by lack of sensory stimuli. The vocal responses, particularly the nature, frequency and quality are noted. Subsequently, fine motor skills should be assessed, including the interest, alertness and rapidity of responses.

The annoying maneuvers, such as assessment of reflexes, measuring head circumference, and performing ventral suspension or pull to sit should be done at the end. It is preferable to perform the developmental assessment before the systemic examination so that the child's cooperation is solicited.

Box 3.1: Equipment for development assessment

- A red ring (diameter 6–7 cm) tied to a string
- Nine red cubes
- Paper pellets
- Spoon
- Cup with handle
- A book with thick pages
- Picture book
- Red pencil, paper
- Doll and mirror

By the end of the evaluation, one should be able to arrive at a conclusion whether the neurological status and cognitive status are within normal range or not. Significant delay on screening is an indication for a detailed formal assessment of development status. By assessment, one can assign developmental quotient (DQ) for any developmental sphere. It is calculated as:

$$\frac{\text{Average age at attainment}}{\text{Observed age at attainment}} \times 100$$

A DQ below 70% is taken as delay and warrants detailed evaluation. To obtain a DQ of a child, a formal assessment by an individual trained in developmental assessment using appropriate tools/tests is needed. There are several tests to assess DQ. Each test has its own psychometric properties. They give different kinds of estimates of development like an overall score of development and subscores for gross motor, fine motor, visual perception, receptive language, expressive language, etc.

IQ tests mainly assess the cognitive/adaptive behavior part of the development. The age at which a particular test can be applied depends on the test items. However, in younger children (<5 years), it is more meaningful to have a global assessment of abilities; hence DQ testing is more comprehensive. Specific IQ tests (Stanford-Binet intelligence scales) are available to assess IQ starting from 2 years of age.

Interpretation

In babies born preterm, corrected age rather than postnatal age is used for determining developmental status till 2 years of age. For example, a child born at 32 weeks gestation (gestational age) seen at 12 weeks of age (postnatal age) should be considered as a 4-week-old (corrected age) child for developmental assessment.

While drawing any conclusions about development, one should remember the wide variations in normality. For example, let us consider the milestone of standing alone. The average age for attainment of this milestone in a WHO survey was 10.8 months (Fig. 3.43). However, the 3rd and 97th centiles for normal children were 7.7 and 15.2 months, respectively. The same is true for many other milestones as is shown in Fig. 3.43. The bars illustrate the age range for normal children to attain that particular milestone. This range of normalcy should always be kept in mind while assessing development.

Retardation should not be diagnosed or suggested on a single feature. Repeat examination is desirable in any child who does not have a gross delay. Factors such as recent illness, significant malnutrition, emotional deprivation, slow maturation, sensory deficits and neuromuscular disorders should be taken into account.

At times, there can be significant variations in attainment of milestones in individual fields, this is called *dissociation*. For example, a 1-year-old child who speaks 2–3 words with meaning and has finger thumb opposition

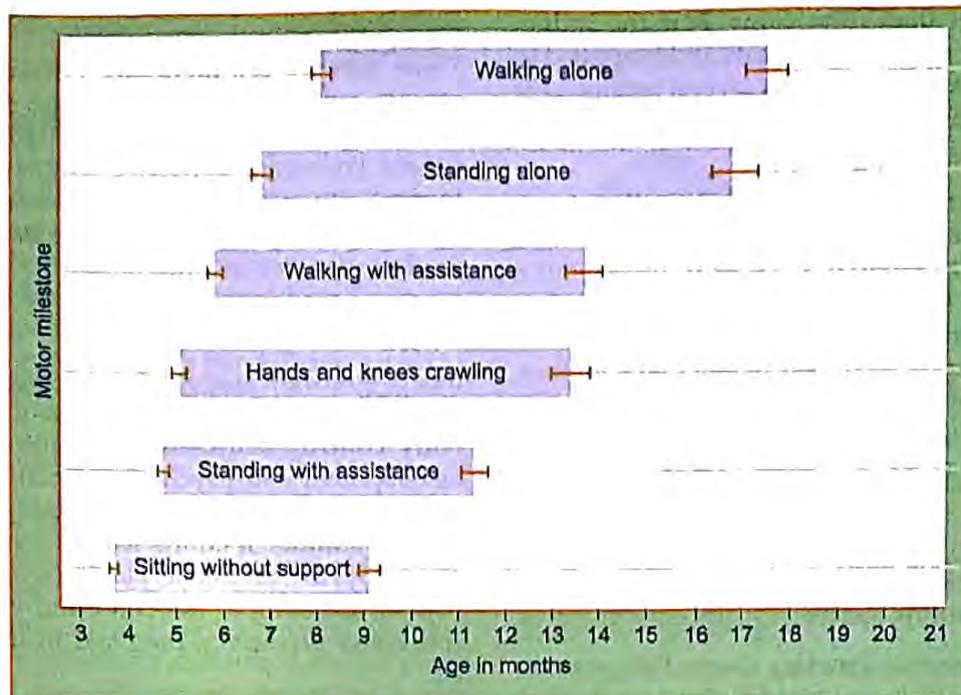


Fig. 3.43: Windows of achievement of six major motor milestones (WHO; Multicenter Growth Reference Study Group, 2006)

(10–12 months), may not be able to stand with support (less than 10 months). Such children require evaluation for physical disorder affecting a particular domain of development. A child having normal development in all domains except language may have hearing deficit.

Table 3.5 gives the upper limits by which a milestone must be attained. A child who does not attain the milestone by the recommended limit should be evaluated for cause of developmental delay.

The predictive value of different domains of development for subsequent intelligence is not the same. Fine motor, personal-social and linguistic milestones predict intelligence far better than gross motor skills. In particular, an advanced language predicts high intelligence in a child.

Table 3.5: Upper limit of age for attainment of milestone

Milestone	Age
Visual fixation or following	2 months
Vocalization	6 months
Sitting without support	10 months
Standing with assistance	12 months
Hands and knees crawling	14 months
Standing alone	17 months
Walking alone	18 months
Single words	18 months
Imaginative play	3 years
Loss of comprehension, single words or phrases at any age	

Adapted from WHO; MGRS group, WHO motor development study. *Acta Paediatr* 2006;450:86–95

Development Screening Tests

Screening is a brief assessment procedure designed to identify children who should receive more intensive diagnosis or assessment. Screening tools are standardized instruments to evaluate development. The administration of these tools should be done after proper training and with a sound knowledge of interpretation of the results. Some tools are parent reported while others require trained personnel. Assessment using screening tools potentially aids in early identification of children who need a more detailed assessment and possibly interventions. It also provides an opportunity for early identification of comorbid developmental disabilities.

Developmental Surveillance

Child development is a dynamic process and difficult to quantitate by one-time assessment. During surveillance, repeated observations on development are made by a skilled physician over time to see the rate and pattern of development. Periodic screening helps to detect emerging disabilities. The physician should choose a standardized developmental screening tool that is practical and easy to use in office setting. Once skilled with the tool, it can be used as screening method to identify at risk children. Screening tests popular in the west include Parents' Evaluations of Development Status (PEDS) and Ages and Stages Questionnaires (ASQ). Screening tools used in India are described below.

Phatak's Baroda screening test: This is India's best known development testing system that was developed by Dr. Promila Phatak. It is meant to be used by child

psychologists rather than physicians. It is the Indian adaptation of Bayley development scale and is applied to children up to 30 months. It requires several testing tools and objects that are arranged according to age. The kit is available commercially.

Ages and stages questionnaire (ASQ-3): It consists of age-based, parent-completed questionnaires that can be used from one month to 5½ years of age. It assesses the following domains: Communication, gross motor, fine motor, problem solving, and personal-social. There are about 30 items per questionnaire about the child's abilities. The questionnaire takes about 10–15 minutes for parents to complete and about 2–3 minutes to score.

Denver II: The revised Denver development screening test (DDST) or Denver II was revised in 1992 and assesses child development in four domains, i.e. gross motor, fine motor adaptive, language and personal-social behavior, which are presented as age norms, just like physical growth curves.

Trivandrum development screening chart: This screener has been revised in 2013. It consists of 51 items for children of 0–6 years. The norms have been adapted from various existing developmental charts/scales. It is primarily a screening tool for use in the community to identify children between 0 and 6 years with developmental delay.

Clinical adaptive test and clinical linguistic and auditory milestone scale (CAT/CLAMS): This easy to learn scale can be used to assess the child's cognitive and language skills. It uses parental report and direct testing of the child's skills. It is used at ages of 0–36 months and takes 10–20 min to apply.

Goodenough-Harris drawing test: This simple nonverbal intelligence test requires only a pencil or pen and white unlined paper. Here the child is asked to draw a man in the best possible manner and points are given for each detail that the child draws. One can determine the mental age by comparing scores obtained with normative sample.

Definitive Tests

These tests are required once screening tests or clinical assessment is abnormal. They are primarily aimed to accurately define the impairments in both degree and sphere. For example, by giving scores for verbal, performance abilities and personal and social skills, these can be differentially quantified. Some of the common scales used are detailed in Table 3.6.

Early Stimulation

Infants who show suspected or early signs of developmental delay need to be provided opportunities that promote body control, acquisition of motor skills, language development and psychosocial maturity. These inputs, termed early stimulation, include measures such as making additional efforts to make the child sit or walk, giving toys to manipulate, playing with the child, showing objects, speaking to the child and encouraging him to speak and prompting the child to interact with others, etc.

There is a general lack of evidence for effectiveness of these early interventions in improving neurodevelopmental outcome and motor abilities. However, studies in premature babies, cerebral palsy, institutionalized children and other children at high risk for adverse neurodevelopmental outcomes suggest that these interventions are effective, if started early. Systematic reviews suggest that the effect of these interventions is sustained in later childhood.

Promoting Development by Effective Parenting

Comprehensive care to children requires focus on preventive efforts including child-rearing information to parents. Parenting has an immense impact on emotional, social and cognitive development and also plays a role in the later occurrence of mental illness, educational failure and criminal behavior. Creating the right conditions for

Table 3.6: Scales for definitive testing of intellect and neurodevelopment

Name of the test	Age range	Time taken to administer	Scoring details; comments
Bayley scale for infant development II	1 months to 3.5 years	30–60 min	Assesses language, behavior, fine motor gross motor and problem-solving skills; provides mental development index and psychomotor developmental index
Wechsler intelligence scale for children IV	6 to 17 years	65–80 min	Assesses verbal and performance skills, provides full scale IQ and indices of verbal comprehension perceptual reasoning, working memory and processing speed
Stanford-Binet intelligence scales, 5th edition	2 to 85 years	50–60 min	Provides full scale IQ, verbal IQ, nonverbal IQ, 10 subset scores and 4 composite scores
Vineland adaptive behavior scale II	0 to 89 years	20–60 min	Measures personal and social skills as reported by the caregiver or parent, in 4 domains (communication, daily living skills, socialization and motor skills)

early childhood development is likely to be more effective and less costly than addressing problems at a later age.

Television Viewing and Development

Television viewing in younger children has been shown to retard language development. It is a passive mode of entertainment and impairs children's ability to learn and read, and also limits creativity. Children can pick up inappropriate language and habits by watching TV shows and commercials. Violence and sexuality on television can have a lasting impact on the child's mind. Parents need to regulate both the quantity and quality of TV viewing, limiting the time to 1–2 hours per day and ensuring that the content they see is useful.

Child Development in Global Perspective

According to estimates, 250 million children (43% of all children) under the age of five in developing countries are at high risk of not reaching their developmental potential due to stunting, poverty and disadvantaged environment. Experts have drawn attention towards this critical aspect of care of children, emphasizing the importance of nutrients and nurturing during the critical first 1000 days of life. *Nurturing care* is care which ensures health, nutrition, responsive caregiving, safety and security, and early learning (Fig. 3.44). Early childhood development programs and other interventions such as breastfeeding, nutrition, interactive play and stimulation, prevention of infections, and learning at home, lay the foundation for learning in school. Effective parent support programs, like the WHO/UNICEF *Care for Child Development* and *Reach Up and Learn*, have been shown to be effective.

Useful Internet Resources

<http://www.nlm.nih.gov/medlineplus/childdevelopment.html>
<http://kidshealth.org/parent/growth/>
<http://www.nichd.nih.gov/>
<http://www.med.umich.edu/yourchild/>
<http://www.bridges4kids.org/disabilities/SLI.html>
<http://www.zerotothree.org/>

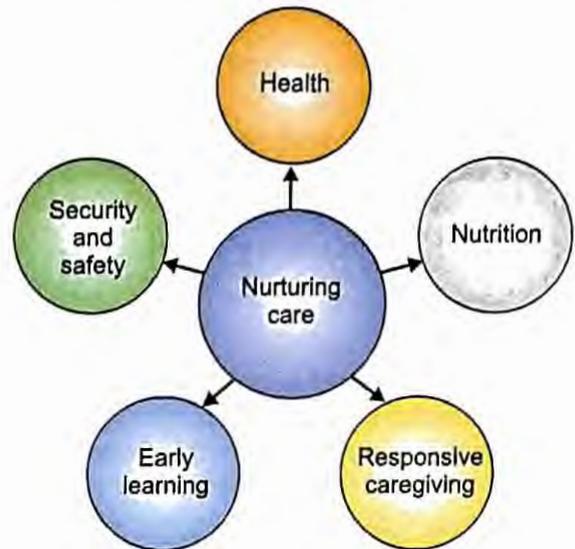


Fig. 3.44: Components of nurturing care

Suggested Reading

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Developmental and Behavioral Disorders

Biswaroop Chakrabarty • Sheffali Gulati

The cognitive growth and behavioral phenotype of an individual chiefly reflect the growth and development of the body, particularly the brain, during early years. Factors like nutrition, environment and social and emotional milieu play a significant role.

GLOBAL DEVELOPMENTAL DELAY, INTELLECTUAL DISABILITY

Global developmental delay is defined as delay in acquiring milestones in two or more of the following domains, namely gross and fine motor, speech and language, cognition, socio-personal and activities of daily living. Above 5 years of age, the term intellectual disability is used, replacing the previously used term mental retardation. The estimated prevalence varies between 2.5 and 5%.

Developmental Deviance and Dissociation

Deviance is the acquisition of milestones in a sequence that is different from usual. For example, children with cerebral palsy may show early standing with support secondary to increased extensor tone. This may also be seen in normally developing children; children may not crawl and directly

start walking from sitting and standing without support. Dissociation is defined as the acquisition of developmental milestones in various domains at differing rates, e.g. isolated speech delay with normal development in other spheres, as in patients with congenital hearing loss.

Etiology

An etiology can be defined in 70% patients with developmental disorders (Table 4.1). In developed countries, antenatal factors predominate; whereas in the developing world, perinatal and postnatal factors are more common. Patients with developmental delay may have various comorbidities depending on the etiology (Table 4.2). Depending on the etiology, the yield of diagnostic tests varies from 10 to 80% (Table 4.3).

Management

A child with developmental delay is managed by a multidisciplinary team comprising of a pediatric neurologist, geneticist, psychologist, psychiatrist, occupational and physiotherapist, speech therapist, audiologist, ophthalmologist, nutritionist and social worker. Early intervention is important to achieve the maximum potential.

Table 4.1: Etiology of developmental delay according to the time of insult

Antenatal	Syndromes (fragile X, Rett syndrome) Chromosomal disorders (Down syndrome) Cortical malformations Intrauterine infections Inborn errors of metabolism (aminoacidopathy, organic acidemia, mitochondrial disorder, urea cycle disorder, disorders of glycosylation) Teratogen exposure Neuromuscular disorders (predominantly motor delay)
Perinatal, neonatal	Hypoxic ischemic encephalopathy Kernicterus After meningitis or encephalitis Hypoglycemic brain injury Hypothyroidism After head trauma
Postnatal	Deficiency of vitamin B ₁₂ , iodine or B ₁ ; toxins (lead)

Table 4.2: Comorbidities in patients with developmental disorders

<i>Developmental delay, Intellectual disability</i>
Seizures
Vision abnormalities, hearing impairment, speech disorders
Feeding problems
Behavioral problems, sleep disturbances
Contractures, bed sores
<i>Autism spectrum disorder</i>
Seizures
Feeding problem
Behavioral problems: Aggression, impulsivity, hyperactivity, inattention, sleep related problems
Cognitive impairment
<i>Attention deficit hyperactivity disorder</i>
Sleep problems
Enuresis, encopresis; obesity
Learning disability
Behavioral comorbidities: Autism spectrum disorder, tics, conduct disorder, delinquency
Anxiety, bipolar illness
<i>Specific learning disability</i>
Epilepsy
Attention deficit hyperactivity disorder, tics
Obsessive compulsive disorder
<i>Tic disorder</i>
Obsessive compulsive disorder; anxiety, depression
Attention deficit hyperactivity disorder
Learning disability
Autism spectrum disorder

Autism Spectrum Disorder

Autism spectrum disorder (ASD) is characterized by the triad of qualitative impairment of social behavior, communication (verbal and non-verbal) skills and associated stereotypic and restrictive behavioral patterns, with onset before 3 years of age (Table 4.4). The estimated global prevalence is 1 to 2%.

Etiopathogenesis

The pathogenesis of autism is not clear. Abnormalities in neural connectivity and migration, dendritic and synaptic morphology and functioning of mirror neurons have been implicated. Genetic causes such as fragile X syndrome, tuberous sclerosis, Angelman syndrome and metabolic diseases like phenylketonuria and hypothyroidism account for 10% cases.

Diagnostic Approach

The Diagnostic and Statistical Manual of Mental Disorders (DSM) IV required fulfillment of a minimum number of symptoms listed in the three domains (social interaction, communication and behavior) to label a child as having an ASD. Guidelines, according to DSM 5, have combined social interaction and communication domains into one. Thus to be labeled as having an ASD, a child has to fulfill a minimum number of symptoms in two domains (social interaction and communication, and behavior). Common comorbidities are shown in Table 4.2.

Management

The chief therapy is behavioral intervention; the role of pharmacotherapy is limited (Table 4.5).

Attention Deficit Hyperactivity Disorder

Attention deficit hyperactivity disorder (ADHD) is the most common neurobehavioral disorder of childhood. Its prevalence in India was estimated at 1.3 per 1000. The American Academy of Pediatrics recommends evaluating any child between 4 and 18 years of age for ADHD, if he or she presents with academic or behavioral problems with symptoms of inattention, hyperactivity and impulsivity (Table 4.4).

Diagnosis

ADHD is diagnosed clinically. The DSM 5 criteria require fulfillment of predefined number of criteria in inattention, hyperactivity and impulsivity domains. The onset of symptoms can be up to 12 years of age and they should

Table 4.3: Diagnostic tests in evaluation of developmental delay

<i>Investigation</i>	<i>Indication</i>
Neuroimaging (MRI preferred over CT)	Specifically if abnormal head size and/or abnormality on neurological examination
Metabolic tests (ammonia, bicarbonate, lactate, sugar; blood TMS; urine GCMS)	Clues on history or examination (recurrent encephalopathy, vomiting, seizures, regression of milestones, organomegaly, cataract, retinopathy)
Genetic studies (cytogenetic studies, karyotyping)	Developmental delay without a known cause, irrespective of dysmorphic features
Thyroid function tests; blood and urine lead; micronutrient levels	If indicated clinically
Electrophysiological tests	Where indicated: Electroencephalogram, visual evoked responses, brainstem evoked response, audiometry, nerve conduction studies, electromyography

MRI: Magnetic resonance imaging; GCMS: Gas chromatography mass spectrophotometry; TMS: Tandem mass spectrophotometry

Table 4.4: Clinical features of autism, ADHD and specific learning disability

Disorder	Salient clinical features
Autism spectrum disorder	Onset before 3 years of age Impaired verbal and gestural communication Defect in social and emotional reciprocity Stereotypic and restrictive behavioural patterns
Attention deficit hyperactivity disorder (ADHD)	Onset up to 12 years of age Present in at least 2 different social settings Interfering with social, academic and occupational functioning Inattention (difficulty sustaining attention, prone to careless mistakes, easily distracted) Hyperactivity (often on the go, fidgety) Impulsivity (intrusive, interruptive, cannot wait for turn)
Specific learning disability*	Dyslexia (difficulty in reading) Dysgraphia (illegible handwriting, spelling mistakes) Dyscalculia (difficulty performing simple calculations)

*Preserved intelligence, vision and hearing

Persistent for at least 6 months despite interventions targeting specific disability

Table 4.5: Pharmacotherapy for autism spectrum disorder

Medication	Indication
Antipsychotics (risperidone, olanzapine)	Anxiety, aggression, repetitive behavior
Methylphenidate	Inattention, hyperactivity, impulsivity
Alpha-2 agonists (clonidine, atomoxetine)	Hyperactivity
Melatonin	Sleep-related problems
Iron supplements	If deficiency is documented

be present in at least two different settings interfering with the social, academic and occupational functioning of an individual. The associated morbidities are summarized in Table 4.2.

Management

The cornerstone of management is psychotherapy tailored for each individual and the family. In patients with inadequate response to psychological interventions, drugs like methylphenidate and atomoxetine are indicated.

Specific Learning Disability

Specific learning disability is defined as a persistent impairment in reading (dyslexia), writing (dysgraphia) and/or arithmetic (dyscalculia) skills in an individual with

preserved cognition, vision, hearing and adequate opportunities (Table 4.4). It affects 5–15% of school-going children. Dyslexia accounts for 80% of all specific learning disabilities. These disorders are probably caused by functionally disrupted networks in the cerebral cortex with intact anatomy.

Diagnosis

Features suggestive of specific learning disabilities include reading slowly and incorrectly, skipping lines while reading aloud, making repeated spelling mistakes, untidy/illegible hand-writing with poor sequencing, and inability to perform even simple mathematics, incoherent to the child's intelligence level. The DSM 5 diagnosis of SLD requires fulfilling a predefined number of criteria in reading, writing and arithmetic skills, and these impairments should persist despite interventions targeting the specific disability for at least 6 months.

Management

Management revolves around remedial education with active participation from both school and parents.

Tic Disorder and Stereotypies

Tics are abrupt onset, fast, paroxysmal, non-rhythmic motor or vocal manifestations which may be simple or complex

Table 4.6: Common tics in children

Motor tics	Vocal tics
Simple Eye blinking, neck jerking, shoulder shrugging	Simple Throat clearing, sniffing, coughing
Complex Foot tapping, echopraxia (imitating others), copropraxia (obscene gestures)	Complex Words out of context, coprolalia (obscene words), echolalia (repeating heard phrases or words), palilalia (repeating own words or phrases)

(Table 4.6). The age of onset is 4–6 years with peak at 10–12 years and significant attenuation by 18–20 years. The prevalence is around 10–15% with higher rate in boys.

Tourette syndrome is characterized by onset before 18 years of age, presence of both motor and vocal tics and persistence beyond 1 year, including the waning phase. Tics can be associated with neurological ailments like Huntington and Wilson disease, or with parainfectious illnesses, e.g. pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS).

It is important to differentiate stereotypies from tics. Although stereotypies may have similar vocal and motor manifestations, classically they are rhythmic and distractible, and usually remain stable over a time period, unlike tics which may evolve temporally. Stereotypies usually have an early onset (before 3 years of age) and, along with neurodevelopmental disorders, may affect normal children, as well.

Management

The essential component is behavioral therapy. Medications like haloperidol and clonidine are considered in situations where the tics are socially and functionally disabling despite adequate behavioral therapy.

Eating Disorders

This group consists of primarily two disorders, anorexia nervosa and bulimia that chiefly affect girls and have in common a disturbed body image perception. Anorexia nervosa usually affects 15–19 years old girls. Characteristic features are an intense fear of becoming fat even though the child is underweight, with body weight <85% of expected. Two subtypes are recognised, with either restricted eating or increased physical activity. Induced vomiting or use of laxatives and diuretics may be present. Complications include secondary amenorrhea and metabolic complications related to malnutrition.

Bulimia affects 10–19 years old children, chiefly girls. There are recurrent episodes of binge eating alternating with inappropriate compensatory behavior such as self-induced vomiting, misuse of laxatives, diuretics or enemas, each occurring at least twice a week for 3 months. Depression, anxiety, suicidal ideation and/or obsessive compulsive disorder are often present. Management of both conditions focuses on psychotherapy, along with nutritional rehabilitation and treating comorbidities and complications.

Pica

Pica is the persistent ingestion of non-nutritive substances such as plaster, charcoal, paint and soil for at least 1 month, inappropriate to the child's development level and cultural practice. It is common in children less than 5 years of age. Poor socioeconomic status, malnutrition and iron deficiency are commonly associated. Developmental

delay, psychosocial stress (maternal deprivation, parental neglect and abuse) and other behavioral disorders can predispose to pica. Children with pica are at increased risk for lead poisoning and parasitic infestations. Management comprises behavior modification, alleviating the psychosocial stress, screening for lead poisoning, deworming and iron supplementation.

Temper Tantrums

Temper tantrums are a child's response to physical or emotional challenges by attention seeking tactics like yelling, biting, crying, kicking, pushing, throwing objects, hitting and head banging. Tantrums typically begin at 18–36 months of age and gradually subside by the age of 3–6 years. Parents are counseled to handle this behavioral problem strategically, by staying calm, firm and consistent so that the child is unable to take advantage from such behavior. The child should be protected from injuring himself or others. Distraction and 'time out' techniques are useful.

Breath-Holding Spells

Breath-holding spells are reflex events typically initiated by a provocation that causes anger, frustration or pain making the child cry. The crying stops at full expiration, and the child becomes apneic and cyanotic or pale. In some cases, the child may become unconscious and hypotonic. In prolonged events, brief tonic-clonic movements may happen. Breath-holding spells are rare before 6 months of age, peak at 2 years and abate by 5 years of age. The differential diagnoses include seizures and cardiac arrhythmias. The history of a provoking event and stereotyped pattern of events help in distinguishing breath-holding spells from seizures. In relevant clinical scenarios, seizures and cardiac arrhythmias including long QT syndrome should be ruled out.

The essential component of management is parental reassurance. The family should be advised to be consistent in handling the child, to remain calm during the event, turn him sideways so that secretions can drain and avoid picking the child up (since this decreases blood flow to the brain). The family should avoid exhibiting undue concern nor give into the child's demands, if the spell was provoked by anger or frustration.

Thumb Sucking

This entity is normal in infants and toddlers. It peaks by 18–21 months of age and usually disappears by the age of 4 years. Its persistence in older children is socially unacceptable and can lead to dental malalignment. In children below 4 years, parents should be reassured. Beyond 4 years of age, the child should be motivated to refrain from this habit. Both positive and negative reinforcements can be used.

Stuttering

Stuttering is a defect in speech characterized by hesitation or spasmodic repetition of some syllables with pauses. There is difficulty in pronouncing the initial consonants caused by spasm of lingual and palatal muscles. It can affect up to 5% of children between 2 and 5 years of age. In this age group, parents should be reassured as most of them show resolution. If it persists beyond or appears after 5 years of age, opinion of psychologist and speech therapist should be sought.

Enuresis

Enuresis is defined as passage of urine in the clothes beyond an age when bladder control should be established (usually 5 years). Both psychological stressors and physiological dysfunction (hyposecretion of vasopressin) can be seen in affected individuals.

Enuresis may be primary or secondary (loss of control after an initial bladder control for 6 months or more), diurnal or nocturnal. Primary monosymptomatic nocturnal enuresis is the commonest variety. Before labeling as primary enuresis, diabetes, urinary tract anomalies, infection and bowel bladder dysfunction should be ruled out. The most important aspect of management is behavioral therapy with positive reinforcement. Bladder alarms or desmopressin is reserved for patients resistant to behavioral interventions (also *see* Chapter 17).

Encopresis

Encopresis is defined as passage of stools in clothes beyond an age when bowel control should have been achieved (usually 4 years). It may be retentive (associated with constipation) or non-retentive, primary (never achieved bowel control) or secondary (loss of control after an initial phase of control for at least 6 months). Primary encopresis is usually associated with constipation, while secondary is associated with significant psychological stressors. Behavioral therapy with positive reinforcement and treatment of constipation are necessary.

Oppositional Defiant Disorder

Oppositional defiant disorder is a repetitive and persistent pattern of opposing, defiant, disobedient and disruptive behavior towards authority figures persisting for at least 6 months. Many children are later diagnosed with conduct disorders. Diagnostic criteria for labeling the condition have been developed. Oppositional defiant disorder results from interplay of factors in the child's characteristics, parental interactions and environmental factors. Family history of mental health problems such as depression, ADHD or antisocial personality is often seen. The management should focus on alleviating risk factors or stresses that might contribute to oppositional behavior. Use of stimulant medication is effective in patients with ADHD.

Conduct Disorder

Conduct disorder is characterized by aggressive and destructive activities that cause disruption in the child's environments such as home, school or the neighborhood. The overriding feature is the repetitive and persistent pattern of behaviors that violate societal norms and the rights of other people, for a period of at least one year. Management consists of behavioral and psychotherapy.

Juvenile Delinquency

Children who show oppositional defiant behavior or conduct disorders and come into conflict with the juvenile justice system are called juvenile delinquents. The term refers to a person under 18 years of age who is brought to the attention of the juvenile justice system for committing a criminal act or displaying other illegal behaviors, like the use of alcohol or illicit drugs. Family and parenting interventions have been shown to reduce the risks of re-incarceration and criminal behavior by juvenile delinquents. In some cases, placement in foster care is recommended with similar interventions being administered by the foster family.

Munchausen by Proxy

Munchausen syndrome by proxy is a disorder in which a caregiver, usually mother, deliberately makes up a history of illness in her child and/or harms the child to create illness. The name is derived from Munchausen syndrome in which a person self-induces or acts out illness to gain medical attention. In Munchausen by proxy, the abusing caregiver gains attention from the relationships formed with health care providers, or her family, as a result of the problems created.

Confirmation of diagnosis needs careful history and reviewing of past and current hospital records. Once the diagnosis is made, the offending caregiver should be confronted, separated from the child and provided psychotherapy.

Parasomnias

Parasomnias are defined as abnormal behavioural and/or motor manifestations seen in sleep. During the first half of sleep, the non rapid eye movement stage (NREM) parasomnias predominate, which are more common and consist of sleep walking (awake and ambulatory), confusional arousals (awake but not ambulatory) and sleep terrors (terrorised child, inconsolable and presence of a spine chilling scream).

The relatively uncommon REM (rapid eye movement stage) parasomnias are seen in the second half of the sleep and comprise of nightmares (unpleasant dreams) and bizarre movements and behavioral manifestations. The child is more likely to remember REM than NREM parasomnias on waking up. The conditions are self limiting and management

is targeted at reassurance and management of stress if any; benzodiazepines may occasionally be used.

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Adolescent Health and Development

Tushar R Godbole • Vijayalakshmi Bhatia

Adolescence is a stage of transition from childhood to adulthood. During this stage of life, a youth undergoes rapid changes in body structure, mediated by the sex hormones. The appearance of sexual characters is coupled with changes in cognition and psychology. Whereas adolescence refers to this entire process, puberty refers to the physical aspect. The age group 10–19 years is considered as the period of adolescence, and puberty marks the early half of adolescence. Though it is a continuous process, for convenience sake, adolescence is generally divided into three phases: Early (10–13 years), mid (14–16 years) and late (17–19 years) puberty.

PHYSICAL ASPECTS

The onset of puberty is triggered by various genetic and environmental factors including the body fat stores. The

activation of the hypothalamic-pituitary-gonadal axis leads to the production of gonadotropins [luteinizing hormone, follicle-stimulating hormone] and sex steroids [estrogen and testosterone]. Gonadal sex steroids bring about secondary sexual characters (breast development, increase in penile and testicular size and menarche), whereas adrenal androgens cause development of sexual hair, acne and underarm odor. Details of hormonal mechanisms of onset and progression of puberty are dealt with in Chapter 18.

Onset and Sequence of Puberty

Puberty in girls starts with breast development (thelarche) between 8 and 13 years (Fig. 5.1). This is then followed by appearance of pubic hair (pubarche) and then, menstruation (menarche) occurring at an average of 12.6

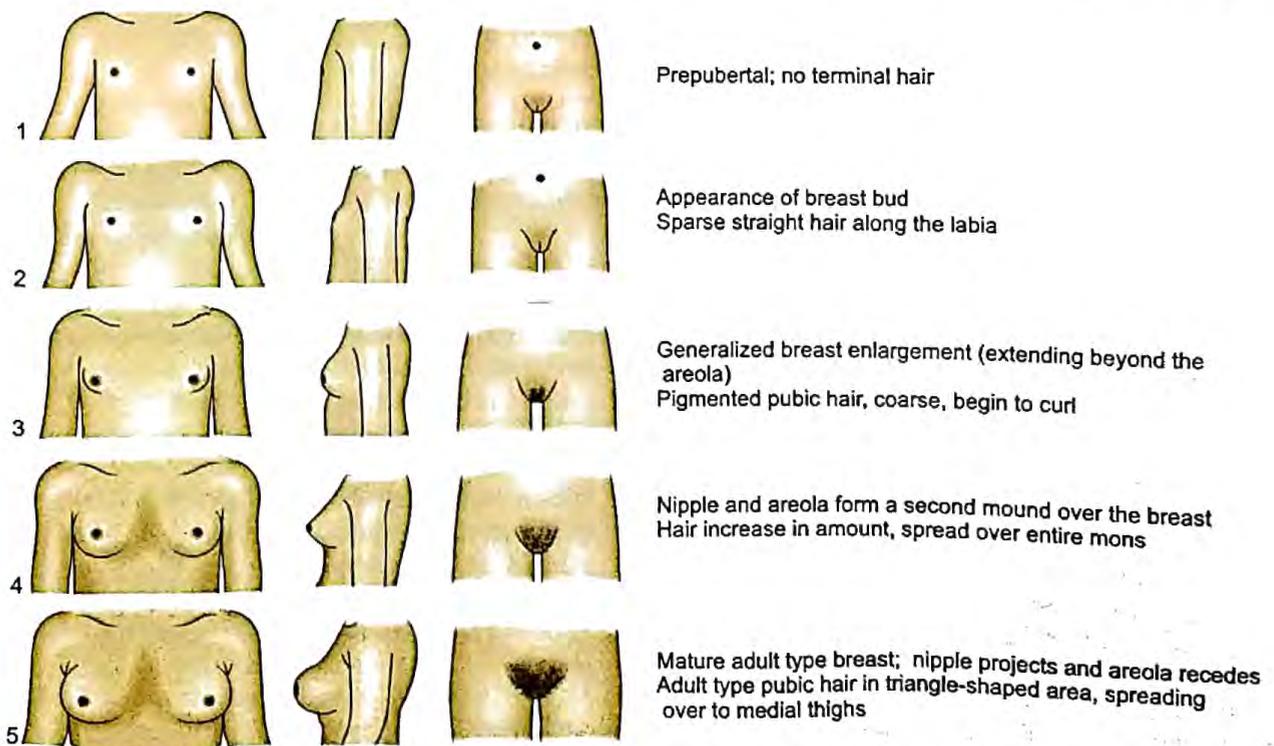


Fig. 5.1: Sexual maturity rating (1–5) in girls (Courtesy: Anil Kumar, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow)

years (range 10–16 years); experts now believe the age of menarche is advancing to ~9 years in many populations. The breast buds may be tender and there may be asymmetry in the breast size during early phases of puberty. Menarche usually occurs after 2–2½ years of thelarche.

In boys, the earliest change is increase in testicular size (volume reaching 4 mL or length 2.5 cm) that occurs between 9 and 14 years (Fig. 5.2). This is followed by appearance of pubic hair and lengthening of the penis. Spermarche or production of sperms starts during mid-adolescence. Laryngeal growth under androgenic stimulus, manifesting as cracking of voice, begins in midpuberty in males and deepening of voice is complete by the end of puberty. Mild degree of breast enlargement is seen in more than half of boys in early puberty which subsides spontaneously over several months. The onset of puberty is variable; thus in an age cohort (e.g. students of 7th class), many will have advanced puberty while others will be awaiting its onset.

Physical Growth and Nutritional Requirements

During puberty, boys gain about 20–30 cm and girls about 16–28 cm. Peak growth velocity in girls occurs before attainment of menarche (stage 3), while boys show peak growth velocity during later stages of puberty (stages 4–5). The growth spurt affects the distal skeleton first, hence enlargement of limbs and extremities is followed by

increase in trunk size. There is an exuberant increase in muscle mass and bone diameter, particularly in boys and total bone mass in both the sexes. Lean body mass increases during the early stages in both the sexes, fat mass increases in girls at later stages of puberty. Under the influence of sex steroids, rapid calcium accretion occurs during puberty, achieving almost 50% of adult bone mass. The recommended dietary allowance (RDA) for calcium is 800 mg/day and an intake of 500 mL milk is recommended in order to achieve this with a cereal-based Indian diet. With minimal sun exposure, the RDA for vitamin D is 600 IU/day. Since dietary vitamin D is mainly available from fatty fish, intake as a pharmacological supplement may be necessary. Increase in body structure is paralleled by increase in blood volume and muscle mass; both of these tissues have high iron content. With commencement of menstruation, nutritional requirements of iron are further increased. With predominantly cereal-based diet and poor bioavailability, an adolescent needs to have a daily intake of 25–30 mg iron in order to meet the daily requirements of 1.3 mg.

Cognitive and Social Development

Volumetric and functional imaging techniques show that the adolescent brain undergoes subtle structural changes and differential growth. Though the exact implications of these changes are largely unknown, these indicate re-organizational or accommodating effort of brain

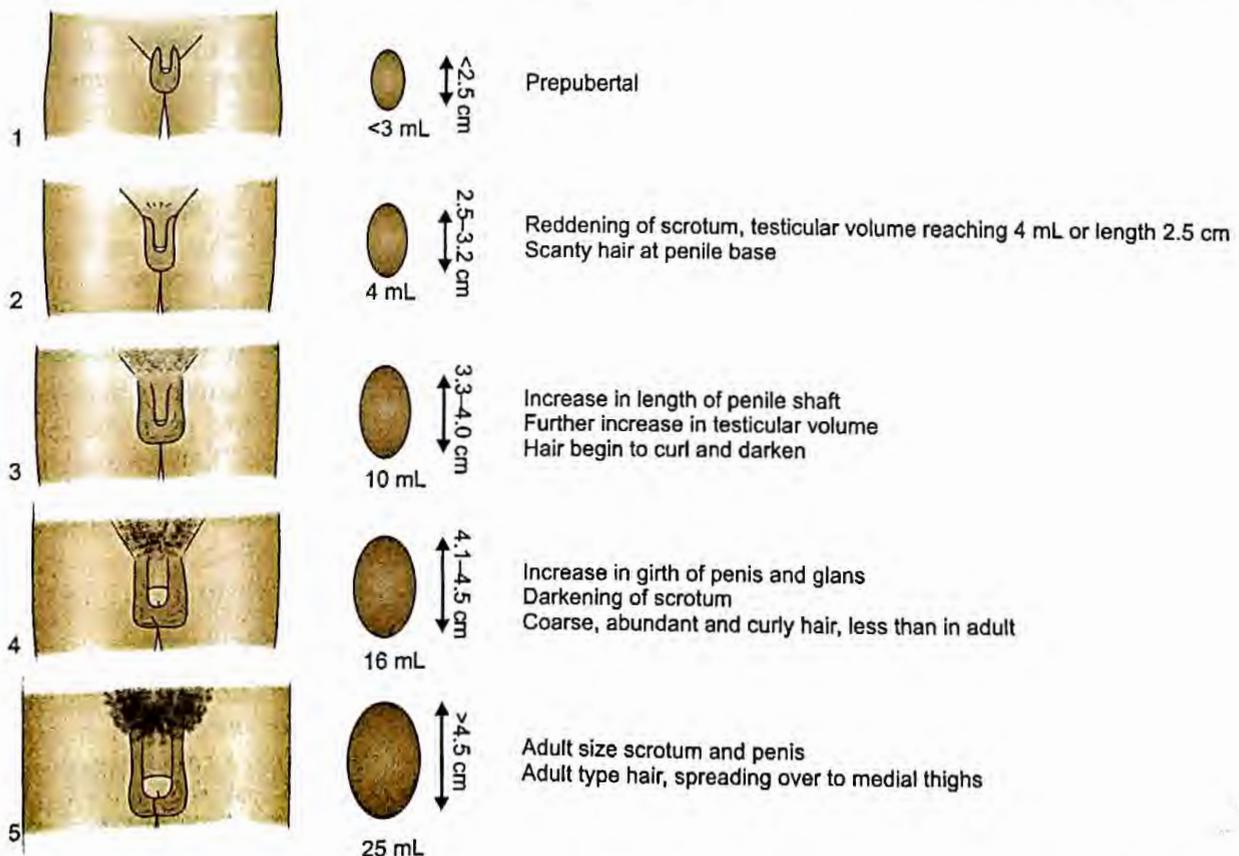


Fig. 5.2: Sexual maturity rating (1–5) in boys (Courtesy: Anil Kumar, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow)

paralleling the multi-fold increase in its functional capabilities.

Early phase: The 'concrete thinking model' of childhood persists into early adolescence, where the concepts are perceived more 'literally'. Teens are impulsive and have limited ability to perceive future implications of their current behavior. They prefer same sex peers. Many are excessively conscious of other people's concerns about their appearance and actions. Curiosity about sexual anatomy and comparison with peers is common.

Mid-phase: This phase is marked by emotional autonomy; they might seem detached from their family. The youth starts to think beyond self and there is beginning of abstract reasoning. Acceptance by the peer group becomes important. Sexual experimentation, such as masturbation, starts at this age.

Late phase: By this time, most of the pubertal changes are already achieved. Moral values and strong self identity are now established. They are now able to suppress impulsivity and are less affected by peer pressure. Personal relations become more important than the peer group. The youth becomes career-oriented and starts short- and long-term planning for his or her goals in life. Many start engaging in sexual activity.

Attitude Towards Health

Adolescents are considered to be at the peak of their health; yet, adolescence coincides with the onset of many health disorders. Girls are often unprepared for their first periods. High-risk behavior is common in mid-adolescent age group. The National Family Health Survey 4 (NFHS4) reported the median age of sexual debut in boys and girls to be 24 years and 19 years, respectively, but a significant proportion are sexually active much before. Knowledge about contraception is improving among adolescents. Though awareness about HIV is increasing among Indian youth, most of them lack comprehensive knowledge of the disease.

PROBLEMS FACED BY ADOLESCENTS

Adolescents are under immense pressure because of the rapid changes in their hormonal milieu, changing ideas and concepts about the world, having to cope up with the expectations from the society and the need to establish their own identity. The problems faced by an adolescent in India are diverse and are often not addressed by the health care system.

Health Problems

Nutrition and eating disorders: There is increase in nutritional requirements during this period of rapid growth, micronutrients being as important as energy and protein (see Chapter 8). Data from the NFHS4 shows that

53% Indian adolescent girls are anemic; the prevalence of anemia has remained unchanged over the last two decades. There is lack of sun exposure due to clothing coupled with dark skin pigment. Insufficient intake of dairy products results in poor intake of calcium and vitamin B₁₂. The resulting low bone mineral density is more pronounced in underprivileged girls as they have low protein intake in addition to calcium and vitamin D deficiency. Vitamin A deficiency is also an important issue in economically deprived adolescents. Undernutrition often delays the onset of puberty and sexual maturation, results in stunting, poor bone mass accrual and reduced work capacity. Girls from poor families are likely to suffer from malnutrition due to gender discrimination in food distribution, whereas girls from urban upper socio-economic group show malnutrition due to eating disorders. Anorexia nervosa and bulimia are increasingly reported.

Mental health problems: Adjustment and anxiety disorders, depression, suicide, delinquent behavior, poor body image and low self-esteem are major concerns. Suicide rates are increasing, with higher number of completed suicide in boys and attempted suicides in girls. Adolescents are at high risk of committing suicide because of cognitive immaturity and impulsivity. Psychological disorders like depression or mood disorders, substance abuse, parent-child conflict, physical or sexual abuse and family history of suicide make them prone for such attempts.

Sleep disturbances: During the period of rapid growth, adolescents have increased sleep requirements. Under the effect of physiologic delay in melatonin secretion, adolescents have a delay in sleep onset and awakening by almost an hour. In urban adolescents, this may be compounded by increasing academic activity or watching television late into the night. Poor sleep habits are likely to reflect in school performance and cause daytime drowsiness, aggressive behavior, conduct disorders, anxiety, restless leg syndrome and depression.

Infections: With increased outdoor activity, teens are exposed to TB, HIV, skin and parasitic infections and sexually transmitted diseases. Early sexual activity is not uncommon. Various biological (immature, incompletely estrogenized mucosa) and psychosocial factors (lack of preparedness, knowledge regarding barrier contraceptives) make adolescents susceptible to these infections.

Problems Specific to Females

It is common to have anovulatory and irregular menstrual cycles during first two years after menarche. The polycystic ovary syndrome, a combination of menstrual irregularities and ovarian cysts with androgen excess like acne or hirsutism, occurs in ~9% adolescent girls. The condition is associated with other metabolic derangements like obesity, insulin resistance and type 2 diabetes.

Menstrual hygiene: There are many social taboos about menstruation in Indian families. Many adolescent girls are found to miss school during their menstruation because of lack of access to safe sanitary products or lack of privacy. Poor menstrual hygiene may contribute to reproductive infections. With the introduction of government and private run 'Menstrual Hygiene Schemes', 57% young women now use hygienic methods during menses. [NHFS4]

Genital infections and sexually transmitted infections: Vaginal discharge is common in adolescent girls and may indicate physiological leukorrhea of puberty, and endogenous or sexually transmitted infections. Gonorrhoea can cause vulvovaginitis, urethritis or proctitis; Chlamydia may cause intermenstrual or post-coital bleeds. Both may be asymptomatic in majority and can cause vaginal discharge. Candidal infections become common with starting of menstruation and often have a cyclic nature. Pelvic inflammatory disease (PID) is a spectrum of inflammatory disorder of female genital tract, which occurs in sexually active females and can present with abdominal pain with vaginal discharge. Lower abdominal, cervical or adnexal tenderness is suggestive of the diagnosis (Table 5.1).

Lifestyle diseases: Obesity is the other end of the spectrum of malnutrition and is epidemic in the urban settings. Among Delhi school children, 5% obesity and 17–19%

overweight have been reported and similar figures are available from other parts of urban India as well. The prevalence of obesity and overweight is higher in boys than girls. Obesity has strong association with asthma, sleep disorders, reflux disease, Blount disease, slipped femoral epiphysis, gallstones, fatty liver and metabolic derangements like type 2 diabetes, dyslipidemia, hypertension and polycystic ovary disease. Essential hypertension is rising, with prevalence of 6% in urban and 3.4% in rural youth in some studies from India.

Substance abuse: Most tobacco and alcohol use starts during adolescence, in urban as well as rural India. The Global Youth Tobacco Survey 2009 showed that 14% of school youth reported using tobacco currently. Apart from tobacco, alcohol (21%), cannabis (3%) and opium (0.4%) are most abused substances. Addicts are prone to accidents, injuries, violence, trading sex-for-drugs, HIV, hepatitis C, sexually transmitted diseases and tuberculosis.

Vulnerability

Abuse and violence (physical and sexual): Physical and sexual violence is common in India, with 20–30% young females suffering from domestic violence and 5–9% young females reporting sexual violence (NFHS4). Accidents are the major cause of mortality in this age group. Road traffic accidents, burns and poisoning are leading causes of traumatic mortality and disability in Indian youth. Motor

Table 5.1: Sexually transmitted infections: Salient features and treatment

Disease	Salient features	Specific treatment
Gonorrhoea	Coinfection common	Ceftriaxone 125 mg IV or IM single dose
Chlamydia infection	Urethritis, vaginal discharge	Oral azithromycin 1 g single dose, or doxycycline 100 mg twice daily for 14 days
Herpes	Multiple painful vesicles and ulcers; tend to recur	Oral acyclovir 400 mg thrice daily for 7 days
Primary syphilis	Painless genital ulcer	Benzathine penicillin 2.4 MU IM (after test dose); oral doxycycline, if allergic to penicillin
Genital warts (papilloma virus)	Tend to recur	Local application of podophyllin weekly, cryotherapy or surgical removal; preventable with vaccination
Chancroid	Painful ulcer with lymphadenopathy	Oral azithromycin 1 g single dose or ciprofloxacin 500 mg twice daily for 3 days
Trichomoniasis	Malodorous yellow green discharge	Oral metronidazole or tinidazole 2 g single dose
Candidiasis	Itching, redness, white discharge	Clotrimazole cream or pessary for 7 days, miconazole pessary for 3 days or oral fluconazole 150 mg single dose
Pelvic inflammatory disease	Polymicrobial; varied disease spectrum	<i>Mild to moderate illness.</i> Oral cefixime 400 mg twice daily for 7 days, metronidazole 400 mg orally twice daily for 14 days and doxycycline 100 mg twice daily for 14 days; abstinence; symptomatic treatment <i>Severe disease.</i> IV antibiotics
Pediculosis pubis	Pruritus	Local application of 1% permethrin, wash after 10 minutes
Scabies	Pruritus and rash	Local application of 5% permethrin; oral ivermectin 2 doses 14 days apart

All patients should be screened for HIV infection; partners should be treated if affected; IM: Intramuscular; IV: Intravenous

vehicle and industrial accidents are common in boys whereas burns are more common in girls.

Migration: Many adolescents migrate from rural to urban settings, for labor or educational opportunities. Trafficking of youth is a serious problem in India and happens for industrial or domestic labor, forced marriages and prostitution. In states like Bihar, 70% of new HIV infections are related to outward male migration.

Adolescent pregnancy: Unmarried adolescents are likely to resort to unsafe methods of abortions, which increase risk of septicemia and mortality. As compared to adult pregnancy, they are also at a higher risk for pre-eclampsia, preterm labor and postpartum hemorrhage. Prolonged and obstructed labor are common in adolescent pregnancies and they are 2–4 times more likely to die during childbirth as compared to adult females. Neonatal, infant and child mortality rates are higher in children delivered to adolescent mothers. Fortunately, the prevalence of adolescent pregnancy [8%] is lower in the results of NFHS 4, due to schooling and knowledge about contraception.

Lack of sex education: The majority of Indian youth do not get formal sex education in an effective way. Peers, books and magazines are their main sources of information about sex. Parents and teachers often fail to discuss issues like masturbation, safe sex, dating, abortion, HIV and sexually transmitted diseases.

Environmental and Social Challenges

Pollution: The incidence of asthma is increasing. There is ongoing research into the role of electromagnetic exposure from communication devices in disorders like childhood leukemia, brain tumors and immune dysregulation.

Media: With easy availability of electronic media, adolescents are exposed to unsupervised information from all across the world. Adolescents often succumb to glamorous portrayal of tobacco or alcohol consumption, unrealistic expectations, physical aggression, destructive behavior and unprotected sex. Spending much of spare time indoors on social networking sites, teenagers are deprived of sunlight and physical activity and socially isolated.

Peer pressure: Peer formation is a part of adolescent social development. Pressure for conforming to norms drives many of their actions and decisions, including risk taking behavior and initiation of substance abuse.

Poverty: Adolescents belonging to poorer families are likely to have inadequate diets. Studies have shown that children belonging to poorer families had higher chances of having depression, anti-social behavior and engaging in drugs or sexual activity at earlier ages.

Illiteracy: Though the situation is improving over the years, still 33% of Indian youth are not able to complete their primary education. Female gender and families from rural and poor background are the risk factors for illiteracy.

Academic and emotional stress: Examinations cause significant physiological and psychological stress. Apart from change in body structure, various other factors like peer acceptance, discrimination, academic burden, parental expectations and changing social environments cause stress among youth. Switching from vernacular to English medium schools, long hours of school and tuitions are additional stress factors that are un-addressed. While most adolescents have adequate coping skills, some have serious adjustment problems resulting in psychological and somatic effects.

Early marriage: Though the legal age for marriage in India is 18 years for girls (Table 5.2), many states still have the practice of childhood and early marriage. Almost 30% of Indian girls between the ages of 15 and 19 years are married; the proportions are higher in rural areas.

Discrimination: Young people are often treated as second class citizens, under the control of adults and often not involved in any decision making. Adolescent girls are often asked to limit their outdoor/extracurricular activities, confined to their houses and expected to do the household work. Gender-based discrimination is seen in education and even food distribution.

Role of Health Care Provider

A checklist for the adolescent clinic visit is provided in Table 5.3. During each visit, the following are important:

Identifying risks: The physician needs to detect risk factors like obesity, hypertension, possible substance/drug abuse, behavioral and social problems and risky behavior. Subtle cues like sad or depressed mood, avoidance of eye contact, bruises or undue resistance to examination are the likely pointers towards physical or sexual abuse.

Table 5.2: Legal age definitions relevant to adolescence

Definition of child	Below 18 years
Minimum age for marriage	Boys 21 years; girls 18 years
Responsibility for crime	12 years
Juvenile criminal	12–18 years
Compulsory free education	6–14 years
Consumption of alcohol	Beyond 18–25 years in different states (illegal in some states and union territories)
Employment in hazardous occupation or hotels	14 years

Table 5.3: Checklist for adolescent health visit

History from parents and adolescent	History of presenting problems Parental concerns on growth, development Academic success; school absenteeism Diet history including calcium, protein and iron intake; junk food Menstrual history; sleep problems
History on separate questioning of adolescent	Emotional problems; relationship with family and peers Outlook towards physical and sexual changes Involvement in relationship or sexual activity Awareness about safe sex and contraception Specific problems related to sex organs Tobacco or other substance use Counsel and clear doubts on sensitive topics
History on separate questioning of parents	Relationship with family Level of communication on sensitive matters
Physical examination	Anthropometry Blood pressure, markers of obesity, acanthosis Sexual maturity rating Signs of malnutrition, anemia and vitamin deficiencies Signs of skin and genital infections Level of general hygiene Signs of trauma; abuse Signs of drug abuse or tobacco use
Counseling	Nutritional intervention Hygienic practices Building rapport between parents and adolescent Providing information and sources on sex education
Investigations	Hemoglobin level Blood sugar, lipid profile Genital swabs Ultrasound of ovaries
Referrals	Counselor Dietitian Psychiatrist Gynecologist Voluntary and confidential HIV testing Social services, child protection agencies, support groups

Establishing rapport: Being empathetic and non-judgmental is the key to effective communication. Direct questioning of the adolescent is as important as questioning the parents. Beginning the interview with icebreakers, use of open-ended non-sensitive questions and then moving to sensitive/targeted questions is helpful.

Confidentiality: One may need to interview a young patient separately, as he/she may not want to discuss sensitive topics in the presence of parents. While examining the genitalia, the doctor can ask patient's preference for presence of their parent inside the examination room. A boy may prefer his parents standing outside the exam room, whereas a girl may find it comforting, if her mother accompanies her during the examination.

Consent: For a child who is less than 12 years, consent for examination or medical/surgical procedure is obtained from the parent or guardian. While an adolescent aged 12–18 years can give consent for examination, consent for medical/surgical procedure can be given only after 18 years. This also includes consent for medical termination of pregnancy, blood and organ donation.

Nutritional intervention: Improving the nutritional status of adolescent girls helps in two ways. It breaks the cycle of malnutrition and low birth weight babies, and prevents long-term complications of the latter in future generations.

Providing health information: The adolescent health visit is an excellent opportunity to talk to the parents and their adolescent about the pubertal changes. It is likely that they

have not received any formal sex education in school and need to be provided correct educational resources for the same.

Referral to social services, psychological evaluation and support: National Commission for Protection of Child Rights Act 2005 considers a person below 18 years as a 'child'. It is mandatory for a health care provider to report all cases of child abuse (even suspected) to the Chairperson of the Commission; the complaint can be lodged online or in writing. Doctors are protected in case of erroneous reporting but punishable, if they fail to report. Adolescents with special needs or victims of any kind of abuse need social and psychological support.

Adolescent-friendly health services: Adolescents have diverse problems and special needs. The services include provision of reproductive health services, nutritional counseling, sex education and life skill education. Confidentiality, easy accessibility, friendly attitude and quick comprehensive health care delivery have made a positive impact on adolescent clients. 'Adolescent reproductive and sexual health' has been identified as a key strategy under RCH II programme. Adolescent friendly clinics are functional at many centers in the country. Box 5.1 lists the key services and interventions that should be provided for comprehensive care for adolescents.

Management of sexual violence: This includes the following measures:

- i. Forensic examination and collection of blood or body fluid samples by trained staff.
- ii. Care of the injuries.
- iii. Prophylaxis against pregnancy: Two doses of levonorgestrel 12 hours apart, first dose being given within 72 hours of intercourse.
- iv. Prophylaxis against sexually transmitted infections includes a single oral dose of azithromycin 1 g along with cefixime 400 mg and metronidazole or tinidazole 2 g, protects against syphilis, gonorrhoea, *Chlamydia* and *Trichomonas*. Hepatitis B vaccination is recommended, if the person is not previously immunized.
- v. Prophylaxis against HIV requires referral to the nearest integrated counseling and testing center.
- vi. Psychological support includes counseling and referral to a psychiatrist. Informing concerned authorities or social services is important as patient may need shelter and legal help. A teen may not be willing to disclose this assault to his parents. Childline (1098) is a support service provided by Government of India focussed on child care and protection.

Protection of Children from Sexual Offenses [POCSO] Act 2012: The POCSO Act protects individuals below 18 years from sexual offense or harassment of any form, be it physical or pornographic. It also explicitly states that an

Box 5.1: Healthy adolescence: Package of Interventions

Healthy lifestyle

- Healthy food
- Exercise and Yoga
- No to tobacco, alcohol, drugs
- Safe conduct on road

Vaccines

- Papilloma virus, rubella

Anemia

- Prevention, detection and management of anemia, especially for adolescent girls

Sexual health

- Sexuality education
- Menstrual hygiene
- Marriage after 18 years, childbirth after 20 years
- Counseling and services for comprehensive sexual and reproductive health, including contraception

Mental health

- Supportive family; counseling and peer/family support in anxiety, depression
- Prevention and management of hazardous and harmful substance use
- Prevention of suicide and management of self-harm/suicide risk

Violence prevention

- Prevention and management of unintentional injury
- Prevention of and response to sexual and other forms of gender-based violence

Communicable and non-communicable diseases

- Prevention, detection and treatment of communicable and non-communicable diseases

Preparing for adulthood

- Parenting skills, responsible husband, wife and father

event of abuse must be informed to legal authorities; failing which, the knowing person [including the health care provider] is liable to legal actions including imprisonment.

Contraception: A pediatrician should advocate for abstinence and delayed initiation of sex to adolescent patients. In case the adolescent is already sexually active, condom seems a better choice compared to other methods. Adolescents with disabilities or mental retardation are wrongly assumed to be at low risk for STIs and pregnancy. Parents of such children need to be counseled regarding these issues.

Adolescent immunization: India has low coverage for booster doses of TT at 10 and 16 years. Papilloma virus vaccine is recommended for peripubertal girls (before initiation of sexual activity) for prevention of infection with human papillomavirus and cervical cancer. Parents need to be counseled thoroughly as the principle behind giving the vaccine might alarm them (Table 5.4).

Table 5.4: Immunization during adolescence

Tetanus and diphtheria toxoids and acellular pertussis (Tdap) vaccine [TT at 10 and 15 years as per Universal Immunization Program]	10–12 years, and every 10 years thereafter
Papillomavirus	2 doses, if given between 9 and 14 years 3 doses, if given beyond age 15 years
Influenza	Annually
Catch-up vaccination is discussed in Chapter 10	

Transition to adult care: With better medical care, a large number of chronically ill or disabled children are surviving into adulthood. As the problems of these children are diverse, they need multidisciplinary care even in their adulthood. Transition to adult care is not mere transfer of the case to a different physician. It is a gradual and planned process; keeping in mind the abilities of the child to participate in self-care, taking responsibilities and decision making. The age at transfer is not fixed; a window of age 14–18 years is used in some countries for a gradual transfer.

GOVERNMENT INTERVENTIONS IN ADOLESCENT HEALTHCARE

Kishori Shakti Yojana and SABLA Yojana aim to provide health, nutrition, education and vocational skills to adolescent girls. National Youth Policy believes in youth empowerment through education. Recognizing the contribution of adolescent care to maternal and child

health, National Health Mission now follows Reproductive, Maternal, Neonatal, Child and Adolescent Health (RMNC+A) approach. Under this program, weekly iron and folic acid supplementation (WIFS) program provides 100 mg of iron and 500 µg folic acid with biennial deworming to all adolescents attending government schools.

Suggested Reading

1. National Family Health Survey [NFHS3, 2005-6] and [NFHS4, 2015-16]. International Institute for Family Survey, Mumbai.
2. WHO Media Centre Fact Sheet 2014. Adolescents: health risks and solutions.
3. Contraception and Adolescents: Committee on Adolescents, Pediatrics 2007;120:1135.
4. National Guidelines on Prevention, Management and Control of RTIs/STIs. Ministry of Health and Family Welfare, Govt of India, 2007.
5. Dietary Guidelines for Indians [Second Edition]. National Institute of Nutrition, 2011.
6. Juvenile Justice Act 2015. The Gazette of India, Ministry of Law and Justice.

Fluid and Electrolyte Disturbances

Kamran Afzal

COMPOSITION OF BODY FLUIDS

The major component of body mass is water. The contribution of total body water to body weight varies with age, lean body weight and adiposity. Total body water (TBW) as a percentage of body weight declines from as high as 90% in early fetal life to nearly 75–80% at the time of birth. Thereafter, it declines progressively to 60% by the end of the first year and remains so till puberty. Since adipose tissue has lower water content, therefore, adolescent females and overweight children have lower TBW as a percentage of body weight.

Total body water is distributed in two major compartments, two-thirds is intracellular fluid (ICF) and one-third is extracellular fluid (ECF). Nearly one-fourth of ECF is distributed in the intravascular space (plasma water) and the remaining in the extravascular (interstitial) space (Fig. 6.1). The relative size of the two main compartments varies with age. Increase in extracellular fluid volume contributes to the increased TBW in neonates, especially preterm babies.

The interstitial fluid component of extracellular fluid is actually a matrix, a collagen/gel substance that allows the interstitium to provide structural rigidity during extra-

cellular volume depletion. The interstitial space, especially in skin and connective tissue, is an important reservoir of extracellular fluid.

Water Balance

In the steady state, water balance represents the difference between water intake (including that generated from endogenous metabolism) and water losses (Fig. 6.2). Much of the water output involves obligatory losses in the urine, stool and, by evaporation from the moist surfaces of the skin and respiratory tract (insensible losses). The kidneys are the major regulators of water output with nearly two-thirds of daily water losses being urine. The obligatory renal water loss is directly related to solute excretion. The evaporative losses play an important role in thermoregulation. In contrast to these insensible losses, sweat which is hypotonic (Na^+ concentration 35 to 65 mEq/L) is actually 'sensible loss'. It also contributes to thermoregulation and may reflect the majority of total daily loss of water in presence of high ambient temperatures or when endogenous heat production is enhanced, as with exercise or fever.

Changes in sodium concentration in the extracellular fluid are linked to extracellular fluid volume and are associated with dysregulated water balance. The effectors for volume regulation are primarily renin-angiotensin-aldosterone system and atrial natriuretic peptide, both of which affect Na^+ excretion. Besides this regulation of body water is made possible by interplay of multiple other factors, including vasopressin, prostaglandins, dopaminergic receptors, α -adrenergic receptors, thirst mechanism and intrinsic renal properties.

Electrolyte Composition of Body Compartments

The extracellular fluid compartment contains high concentration of sodium, chloride, and bicarbonate (Fig. 6.3). Potassium, organic phosphates and proteins are the predominant ICF osmoles. Because of variability in ECF and ICF distribution, the serum concentrations do not necessarily reflect the total body content of a particular electrolyte. Permeability to ions varies in each organ with

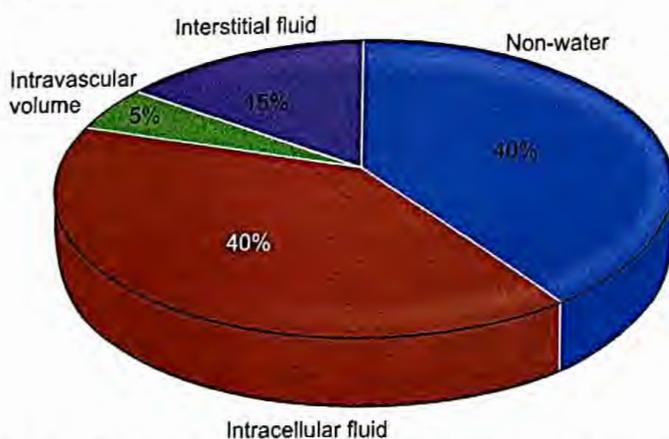


Fig. 6.1: Body composition. Nearly 60% of the body weight is water. Of this two-thirds is intracellular, while the rest is extracellular (ECF), which is distributed between the interstitial and intravascular compartments in 3:1 ratio

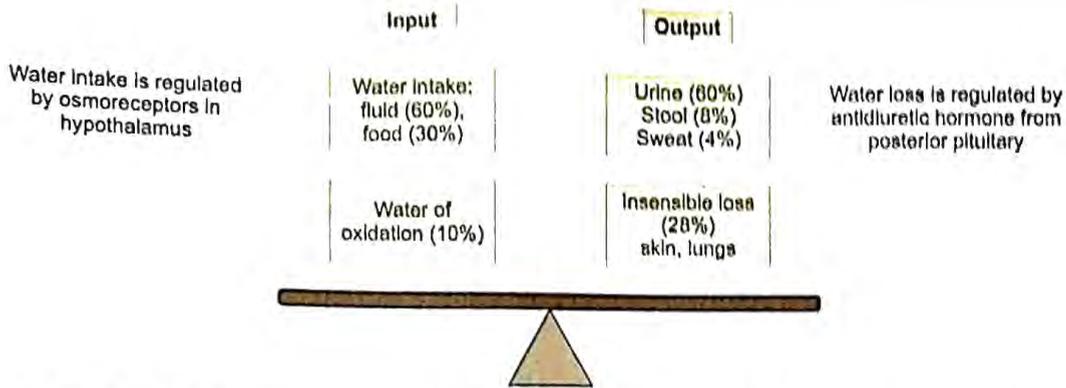


Fig. 6.2: Balance of water intake and losses maintains normal plasma osmolality. Only water intake and urinary losses can be regulated

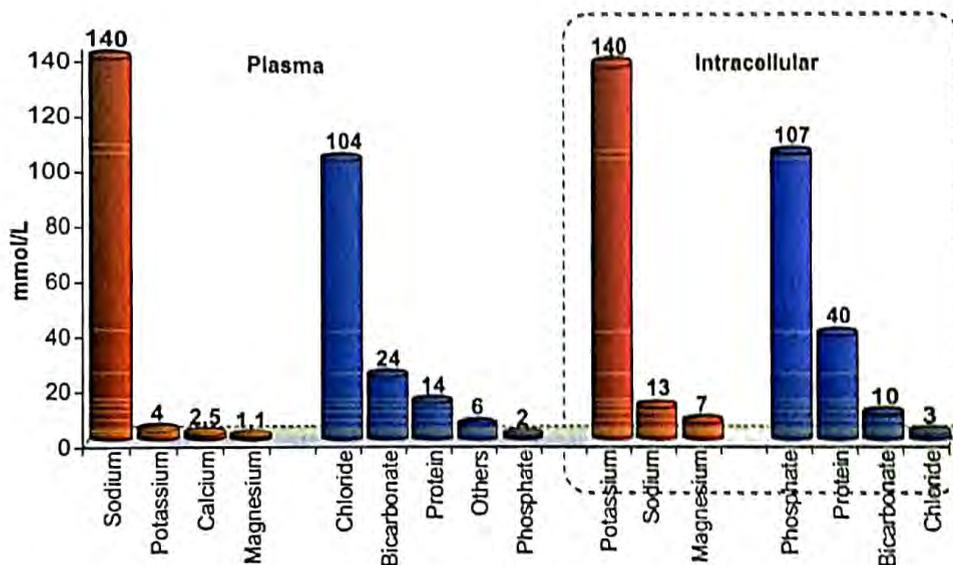


Fig. 6.3: Electrolyte composition of Intracellular and extracellular fluid compartments

the brain having the least and the liver the most permeability. However, water readily crosses cell membranes to achieve an osmotic equilibrium between the two compartments. The balance and appropriate distribution of fluid within these spaces is maintained by the colloid oncotic pressure, membrane permeability and hydrostatic pressure. Plasma and interstitial fluid are rich in proteins, which determine plasma colloid oncotic pressure.

Osmolality

Osmolality (expressed as milliosmoles per kilogram of water, mOsm/kg) is the solute concentration of a fluid. Changes in osmolality can produce grave neurologic consequences and even death, primarily due to water movement into and out of the brain. To prevent this, the plasma osmolality, which is primarily determined by the plasma Na⁺ concentration, is normally maintained closely between 1 and 2% of the normal (285 to 295 mOsm/kg) by appropriate variations in water intake and water excretion. This regulatory system is governed by different osmoreceptors in the hypothalamus that influence both thirst

and the secretion of antidiuretic hormone (ADH) (Fig. 6.4). Plasma osmolality can be measured directly using osmometers, as well as estimated indirectly as follows:

$$\text{Plasma osmolality} = 2[\text{Na}^+] + \frac{\text{glucose}}{18} + \frac{\text{blood urea nitrogen}}{2.8}$$

Measured values are generally higher than calculated values by up to 10 mOsm/kg and this difference is called osmolal gap. Increase in osmolal gap may occur due to increase in unmeasured osmoles.

Normal Maintenance Fluid and Electrolyte Requirements

The normal maintenance water requirement is equal to the insensible and urinary water losses. Holliday and Segar guidelines (1957) calculate maintenance fluid volumes to match electrolyte-free water requirements from estimates of water of evaporation (heat dissipation) and caloric expenditure (heat production). They estimated a daily sodium requirement of 3 mEq/kg, potassium and chloride 2 mEq/kg each and daily glucose requirement as 5 g/kg

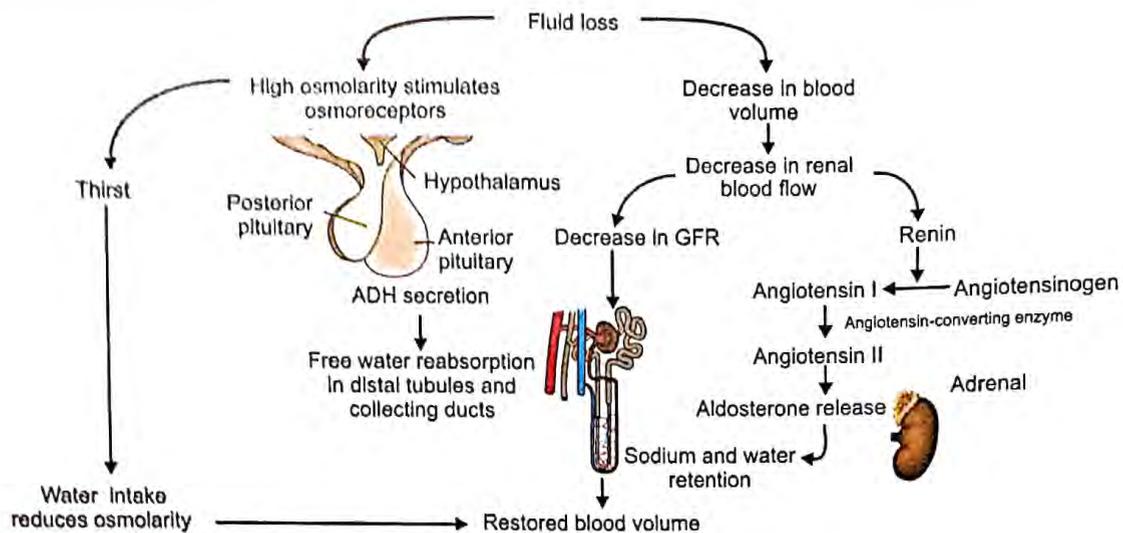


Fig. 6.4: Regulation of sodium and water balance

Table 6.1: Maintenance fluid requirement in healthy children

Body weight	Per day	Per hour
0–10 kg	100 mL/kg	4 mL/kg
10–20 kg	1000 mL for first 10 kg + 50 mL/kg for each kg beyond 10 kg	40 mL + 2 mL/kg for each kg beyond 10 kg
>20 kg	1500 mL + 20 mL/kg for each kg beyond 20 kg	60 mL + 1 mL/kg for each kg beyond 20 kg

based on the electrolyte composition of human and cow milk and recommended 30 mEq/L sodium chloride (saline) for maintenance fluid in children. Maintenance IV fluids in an unwell child may be initiated with 0.45% normal saline along with 5% dextrose and 20 mEq/L of potassium chloride (provided urine output is adequate). This composition may be modified according to the clinical state. The guidelines for maintenance volume (Table 6.1) assume average calorie expenditure in a healthy child. Fluid requirements change considerably in different clinical conditions (Table 6.2).

IV fluid with osmolality lower than plasma osmolality can cause movement of free water from plasma to red blood cells leading to hemolysis. Therefore, infusing plain

5% dextrose in water or 0.2% or 0.45% saline (without dextrose) should be avoided. There is considerable evidence that use of hypotonic fluids in sick hospitalized patients increases the risk of hyponatremia several fold. Normal saline (0.9%) can be safely administered in standard maintenance volume without risks of hypernatremia or fluid overload, except in patients who are fluid restricted (e.g. congestive heart failure, liver and renal failure) and those with renal concentrating defect (e.g. diabetes insipidus). Hypotonic fluid should only be used to achieve a positive free-water balance as in replacing renal or non-renal loss of electrolyte-free water.

The ideal volume for maintenance fluid is debated. Conventional calculation using weight-based formulae often lead to overestimation of electrolyte-free water, and excess free water retention that predispose to hyponatremia. Therefore, it may be prudent to restrict maintenance fluids to 40–60%, especially in critically sick children. Fluids should be limited around 400 mL/m² in renal failure with oliguria. There is no single maintenance intravenous fluid which is suitable for all clinical scenarios and maintenance fluid prescriptions should be individualized. All children receiving IV maintenance fluid should be monitored with daily weight, fluid balance, clinical and biochemical parameters in order to maintain homeostasis. Additionally, maintenance IV fluids do not replace daily nutrient requirements and provide only 20% of daily calories (enough to avoid starvation ketoacidosis and diminish protein degradation).

Table 6.2: Conditions that alter maintenance fluid needs

Increased fluid requirement	Decreased fluid requirement
Fever (10–15% per °C above 38°C)	Oliguria or anuria
Radiant warmer, phototherapy	Humidified ventilator or incubator
Burns, sweating	Hypothyroidism
Physical activity; hyperventilation	
Diarrhea, vomiting	
Polyuria, renal concentrating defects	
Very low birth weight babies (large surface area)	

Table 6.3: Clinical assessment of dehydration

	No dehydration	Some dehydration	Severe dehydration
Decrease in body weight	<5% in infants; <3% in older children	5–10% in infants; 3–6% in older children	>10% in infants; >6% in older children
Mental status	Normal	Irritable	Lethargic to comatose
Thirst	Normal	Increased	Unable to drink
Skin color and elasticity (turgor)	Normal	Cool, pale; mild delay in turgor	Cold, mottled; tenting
Sunken eyes	Normal	Sunken	Very sunken
Mucous membrane	Normal	Dry	Very dry
Pulse rate	Normal	Slightly increased	Tachycardia
Capillary refill	2–3 sec	3–4 sec	>4 sec
Blood pressure	Normal	Normal	Normal or low
Urine output	Slightly decreased	Decreased	Oliguria, anuria

DEFICIT THERAPY

The degree of volume depletion is assessed by physical examination (Table 6.3). The process of hypernatremia or hypertonicity decreases the severity of physical signs of volume depletion. All fluid lost should be replaced daily to maintain euvolemic state. Steps for providing fluids and electrolytes to volume depleted patients are:

- If the patient shows signs of shock, compensated shock or features of severe dehydration (Table 6.3), rapidly infuse isotonic fluids to restore intravascular volume. This is done by infusing 1 to 3 fluid boluses of isotonic saline or Ringer’s lactate, 20 mL/kg body weight.
- Provide fluids to replace calculated/observed volume deficit. This is calculated as volume at the rate of 10 mL for each percentage weight loss. For example, in patients with moderate (some) dehydration, which is on an average 7.5% weight loss, the replacement volume is 75 mL/kg body weight. If the pre-dehydration weight is known, the volume of fluid needed is 1 liter for every kg of weight loss.
- Provide fluid and electrolytes to replace the amounts lost in normal daily metabolism (maintenance fluids).
- Provide enough fluid to replace ongoing losses of various body fluids (Table 6.4).

While current literature does not advocate use of one type of fluid over another, there is a growing concern of hyperchloremic metabolic acidosis with fluid resuscitation with normal saline. Balanced fluids, such as Ringer’s

lactate, that mimic plasma composition better than normal saline may be considered, especially in the setting of acidosis.

SODIUM

Physiology

Sodium is the most abundant ion of the extracellular fluid compartment and is critical in determining extracellular and intracellular osmolality. Normal serum sodium concentration varies between 135 and 145 mEq/L. Extracellular sodium balance is determined by sodium intake relative to sodium excretion. Daily sodium requirement is 2 to 3 mEq/kg body weight although intakes are generally well in excess. The requirement varies with age. It is nearly two- to threefolds higher in term and very low birth weight preterm babies, a reflection of immaturity of renal tubular function and higher requirements for growth. Adult requirements decrease to 1.5 mEq/kg/d. Urinary sodium excretion represents the majority of sodium losses and approximately equals the daily intake of sodium. Fractional excretion of sodium is generally less than 1% of filtered load. Extrarenal sodium losses can be significant *via* profuse sweating, burns, severe vomiting or diarrhea.

A fall in blood pressure, decrease in sodium delivery to the macula densa, or sympathetic stimulation may activate the renin–angiotensin axis, generating angiotensin II. This results in increase in blood pressure and sodium retention caused by enhanced aldosterone secretion. The effective circulating volume refers to that part of the extracellular fluid that is in the arterial system and is effectively perfusing the tissues. The effective circulating volume usually varies directly with the extracellular fluid volume, and both are proportional to total body Na⁺ stores. As a result, the regulation of Na⁺ balance (by alteration in its urinary excretion) and maintenance of effective circulating volume are closely related. Sodium loading tends to produce volume expansion, whereas loss leads to volume depletion.

Table 6.4: Electrolyte composition of body fluids

Losses	Na ⁺ (mEq/L)	K ⁺ (mEq/L)	Cl ⁻ (mEq/L)	HCO ₃ ⁻ (mEq/L)
Gastric	60–100	5–20	90–130	0
Small intestine	80–140	5–15	90–140	40
Colon	60	30	40	15
Pancreas	135–145	5–10	70–90	95–120
Diarrhea	10–90	10–80	90–130	40

Hyponatremia

Hyponatremia, defined as plasma sodium less than 135 mEq/L, can result from excessive loss of sodium from excessive sweating, vomiting, diarrhea, burns and the administration of diuretics (Table 6.5). The most common cause of hyponatremia, however, is not a deficiency of total body sodium, but an excess of total body water, as in the syndrome of inappropriate antidiuresis (SIAD).

SIAD is seen in association with pulmonary and cranial disorders and postoperatively. High levels of vasopressin or antidiuretic hormone (ADH) are secreted at a low threshold or continuously despite low osmolality. The presence of hyponatremia plus a urine osmolality higher than maximal dilution confirms the diagnosis. SIAD should be differentiated from cerebral salt wasting which is also associated with central nervous system disorders. In the latter, there is hypovolemic hyponatremia and high urinary sodium (>80 mEq/L) due to increase in blood levels of natriuretic factor(s). SIAD is characterized by euvolemia or mild volume expansion, inappropriate urinary concentration (urine osmolality >100 mOsm/kg), and high urine sodium (>20–30 mEq/L). In presence of elevated ADH levels, there is impaired ability to excrete free water with the urine osmolality exceeding that of plasma. The treatments are different, as cerebral salt wasting requires replacement of urinary salt-water losses while SIAD is managed by fluid restriction.

Hyperosmolality resulting from non-sodium molecules (hyperglycemia, mannitol overdose) draws water from the intracellular space to dilute the extracellular sodium concentration. Factitious hyponatremia, reported when hyperlipidemia (chylomicronemia) or hyperproteinemia coexist, is uncommon due to use of ion-selective electrodes.

Patients are generally symptomatic when serum sodium concentration falls below 125 mEq/L or the decline is acute (<24 hours). Early features include headache,

nausea, vomiting, lethargy and confusion. Advanced manifestations are seizures, coma, decorticate posturing, dilated pupils, anisocoria, papilledema, cardiac arrhythmias, myocardial ischemia and central diabetes insipidus. Cerebral edema occurs at levels of 125 mEq/L or less.

Hypo-osmolality causes influx of water into the intracellular space, which results in cytotoxic cerebral edema and increased intracranial pressure and can lead to brain ischemia, herniation and death. The brain's primary mechanism in adapting to hyponatremia is the extrusion of intracellular electrolytes and organic osmolytes. Some of these organic osmolytes are excitatory amino acids, such as glutamate and aspartate that can produce seizures in the absence of detectable cerebral edema. Major risk factors for developing hyponatremic encephalopathy are young age, hypoxemia and neurological disease. Children are at significantly higher risk than are adults for developing hyponatremic encephalopathy due to their relatively larger brain to intracranial volume ratio compared with adults. Hyponatremia in association with increased intravascular volume can result in pulmonary edema, hypertension and heart failure. Asymptomatic hyponatremia in preterm neonates is associated with poor growth and development, sensorineural hearing loss and a risk factor for mortality in neonates who suffered perinatal birth asphyxia.

Treatment

The first step is to determine whether hyponatremia is acute (<48 hours) or chronic (>48 hours), symptomatic or asymptomatic and evaluate the volume status. In hypovolemic hyponatremia with hypotension, volume resuscitation with normal saline takes precedence over treatment of hyponatremia even at the risk of sudden increase in serum sodium. Symptomatic hyponatremia requires early recognition and prompt management with IV boluses of hypertonic saline irrespective of the chronicity of hyponatremia. Close biochemical and clinical monitoring should be provided during management (Box 6.1).

In asymptomatic cases, the underlying etiology needs to be evaluated and corrected. Losses due to renal or adrenocortical diseases are suggested by urinary sodium concentration of more than 20 mEq/L in the presence of clinically relevant volume depletion (Fig. 6.5). Chronic hyponatremia should be slowly corrected over 48–72 hours. Aggressive therapy with hypertonic saline in patients with chronic hyponatremia (where brain adaptation to hypo-osmolality is set in by extrusion of intracellular electrolytes and organic osmoles) can lead to osmotic demyelination syndrome. Patients who develop the demyelination syndrome show a biphasic course, with neurological improvement followed by deterioration 2–7 days later manifested by mutism, dysarthria, lethargy, spastic quadriparesis and pseudobulbar palsy. In clinical practice, the distinction between acute and chronic hyponatremia

Table 6.5: Causes of hyponatremia

Hypovolemic hyponatremia (sodium loss in excess of free water)

Renal loss: Diuretic use, osmotic diuresis, renal salt-wasting, adrenal insufficiency, pseudohypoaldosteronism

Extrarenal loss: Diarrhea, vomiting, drains, fistula, sweat (cystic fibrosis), cerebral salt wasting syndrome, third-spacing (effusions, ascites)

Normovolemic hyponatremia (conditions that predispose to SIAD)

Inflammatory central nervous system disease (meningitis, encephalitis), tumors

Pulmonary diseases (severe asthma, pneumonia)

Drugs (cyclophosphamide, vincristine)

Nausea, postoperative

Hypervolemic hyponatremia (excess free water retention)

Congestive heart failure, cirrhosis, nephrotic syndrome, acute or chronic kidney disease

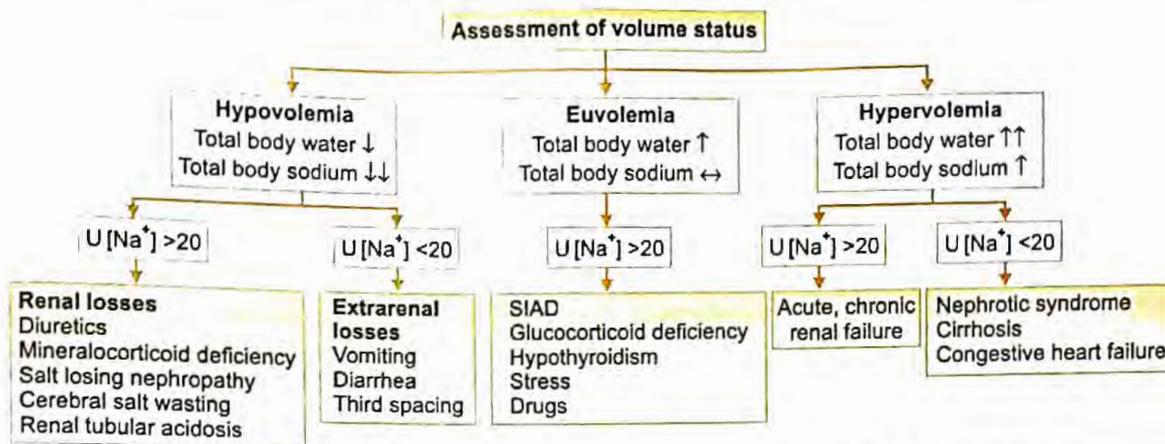


Fig. 6.5: Diagnostic approach to hyponatremia. U[Na⁺] urinary sodium, mEq/L; ↑ Increased; ↓ decreased

Box 6.1: Treatment of hyponatremia

- Treat hypotension first with 20 mL/kg of normal saline or Ringer's lactate
- Symptomatic hyponatremia
 - 3–5 mL/kg 3% sodium chloride infused over 1 hour, monitor sodium hourly.
 - Aim for first hour of management is to increase serum sodium by 5–6 mEq/L with resolution of symptoms, indicating that patient is awake, alert, responding to commands with no headache and nausea
 - Continue 3% saline infusion till patient is asymptomatic and serum sodium approaches 130 mEq/L or rises 10 mEq/L in 4–6 hours; monitor serum sodium 2–4 hourly
- Asymptomatic and chronic hyponatremia
 - Treat underlying etiology
 - Calculate Na⁺ deficit (mEq/kg) = (130 – serum Na⁺) × 0.6 × body weight (kg)
 - Rise of serum sodium should not exceed 0.5 mEq/hour or 10 mEq/L in the first 24 hours and an additional 8 mEq/L during every next 24 hours thereafter until the serum sodium reaches 130 mEq/L.
 - *Hypovolemia*: Sodium deficit estimated is given as normal saline; WHO ORS rehydration solution is preferable for patients able to accept orally
 - *SIAD*: Fluid restriction; furosemide and oral salt supplementation, if required
 - *Hypervolemia*: Sodium and fluid restriction, diuretics
 - *Cerebral salt wasting*: Fludrocortisone

is often unclear at initial evaluation. Therefore, hyponatremia should be assumed as chronic and corrected gradually (≤ 10 – 12 mEq/L/day).

In a volume expanded state, fluid restriction alone or in combination with diuretics is useful. Fluid restriction alone has no role in the management of symptomatic hyponatremia. Normal saline is also inappropriate for treating hyponatremic encephalopathy due to non-hemodynamic states of vasopressin excess, such as SIAD and postoperative hyponatremia, as it is not sufficiently hypertonic to induce reduction in cerebral edema. V₂ receptor antagonists or vaptans that block the binding

of ADH to its V₂ receptor, are yet not recommended for treatment of hyponatremic encephalopathy. These agents may have a role in treating euvolemic hyponatremia from SIAD and hypervolemic hyponatremia in congestive heart failure.

Hypernatremia

Hypernatremia is defined as increase in serum sodium concentration to levels more than 150 mEq/L. It may be accompanied by the presence of low, normal or high total body sodium content. The major cause of hypernatremia is loss of body water, inadequate intake of water, a lack of antidiuretic hormone (ADH), or excessive intake of sodium (e.g. solutions with high sodium such as sodium bicarbonate) (Table 6.6). Diabetes insipidus may result from a deficiency of ADH or its end organ unresponsiveness.

In the presence of an intact thirst mechanism, a slight increase in serum sodium concentration (3 to 4 mEq/L) above normal elicits intense thirst. The lack of thirst in the presence of hypernatremia in a mentally alert child indicates a defect in either the osmoreceptors or the cortical thirst center. The most objective sign of hypernatremia is lethargy or mental status changes, which proceeds to coma and convulsions. With acute and severe hypernatremia, the osmotic shift of water from neurons leads to shrinkage of the brain and tearing of the meningeal vessels and intracranial hemorrhage; slowly developing hypernatremia is generally well tolerated. The latter adaptation occurs initially by movement of electrolytes into cells and later by intracellular generation of organic osmolytes, which counter plasma hyperosmolality.

Treatment

Treatment involves restoring normal osmolality and volume. The speed of correction depends on the rate of development of hypernatremia and associated symptoms (Box 6.2). Because chronic hypernatremia is well tolerated, rapid correction offers no advantage and may be harmful since it may result in brain edema. Usually, a maximum of 10% of the serum sodium concentration or about

Table 6.6: Causes of hypernatremia**Net water loss***Pure water loss*

Insensible losses

Diabetes insipidus

Inadequate breastfeeding

*Hypotonic fluid loss**Renal:* Loop, osmotic diuretics, postobstructive, polyuric phase of acute tubular necrosis*Gastrointestinal:* Vomiting, nasogastric drainage, diarrhea; lactulose**Hypertonic sodium gain***Excess sodium intake*

Sodium bicarbonate, saline infusion

Hypertonic feeds, boiled skimmed milk

Ingestion of sodium chloride

Endocrine: Primary hyperaldosteronism, Cushing syndrome**Box 6.2:** Treatment of hypernatremia

- Restore intravascular volume with 20 mL/kg normal saline over 20 min (repeat until intravascular volume restored)
- Determine time for correction on basis of initial sodium concentration:

Serum sodium level	Time
145–157 mEq/L	24 hours
158–170 mEq/L	48 hours
171–183 mEq/L	72 hours
184–196 mEq/L	84 hours
- Fluid for correction D5 N/3 to N/4 normal saline (with 20 mEq/L KCl unless contraindicated)
- Fluid rate: 1.25–1.5 times maintenance
- Monitor serum sodium q 4 hourly; should not fall by >0.5 mEq/L/hour
- Adjust fluid on basis of clinical status and serum sodium concentration; if child develops seizures (due to rapid correction) 3% NaCl (4–6 mL/kg over 30 min) is indicated.
- Replace ongoing losses as they occur
- Identify and treat the underlying cause

0.5 mEq/L/hr should be the goal rate of correction. Renal replacement therapy is indicated for concurrent renal failure and volume overload.

POTASSIUM**Physiology**

Potassium being a predominantly intracellular cation, its blood level is unsatisfactory indicator of total body stores. Normal serum concentration of potassium ranges between 3.5 and 5 mEq/L. Common potassium-rich foods include meats, beans, fruits and potatoes. Gastrointestinal absorption is complete and potassium homeostasis is maintained predominantly through the regulation of renal excretion. The fractional excretion of potassium is about 10%, chiefly regulated by aldosterone at the collecting duct. Renal adaptive mechanisms maintain potassium homeo-

stasis until the glomerular filtration rate drops to less than 15–20 mL/min. Excretion is increased by aldosterone, high sodium delivery to the collecting duct (e.g. diuretics), urine flow (e.g. osmotic diuresis), blood potassium level, glucocorticoids, ADH and delivery of negatively charged ions to the collecting duct (e.g. bicarbonate). In renal failure, the proportion of potassium excreted through the gut increases, chiefly by the colon in exchange for luminal sodium.

Aldosterone and insulin play important roles in potassium homeostasis. Insulin stimulated by potassium ingestion increases uptake of potassium in muscle cells, through increased activity of the sodium pump. High potassium levels stimulate its renal secretion *via* aldosterone-mediated enhancement of distal expression of secretory potassium channels (ROMK). Insulin, beta-adrenergic stimuli and alkalosis enhance potassium entry into cells. The reverse happens with glucagon, α -adrenergic stimuli and acidosis.

Hypokalemia

Hypokalemia is defined as a serum potassium level below 3.5 mEq/L. The primary pathogenetic mechanisms resulting in hypokalemia include increased losses, decreased intake or transcellular shift (Table 6.7). Vomiting, a common cause of hypokalemia, produces volume depletion and metabolic alkalosis. Volume depletion leads to secondary hyperaldosteronism, which enhances sodium resorption and potassium secretion in the cortical collecting tubules. Metabolic alkalosis also increases potassium secretion due to the decreased availability of hydrogen ions for secretion in response to sodium reabsorption.

Regardless of the cause, hypokalemia produces similar signs and symptoms. Symptoms are nonspecific and predominantly are related to muscular or cardiac function. Severe hypokalemia (<2.5 mEq/L) may cause muscle weakness (neck flop, abdominal distension, ileus) and produce cardiac arrhythmias. Chronic hypokalemia is associated with interstitial renal disease of uncertain pathogenesis. Hypokalemia increases the risk of digoxin toxicity by promoting its binding to myocytes, potentiating its action and decreasing clearance.

Treatment

Patients should be evaluated to determine the underlying causes and determine whether it is associated with hypertension and acidosis or alkalosis (Fig. 6.6). Hypertension may be a clue to primary hyperaldosteronism, renal artery stenosis, or the rarer forms of genetically inherited hypertension such as congenital adrenal hyperplasia, glucocorticoid remediable hypertension or Liddle syndrome. Relative hypotension and alkalosis suggests diuretic use, or a tubular disorder such as Bartter or Gitelman syndrome.

Therapy involves decreasing ongoing losses (e.g. discontinuation of diuretics, α_2 -agonists), replenishing

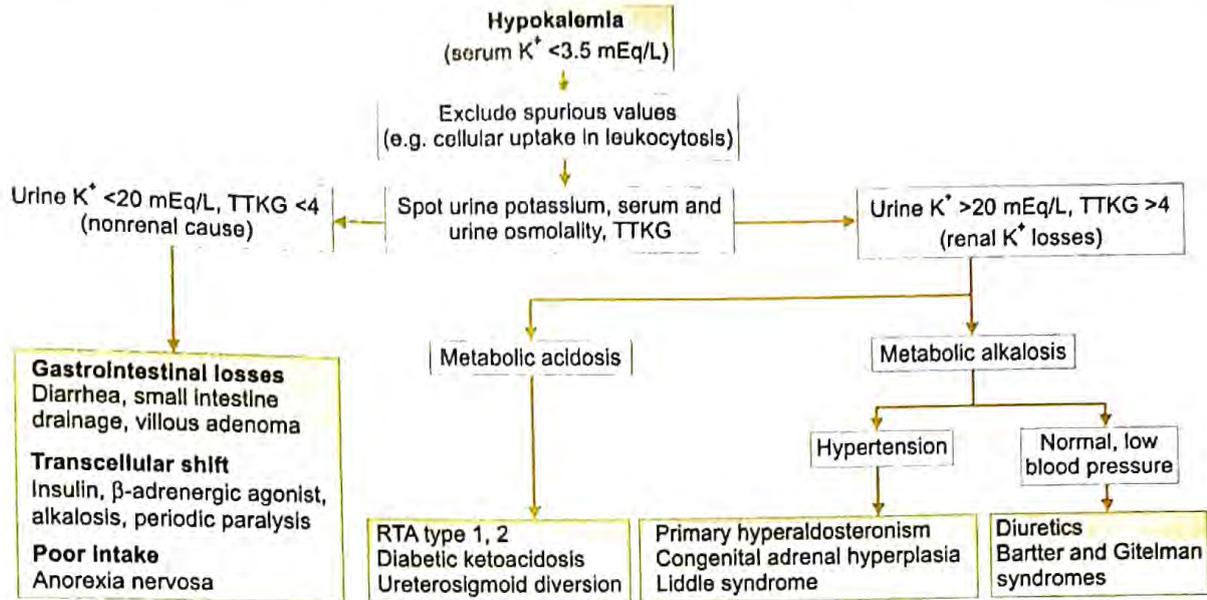


Fig. 6.6: Diagnostic approach to hypokalemia. K⁺ potassium; RTA renal tubular acidosis; TTKG transtubular potassium gradient

Table 6.7: Causes of hypokalemia

Increased losses

Renal

- Renal tubular acidosis (proximal or distal)
- Drugs (loop and thiazide diuretics, amphotericin B, aminoglycosides, corticosteroids)
- Cystic fibrosis
- Gitelman syndrome, Bartter syndrome, Liddle syndrome
- Ureterosigmoidostomy
- Mineralocorticoid excess (Cushing syndrome, hyperaldosteronism, congenital adrenal hyperplasia (11β-hydroxylase, 17α-hydroxylase deficiency)
- High renin conditions (renin secreting tumors, renal artery stenosis)

Extrarenal

- Diarrhea, vomiting, nasogastric suction, sweating
- Potassium binding resins (sodium polystyrene sulfonate)

Decreased intake or stores

- Malnutrition, anorexia nervosa
- Potassium-poor parenteral nutrition

Intracellular shift

- Alkalosis, high insulin state, medications (β₂-adrenergic agonists, theophylline, barium, hydroxychloroquine), refeeding syndrome, hypokalemic periodic paralysis, malignant hyperthermia, thyrotoxic periodic paralysis

potassium stores (oral or intravenous administration of potassium chloride) and disease-specific therapy for the conditions such as Bartter and Gitelman syndrome (e.g. indomethacin, angiotensin-converting enzyme inhibitors) (Box 6.3).

Hyperkalemia

Hyperkalemia, defined as serum potassium level exceeding 5.5 mEq/L, is most commonly associated with

Box 6.3: Treatment of hypokalemia

- IV supplementation
 - Indication: Symptomatic patients, severe hypokalemia (<2.5 mEq/L), ECG abnormalities
 - Potassium chloride (15%; 2 mEq/mL; 0.5–1 mEq/kg/dose) given as IV infusion over 1–2 hr. Infusion rate should not exceed 1 mEq/kg/hr; concentration of potassium should not exceed 60 mEq/L (peripheral line) and 80 mEq/L (central line)
- Oral supplementation
 - Dose: 2–4 mEq/kg/day in 3–4 divided doses
 - Potassium chloride (10%; 20 mEq/15 mL); potassium citrate used in renal tubular acidosis. Liquid preparations are bitter and may be diluted with juice or water
- Stop and replace ongoing losses, volume resuscitation with normal saline, correct hypomagnesemia, treat underlying etiology

renal insufficiency, acidosis and diseases that involve defects in mineralocorticoid, aldosterone and insulin function. Sudden and rapid onset of hyperkalemia is one of the most serious electrolyte disturbances and result in severe cardiac arrhythmia.

Factitious or pseudohyperkalemia can occur because of the practice of squeezing of extremities during phlebotomy or blood sampled from a limb being infused with potassium-containing fluid or hemolysis of a standing sample. Thrombocytosis and leukocytosis can also lead to false elevation of serum potassium levels. True hyperkalemia is caused by one or more of three mechanisms: Increased potassium intake, extracellular potassium shifts and decreased excretion (Table 6.8). Increased potassium intake may result from inappropriate intravenous or oral potassium supplementation. Packed red blood cells have high concentrations of potassium that can lead to hyperkalemia. Acidosis results in transcellular potassium

Table 6.8: Causes of hyperkalemia**Decreased losses***Renal failure*

Renal tubular disorders: Pseudohypoaldosteronism, urinary tract obstruction

Drugs: ACE inhibitors, angiotensin receptor blockers, potassium sparing diuretics, NSAIDs, heparin

Mineralocorticoid deficiency: Addison disease, 21-hydroxylase deficiency, 3 β -hydroxysteroid dehydrogenase deficiency

Increased intake

Intravenous or oral potassium intake; packed red cells transfusion

Extracellular shift

Acidosis, low insulin state, medications (β -adrenergic blockers, digitalis, succinylcholine, fluoride), hyperkalemic periodic paralysis, malignant hyperthermia

Cellular breakdown

Tumor lysis syndrome, rhabdomyolysis, crush injury, massive hemolysis

shift, but any cellular injury that disrupts the cell membrane (e.g. tumor lysis syndrome, rhabdomyolysis, crush injury, massive hemolysis) can cause hyperkalemia.

Patients may report nausea, vomiting and paresthesias or nonspecific findings of muscle weakness (skeletal, respiratory), fatigue and ileus. Clinical manifestations are related to the effects of elevated potassium levels on cardiac conduction since they interfere with repolarization of the cellular membrane. ECG changes appear progressively with rising serum potassium and include tall, peaked T waves (5.5 to 6.5 mEq/L), prolonged PR interval, flat P waves, wide QRS complex (6.5 to 8.0 mEq/L), absent P waves, bundle branch blocks and eventually sine waves (>8.0 mEq/L).

The transtubular potassium gradient (TTKG) accounts for the confounding effect of urine concentration on interpretation of urine potassium excretion.

$$\text{TTKG} = \frac{(\text{urine potassium} \times \text{serum osmolality})}{(\text{serum potassium} \times \text{urine osmolality})}$$

This test cannot be applied when the urine osmolality is less than the serum osmolality. Normal TTKG varies between 6 and 12. It should rise to >10 in patients with hyperkalemia. A value <5 signifies in appropriate aldosterone effect. An increase in TTKG >7 after administration of physiologic dose of fludocortisone suggests mineralocorticoid deficiency; <7 suggests resistance.

Treatment

Hyperkalemia is a medical emergency, requiring prompt discontinuation of potassium-containing fluids and administration of medications that ensure stability of myocardial membrane, intracellular shift of potassium and enhance its elimination (Box 6.4). Continuous ECG moni-

Box 6.4: Treatment of hyperkalemia

- Prompt discontinuation of potassium-containing fluids and medications that lead to hyperkalemia
- Stabilize myocardial cell membrane to prevent cardiac arrhythmia. Use IV 10% calcium gluconate (or calcium chloride), at 0.5–1 mL/kg over 5–10 minutes under cardiac monitoring. Discontinue, if bradycardia develops
- Enhance cellular uptake of potassium
 - Regular insulin and glucose IV: (0.3 U regular insulin/g glucose over 2 hr)
 - Sodium bicarbonate IV: 1–2 mEq/kg body weight over 20–30 minutes
 - β -adrenergic agonists (salbutamol, terbutaline) nebulized or IV
- Total body potassium elimination
 - Sodium polystyrene sulfonate (Kayexalate) oral/per rectal: 1 g/kg (max. 15 g/dose) oral or rectal enema in 20–30% sorbitol
 - Loop or thiazide diuretics (if renal function is maintained)
- Hemodialysis: For severe symptomatic hyperkalemia, particularly in patients with impaired renal functions or tumor lysis
- Primary or secondary hypoaldosteronism: Require maintenance steroids and mineralocorticoid supplements

toring should be performed. Treatment should be individualized based upon the presentation, potassium level, and ECG changes. If the hyperkalemia is severe (potassium >7.0 mEq/L) or the patient is symptomatic with ECG changes, therapy should be initiated promptly with intravenous calcium gluconate, followed by sodium bicarbonate, insulin-glucose infusion and/or nebulized β_2 -agonists. Hemodialysis may be needed in the more refractory patients. Milder elevations (5.5–6.5 mEq/L) are managed with elimination of potassium intake, discontinuation of potassium sparing drugs and treatment of the underlying etiology. Children with primary or secondary hypoaldosteronism require stress-dose steroid supplements and mineralocorticoids.

CALCIUM**Physiology**

Ninety-eight percent of body calcium is found in the skeleton which is in equilibrium with the extracellular concentration of calcium. Approximately 1 to 2% of body calcium exists in the ECF for physiological functions like blood coagulation, cellular communication, exocytosis, endocytosis, muscle contraction and neuromuscular transmission. Calcium affects the intracellular processes, through its calcium-binding regulatory protein, calmodulin.

Most of the filtered calcium is reabsorbed in the proximal tubule (70%), ascending loop of Henle (20%) and the distal tubule and collecting duct (5–10%). Factors that promote calcium reabsorption include parathormone (PTH), calcitonin, vitamin D, thiazide diuretics and

volume depletion. Volume expansion, increased sodium intake and diuretics such as mannitol and frusemide promote calcium excretion.

The intestine serves as a long-term homeostatic mechanism for calcium. Although the major source of calcium is dietary, less than 15% of dietary calcium is absorbed, primarily in the ileum and jejunum by means of active transport and facilitated diffusion. Calcium is controlled primarily by major regulatory hormones, PTH, calcitonin and vitamin D. Additionally thyroid hormones, growth hormone, adrenal and gonadal steroids also have minor influences on calcium metabolism.

Role of the calcium-sensing receptor. The calcium-sensing receptor (CaSR) is a G protein-coupled receptor, which allows the parathyroid chief cells, the thyroidal C cells and the ascending limb of the loop of Henle (renal tubular epithelial cells) to respond to changes in the extracellular calcium concentration. The ability of the CaSR to sense the serum calcium is essential for the appropriate regulation of PTH secretion by the parathyroid glands and for the regulation of passive paracellular calcium absorption in the loop of Henle. Calcitonin secretion and renal tubular calcium reabsorption are directly regulated by the action of calcium ion on its receptor. Ionized calcium acts through calcitonin, to inhibit its release from

bones. Decrease in extracellular calcium concentration, stimulates the CaSR in parathyroid glands, resulting in an increase in PTH secretion (Fig. 6.7). PTH increases distal renal tubular reabsorption of calcium within minutes and stimulates osteoclast activity, with release of calcium from the skeleton within 1–2 hours. More prolonged PTH elevation stimulates 1α -hydroxylase activity in the proximal tubular cells, which leads to 1, 25-dihydroxyvitamin D production. In the kidney, vitamin D and PTH stimulate the activity of the epithelial calcium channel and the calcium-binding protein (i.e. calbindin) to increase active transcellular calcium absorption in the distal convoluted tubule. These mechanisms help to maintain normal levels of serum calcium.

Plasma calcium exists in three different forms: 50% as biologically active ionized form, 45% bound to plasma proteins (mainly albumin) and 5% complexed to phosphate and citrate. In the absence of alkalosis or acidosis, the proportion of albumin-bound calcium remains relatively constant. Metabolic acidosis leads to increased ionized calcium from reduced protein binding and alkalosis has the opposite effect. Plasma calcium is tightly regulated despite its large movements across the gut, bone, kidney and cells in the normal range of 9–11 mg/dL.

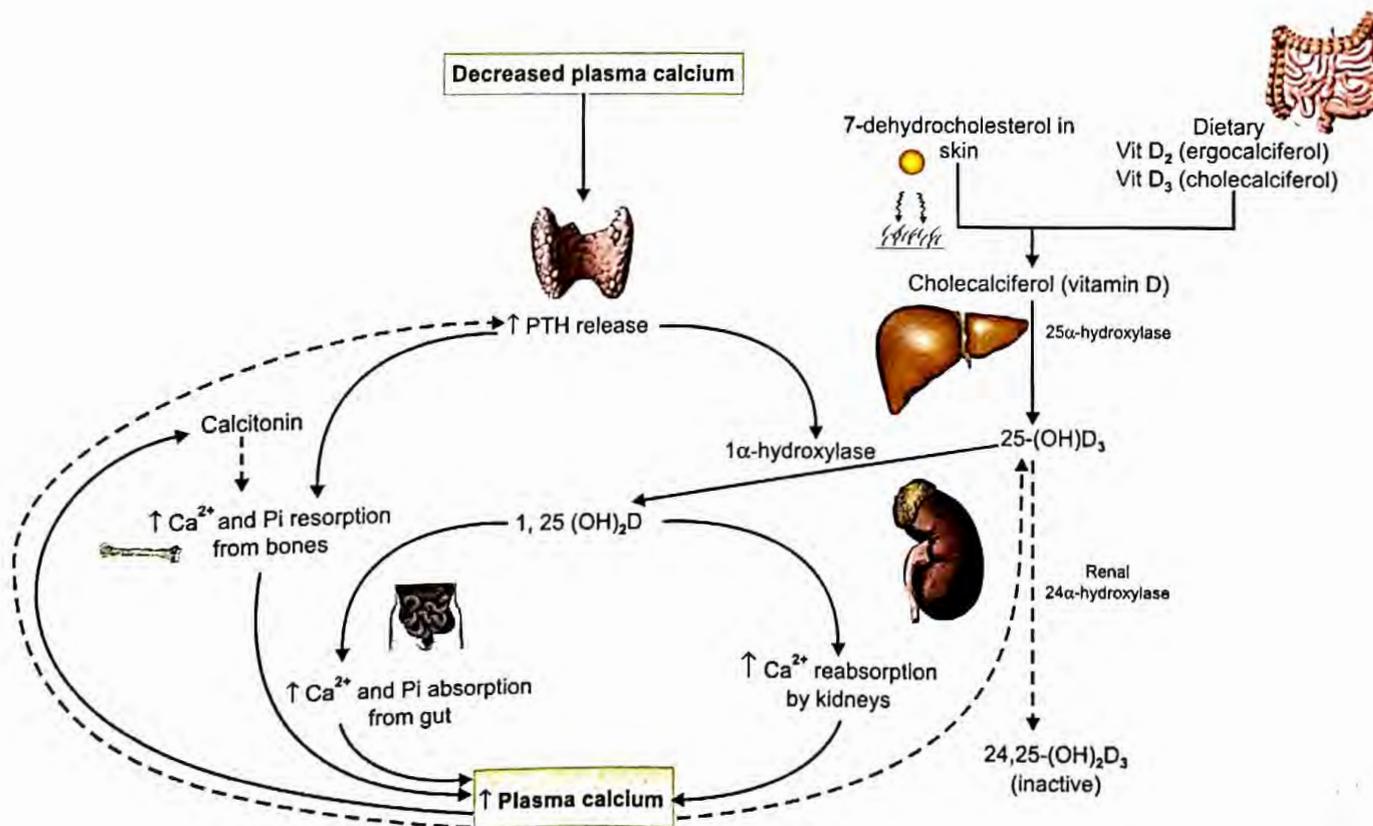


Fig. 6.7: Regulation of plasma calcium. Reduction in ionized calcium results in parathormone secretion, which through direct and indirect actions on the bones, intestine and the kidneys results in positive calcium balance. Calcitonin results in accretion of bone mass. Discontinuous lines indicate inhibitory control

Because calcium binds to albumin and only the unbound (free or ionized) calcium is biologically active, the serum level must be adjusted for abnormal albumin levels. For every 1 g/dL drop in serum albumin below 4 g/dL, measured serum calcium decreases by 0.8 mg/dL. Corrected calcium can be calculated using the following formula:

$$\text{Corrected Ca} = [4 - \text{plasma albumin in g/dL}] \times 0.8 + \text{measured serum calcium}$$

Alternatively, serum free (ionized) calcium levels can be directly measured, negating the need for correction for albumin.

Hypocalcemia

Hypocalcemia is defined as serum calcium less than 8 mg/dL or ionized calcium below 4 mg/dL. The causes and algorithm for investigating the etiology are shown in Table 6.9 and Fig. 6.8. Hypocalcemia manifests as central nervous system irritability and poor muscular contractility. Newborns present with nonspecific symptoms such as lethargy, poor feeding, jitteriness, vomiting, abdominal distension and seizures. Children may develop seizures, twitching, cramps and rarely laryngospasm (Box 6.5). Tetany and signs of nerve irritability may manifest as muscular twitching, carpopedal spasm and stridor. Latent tetany can be diagnosed clinically by clinical maneuvers such as Chvostek sign (twitching of the orbicularis oculi and mouth elicited by tapping the facial nerve anterior to the external auditory meatus) and the Trousseau sign

Table 6.9: Causes of hypocalcemia

Neonatal: Early (within 48–72 hours after birth) or late (3–7 days after birth) neonatal hypocalcemia; prematurity; infant of diabetic mother; neonates fed high phosphate milk

Parathyroid: Aplasia or hypoplasia of parathyroid glands, DiGeorge syndrome, idiopathic; pseudohypoparathyroidism; autoimmune parathyroiditis; activating mutations of calcium sensing receptors

Vitamin D: Deficiency; resistance to vitamin D action; acquired or inherited disorders of vitamin D metabolism

Others: Hypomagnesemia; hyperphosphatemia (excess intake, renal failure); malabsorption syndromes; metabolic alkalosis; hypoproteinemia; acute pancreatitis

Drugs: Prolonged therapy with furosemide, corticosteroid or phenytoin

Box 6.5: Clinical features of hypocalcemia

- Carpopedal and muscle spasms
- Tetany
- Laryngospasm
- Paresthesias
- Seizures
- Irritability, depression, psychosis
- Intracranial hypertension
- Prolonged QTc interval

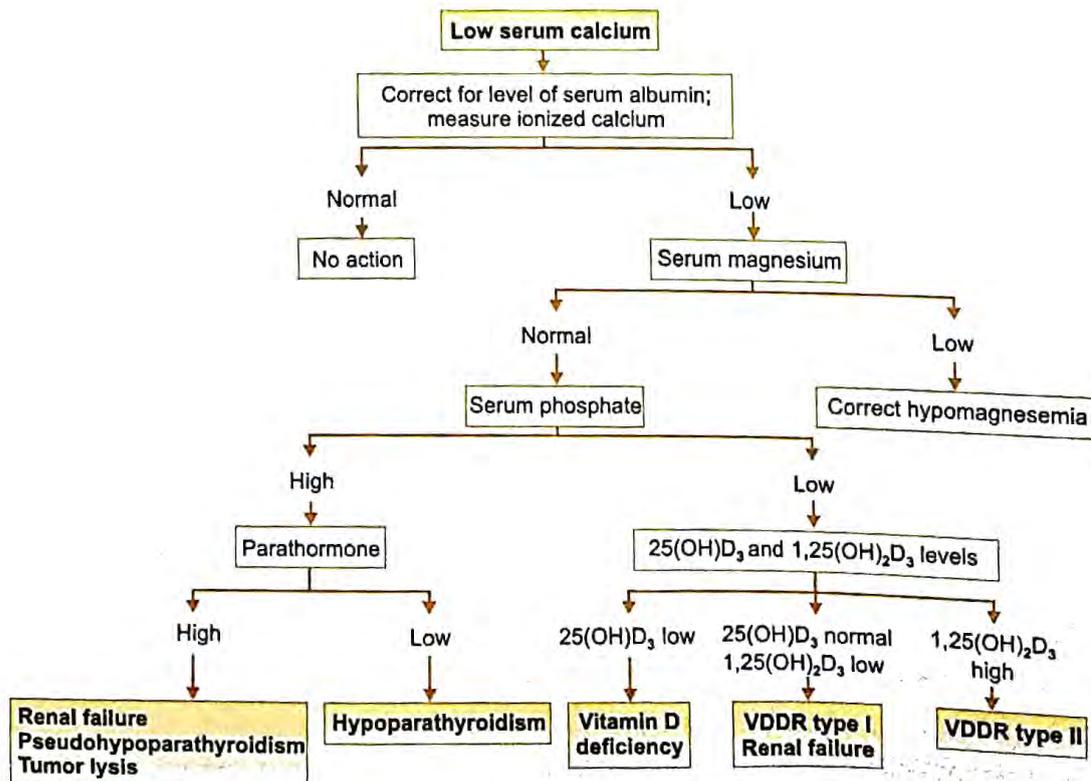


Fig. 6.8: Algorithm for evaluation of hypocalcemia. VDDR vitamin D dependent rickets

(carpopedal spasm elicited by inflating a blood pressure cuff on the arm to a pressure above the systolic pressure for 3 min). ECG shows prolonged corrected QT interval (QTc) to more than 0.45 seconds. Cardiac function may be impaired because of poor muscle contractility. Prolonged hypocalcemia can present with features of rickets.

Management

Tetany, laryngospasm and seizures must be treated immediately with 2 mL/kg of 10% calcium gluconate, administered IV slowly under cardiac monitoring. Calcium gluconate 10% (100 mg/mL) IV solution contains 9.8 mg/mL (0.45 mEq/mL) elemental calcium; calcium chloride 10% (100 mg/mL) contains 27 mg/mL (1.4 mEq/mL). Initially, IV calcium boluses are given every 6 hr. Thereafter, oral calcium supplementation is provided at 40–80 mg/kg/day. Oral calcium therapy is used in asymptomatic patients and as follow-up to intravenous (IV) calcium therapy. Intravenous infusion with calcium-containing solutions can cause severe tissue necrosis; therefore, integrity of the IV site should be ascertained before administering calcium through a peripheral vein. Rapid infusion of calcium-containing solutions through arterial lines can cause arterial spasm and if administered via an umbilical artery catheter, intestinal necrosis. Magnesium administration is necessary to correct any hypomagnesemia because hypocalcemia does not respond until the low magnesium level is corrected. In patients with concurrent acidemia, hypocalcemia should be corrected first. Acidemia increases the ionized calcium levels by displacing calcium from albumin. If acidemia is corrected first, ionized calcium levels decrease.

Calcium carbonate is an oral supplement providing 40% elemental calcium. Therapy with cholecalciferol is used in patients with vitamin D deficiency. Calcitriol, an active metabolic form of vitamin D (i.e. 1,25-dihydroxycholecalciferol), is administered in liver or renal disease.

Hypercalcemia

Hypercalcemia is defined as a serum calcium level greater than 11 mg/dL. Because calcium metabolism normally is tightly controlled by the body, even mild persistent elevations should be investigated. Etiologies of hypercalcemia vary by age and other factors (Table 6.10). Hypercalcemia is often asymptomatic, although it can cause symptoms at levels as low as 12 mg/dL and consistently at values above 15 mg/dL. Such high values are, however, rarely encountered and present as stupor and coma. Neonates may be asymptomatic or may have vomiting, hypotonia, hypertension or seizures. Clinical features in older children are summarized in Box 6.6 and include irritability, malaise, headache, confusion, unsteady gait and proximal muscle weakness. Abdominal pain with paralytic ileus, nausea, vomiting and constipation are often observed. Ectopic calcification can lead to symptoms of pancreatitis,

Table 6.10: Causes of hypercalcemia

Neonates

Neonatal primary hyperparathyroidism, secondary hyperparathyroidism
Familial hypocalciuric hypercalcemia
Excessive supplementation of calcium
William syndrome, hypophosphatasia, idiopathic infantile hypercalcemia

Older children

Hyperparathyroidism (parathyroid adenoma, autosomal dominant hereditary hyperparathyroidism, multiple endocrine neoplasia type 1)

Malignancies: Non-Hodgkin or Hodgkin lymphoma, Ewing sarcoma, neuroblastoma, Langerhans cell histiocytosis, rhabdomyosarcoma

Granulomatous disease: Sarcoidosis, tuberculosis, Wegener disease, berylliosis

Others: Vitamin D or A intoxication; thiazide diuretics; milk-alkali syndrome; dietary phosphate deficiency; subcutaneous fat necrosis; thyrotoxicosis; prolonged immobilization

with epigastric pain and vomiting. Ectopic calcification can manifest as conjunctivitis or band keratopathy. Renal manifestations due to renal stones and nephrocalcinosis can progress to renal failure, and polyuria and polydipsia occur due to nephrogenic diabetes insipidus.

Treatment

The initial treatment of hypercalcemia involves hydration to improve urinary calcium excretion. Rapid lowering of serum calcium can be expected with isotonic sodium chloride solution, because increasing sodium excretion increases calcium excretion. Addition of a loop diuretic inhibits tubular reabsorption of calcium but attention should be paid to other electrolytes (e.g. magnesium, potassium) during saline diuresis. Bisphosphonates serve to block bone resorption and decrease serum calcium within a couple of days but have not been used extensively in children. Pamidronate and etidronate have been used in the treatment of hypercalcemia due to malignancy, immobilization and hyperparathyroidism but may cause mineralization defects. IV calcitonin may also be used with bisphosphonates.

Peritoneal dialysis or hemodialysis can be used in extreme situations, particularly in patients with renal failure. Calcimimetics (cinacalcet hydrochloride) change the

Box 6.6: Clinical features of hypercalcemia

Lethargy, confusion, depression, coma	Bradycardia, systemic hypertension, headache
Hyporeflexia	Nephrocalcinosis, nephrolithiasis
Muscle weakness	Reduced QTc interval
Constipation	
Polyuria	

configuration of the CaSR in a manner that makes it more sensitive to serum calcium. Surgical intervention may be needed in patients with hyper-parathyroidism, particularly with recurrent renal stones or serum calcium levels higher than 12.5 mg/dL. Subtotal parathyroidectomy can be performed, or complete parathyroidectomy can be chosen with reimplantation of a small amount of tissue in the forearm.

MAGNESIUM

Physiology

Magnesium is the third-most abundant intracellular cation predominantly located in muscle and liver cells. Most intracellular magnesium is bound to proteins; only approximately 25% is exchangeable.

Magnesium plays a fundamental role in many functions of the cell, including energy transfer and storage and nerve conduction. Magnesium also plays important role in protein, carbohydrate, and fat metabolism, maintenance of normal cell membrane function and regulation of PTH secretion.

Dietary sources include green leafy vegetables, cereals, nuts and meats. Absorption of magnesium takes place primarily in the small intestine and is inversely related to the amount of magnesium, calcium, phosphate and fat. PTH and glucocorticoids increase magnesium absorption. Absorption is diminished in presence of substances that complex with magnesium (free fatty acids, fiber, phytate, phosphate, oxalate); increased intestinal motility and calcium also decrease magnesium absorption. Vitamin D and PTH enhance absorption. Renal excretion is the principal regulator of magnesium balance. Reabsorption occurs chiefly in the thick ascending loop of Henle (70%) and to a smaller extent in the proximal (15%) and distal (5–10%) tubules. Fractional excretion of magnesium exceeding 4% indicates renal magnesium wasting.

Hypomagnesemia

Hypomagnesemia develops from decreased intake or more commonly increased losses which could be gastrointestinal (diarrhea, vomiting, nasogastric suction) or renal (chronic use of thiazide diuretics, recovery phase of acute tubular necrosis, Gitelman syndrome, familial hypomagnesemia-hypercalciuria-nephrocalcinosis). Symptomatic magnesium depletion (occurs at levels below 1.2 mg/dL) is often associated with multiple biochemical abnormalities, including hypokalemia, hypocalcemia and metabolic acidosis. As a result, hypomagnesemia is sometimes difficult to attribute solely to specific clinical manifestations. Hypomagnesemia often leads to hypocalcemia, possibly by inhibition of PTH activity. Neuromuscular manifestations of hypomagnesemia include muscle weakness, tremors, seizures, paresthesias, tetany, positive Chvostek sign, Trousseau signs and nystagmus. Cardiovascular manifestations include

nonspecific T wave changes, U waves and prolonged QT interval and arrhythmias.

Treatment

Therapy can be oral for patients with mild symptoms or intravenous for patients with severe symptoms or those unable to tolerate oral administration. Severe hypomagnesemia is treated with slow intravenous infusion of magnesium sulfate (50% solution) at a dose of 25–50 mg/kg (2.5–5.0 mg/kg of elemental magnesium). The dose is repeated every 6 hr, for a total of 2–3 doses. Doses need to be reduced in children with renal insufficiency. Oral replacement should be given in the asymptomatic patient, or those requiring long-term replacement, preferably with a sustained-release preparation to avoid diarrhea. Oral magnesium preparation provides 5–7 mEq of magnesium per tablet. Two to four tablets may be sufficient for mild, asymptomatic disease while severe cases require up to six to eight tablets, to be taken daily in divided doses. Patients with renal magnesium wasting may benefit from diuretics with magnesium-sparing properties, such as spironolactone and amiloride.

Hypermagnesemia

Serum magnesium >2.5 mg/dL is uncommon in children and may be seen in the setting of renal insufficiency, prolonged use of magnesium containing antacids or in neonates born to mothers given magnesium sulfate as a treatment for eclampsia. Symptoms of hypermagnesemia are nonspecific at lower levels: nausea, vomiting, flushing, lethargy, weakness and dizziness. At higher levels, deep tendon reflexes are depressed which may progress to coma and respiratory depression. Effects on the heart may result in prolongation of intervals on ECG or manifest as arrhythmias, complete heart block and asystole.

Treatment

In patients with mildly increased levels, the source of magnesium may simply be removed. Intravenous calcium directly antagonizes the cardiac and neuromuscular effects of excess extracellular magnesium. Dialysis may be used for patients with severe hypermagnesemia and renal impairment, or those with serious cardiovascular or neuromuscular symptoms.

ACID-BASE DISORDERS

Regulation of Acid-Base Equilibrium

The body is sensitive to changes in blood pH level, as disturbances in acid-base homeostasis can result in denaturation of proteins and inactivation of enzymes that may be potentially fatal. Strong mechanisms exist to regulate acid-base balance and maintain arterial pH (7.35 to 7.45), pCO₂ (35 to 45 mm Hg) and HCO₃⁻ (20 to 28 mEq/L) within a narrow range.

pH of body fluids is calculated using the Henderson-Hasselbach equation:

$$\text{pH} = \text{pK} + \log \left(\frac{\text{HCO}_3^-}{\text{pCO}_2} \right)$$

where pK is the dissociation constant of the acid. Alteration in either serum bicarbonate concentration or the partial pressure of carbon dioxide causes acidosis (pH <7.35) or alkalosis (pH >7.45). Metabolic activity results in production of two types of acids, carbonic acid (a volatile acid, derived from carbon dioxide) and nonvolatile acids (including sulfuric acid, organic acids, uric acid and inorganic phosphates). Accumulation of H⁺ ions of nonvolatile acids due to excess production or inadequate buffering, failure to excrete H⁺ or loss of bicarbonate results in metabolic acidosis. If the reverse occurs, it results in metabolic alkalosis. The principle mechanism for carbon dioxide handling is by the lungs. Hyperventilation results in CO₂ washout and drop in arterial pCO₂ (respiratory alkalosis), hypoventilation has the opposite effect (respiratory acidosis). When only one primary acid-base abnormality occurs and its compensatory mechanisms are activated, the disorder is classified as simple acid-base disorder. A simple algorithm for defining simple acid-base disorders is shown in Fig. 6.9. When a combination

of disturbances occurs, the disorder is classified as a mixed acid-base disorder. The latter are suspected when the compensation in a given patient differs from the predicted values in Table 6.11.

In order to maintain body homeostasis, changes in pH are resisted by a complex system of intracellular and extracellular buffers that reversibly bind hydrogen ions and resist change in pH. In metabolic disorders, the extracellular buffers rapidly titrate the addition of strong acids or bases. Intracellular buffers chiefly accomplish the buffering of respiratory disorders. Secondary respiratory compensations to metabolic acid-base disorders occur within minutes and is completed by 12 to 24 hours. In contrast, secondary metabolic compensation of respiratory disorders begins more slowly and takes 2 to 5 days for completion. The compensatory mechanisms do not return the pH to normal until the underlying disease process has been appropriately treated. Extracellular buffers include bicarbonate and ammonia, whereas proteins and phosphate act as intracellular buffers. Hemoglobin is a powerful intracellular buffer because its negatively charged histidine moieties accept H⁺, normalizing the pH. Other proteins also have negative charges that can accept H⁺.

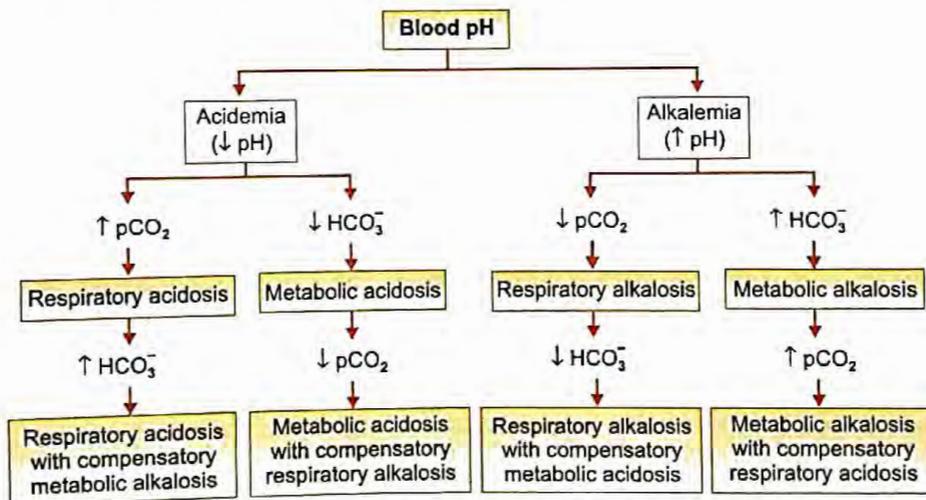
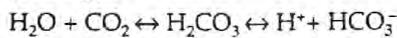


Fig. 6.9: Algorithm for simple acid-base disorders

Table 6.11: Compensation for primary acid-base disorders

Disorder	Primary event	Compensation	Expected Compensation
Metabolic acidosis	↓ [HCO ₃ ⁻]	↓ pCO ₂	pCO ₂ ↓ by 1–1.5 mm Hg for 1 mEq/L ↓ [HCO ₃ ⁻]
Metabolic alkalosis	↑ [HCO ₃ ⁻]	↑ pCO ₂	pCO ₂ ↑ by 0.5–1 mm Hg for 1 mEq/L ↑ [HCO ₃ ⁻]
Respiratory acidosis			
Acute (<24 hours)	↑ pCO ₂	↑ [HCO ₃ ⁻]	[HCO ₃ ⁻] ↑ by 1 mEq/L for 10 mm Hg ↑ pCO ₂
Chronic (3–5 days)	↑ pCO ₂	↑↑ [HCO ₃ ⁻]	[HCO ₃ ⁻] ↑ by 4 mEq/L for 10 mm Hg ↑ pCO ₂
Respiratory alkalosis			
Acute (<24 hours)	↓ pCO ₂	↓ [HCO ₃ ⁻]	[HCO ₃ ⁻] ↓ by 1–3 mEq/L for 10 mm Hg ↓ pCO ₂
Chronic (3–5 days)	↓ pCO ₂	↓↓ [HCO ₃ ⁻]	[HCO ₃ ⁻] ↓ by 2–5 mEq/L for 10 mm Hg ↓ pCO ₂

Bicarbonate-carbonic acid buffer in the extracellular fluid, is the key buffer as carbon dioxide (CO_2) can be shifted through carbonic acid (H_2CO_3) to hydrogen ions and bicarbonate (HCO_3^-):



Acid-base imbalances that overcome the buffer system can be compensated in the short-term by altering the rate of ventilation, which alters the pCO_2 . While this is a relatively weak buffer, it accounts for 55% of the buffering capacity because of its sheer abundance. When H^+ concentration increases the above reaction shifts to the left, more CO_2 is generated and exhaled from the lungs, moderating the change in pH.

Renal Regulation of Acid-Base Balance

The kidneys are slower to compensate, but renal physiology has several powerful mechanisms to control pH by the excretion of excess acid or base. Kidneys are the principal regulators of bicarbonate mainly by two methods: (i) resorption of HCO_3^- mostly in proximal convoluted tubules and (ii) excretion of H^+ and, therefore, generation of HCO_3^- , primarily by the distal tubules and collecting ducts. In response to acidosis, tubular cells reabsorb more bicarbonate from the tubular fluid, collecting duct cells secrete more hydrogen and generate more bicarbonate, and ammoniogenesis leads to increased formation of renal ammonia (Fig. 6.10). In responses to alkalosis, the kidneys excrete more bicarbonate by decreasing hydrogen ion secretion from the tubular epithelial cells, and lowering rates of glutamine metabolism and ammonia excretion.

Bicarbonate-carbonic acid in the kidney tubules: H^+ ions secreted from the tubular cells combines with luminal HCO_3^- to form water and CO_2 . The CO_2 enters the tubular cell and combines with water, in presence of carbonic

anhydrase, to regenerate HCO_3^- that is reabsorbed into the bloodstream, thus conserving the filtered HCO_3^- .

Monohydrogen phosphate-dihydrogen phosphate buffer: This luminal buffer system buffers H^+ ions secreted from the tubular cells, as follows:

$\text{H}^+ + \text{Na}_2\text{HPO}_4 \rightarrow \text{NaH}_2\text{PO}_4 + \text{Na}^+$. The weakly acidic sodium dihydrogen phosphate is excreted in the urine.

Ammonia-ammonium buffer: In tubular cells, glutamine is converted to glutamic acid and ammonia, the reaction catalyzed by glutaminase. Ammonia is secreted in the lumen and combines with H^+ to form ammonium ions, which are excreted in urine.

Sodium-hydrogen exchange in the distal tubule: The distal tubular cells actively reabsorb Na^+ ; to maintain electro-neutrality, H^+ ions are exchanged. The latter combine with either monohydrogen phosphate or ammonia and are excreted.

Anion Gap

To achieve electrochemical balance, the number of negatively charged ions (anions) should equal the positively charged ions (cations). Measured plasma anions are chloride and bicarbonate, and the unmeasured anions include phosphates, sulfates and proteins (e.g. albumin). Under typical conditions, unmeasured anions exceed unmeasured cations; this is referred to as the anion gap and can be represented by the following formula:

$$\text{Anion gap} = (\text{Na}^+) - (\text{Cl}^- + \text{HCO}_3^-)$$

The anion gap is normally 8 to 12 mEq/L. When a strong acid is added to or produced in the body, hydrogen ions are neutralized by bicarbonate, resulting in a fall in bicarbonate. These acids include inorganic (e.g. phosphate or sulfate), organic (e.g. ketoacids or lactate) or exogenous (e.g. salicylate) acids incompletely neutralized by bicar-

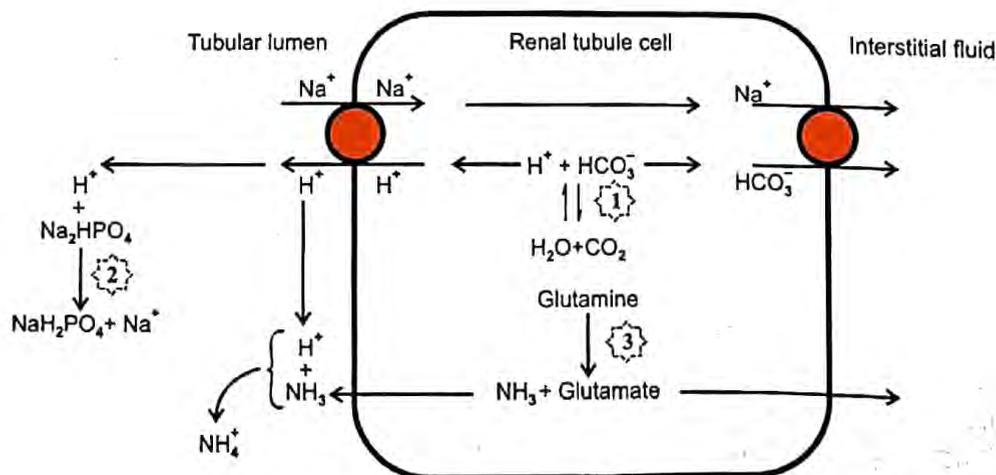


Fig. 6.10: Renal regulation of acid-base disorders. 1 = bicarbonate-carbonic acid buffer; 2 = monohydrogen phosphate-dihydrogen phosphate buffer; 3 = ammonia-ammonium buffer

bonate. The accompanying unmeasured anion results in increased anion gap proportional to the fall in bicarbonate. In contrast, when the bicarbonate is lost from the body, no new anion is generated; therefore, there is a reciprocal increase in chloride ions (proportional to the fall in bicarbonate) resulting in normal anion gap. Hypoalbuminemia is the most common cause of a low anion gap. Albumin represents about half of the total unmeasured anion pool; for every decrease of 1 g/dL of plasma albumin, the plasma anion gap decreases by 2.5 mEq/L.

Metabolic Acidosis

Metabolic acidosis is an acid-base disorder characterized by a decrease in serum pH that results from either a loss in plasma bicarbonate concentration or an increase in hydrogen ion concentration (Table 6.12). Primary metabolic acidosis is characterized by an arterial pH of less than 7.35 due to a decrease in plasma bicarbonate in the absence of an elevated PaCO₂. If the measured PaCO₂ is higher than the expected PaCO₂, a concomitant respiratory acidosis is also present (caused by a depressed mental state, airway obstruction or fatigue). Acutely, medullary chemoreceptors compensate for metabolic acidosis through increase in alveolar ventilation, which results in tachypnea and hyperpnea that washes off CO₂ and corrects pH.

Calculation of plasma anion gap helps to classify metabolic acidosis into those with elevated anion gap (i.e. >12 mEq/L as in increased acid production or decreased losses) and those with normal anion gap (i.e. 8–12 mEq/L

as in gastrointestinal or renal loss of bicarbonate or when hydrogen ions cannot be secreted because of renal failure) (Table 6.12).

Another useful tool in the evaluation of metabolic acidosis with normal anion gap is urinary anion gap.

$$\text{Urinary anion gap} = \text{urinary } [\text{Na}^+] + [\text{K}^+] - [\text{Cl}^-]$$

Urinary anion gap is negative in patients with diarrhea regardless of urinary pH, and urinary anion gap is positive in renal tubular acidosis. An elevated osmolal gap (>20 mOsm/kg) with metabolic acidosis suggests the presence of osmotically active agents such as methanol, ethylene glycol or ethanol.

Clinical Features

Initially, patients with a metabolic acidosis develop a compensatory tachypnea and hyperpnea, which may progress if the acidemia is severe, and the child can present with significant work of breathing and distress (Kussmaul breathing). An increase in H⁺ concentration results in pulmonary vasoconstriction, which raises pulmonary artery pressure and pulmonary vascular resistance. Tachycardia is the most common cardiovascular effect seen with mild metabolic acidosis. Cerebral vasodilation occurs as a result of metabolic acidosis and may contribute to an increase in intracranial pressure. Acidosis shifts the oxygen-hemoglobin dissociation curve to the right, decreasing hemoglobin's affinity for oxygen. During metabolic acidosis, excess hydrogen ions move toward the intracellular compartment and potassium moves out of the cell into the extracellular space. Untreated severe metabolic acidosis may be associated with life-threatening arrhythmias, myocardial depression, respiratory muscle fatigue, seizures, shock and multiorgan failure.

Treatment

It is important to identify the cause of metabolic acidosis as most cases resolve with correction of the underlying disorder. The role of alkali therapy in acute metabolic acidosis is limited. It is definitely indicated in some situations, e.g. salicylate poisoning, inborn errors of metabolism, or in those with pH below or equal to 7.0 or [HCO₃⁻] less than 5 mEq/L, as severe acidosis can produce myocardial dysfunction. The amount of bicarbonate required is

$$\text{Body weight (kg)} \times \text{base deficit} \times 0.3.$$

One mL of 7.5% sodium bicarbonate provides 0.9 mEq bicarbonate. The recommendation is to replace only half of the total bicarbonate deficit during the first few hours of therapy. This amount is given as continuous infusion over two hours. Rapid correction of acidosis with sodium bicarbonate can lead to extracellular volume expansion, exacerbating pulmonary edema in patients with cardiac failure. In the latter, the rate of infusion should be slower. If hypernatremia is a concern, sodium bicarbonate may be used as part of the maintenance intravenous solution.

Table 6.12: Causes of metabolic acidosis

Normal anion gap (hyperchloremic acidosis)

Renal loss of bicarbonate

Proximal (type 2) renal tubular acidosis, carbonic anhydrase inhibitors (e.g. acetazolamide), tubular damage due to drugs or toxins

Gastrointestinal bicarbonate loss

Diarrhea, ureteral sigmoidostomy, rectourethral fistula, fistula or drainage of small bowel or pancreas

Decreased renal hydrogen ion excretion

Renal tubular acidosis type 1 and type 4 (aldosterone deficiency)

Potassium sparing diuretics

Increased hydrogen chloride production

Parenteral alimentation, increased catabolism of lysine and arginine

Ammonium chloride ingestion

Elevated anion gap

Increased acid production/accumulation: Sepsis, shock, poisonings (ethanol, methanol, ethylene glycol); inborn errors of metabolism

Ketoacidosis: Diabetic ketoacidosis, starvation

Exogenous acids: Salicylates, iron, isoniazid, paraldehyde

Failure of acid excretion: Acute or chronic kidney disease

During correction of acute metabolic acidosis, the effect of sodium bicarbonate in lowering serum potassium and ionized calcium concentrations must also be considered and monitored. Since bicarbonate therapy generates large amount of CO_2 , ventilation should increase proportionately otherwise this might worsen intracellular acidosis. The inability to compensate may be especially important in patients with diabetic ketoacidosis who are at risk for cerebral edema. In diabetic ketoacidosis, insulin therapy generally corrects the acidosis.

In newborns, frequent administration of hypertonic solutions such as sodium bicarbonate have led to intracranial hemorrhage resulting from hyperosmolality and resultant fluid shifts from the intracellular space. Children with inherited metabolic abnormalities, poisoning, or renal failure may require hemodialysis.

Mild to moderate acidosis in renal failure or renal tubular acidosis improves on oral alkali therapy, the dose being 0.5 to 2 mEq/kg/day of bicarbonate in 3–4 divided doses. In cases of acidosis due to volume depletion, the volume deficit should be corrected.

Metabolic Alkalosis

Metabolic alkalosis ($\text{pH} > 7.45$) is an acid–base disturbance caused by elevation in the plasma bicarbonate (HCO_3^-) concentration in the extracellular fluid that results from a net loss of acid, net gain of base or loss of fluid with more chloride than bicarbonate. There are two types of metabolic alkalosis classified based on the amount of chloride in the urine, i.e. chloride-responsive or chloride resistant (Table 6.13). Chloride-responsive metabolic alkalosis shows urine chloride levels of less than 10 mEq/L and is characterized by decreased ECF volume and low serum chloride levels, such as occurs with vomiting or use of diuretics. This type responds to administration of chloride salt (usually as normal saline). Chloride-resistant metabolic alkalosis is characterized by urine chloride levels of more than 20 mEq/L. Primary aldosteronism is an example of chloride-resistant metabolic alkalosis and this type resists administration of therapy with chloride.

The body compensates for metabolic alkalosis through buffering of excess bicarbonate and hypoventilation. Intracellular buffering occurs through sodium-hydrogen and potassium-hydrogen ion exchange, with eventual formation of CO_2 and water from HCO_3^- . Within several hours, elevated levels of HCO_3^- and metabolic alkalosis inhibit the respiratory center, resulting in hypoventilation and increased pCO_2 levels. This mechanism produces a rise in pCO_2 of as much as 0.7 to 1 mm Hg for each 1 mEq/L increase in HCO_3^- .

Clinical Features

Signs and symptoms observed with metabolic alkalosis usually relate to the specific disease process that caused the acid–base disorder. Increased neuromuscular excitability (e.g. from hypocalcemia), sometimes causes tetany or

Table 6.13: Causes of metabolic alkalosis

Chloride responsive

Gastric fluid loss (e.g. vomiting, nasogastric drainage)
Volume contraction (e.g. loop or thiazide diuretics, metolazone)
Congenital chloride diarrhea, villous adenoma
Cystic fibrosis
Post-hypercapnia syndrome (mechanically ventilated patients with chronic lung disease)

Chloride resistant

Primary aldosteronism (adenoma, hyperplasia)
Renovascular hypertension, renin secreting tumor
Barter and Gitelman syndromes
Apparent mineralocorticoid excess
Glucocorticoid remediable aldosteronism
Congenital adrenal hyperplasia (11β - and 17α -hydroxylase deficiency)
Liddle syndrome
Excess bicarbonate ingestion

seizures. Generalized weakness may be noted, if the patient also has hypokalemia. Patients who develop metabolic alkalosis from vomiting can have symptoms related to severe volume contraction, with signs of dehydration. Although diarrhea typically produces a hyperchloremic metabolic acidosis, diarrheal stools may rarely contain significant amounts of chloride, as in the case of congenital chloride diarrhea. Children with this condition present at birth with watery diarrhea, metabolic alkalosis, and hypovolemia. Weight gain and hypertension may accompany metabolic alkalosis that results from a hypermineralocorticoid state.

Treatment

The overall prognosis in patients with metabolic alkalosis depends on the underlying etiology. Prognosis is good with prompt treatment and avoidance of hypoxemia. Mild or moderate metabolic alkalosis or alkalemia rarely requires correction. For severe metabolic alkalosis, therapy should address the underlying disease state, in addition to moderating the alkalemia. The initial target pH and bicarbonate level in correcting severe alkalemia are approximately 7.55 and 40 mEq/L, respectively.

Therapy with diuretics (e.g. furosemide, thiazides) should be discontinued. Chloride-responsive metabolic alkalosis responds to volume resuscitation and chloride repletion. Chloride-resistant metabolic alkalosis may be more difficult to control. As with correction of any electrolyte or acid–base imbalance, the goal is to prevent life-threatening complications with the least amount of correction.

For persistent severe metabolic alkalosis in the setting of fluid overload, wherein saline cannot be given, cautious use of HCl or ammonium chloride may be considered. Acetazolamide may help patients with chloride-resistant metabolic alkalosis provided GFR is adequate. Correction of metabolic alkalosis in patients with renal failure may require hemodialysis or continuous renal replacement

therapy with a dialysate that contains high levels of chloride and low HCO_3^- .

Respiratory Acidosis

Respiratory acidosis occurs when the alveolar ventilation falls or when carbon dioxide production is increased, so that the arterial partial pressure of carbon dioxide (PaCO_2) is elevated above the normal range (>45 mm Hg) leading to a blood pH lower than 7.35 (Table 6.14). pCO_2 is directly proportional to carbon dioxide production and inversely proportional to alveolar ventilation. The kidneys compensate for respiratory acidosis by increasing HCO_3^- reabsorption, a process that begins in 6–12 hours but takes 3–5 days for maximal compensation.

The kidneys increase excretion of hydrogen ions (predominantly in the form of ammonium) that increases the plasma bicarbonate concentration by approximately 3.5–4 mEq/L for every 10 mm Hg increase in CO_2 .

Clinical Features

Patients with acute respiratory acidosis frequently demonstrate air-hunger with retractions and use of accessory muscles. Neurologic findings include anxiety, disorientation, confusion and lethargy followed by tremors, somnolence or coma at higher pCO_2 . Hypercapnic neurologic changes are reversible with no residual effect. Cardiovascular findings include tachycardia, bounding arterial pulses and in severe cases hypotension.

Treatment

The goal of therapy is to correct or compensate for the underlying pathologic process. Failure to consider a mixed acidosis can lead to missed therapies and diagnosis. Assisted ventilation is required in many cases.

Respiratory Alkalosis

Respiratory alkalosis occurs in the setting of a primary decrease in pCO_2 as a consequence of hyperventilation

Table 6.14: Causes of respiratory acidosis

Decrease in alveolar ventilation

Depressed central respiratory drive
Acute paralysis of the respiratory muscles
Acute or chronic parenchymal lung and airway diseases
Progressive neuromuscular disease
Worsening scoliosis (restrictive lung disease)

High carbon dioxide production and inability to increase minute ventilation

Extensive burn injury
Malignant hyperthermia
Fever

(Table 6.15). In a child, this may result from high fever, sepsis, mild bronchial asthma, central nervous system disorders or overventilation of an intubated child in intensive care setting. In acute respiratory alkalosis, titration is done by intracellular buffers. Renal compensation begins within several hours and takes several days for the maximal response.

Clinical Features

Patients primarily have clinical manifestations of the underlying disorder. Alkalosis, by promoting the binding of calcium to albumin, can reduce the fraction of ionized calcium in blood which may manifest as feeling of tingling, paresthesias, dizziness, palpitations, tetany and seizures. Therapy is directed towards the causal process.

Table 6.15: Causes of respiratory alkalosis

Hypoxia and hypoxemia

High altitude or low fraction of inspired oxygen, anemia, hypotension or lung disease

Pulmonary disorders

Pulmonary edema, embolism, airway obstruction, pneumonia, interstitial lung disease

Mechanical ventilation (ventilatory rate or tidal volume too high)

Extrapulmonary disorders (severe respiratory alkalosis)

Stress, neurologic disease (stroke, infection, trauma, tumor)
Medications: Catecholamines, progesterone, methylxanthines, salicylates, doxapram, nicotine
Hyperthermia, hepatic encephalopathy, sepsis, recovery from metabolic acidosis

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Nutrition

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FOOD

Our food is made up of essential, natural substances called nutrients. Human body needs over 50 nutrients on a daily basis to stay healthy. Nutrients are categorized as macronutrients including carbohydrates, proteins, fat; and micronutrients such as vitamins, minerals and trace elements.

Macronutrients are needed in large quantities and are referred to as the energy yielding components of diet, i.e they breakdown into simpler compounds to provide energy.

Micronutrients are needed in small quantities, but are very essential to keep us healthy. They do not yield energy but have a protective role and are needed to enhance immunity. Micronutrients are discussed in detail in Chapter 8.

All nutrients work together to maintain overall health. Each of these nutrients is required in a specific amount by the body. The deficiency and excess of nutrients can be harmful, leading to a variety of complex diseases.

Carbohydrates, proteins and fats comprise macronutrients and contribute to energy intake by humans as shown in Table 7.1.

Carbohydrates

Carbohydrates are the main source of energy in the Indian diet. Carbohydrates contribute to taste, texture and bulk to the diet. They are essential for digestion and assimilation of other foods. Lack of carbohydrates (less than 30%) in the diet may produce ketosis, loss of weight and breakdown of proteins.

Carbohydrates are divided into simple carbohydrates

Table 7.1: Energy content of macronutrients

Nutrient	Energy (kcal) per gram
Carbohydrate	4 kcal
Protein	4 kcal
Fat	9 kcal
Fiber and water	0 kcal

(monosaccharides and disaccharides such as glucose and fructose found in fruits, vegetables and honey, sucrose in sugar and lactose in milk) and complex carbohydrates (oligosaccharides and polysaccharides such as starch in cereals, millets, pulses and root vegetables).

The main source of energy in the body is glucose derived from starch and other sugars present in the diet. Glucose is used as a fuel by the cells and is converted to glycogen by liver and muscles. Excess carbohydrates are converted to fat.

Fiber: Fiber determines the quality of carbohydrates. Dietary fibers are also called "non-digestible or unavailable carbohydrates" as they are not digested by the enzymes in the gut. They have very little nutritional value but are essential for the normal functioning of the gut, elimination of waste, bile acid binding capacity and for maintaining the growth of normal intestinal microflora.

Polysaccharides such as cellulose, hemicelluloses, pectin, gums, mucilage and lignin are some examples of fiber, mainly provided by cereals, millets, vegetables and fruits.

Requirements: As much as 55–60% of total energy intake should come from carbohydrates.

Proteins

Protein is the second most abundant substance in the body after water. They are required for the growth and synthesis of tissues in the body; formation of digestive juices, hormones, plasma proteins enzymes, vitamins, hemoglobin; as buffers to maintain acid–base equilibrium in the body; and as an alternate source of energy for the body. Proteins are made of amino acids. Amino acids that can be synthesized in the body are called non-essential amino acids, while essential amino acids require to be supplied in the diet.

Essential amino acids include leucine, isoleucine, lysine, methionine, phenylalanine, threonine, tryptophan and valine. Histidine and arginine are essential during infancy because the rate of their synthesis is inadequate for sustaining growth.

Protein quality: Food proteins differ in their nutritional quality depending on their amino acid profile and digestibility. Cereal grains are deficient in lysine, threonine or tryptophan, whereas pulses are rich in lysine but are limited in sulfur-containing amino acids, mainly methionine. When cereals are taken in combination with the pulses, the deficiency in one is made good by an excess in other; thereby improving the overall quality of proteins in food.

Egg protein has the highest nutritive value and is therefore taken as the reference protein, and the value of others is expressed as relative to the egg (taken as 100%).

Generally, animal proteins have a higher biological value than the plant proteins. The nutritive value of a mixture of two proteins may be higher than the mean of the two because of mutual complementary effects.

Requirements: Nearly 10–12% of the total energy should be provided from protein sources. An intake of 8% proteins may be sufficient for food having a higher content of animal proteins or high value proteins in the diet.

Fats

Fats function as structural elements of the cell membranes, act as vehicle for absorption and transport of fat-soluble vitamins (A, D, E and K) and are precursors of prostaglandins and hormones. Fats are made of fatty acids and dietary fats are mixture of largely triglycerides, small proportion of phospholipids and cholesterol.

Fatty acids are classified into 3 groups: Saturated fatty acids (SFAs), monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs) (Fig. 7.1). Humans can synthesize SFAs and MUFAs besides obtaining them from diet, but PUFAs cannot be synthesized in the body and have to be provided through diet.

- Saturated fatty acids (SFA) consisting of straight, even numbered chains of 4–24 carbon atoms. They are classified as short (C<10), medium (C12:0 and C12:0) or long (C16:0–C24:0) chain fatty acids based on carbon chain length. The degree of saturation determines whether the fat is solid or liquid at room temperature—more the saturation, harder and more solid is the fat.

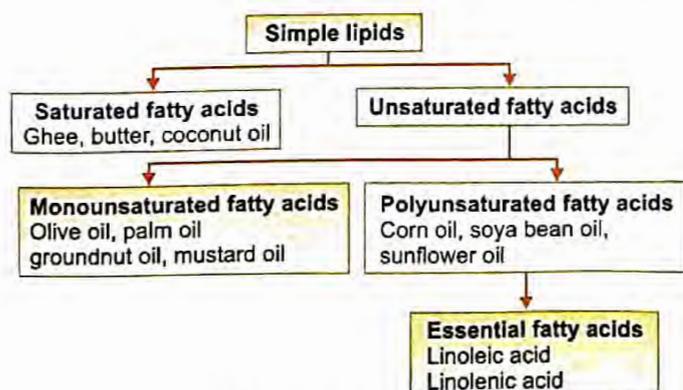


Fig. 7.1: Classification of fats

- Unsaturated fatty acids (MUFAs and PUFAs) have double bonds in *cis* or *trans* configuration. Double bonds in *cis* configuration are nutritionally good, while in *trans* configuration (*trans* fatty acids) are bad for health. Thus, *trans* fats are a type of unsaturated fats. These occur naturally in small quantity. Artificial *trans* fats are created when hydrogen is passed through liquid vegetable oils to make them more solid ('vanaspati'). Such fats are used in household cooking as well as in snack foods (packaged baked food, samosas, mathris, kachoris, pizzas, burgers, French fries, etc.). *Trans* fats increase the risk of coronary artery disease due, in part, by increasing levels of low density lipoproteins (LDL) and lowering high density lipoprotein (HDL). Hence, *trans* fat intake is best avoided.
- PUFAs are grouped into two series, namely, linoleic acid (LA, C18:2n-6) and alpha-linolenic acid (ALA, C18:3n-3) depending on the position of double bond. LA and ALA are long chain dietary essential fatty acids. LA gets metabolized to arachidonic acid (AA), while ALA to eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA).

Medium chain triglycerides (MCT) are an immediate source of energy as they are transported directly from the small intestine to liver by portal vein and burned immediately to produce energy. MCT improves endurance performance, promotes fat burning, spares muscle glycogen, increases metabolic rate, maintains muscle mass and lowers blood cholesterol level. Supplementation with MCT is used in the dietary management of cystic fibrosis, obesity, pancreatic insufficiency, AIDS, epilepsy, gallstones, high blood cholesterol levels, fat malabsorption, intestinal lymphangiectasia, and are used as energy supplements in athletes. Sources of MCTs are coconut oil, palm kernel oil, butter (15% of MCT). Prolonged use of MCTs alone leads to essential fatty acid (EFA) deficiency.

Long chain triglycerides (LCT) provide essential fatty acids (EFAs) and require carnitine to produce energy. MCT and LCT should be ideally used in combination to prevent EFA deficiency.

Essential fatty acids (EFAs) cannot be synthesized in the body and have to be supplied through dietary fat. EPA and DHA are important components of gray matter of the brain and improve intellectual performance. Deficiency of EFA leads to cessation of growth, alopecia, diarrhea, impaired wound healing, decreased calcium absorption, decreased calcium deposits in bones and decreased bone strength. It is recommended that ALA (n-3 fatty acid) content of the diet should be about 0.5% of the total calories or 1.0–1.5 g/day.

Cholesterol is the component of cell membrane, helps the body produce steroid hormones and bile acids.

Requirements: Fats are major source of energy in diet. In normally growing children, about 25–30% of energy intake

should be derived from fat which includes 10–15% invisible fat. However, in malnourished children, up to 45% of calories can be safely provided from fat.

Invisible fat: Fat present naturally in our food but cannot be seen and separated from food such as milk and milk products, egg and meat, nuts contain good amount, while cereals, pulses, vegetables and fruits contain negligible amount.

Visible fat: Fat which is used for cooking or added while cooking such as edible vegetable oils and ghee.

To provide a healthy balance of visible fat, daily diet should provide <7% saturated fat, 10% polyunsaturated fat and rest 13% should be derived from monounsaturated fats. A minimum of 3% energy should be derived from linoleic acid and 0.3% from linolenic acid.

There is no single oil/fat with the ideal composition; it is recommended to use blend of two or more vegetable oils.

7 Energy

Energy needs of children are computed keeping in mind the increase in body size, high metabolic rate that regulates body temperature and maintains high level of activities, and marked developmental changes in organ function and composition.

Energy requirements vary through childhood because of variations in growth rate and physical activity. Although growth rate slows in toddlers, their activity levels are high, and appetite and food intake tends to be erratic. In older children, growth is more constant but energy needs vary within and between individuals. During adolescence, energy needs increase due to rapid growth and development.

There are three critical periods in early life of a young child with regards to energy requirements: Around 6 months when complementary feeding is initiated, between 1 and 2 years when physical activity is increased and between 10 and 12 years for girls and 15–18 years for boys when puberty is attained.

Calculation of energy requirement should account for the level of physical activity and the energy required allowing for optimal growth. For children with normal

Table 7.2: Simple calculation of daily energy requirements for children

At 10 kg body weight	1000 kcal
Weight >10 kg–20 kg	1000 kcal + 50 kcal for each kg above 10 kg, e.g. for a 15 kg child, requirement will be 1250 kcal
Weight >20 kg	1500 kcal + 20 kcal for each kg above 10 kg, e.g. for a 30 kg child, requirement will be approximately 1700 kcal

body weights, the energy requirements are calculated roughly as shown in Table 7.2.

DIETARY STANDARDS

Infants and children have higher requirements of nutrients than adults. While adults need nutrients for maintaining constant body weight and functions, infants and children require nutrients not only for maintenance but also for promoting and supporting their rapid rate of growth and development.

A range of acceptable or safe intake levels have been established for almost all the important nutrients at different ages, which are recognized as recommended dietary allowances (RDA).

Recommended Dietary Allowances (RDAs)

RDAs are nutrient specific and technical in nature. These are formulated based on the current knowledge of nutritional requirements of different age and sex groups depending on anthropometry (weight, height), body composition, climate and environment, physical activity, physiological status and body demands. All these factors lead to differences in food intake and nutrient requirements.

Summary of Recommended Dietary Allowances (RDA) for energy and protein revised in 2010 is shown in Table 7.3.

Nutritive Value of Some Common Foods

Table 7.4 portrays energy, protein, carbohydrates and fat composition of common Indian food items and portions.

Table 7.3: Daily energy and protein requirements at different ages

Group	Age	Energy (kcal/d)	Protein (g/d)
Infants	0–6 months	90 kcal/kg/d	1.2 g/kg/d
	6–12 months	80 kcal/kg/d	1.7 g/kg/d
Children	1–3 years	1050	17
	4–6 years	1350	20
	7–9 years	1700	30
Boys	10–12 years	2200	40
Girls	10–12 years	2000	40
Boys	13–15 years	2750	54
Girls	13–15 years	2300	52
Boys	16–17 years	3000	62
Girls	16–17 years	2450	56
Adult male	Sedentary	2300	60
Adult female	Sedentary	1900	55

Adapted from Nutrient Requirements and Recommended Dietary Allowances for Indians, ICMR 2010 [Values have been rounded off at places]

Table 7.4: Approximate nutritive value of common food items

Food items	Raw edible amount (g or mL)	Household measures (cooked) or portion	Energy (kcal)	Protein (g)	Carbohydrate (g)	Fat (g)
Milk and milk products						
Human milk	100 mL	-	65	1.1	7.4	3.4
Milk (cow)	100 mL	½ glass	73	3.2	4.9	4.4
Milk (buffalo)	100 mL	½ glass	107	3.6	8.3	6.5
Paneer (home made—cow milk)	30 g	1 small piece	76.5	5.5	3.5	4.5
Curd (homemade—cow milk)	100 mL	1 small cup	62	3.2	3.2	4.0
Meat and poultry						
Chicken, thigh, skinless	100 g	1 serving	200	18.0	-	14.0
Meat (flesh)	100 g	4 pieces	135	20.0	-	6.0
Fish (rohu)	100 g	2–3 pieces	100	20.0	-	2.4
Egg whole (hen)	45 g	1 No.	74	5.0	-	6.0
Egg white (from 1 egg)	25 g	-	11	4.0	-	0.01
Egg yolk (from 1 egg)	20 g	-	60	3.2	-	5.2
Cereals and millets						
Chapati	25 g wheat flour	1 medium size	80	2.5	16.0	0.3
Bread (white)	30 g maida	1 big slice	72	2.5	14.5	0.5
Wheat daliya/suji/sevian	25 g raw	1 katori cooked	80	2.5	16.0	0.3
Rice	25 g raw	1 katori cooked	90	2.0	19.5	0.1
Biscuits	10 g	2 nos	50	1.0	7.0	2.0
Cake	30 g	1 small piece	129	1.8	18.0	5.5
Sago/arrowroot/corn flour	25 g	5 tsp	88	-	22.0	-
Millet grains (bajra, jowar, jau, oats, kottu, etc.)	25 g	5 tsp	94	3.0	16.0	2.0
Khichri [raw rice 20 g plus raw dal 5 g (4:1)]	25 g raw	1 katori cooked (100 g)	85	3.0	18.0	0.1
Pulses						
Dhooli dals (moong/arhar, etc.)	25 g raw] 1 katori cooked (100–125 g)	80	6.0	14.0	0.3
Sabut dals (Rajma/Chana, etc.)	25 g raw		70	5.0	10.0	1.0
Soyabean (white)	25 g raw		95	10.0	2.5	5.0
Vegetables						
Green leafy and seasonal vegetables (spinach, bathua, bhindi, cauliflower, beans, etc.)	100 to 125 g	½ katori cooked	25	2.0	2.5	0.6
Root vegetables (includes arbi, potato, zimikand, etc.)	100 g	1 small size	60	1.5	13.0	0.2
Peas fresh	100 g	1 katori	80	7.0	13.0	0.1
Low carb vegetables (Lauki/tori/ tinda/kaddu/cucumber)	100 g	½ katori	10	0.53	1.7	0.13
Dried nuts						
Groundnuts	25 g	Handful	130	6.0	4.0	10.0
Almond/walnuts/	25 g	-do-	150	4.5	1.0	14.5
Cashew nuts	25 g	-do-	140	4.5	6.5	10.0
Fruits						
Banana	100 g	1 small	110	1.5	25.0	0.5
Mango/chikoo/apple	100 g	1 medium	70	0.6	13.0	1.7
Guava/pear/orange	100 g	1 medium	35	1.0	7.0	0.2
Kharbooja/papaya	100 g	2 pieces	25	0.5	5.0	0.2
Tomato/water melon	100 g	A few pieces	20	0.8	3.0	0.3

(Contd...)

Table 7.4: Approximate nutritive value of common food items (Contd...)

Food items	Raw edible amount (g or mL)	Household measures (cooked) or portion	Energy (kcal)	Protein (g)	Carbohydrate (g)	Fat (g)
Fats and oils						
Refined oil/ghee	5 mL/g	1 tsp	45	-	-	5.0
Butter	5 g	1 tsp	36	-	-	4.0
Coconut oil	5 mL	1 tsp	42	-	-	5.0
Sugars						
Sugar	5 g	1 levelled tsp	20	-	5.0	-
Honey/jam	5 g	1 levelled tsp	16	-	4.0	-
Jaggery	5 g	1 tsp	18	-	4.5	-
Drinks						
Sugarcane juice	100 mL	½ glass	60	-	15.0	-
Coconut water	100 mL	½ glass	14	0.2	3.0	0.1
Soft drinks	100 mL	½ glass	37	-	9.2	-
Processed dairy products						
Full cream milk	100 mL	½ glass	90	3.5	5.0	6.2
Toned milk	100 mL	½ glass	58	3.2	4.5	3.0
Double toned milk	100 mL	½ glass	48	3.0	5.0	2.0
Skimmed milk	100 mL	½ glass	33	3.0	5.0	-
Dahi (plain)/Curd	100 mL	1 cup	75	3.7	5.0	4.5
Buttermilk (lassi-plain)	100 mL	½ glass	32	2.0	2.0	2.0
Sweet lassi	100 mL	½ glass	95	2.5	15.5	2.5
Salted lassi	100 mL	½ glass	32	1.8	2.0	1.8
Cottage cheese	30 g	1 small pc	93	5.5	0.7	7.5
Ice cream	100 mL	1 small cup	180	4.0	23.0	8.0
Ice cream (sugar free)	100 mL	1 small cup	113	5.0	12.0	5.0

kcal: Kilocalories; tsp: Tea spoon

NB: Some approximations made in values of nutrient contents

Adapted from:

1. Indian Food Composition tables, NIN, ICMR, 2017
2. Compilation of Food Exchange list (Technical series 6), Lady Irwin College, Delhi University, 2017
3. For processed foods, nutritional facts are taken from the packets

BALANCED DIET

Balanced diet is defined as nutritionally adequate and appropriate intake of food items that provide all the nutrients in required amounts and proper proportions, to ensure normal growth, development and disease free optimum health amongst children and adolescents. Wide variety and combination of foods are used to formulate balanced diet for various categories of people to meet their needs as per nutritional standards (RDA).

In order to plan nutritionally adequate balanced diet as per RDA, "food group system" is used that converts quantitative nutrient data into food-based information.

Based on major content of nutrients, foods are conventionally placed into 5 groups: (i) Cereals, millets and cereal grains; (ii) Pulses, legumes and nuts; (iii) Milk, egg and flesh foods; (iv) Vegetables and fruits; (v) Fats and sugar. Food groups differ in their nutrient quality and quantity and hence while planning a diet, inclusion of one

or more food items from each of these groups is essential to label a diet as 'balanced'.

The nutrient characteristics of common foods are depicted in Table 7.5.

Cereals, millets and pulses are the major source of most nutrients in Indian diet. Milk provides good quality protein and calcium and hence is an essential item of our diet. Eggs, flesh foods and fish enhance the quality of diet but Indians are predominantly vegetarian society and most of our nutrients are derived from cereal/pulse and milk based diets. Oils and nuts are calorie rich foods and are useful in increasing the calorie density. Vegetables and fruits provide protective substances such as vitamins, minerals, fiber and antioxidants.

In a normal balanced Indian diet, recommended macronutrients as a proportion of total energy intake should be: carbohydrates (55–60%), fats (25–30%) and proteins (10–12%).

Table 7.5: Nutritional characteristics of common food items

Foods	Main nutrients	Other characteristics
Milk and milk products	Protein, fat, calcium, phosphorus, vitamin B ₂	Provide high quality protein lactose and saturated fats; lack in iron and vitamin C
Egg (hen)	Protein, fat, phosphorus, riboflavin	Provide high quality protein and vitamin B ₁₂ ; lacks in carbohydrates and vitamin C; contains saturated fats and is rich in cholesterol
Chicken	Protein, phosphorus	Provides high quality protein and all B vitamins; does not provide carbohydrate, fat and iron
Fish	Protein, fat, calcium, vitamin B ₁₂	Lacks in carbohydrates; good source of high quality protein and fat containing omega-3 fatty acids
Cereals grains and products	Carbohydrate, fiber, folic acid, vitamins B ₁ and B ₂ , phytates, iron	Good source of energy; has poor quality protein that lacks in lysine; provides negligible amounts of unsaturated fat; phytates hinder the absorption of iron
Pulses, peas, beans	Carbohydrate, protein, folic acid, calcium, fiber, vitamins B ₁ and B ₂ , iron, phosphorus	Good source of energy; contain proteins of lower quality that lack in methionine; provides negligible amount of unsaturated fat; absorption of iron is hindered by phytates
Soya bean	Protein (35%), fiber, fat (40%), calcium, iron, zinc, copper, magnesium, selenium, folic acid, potassium, all B vitamins, carotenoids, fiber, isoflavones	Source of high quality protein (twice of that in pulses) and fat (three times that in pulses); contains polyunsaturated, monounsaturated and saturated fats; vegetarian source of omega-3 fatty acids; deficient in sodium and vitamin C and B ₁₂ ; phytates hinder the absorption of iron and calcium
Seasonal vegetables	Carotenoids, folic acid, calcium, fiber, vitamin C	Good source of carbohydrates in the form of roughage and fiber that provide bulk in diet; deficient in proteins and fat
Green leafy vegetables	Carotenoids, folic acid, calcium	Good source of soluble fiber; deficient in protein and fat fiber, vitamin C, iron, riboflavin
Root vegetables	Carbohydrate (chiefly starch)	Good source of energy; deficient in protein, fat and folic acid; carrots are a rich source of carotene, potatoes provide vitamin C; tapioca is rich in calcium
Fruits	Carbohydrate, potassium	Good source of fiber and roughage; deficient in proteins, fat and folic acid; juicy fruits have high potassium content; banana is a good source of energy but poor source of potassium
Nuts	Energy, protein, fat and B vitamins	Groundnuts are particularly rich in thiamine and nicotinic acid

Adapted from The 2010 recommendations of the National Institute of Nutrition (ICMR), Hyderabad on the Nutritive Value of Indian Foods

NORMAL BALANCED DIET FOR VARIOUS AGE GROUPS

Exclusive Breastfeeding (0–6 months of age)

An infant should be exclusively breastfed till six months of age. During this phase, additional food or fluids are not required as breast milk is nutritionally complete for the child's growth and development; it protects from infections and strengthens immune system. Breastfeeding issues are discussed in Chapter 8.

Complementary Feeding (6 months onwards)

After six months of age, breast milk alone is not enough to make an infant grow well. Complementary feeding refers to food which complements breast milk and ensures that the child continues to have enough energy, protein and other nutrients to grow normally.

Complementary feeding is started six months of age (180 days), while continuing breastfeeding.

Breastfeeding is encouraged up to two years of age or more in addition with normal food. Key recommendations

for breastfeeding and complementary feeding are given in Table 7.6.

Between 6 and 12 months, child goes through a major food transition that depends on several cardinal factors, essential to be considered in feeding the child.

Factors to be Considered while Planning Food for Young Child

Energy density: Most of our traditional foods are bulky and a child cannot eat large quantities at a time. Children have low stomach capacity. Hence, it is important to give small energy-dense feeds at frequent intervals to ensure adequate energy intakes by the child.

Energy density of foods given to infants and young children can be increased without increasing the bulk by adding:

- **Oil or ghee:** Fat is a concentrated source of energy and increases energy content of food without increasing the bulk. The false belief that a young child cannot digest

Table 7.6: Counselling for feeding of Infants and children

Age (months)	Food
Up to 6 months	Breastfeed as often as the child wants, day and night, at least 8 times in 24 hours Do not give any other foods or fluids, not even water <i>Remember:</i> Continue breastfeeding even if the child is sick
6 to 12 months	Breastfeed as often as the child wants <i>Complementary feedings:</i> Give at least one katori serving at a time of mashed roti/bread/biscuit mixed in sweetened undiluted milk; or mashed roti, rice, bread mixed in thick dal with added ghee/oil; or khichri with added oil or ghee Add cooked vegetables in these servings or use sevian, dalia, halwa, kheer prepared in milk or any cereal porridge cooked in milk, or mashed boiled or fried potatoes Offer banana, biscuit, cheeku, mango or papaya as snacks in between the serving <i>Frequency:</i> 3–4 times per day if breastfed; 5 times per day if not breastfed <i>Remember:</i> Keep the child in your lap and feed with your own hands; wash your own and child's hands with soap and water every time before feeding
12 months to 2 years	Breastfeed as often as the child wants; offer food from the family pot Give at least 1½ katori serving at a time of mashed roti/rice bread mixed in thick dal or khichri with added ghee or oil Add cooked vegetables in the servings, or mashed roti/rice/bread/biscuit mixed in sweetened undiluted milk, or sevian, dalia, halwa or kheer prepared in milk or any cereal porridge cooked in milk, or mashed boiled/fried potatoes <i>Frequency:</i> 3–5 times a day Offer banana, biscuit, cheeku, mango or papaya as snacks in between the servings <i>Remember:</i> Sit by the side of child and help him to finish the serving; wash your child's hands with soap and water every time before feeding
2 years and older	Give family food as 3–4 meals each day Twice daily, also give nutritious snacks between meals, e.g. banana, biscuit, cheeku, mango, or papaya <i>Remember:</i> Ensure that the child finishes the serving; teach your child to wash his hands with soap and water every time before feeding

fat is not true. A young infant can digest fat present in breast milk as well as all other foods like cereals and pulses. Sugar and jaggery are also rich in energy though not as high in calories as fat but can easily be added in infant foods.

- *Thickening the gruel:* Thin gruels do not provide enough energy. A young infant particularly during 6–9 months requires thick but smooth mixtures. For instance, advising *dal ka paani* as a complementary food recipe is absurd. Infant should be given medium thickness gruel of 'dal' with added oil instead.
- *Amylase rich foods (ARF)* such as malted foods reduce the viscosity of the foods and therefore the child can eat more quantities at a time. (Malting is germinating whole grain cereal or pulse, drying and then grinding).

Often the energy needs of the child are not well appreciated by caregivers. A child between the age of 1 or two years of age needs as much as 50% the nutrition required by an adult.

Nutrient density of the feed can be ensured by including a variety of foods in order to meet all the nutrients. Even as early as 9 months, infants need small portions of food items from all food groups to be included in their diet

to ensure intakes of all macronutrients and micronutrients.

Amount of feed: At 6 months of age, feed should be started with small amount as much as 1–2 teaspoons and the quantity is increased gradually as the child gets older and starts to accept food better. Child should be given time to adapt gradually to larger quantities from teaspoon to table spoon and then to a katori.

Consistency of feed: Infants can eat pureed, mashed and semi-solid foods beginning at six months. By 8 months, most infants can also eat "finger foods" (snacks that can be eaten by children alone). By 12 months, most children can eat the same types of foods as consumed by the rest of the family. As the child grows older, he should be shifted to more appropriate foods suitable for his age. Help children to accept the usual family food gradually which is safely prepared and fed.

Frequency of feeding: An average healthy breastfed infant needs complementary foods 3–4 times per day at 6–8 months of age and 3–4 times per day at 9–11 months and 4–5 times at 12–24 months of age, with additional nutritious snacks such as a piece of fruit, offered 1–2 times per day or as desired. Snacks are defined as foods eaten

between meals, usually convenient and easy to prepare. If energy density or amount of food per meal is low, or the child is no longer breastfed, more frequent meals may be required.

Hygiene: Good hygiene and proper food handling should be practiced to prevent children from infections and malnutrition. Simple hygiene practices include: (a) Washing hands before food preparation and eating, (b) Serving freshly cooked foods (cooked should not be kept for 2–3 hours), (c) Using clean utensils and covered properly, (d) Using clean cups and bowls when feeding children, and (e) Avoiding use of feeding bottles.

Planning Diet for Individual Child

In clinical practice, it is imperative to plan diets for different conditions among children with various ages, both healthy and sick. In this exercise, it is important to ensure the right balance of macronutrients and food groups. A sample diet plan for 1000 kcal is shown in Table 7.7. This can serve as a template to plan diets of lower or higher energy content by varying amounts of ingredients.

UNDERNUTRITION

Undernutrition is a set of conditions that result from inadequate consumption, poor accretion or excessive loss of nutrients. Overnutrition includes overweight and obesity, and is caused by overindulgence or excessive intake of nutrients, or pathological conditions.

Malnutrition refers to deficiencies, excesses or imbalances in a person's intake of energy and/or nutrients (WHO). Thus, malnutrition connotes both undernutrition as well as overnutrition. In practice, however, often the terms malnutrition and protein energy malnutrition (PEM) are used interchangeably with undernutrition.

In this chapter, we will focus on undernutrition among children less than 5 years of age.

Consequences of Undernutrition

Undernourished children have higher risk of infections and mortality. Undernutrition is associated with 35% of under-5 child deaths. Undernutrition is strongly associated with shorter adult height, poor lean weight, less schooling, low cognition, reduced economic productivity and, for women, lower offspring birthweight. Low birthweight and undernutrition in childhood are important risk factors for diabetes mellitus, hypertension and dyslipidemias in adulthood.

Underweight, Stunting and Wasting

Undernutrition has three subgroups: *Underweight*, *wasting* and *stunting* (Table 7.8 and Fig. 7.2)

An *underweight* child has *low-weight-for-age*. It means that the weight of this child is less than minus 2 standard deviations ($-2SD$) on the WHO Growth Standard for her/his age. An underweight child could be wasted or stunted, or both.

Stunting denotes *low-height-for-age*. The height (or length) of a stunted child is below minus 2 standard deviations ($<-2SD$) at her/his age on the WHO Growth Standard. A stunted child is short for her/his age. Stunting indicates chronic undernutrition.

Wasting implies *low-weight-for-height*. A child whose weight for her/his actual height is less than minus 2 standard deviations ($<-2SD$) at her/his age on the WHO Growth Standard has wasting. A wasted child has a thin appearance. Wasting indicates acute undernutrition as result of recent food deficit or an acute illness such as diarrhea.

Growth charts based on WHO Growth Reference Standards are given in Chapter 2.

Table 7.7: A 1000 kcal sample, balanced diet plan based on the food measures. The food portions are to be spread over 24 hours in multiple meals and snacks

Food	Amount/ready to eat portion	Energy (kcal)	Protein (g)
Cow's milk/curd	1 glass milk (200 mL) plus ½ katori curd (50 mL milk)	180	8.0
Pulses	25 g raw dal (1 katori cooked)	80	6.0
Cereals wheat/rice	100 g 4 chapatis (100 g wheat flour) OR 2 chapatis (50 g wheat flour) plus 2 katoris rice cooked (50 g grain) OR 2 chapatis (50 g wheat flour) plus 1 katori cooked suji (25 g wheat flour) plus 1 katori rice cooked (25 gm raw grain)	340	9–10 g
Vegetables	150 g		
Green/seasonal	100 g (1 katori cooked)	25	2.0
Potato	50 g (1/2 katori cooked)	30	1.0
Fruit (banana)	100 g	110	1.5
Oil/ ghee (4 tsp)	20 mL (in cooking plus added)	180	-
Sugar (3 tsp)	15 g (in cooking plus added)	60	-
Total		~1000 kcal	~28 g

• Note—Energy from protein 11–12% in this sample diet

• tsp: Tea spoon

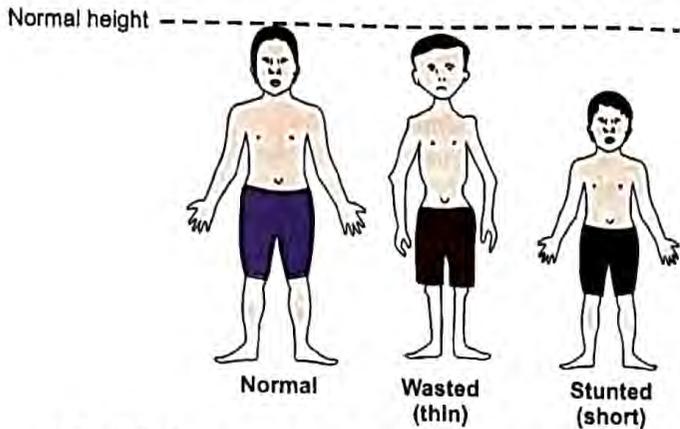


Fig. 7.2: Appearance of undernourished children

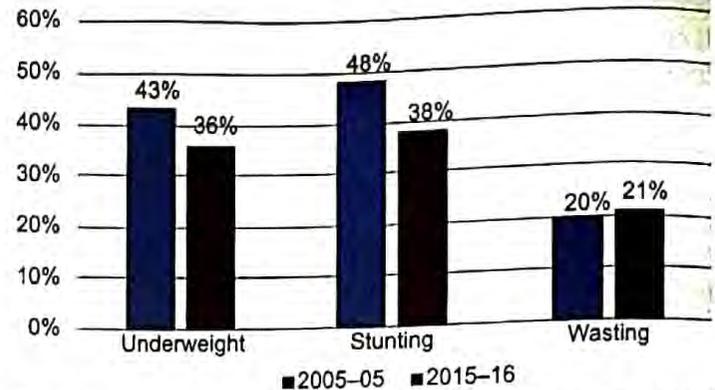


Fig. 7.3: Trends in undernutrition in India: proportion of under-5 children with underweight, stunting and wasting. Source: National Family Health Surveys 3 (2005-06) and 4 (2015-16)]

Table 7.8: Classification of undernutrition

Classification	Criteria	As per WHO growth standards	Sub-classification	As per WHO Reference Standards
Underweight	Low-weight-for-age	Weight-for-age less than minus 2 SD (<-2 SD)	Moderate underweight	Weight-for-age below minus 2 SD and up to minus 3 SD (<-2 SD to -3 SD)
			Severe underweight	Weight-for-age minus 3 SD (<-3 SD)
Stunting	Low-height* (or length) for-age	Height*-for-age less than minus 2 SD (<-2 SD)	Moderate stunting	Height*-for-age below minus 2 SD and up to minus 3 SD (<-2 SD to -3 SD)
			Severe stunting	Height*-for-age below minus 3 SD (<-3 SD)
Wasting	Low-weight-for-height	Weight-for-height less than minus 2 SD (<-2 SD)	Moderate wasting	Weight-for-height below minus 2 SD and up to minus 3 SD (<-2 SD to -3 SD)
			Severe wasting	Weight-for-height below minus 3 SD (<-3 SD)

*'Length' in the first two years of life
SD: Standard deviation

The term 'edematous malnutrition' is used if edema is also present in an underweight child. Clinical classification of undernutrition as marasmus, kwashiorkor and marasmic kwashiorkor is also helpful (discussed below).

Epidemiology

Childhood undernutrition is an underlying cause in an estimated 45% of all deaths among under-5 children. According to the National Family Health Survey (NFHS) 4, carried out in 2015-16, 36% of India's children under the age of five are underweight, 38% are stunted and 21% are wasted (Fig. 7.3). Comparable figures for 2005-06 were 43%, 48% and 20%, respectively. There has been a slow reduction in undernutrition in the country over the years, especially stunting. Yet we continue to have the highest burden of childhood undernutrition in the world.

Undernutrition rates are highest among the scheduled tribes and scheduled caste families. Proportion of underweight children in rural areas (38%) is higher than urban areas (29%).

During the first six months of life, 20-30% of children are already undernourished, often because they were born low birthweight. The proportion of undernutrition and stunting starts rising after 4-6 months of age (Fig. 7.4).

After 6 months of age, breast milk alone is not enough to meet the energy requirement of the child, and therefore solid food (complementary feeding) must be introduced, in addition to continuing breastfeeding. This often does not happen.

It is estimated that only 10% of children between the age of 6-24 months have adequate nutritional intake (NFHS 4). Most children in the country are thus 'nutrition hungry' in this critical phase of life. In addition, the child becomes more prone of infections, particularly diarrhea, due as she becomes mobile and puts unhygienic objects into mouth and ingests unhygienic food products.

Late introduction of complementary feeding and inadequate food intake leads to increasing predisposition to undernutrition. The proportion of children who are stunted or underweight increases rapidly with the child's age until about 18-24 months of age (Fig. 7.4).

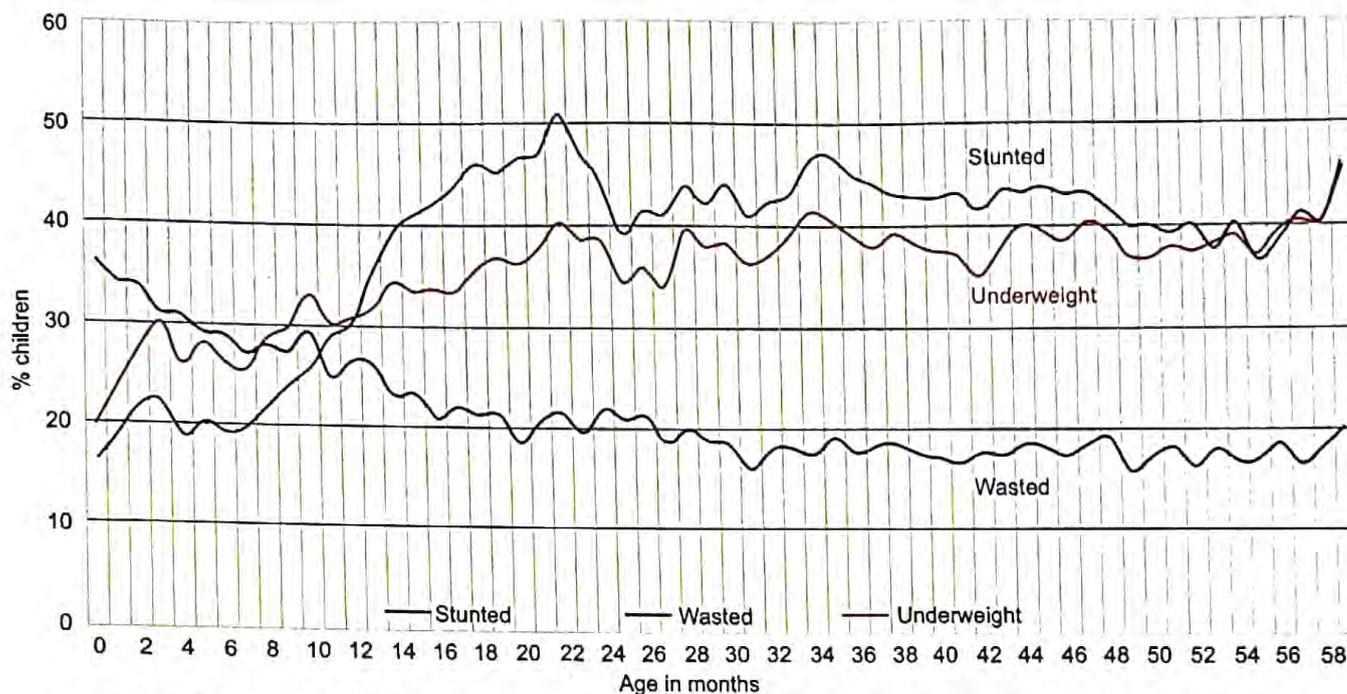


Fig. 7.4: Proportion of malnourished children according to age (National Family Health Survey 4, 2015-16)

Importance of fetal life and the first two years of life (the first 1000 days 'window') for linear and brain growth.

Length at 2 years is the predictor of adult height and productivity. Brain achieves a near adult size by two years of age. It is practically impossible to reverse the height and brain growth deficit after 2 years of age with nutrition and other interventions; it is simply too late.

Thus, nutrition during the first 1000 days since conception, encompassing pregnancy and the first 2 years of life, is of profound importance for realizing the physical and intellectual potential. Nutritional corrections after two years will not change these outcomes.

Hence, ensuring optimum nutrition of the mother before and during pregnancy, and optimum feeding of children in the first 2 years of life (including breastfeeding for first 2 years, and adequate solid feeding after 6 months of age) is absolutely crucial in human life.

Determinants

The causes of malnutrition could be viewed as immediate, underlying and basic as depicted in Fig. 7.5.

The immediate determinants of a child's nutritional status work at the individual level. These include low birthweight, illnesses (particularly infections such as diarrhea and pneumonia) and inadequate dietary intake.

Finally, the underlying determinants are influenced by the basic determinants. These include the socioeconomic status and education level of the families, women's empowerment, cultural taboos regarding food and health, access to water and sanitation, etc. Access to safe water and sanitation, will reduce a significant proportion of undernutrition.

Three cardinal determinants of undernutrition

- 1. Low birth weight:** Infants born small often remain undernourished. About 20% childhood undernutrition is attributable to fetal growth restriction.
- 2. Infections:** Diarrhea, pneumonia and other infections consume energy and hamper growth. Diarrhea causes nutrient loss in stools. About 25% childhood undernutrition is attributable to diarrhea, pneumonia and other infections.
- 3. Low food intake:** Inadequate breastfeeding, delayed complementary feeding and insufficient food intake means less energy and protein available for growth. This underlies about 55% of childhood undernutrition.

Clinical Syndromes of Undernutrition

Moderate and severe malnutrition is associated with one of classical syndromes, namely, marasmus, kwashiorkor, or with manifestations of both. Another classification, the severe acute malnutrition (SAM) is used in the program setting.

Marasmus

Marasmus is characterized by severe form of wasting. There is marked wasting of fat and muscle as these tissues are consumed to make energy. Acute starvation or acute illness over a borderline nutritional status precipitates this form of undernutrition. Severe marasmus is a typical form of severe acute malnutrition (SAM).

- The main sign is severe wasting. The child appears very thin (skin and bones) and has no fat. There is severe wasting of the shoulders, arms, buttocks and thighs (Fig. 7.6).
- The loss of buccal pad of fat creates the aged or wrinkled appearance that has been referred to as monkey facies

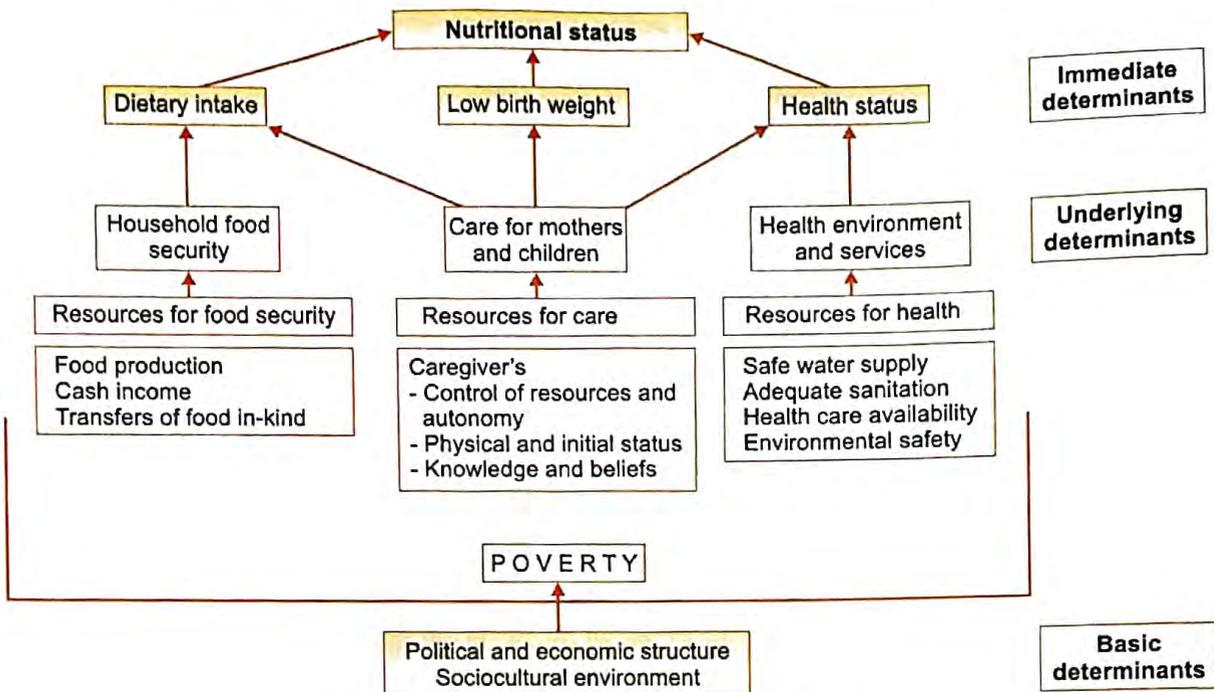


Fig. 7.5: Determinants of a child's nutrition status

(Fig. 7.6a). Baggy pants appearance refers to loose skin of the buttocks hanging down (Fig. 7.6b). Axillary pad of fat may also be diminished

- Affected children may appear to be alert in spite of their condition
- There is no edema

Kwashiorkor

Uncommon in India now, it usually affects children aged 1–4 years. The main sign is pitting edema, usually starting in the legs and feet and spreading, in more advanced cases, to the hands and face. Because of edema, children with kwashiorkor may look healthy so that their parents view them as well fed.

- **General appearance:** Child may have a fat sugar baby appearance.
- **Edema:** It ranges from mild to gross and may represent up to 5–20% of the body weight.
- **Muscle wasting:** It is always present. The child is often weak, hypotonic and unable to stand or walk.
- **Skin changes:** The skin lesions consist of increased pigmentation, desquamation and dyspigmentation. Pigmentation may be confluent resembling flaky paint or in individual enamel spots. The distribution is typically on buttocks, perineum and upper thigh. Petechiae may be seen over abdomen. Outer layers of skin may peel off and ulceration may occur. The lesions may sometimes resemble burns.
- **Mucous membrane lesions:** Smooth tongue, cheilosis and angular stomatitis are common. Herpes simplex stomatitis may also be seen.



Fig. 7.6: A child with severe acute malnutrition. Note the (a) dull, lustless, sparse hair; temporal hollowing; loss of buccal pad of fat; anxious look; (b) Loose folds of skin in the gluteal region giving a 'baggy pants' appearance

- **Hair:** Changes include dyspigmentation, loss of characteristic curls and sparseness over temple and occipital regions. Hair lose their lustre and are easily pluckable. A flag sign which is the alternate bands of hypopigmented and normally pigmented hair pattern is seen when the growth of child occurs in spurts.
- **Mental changes:** Includes unhappiness, apathy or irritability with sad, intermittent cry. They show no signs of hunger and it is difficult to feed them.
- **Neurological changes:** Changes such as tremors are seen during recovery.
- **Gastrointestinal system:** Anorexia, sometimes with vomiting, is the rule. Abdominal distension is characteristic. Stools may be watery or semisolid, bulky with a low pH and may contain unabsorbed sugars.
- **Anemia:** Nutritional anemia is almost always associated.
- **Cardiovascular system:** The findings include cold, pale extremities due to circulatory insufficiency and are associated with prolonged circulation time, bradycardia, diminished cardiac output and hypotension.
- **Renal function:** Glomerular filtration and renal plasma flow are diminished. There is aminoaciduria and inefficient excretion of acid load.

Marasmic Kwashiorkor

It is a mixed form of undernutrition and manifests as edema occurring in children who may or may not have other signs of kwashiorkor and have varied manifestations of marasmus.

Severe Acute Malnutrition (SAM)

This special classification is recommended by WHO for identifying and managing children with life threatening undernutrition in public health programme settings. Children with SAM have a mix of features of marasmus and kwashiorkor.

Severe acute malnutrition (SAM) among children 6–59 months of age is defined by WHO and UNICEF as any of the following three criteria:

- Weight-for-height below -3 standard deviation ($<-3SD$) on the WHO Growth Standard; or
- Presence of bipedal edema; or
- Mid upper arm circumference (MUAC) below 11.5 cm.

In a child below 6 months of age, the MUAC is not used as a criterion.

Children with SAM have a high risk of death. In addition to debilitating undernutrition, they often have serious infections such as diarrhea, pneumonia, sepsis, malaria and skin infections. They require urgent attention.

MANAGEMENT OF MALNUTRITION

The management of malnutrition depends on its severity. While mild to moderate malnutrition can be managed on ambulatory basis, severe malnutrition is preferably

managed in hospital. The management of low birth weight infants is discussed in Chapter 8.

Mild and Moderate Malnutrition

Mild and moderate malnutrition make up the greatest portion of malnourished children and account for $>80\%$ of malnutrition associated deaths. It is, therefore, vital to intervene in children with mild and moderate malnutrition at the community level before they develop complications.

The mainstay of treatment is provision of adequate amounts of protein and energy; at least 150 kcal/kg/day should be given. Nutritious home food is recommended. The ICDS programme provides extra ration for such children.

In order to achieve these high energy intakes, frequent feeding (up to seven times a day) is often necessary. Because energy is so important and because carbohydrate energy sources are bulky, oil is usually used to increase the energy in therapeutic diets. Nutrient-dense foods enable children to consume and maximize the absorption of nutrients in order to fulfil their requirements of energy and all essential nutrients.

According to WHO, animal-source foods are more likely to meet the amino acid and other nutrient needs of recovering children. Milk and eggs are excellent animal origin foods for children. Plant-source foods, in particular legumes or a combination of cereals and legumes, also have high-quality proteins, although they may also contain some anti-nutrients such as phytates, tannins or inhibitors of digestive enzymes, which may limit the absorption of some micronutrients, particularly minerals.

It is recognized increasingly that a relatively small increase over normal protein requirements is sufficient for rapid catchup growth, provided energy intake is high. *A protein intake of 3 g/kg/day is sufficient.* Milk is the most frequent source of the protein used in therapeutic diets, though other sources, including vegetable protein mixtures, have been used successfully. Adequate minerals and vitamins should be provided for the appropriate duration. *The best measure of the efficacy of treatment of mild and moderate malnutrition is weight gain.*

Severe Acute Malnutrition (SAM): Children 6 to 59 Months

The World Health Organization has developed guidelines for the management of severe acute malnutrition (SAM) and these have been updated in 2013. Guidelines are mainly for children of more than 6 months of age.

Once a child, 6 months or older, is diagnosed as SAM, she/he should be thoroughly assessed by a physician for complications by looking for severe edema (+++), lack of appetite, medical complications on clinical examination (e.g. severe anemia, pneumonia, diarrhea, dehydration, cerebral palsy, tuberculosis, HIV, heart disease etc.) and danger signs according to IMNCI algorithm (Fig. 7.7). If any of these are present, it is classified as complicated SAM, and the child is referred for inpatient management.

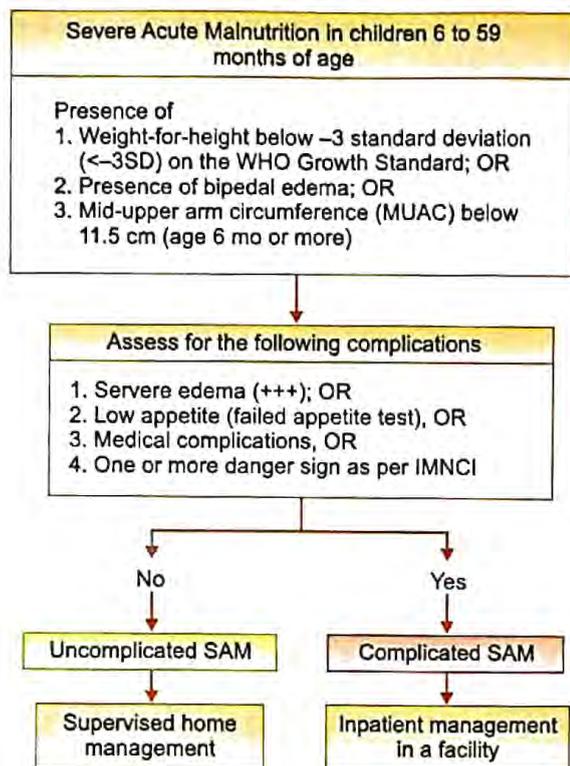


Fig. 7.7: Approach to child with severe acute malnutrition

If the above mentioned signs are absent, the child has uncomplicated SAM and can be managed in the outpatient setting with care at home (Fig. 7.7). Good appetite is critically important in home care of the child with SAM because oral intake of adequate energy dense food is the fundamental requirement for recovery.

Supervised Home Management of Uncomplicated SAM

Children with uncomplicated SAM can be managed at home provided:

- Family is counseled and fully engaged.
- Community health worker(s) and peer counselors are involved to support the family.
- Supply of adequate home food and ready to use therapeutic food (RUTF), if possible.
- Periodic monitoring for growth and medical condition can be ensured.

Mainstay of home management is nutritional rehabilitation with high energy food. This could be adequate home foods prepared from locally available cereals and pulses, sugar, oil, milk and/or eggs etc. ensuring 175 cal/kg body weight/day. Ready to use therapeutic food (RUTF), which avoids cumbersome preparation of recipes at home is a practical option. The available evidence shows that recovery rates are higher with RUTF than home food based regimens even when families are well supported.

RUTF is an energy dense, mineral and vitamin enriched food that has greatly improved the management of SAM. The composition of RUTF is shown in Table 7.9. The RUTF is made of peanut paste, sugar, milk solids and vegetable oil with added minerals and vitamins. RUTF has a pasty, smooth consistency, and good taste. It is easy for the child to eat and digest. RUTF can be locally produced or be commercially available.

Caregiver should wash hands and utensils used for feeding. Breastfeeding should be continued, if the child is breastfed. The caregiver lovingly engages the child, talks to her, plays with her and makes feeding exercise an interactive affair. In addition, the child should be provided sensory stimulation (play, physical activity, laughter, exposure to colors and shapes, storytelling, massage, etc.).

Optimum home management of a child with SAM is not possible without effective support by the health worker. Families will invariably need close facilitation and guidance by the health worker (ASHA ANM or AWW). A home contact every day initially, and then twice a week is essential (Panel 1).

The child should be monitored by health workers for signs of undernutrition (weight, height, MUAC, edema, anemia, etc.) every week.

In addition to nutrition, every child on SAM treatment should receive the following interventions: an antibiotic course (amoxicillin for 5 days), mega dose of vitamin (100 000 units) in the presence of clinical deficiency (xerophthalmia, Bitot's spots or keratomalacia), and albendazole single dose (for children over 2 years of age). (It may be noted that RUTF contains appropriate supplements of minerals and vitamins). The child should

Table 7.9: Composition and nutrition value of the standard ready to use therapeutic food (RUTF)

Composition		Food value per 100 g	
Peanut paste	30%	Energy	543 kcal
Sugar	29%	Nutrients	
Milk solids	20%	Protein	15 g
Vegetable oil	18%	Lipids	35 g
With added mineral mix ¹ , vitamin mix ² , emulsifier and antioxidant		Carbohydrates	43 g

¹Minerals per 100 g: Calcium 400 mg, phosphorus 400 mg, potassium 1100 mg, magnesium 110 mg, sodium <290 mg, iron 10 mg, zinc 12 mg, copper 1.5 mg, iodine 100 µg, selenium 30 µg.

²Vitamins per 100 g: vitamin A 0.9 mg, vitamin D₃ 18 µg, vitamin K 21 µg, vitamin E 27 µg, vitamin C 54 mg, vitamin B₁ 0.5 mg, vitamin B₂ 1.8 mg, vitamin B₆ 0.7 mg, vitamin B₁₂ 1.6 µg, niacin 5.8 mg, Ca-D pantothenate 3 mg, folic acid 225 µg, biotin 70 µg.

Panel 1: Summary of supervised home management of a child with uncomplicated SAM

- I. Nutrition therapy
 - *What to feed:* Initially home foods or RUTF; later home foods. Continue breastfeeding
 - *How much to feed:* Enough to provide 175 kcal/kg/day
 - *How often to feed:* 6–8 times a day
 - *How to feed:* Lovingly, actively; ensuring hygiene
- II. Other treatments
 - Oral amoxicillin for 5 days
 - Mega dose vitamin A, if obvious signs of vitamin A deficiency
 - Albendazole 400 mg single dose
 - Age appropriate vaccines
- III. Sensory stimulation
 - Play, physical activity, interaction
- IV. Supervision and support
 - Home visits by health workers, initially daily, later twice a week; more if necessary
 - Involve a peer counselor, a volunteer woman friend/neighbor to support the family
 - Ensure supply of RUTF
- V. Monitoring by health workers (ASHA/AWW/ANM)
 - Assess intake, solve feeding issues
 - Evaluate for medical problems; treat/refer
 - Assess growth weekly

be provided all the due vaccines as per national immunization schedule.

Nutritional rehabilitation of a child with SAM would require 3–5 months. Hence, home contacts are extremely important. After completion of treatment, the child should be followed up in the Anganwadi regularly.

Management of Complicated SAM in Hospital

All children with complicated SAM should be hospitalized. The government has established nutrition rehabilitation centres (NRCs) in all states.

The child with severe malnutrition has a complex backdrop with dietary, infective, social and economic factors underlying the malnutrition. A history of events leading to the child's admission should be obtained. Socioeconomic history and family circumstances should be explored to understand the underlying and basic causes. Particular attention should be given to: Diet (before the current illness) including breastfeeding. Malnutrition may be the presentation of HIV infection.

Physical features of malnutrition as described above should be looked for. Following clinical features should be particularly looked for: Fever, hypothermia (temperature <35.5°C), signs of dehydration, shock (cold hands, slow capillary refill, weak and rapid pulse), anemia, eye signs of vitamin A deficiency, localizing signs of infections (pneumonia, skin infections, diarrhea, tuberculosis), signs of HIV infection, mouth ulcers and skin changes of kwashiorkor.

The general treatment involves 10 steps in two phases:

- The initial *stabilization phase* focuses on restoring homeostasis and treating medical complications and usually takes 2–7 days of inpatient treatment.
- The *rehabilitation phase* focuses on rebuilding wasted tissues and may take several weeks.

The 10 essential steps and the time frame are shown in Fig. 7.8 and Table 7.10.

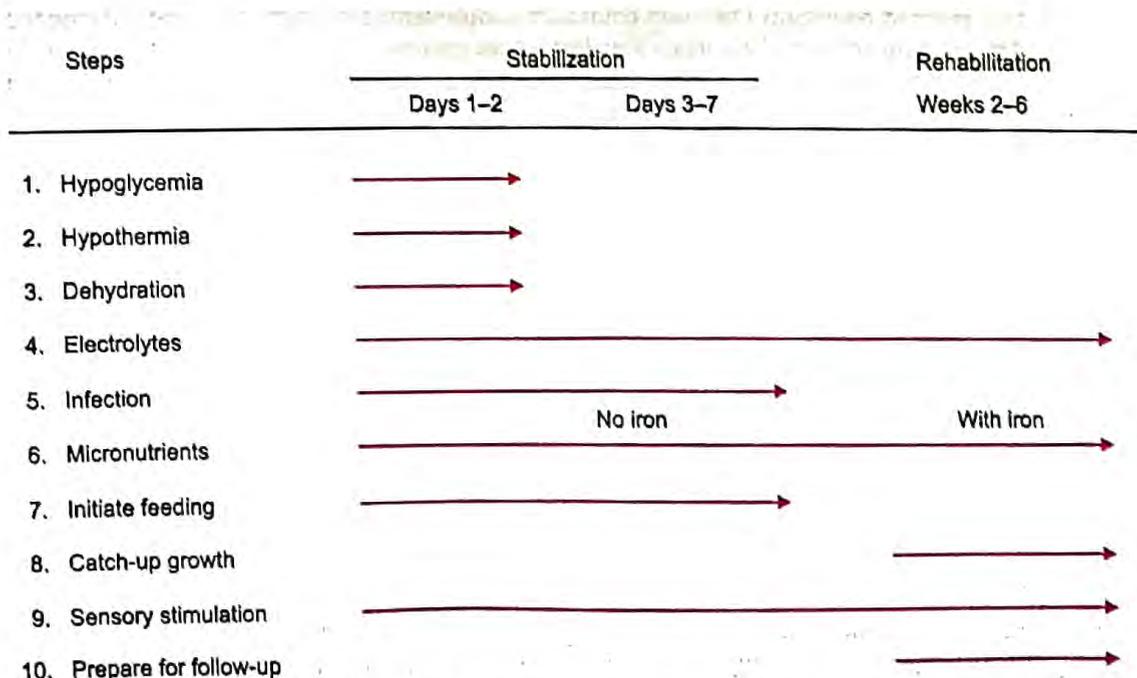


Fig. 7.8: The time frame for initiating and achieving 10 steps

Table 7.10: Summary of the management of severe malnutrition

Hypoglycemia	<p>Blood glucose level <54 mg/dL or 3 mmol/L If blood glucose cannot be measured, assume hypoglycemia Hypoglycemia, hypothermia and infection generally occur as a triad</p> <p>Treatment Asymptomatic hypoglycemia Give 50 ml of 10% glucose or sucrose solution orally or by nasogastric tube followed by first feed Feed with starter F-75 every 2 hourly day and night Symptomatic hypoglycemia Give 10% dextrose IV 5 ml/kg Follow with 50 ml of 10% dextrose or sucrose solution by nasogastric tube Feed with starter F-75 every 2 hourly day and night Start appropriate antibiotics</p> <p>Prevention Feed 2 hourly starting immediately Prevent hypothermia</p>
Hypothermia	<p>Rectal temperature less than <35.5°C or 95.5°F or axillary temperature less than 35°C or 95°F Always measure blood glucose and screen for infections in the presence of hypothermia</p> <p>Treatment Clothe the child with warm clothes; ensure that the head is also covered with a scarf or cap Provide heat using overhead warmer, skin contact or heat convector Avoid rapid rewarming as this may lead to disequilibrium Feed the child immediately Give appropriate antibiotics</p> <p>Prevention Place the child's bed in a draught free area Always keep the child well covered; ensure that head is also covered well May place the child in contact with the mother's bare chest or abdomen (skin-to-skin) Feed the child 2 hourly starting immediately after admission</p>
Dehydration	<p>Difficult to estimate dehydration status accurately in the severely malnourished child Assume that all severely malnourished children with watery diarrhea have some dehydration Low blood volume (hypovolemia) can coexist with edema</p> <p>Treatment Use reduced osmolarity ORS with potassium supplements for rehydration and maintenance Amount depends upon how much the child wants, volume of stool loss, and whether the child is vomiting Initiate feeding within two to three hours of starting rehydration; use F-75 formula on alternate hours along with reduced osmolarity ORS Be alert for signs of overhydration</p> <p>Prevention Give reduced osmolarity ORS at 5–10 mL/kg after each watery stool, to replace stool losses If breastfed, continue breastfeeding Initiate refeeding with starter F-75 formula</p>
Electrolytes	<p>Give supplemental potassium at 3–4 mEq/kg/day for at least 2 weeks On day 1, give 50% magnesium sulfate (equivalent to 4 mEq/mL) IM once (0.3 mL/kg; maximum of 2 mL). Thereafter, give extra magnesium (0.8–1.2 mEq/kg daily) Excess body sodium exists even though the plasma sodium may be low; decrease salt in diet</p>
Infection	<p>Multiple infections are common; assume serious infection and treat Usual signs of infection such as fever are often absent Majority of bloodstream infections are due to gram-negative bacteria Hypoglycemia and hypothermia are markers of severe infection</p> <p>Treatment Treat with parenteral ampicillin 50 mg/kg/dose 6 hourly for at least 2 days followed by oral amoxicillin 15 mg/kg 8 hourly for 5 days; and gentamicin 7.5 mg/kg or amikacin 15–20 mg/kg IM or IV once daily for 7 days</p>

(Contd...)

Table 7.10: Summary of the management of severe malnutrition (Contd..)

If no improvement occurs within 48 hours, change to IV cefotaxime (100–150 mg/kg/day 6–8 hourly) or ceftriaxone (50–75 mg/kg/day 12 hourly)

If other specific infections are identified, give appropriate antibiotics

Prevention

Follow standard precautions like hand hygiene

Give measles vaccine, if the child is >6 months and not immunized, or if the child is >9 months and had been vaccinated before the age of 9 months

Micronutrients

Use up to twice the recommended daily allowance of various vitamins and minerals

On day 1, give vitamin A orally (if age >1 year, give 2 lakh IU; age 6–12 months, give 1 lakh IU; age 0–5 months, give 50,000 IU)

Folic acid 1 mg/day (give 5 mg on day 1)

Zinc 2 mg/kg/day

Copper 0.2–0.3 mg/kg/day

Iron 3 mg/kg/day, once child starts gaining weight; after the stabilization phase

Initiate feeding

Start feeding as soon as possible as frequent small feeds

If unable to take orally, initiate nasogastric feeds

Total fluid recommended is 130 mL/kg/day; reduce to 100 mL/kg/day, if there is severe edema

Continue breastfeeding *ad libitum*

Start with F-75 starter feeds every 2 hourly

If persistent diarrhea, give a cereal based low lactose F-75 diet as starter diet

If diarrhea continues on low lactose diets give, F-75 lactose free diets (rarely needed)

Catch-up growth

Once appetite returns in 2–3 days, encourage higher intakes

Increase volume offered at each feed and decrease the frequency of feeds to 6 feeds per day

Continue breastfeeding *ad libitum*

Make a gradual transition from F-75 to F-100 diet

Increase calories to 150–200 kcal/kg/day, and proteins to 4–6 g/kg/day

Add complementary foods as soon as possible to prepare the child for home foods at discharge

Sensory stimulation

A cheerful, stimulating environment

Age appropriate structured play therapy for at least 15–30 min/day

Age appropriate physical activity as soon as the child is well enough

Tender loving care

Prepare for follow-up

Primary failure to respond is indicated by:

Failure to regain appetite by day 4

Failure to start losing edema by day 4

Presence of edema on day 10

Failure to gain at least 5 g/kg/day by day 10

Secondary failure to respond is indicated by:

Failure to gain at least 5 g/kg/day for consecutive days during the rehabilitation phase

Step 1: Treat/Prevent Hypoglycemia

All severely malnourished children are at risk of hypoglycemia (blood glucose level <54 mg/dL or 3 mmol/L), hence blood glucose should be measured immediately at admission. If blood glucose cannot be measured, one must assume hypoglycemia and treat.

Hypoglycemia may be asymptomatic or symptomatic. Symptomatic hypoglycemia manifesting as lethargy, unconsciousness, seizures, peripheral circulatory failure or hypothermia is more common in marasmus, where energy stores are depleted or when feeding is infrequent.

For correction of asymptomatic hypoglycemia, 50 mL of 10% glucose or sucrose solution (1 rounded teaspoon of sugar in 3½ tablespoons of water) should be given orally or by nasogastric tube followed by the first feed. For correction of symptomatic hypoglycemia, 5 mL/kg of 10%

dextrose should be given intravenously. This should be followed with 50 mL of 10% dextrose or sucrose solution by nasogastric tube. Blood glucose levels must be estimated every 30 min till the glucose level becomes normal and stabilizes. Once stable, the 2 hourly feeding regimens should be started.

Feeding should be started with starter F-75 (Formula 75 which is a WHO recommended starter diet for severe acute malnutrition containing 75 kcal/100 mL of feed (described later) as quickly as possible and then continued 2–3 hourly day and night (initially a quarter of the 2 hourly feed should be given every 30 min till the blood glucose stabilizes). Most episodes of symptomatic hypoglycemia can be prevented by frequent, regular feeds and the child should be fed regularly throughout the night. Hypoglycemia, hypothermia and infection generally occur as a triad.

Step 2: Treat/Prevent Hypothermia

All severely malnourished children are at risk of hypothermia due to impairment of thermoregulatory control, lowered metabolic rate and decreased thermal insulation from body fat. Children with marasmus, concurrent infections, denuded skin and infants are at a greater risk. Hypothermia is diagnosed, if the axillary temperature is less than 35°C or 95°F. It can occur in summers as well.

The child should be rewarmed providing heat using radiation (overhead warmer) or conduction (skin contact) or convection (heat convector). Rapid rewarming may lead to disequilibrium and should be avoided.

In case of severe hypothermia (temperature <32°C), warm humidified oxygen should be given followed immediately by 5 mL/kg of 10% dextrose IV or 50 mL of 10% dextrose by nasogastric route (if IV access is difficult). If clinical condition allows the child to take orally, warm feeds should be given immediately or else the feeds should be administered through a nasogastric tube. If there is feed intolerance or another contraindication for nasogastric feeding, maintenance IV fluids (prewarmed) should be started.

In a hypothermic child, hypoglycemia must be looked for and managed. The child's temperature should be monitored every 2 hours till it rises to more than 37.5°C. Temperature monitoring must be ensured especially at night when the ambient temperature falls.

In most cases, hypothermia may be prevented by frequent feeding. Therefore, the child should be fed immediately and subsequently, every 2 hourly. All children should be nursed in a warm environment, clothed with warm clothes and covered using a warm blanket. The head should also be covered well with a scarf or a cap. The child could also be put in contact with the mother's bare chest or abdomen (skin-to-skin) as in kangaroo mother care to provide warmth. Besides these measures, hypothermia can also be prevented by placing the child's bed in a draught free area away from doors and windows, minimizing exposure after bathing or during clinical examination and keeping the child dry always.

Step 3: Treat/Prevent Dehydration

Dehydration tends to be overdiagnosed and its severity overestimated in severely malnourished children. Loss of elasticity of skin may either be due to loss of the subcutaneous fat in marasmus or loss of extracellular fluid in dehydration. In dehydration, the oral mucosa feels dry to the palpating finger gently rolled on the inner side of the cheek. Presence of thirst, hypothermia, weak pulses and oliguria are other signs of dehydration in severely malnourished children. It is important to recognize that low blood volume (hypovolemia) can coexist with edema. Since estimation of dehydration may be difficult in

severely malnourished children, it is safe to assume that all patients with watery diarrhea have some dehydration.

WHO lays down following guidelines for treating dehydration with ORS in children with SAM:

- Children with severe acute malnutrition who present with some dehydration or severe dehydration but who are not in shock should be rehydrated slowly using ORS for malnourished children.
- Full-strength, standard WHO low-osmolarity oral rehydration solution (75 mmol/L of sodium) should not be used for oral or nasogastric rehydration in children with severe acute malnutrition who present with some dehydration or severe dehydration.
- Give either half-strength standard WHO low-osmolarity oral rehydration solution with added potassium and glucose, unless the child has cholera or profuse watery diarrhea. Dissolve one sachet of standard WHO low-osmolarity oral rehydration solution in 2 L water (instead of 1 L). Add 1 level scoop of commercially available combined minerals and vitamins mix1 or 40 mL of mineral mix solution, and add and dissolve 50 g of sugar.

As the combined minerals and vitamins mix and mineral mix solution are not available, the alternative is to dissolve one sachet of standard WHO low-osmolarity oral rehydration solution in 2 L water (instead of 1 L), add 50 g of sugar (sucrose) and 45 mL of syrup potassium chloride (10% solution in a sugarless base).

ORS is given orally or by nasogastric tube at 5–10 mL/kg/h up to a maximum of 12 hours. Thus, dehydration should be corrected slowly over a period of 12 hours.

Intravenous therapy should be given only for severe dehydration and shock or if the enteral route cannot be used. The exact amount actually depends on how much the child wants, volume of stool loss and whether child is vomiting. Ongoing stool losses should be replaced with approximately 5–10 mL/kg of the ORS after each watery stool. The frequent passage of small unformed stools should not be confused with profuse watery diarrhea as it does not require fluid replacement.

Breastfeeding should be continued during the rehydration phase. Refeeding must be initiated with starter F-75 within 2–3 hours of starting rehydration. The feeds must be given on alternate hr (e.g. 2, 4, 6 hours) with reduced osmolarity ORS (composition as described above) (hr 1, 3, 5). Once rehydration is complete, feeding must be continued and ongoing losses replaced with ORS.

The progress of rehydration should be monitored every half hourly for first 2 hours and then hourly for the next 4–10 hours. Pulse rate, respiratory rate, oral mucosa, urine frequency or volume and frequency of stools and vomiting should be monitored.

One must be alert for signs of overhydration (increase in respiratory rate by 5/minute and pulse rate by 15/minute, increasing edema and periorbital puffiness),

which can be dangerous and may lead to heart failure. In case of signs of overhydration, ORS should be stopped immediately and child reassessed after one hour. On the other hand a decrease in the heart rate and respiratory rate (if increased initially) and increase in the urine output indicate that rehydration is proceeding. The return of tears, a moist oral mucosa, less sunken eyes and fontanelle and improved skin turgor are also indicators of rehydration. Once any four signs of hydration (child less thirsty, passing urine, tears, moist oral mucosa, eyes less sunken, faster skin pinch) are present, ORS for rehydration must be stopped and continued to replace the ongoing losses.

Severe dehydration with shock: It is important to recognize severe dehydration in malnourished children. Severe dehydration with shock is treated with intravenous fluids. Ideally, Ringer lactate with 5% dextrose should be used as rehydrating fluid. If not available, half normal saline (N/2) with 5% dextrose or Ringer lactate alone can be used. After providing supplemental oxygen, the rehydrating fluid should be given at a slow infusion rate of 15 mL/kg over the first hour with continuous monitoring of pulse rate, volume, respiratory rate, capillary refill time and urine output.

If there is improvement (pulse slows, faster capillary refill) at the end of the first hour of IV fluid infusion, a diagnosis of severe dehydration with shock should be considered and the rehydrating fluid repeated at the same rate of 15 mL/kg over the next hour. This should be followed by reduced osmolarity ORS at 5–10 mL/kg/hr, either orally or by nasogastric tube. Patients should be monitored for features of overhydration and cardiac decompensation.

Septic shock: If at the end of the first hour of IV rehydration, there is no improvement or worsening, septic shock must be considered and appropriate treatment started.

Step 4: Correct Electrolyte Imbalance

In severely malnourished children excess body sodium exists even though the plasma sodium may be low. Sodium intake should be restricted to prevent sodium overload and water retention during the initial phase of treatment. Excess sodium in the diet may precipitate congestive cardiac failure.

All severely malnourished children have deficiencies of potassium and magnesium, which may take two weeks or more to correct. Severely malnourished children may develop severe hypokalemia and clinically manifest with weakness of abdominal, skeletal and even respiratory muscles. This may mimic flaccid paralysis. Electrocardiography may show ST depression, T waves inversion and presence of U waves. If serum potassium is <2 mEq/L and presence of U waves, correction should be or <3.5 mEq/L with ECG changes, correction should be

started at 0.3–0.5 mEq/kg/hr infusion of potassium chloride in intravenous fluids, preferably with continuous monitoring of the ECG.

Once severe hypokalemia is corrected, all severely malnourished children need supplemental potassium at 3–4 mEq/kg/day for at least 2 weeks. Potassium can be given as syrup potassium chloride; the common preparation available has 20 mEq of potassium/15 mL.

On day 1, 50% magnesium sulfate (equivalent to 4 mEq/mL) should be given at 0.3 mL/kg to a maximum of 2 mL intramuscularly. Thereafter, 0.8–1.2 mEq/kg magnesium should be given orally as a supplement mixed with feeds.

Step 5: Treat/Prevent Infection

Infection may not produce the classical signs of fever and tachycardia in severely malnourished children. Instead, severe infection may be associated with hypothermia. Localizing signs of infection are often absent. The most common sites for infection are the skin, the alimentary tract, the respiratory tract (including the ears, nose and throat) and the urinary tract. Majority of the infections and septicemia are caused by gram-negative organisms. Therefore, all severely malnourished children should be assumed to have a serious infection on their arrival in hospital. In addition, hypoglycemia and hypothermia are considered markers of severe infection in children.

The following investigations are done for identifying infections: (i) Hb, TLC, DLC, peripheral smear, (ii) urinalysis and culture, (iii) blood culture, (iv) chest X-ray, (v) Mantoux test, (vi) gastric aspirate for AFB, (vii) peripheral smear for malaria (in endemic areas), and (viii) CSF examination (if meningitis is suspected).

All children with suspected infection should be treated with broad spectrum parenteral antibiotics; ampicillin and gentamicin or amikacin (Table 7.11). Antimalarial and antituberculous treatment should only be given when the particular conditions are diagnosed.

Response to treatment will be indicated by resolution of initial symptoms and signs of infection, if any. The child's activity, interaction with parents and appetite should improve. If there is no improvement or deterioration of the symptoms/signs of infection, the child should be screened for infection with resistant bacterial pathogens, tuberculosis, HIV and unusual pathogens.

Prevention of hospital acquired infection: The health care personnel should follow standard precautions. The effectiveness of hand hygiene should be emphasized to all health care providers, attendants and patients. It is essential that adequate safety measures are taken to prevent the spread of hospital acquired infections, since these children are at higher risk of acquiring infections due to their compromised immune status.

Table 7.11: Recommended antibiotics for infections in severely malnourished children

Type of infection	Recommended antibiotics
No obvious infections or complications	Oral cotrimoxazole (5 mg/kg 12 hourly of trimethoprim) or oral amoxicillin 10 mg/kg 8 hourly for 5 days
Infected child or complications	IV ampicillin 50 mg/kg/dose 6 hourly and IV gentamicin 5–7 mg/kg/day in 1–2 doses; add IV cloxacillin 100 mg/kg/day 6 hourly if staphylococcal infection is suspected; revise therapy based on the culture sensitivity report
For septic shock or no improvement or worsening	Add third generation cephalosporin, i.e. IV cefotaxime 100 mg/kg/day 8 hourly
Meningitis in initial 48 hr	IV cefotaxime 200 mg/kg/day IV 6 hourly with IV amikacin 15 mg/kg/day 1–2 doses
Dysentery	Ciprofloxacin 20 mg/kg/day in 2 divided doses; IV ceftriaxone 50 mg/kg/day 12 hourly, if child is sick or has already received nalidixic acid

Step 6: Correct Micronutrient Deficiencies

All severely malnourished children have vitamin and mineral deficiencies. Micronutrients should be used as an adjunct to treatment in safe and effective doses. Up to twice the recommended daily allowance of various vitamins and minerals should be used. Although anemia is common, iron should not be given initially due to danger of promoting free radical generation and bacterial proliferation. It should be added only after a week of therapy when the child has a good appetite and starts gaining weight.

Vitamin A deficiency is not an infrequent association and is an important cause of blindness caused by keratomalacia. Vitamin A should therefore be given to all severely malnourished children on day 1 at 50,000 IU, 100,000 IU and 200,000 IU for infants 0–5 month, 6–12 months and children >1 year of age unless there is definite evidence that a dose has been given in the last month. In presence of xerophthalmia, the same dose should be repeated on the next day and 2 weeks later. Children >1 year but weighing <8 kg should receive half the age related dose. In presence of clinical evidence of xerophthalmia the administration of vitamin A should be considered an emergency as the changes may progress to keratomalacia within hours.

Children with SAM receiving F-75, F-100 or RUTF complying with WHO specifications do not need vitamin A supplementation because these preparations already contain sufficient vitamin A.

Vitamin K should be administered in a single dose of 2.5 mg intramuscularly at the time of admission. Daily multivitamin supplements containing thiamine 0.5 mg/1000 kcal, riboflavin 0.6 mg/1000 kcal and nicotinic acid (niacin equivalents) 6.6 mg/1000 kcal should be given. It is better to give a formulation that is truly multivitamin (e.g. one that has vitamin A, C, D, E and B₁₂). Folic acid 1 mg/day (5 mg on day 1), zinc 2 mg/kg/day and copper 0.2–0.3 mg/kg/day should be given daily. Iron 3 mg/kg/day should be added once child starts gaining weight, after the stabilization phase.

Emergency treatment of severe anemia: If a severely malnourished child has severe anemia with a hemoglobin

less than 4 g/dL or between 4 and 6 g/dL but with respiratory distress, a blood transfusion should be given with whole blood 10 mL/kg bodyweight slowly over 3 hours. Furosemide should be given at the start of the transfusion. If the severely anemic child has signs of cardiac failure, packed cells rather than whole blood should be transfused.

The hemoglobin concentration may fall during the first week of treatment. This is normal and no transfusion should be given. In mild to moderate anemia, iron should be given for two months to replete iron stores but this should not be started until after the initial stabilization phase has been completed.

Step 7: Initiate Refeeding

Feeding should be started as soon as possible with a diet which has osmolarity less than 350 mOsm/L; lactose not more than 2–3 g/kg/day; appropriate renal solute load (urinary osmolarity <600 mOsm/L); initial percentage of calories from protein of 5%; adequate bioavailability of micronutrients and low viscosity. The preparation should be easy to prepare and socially acceptable and there should be facilities for adequate storage, cooking and refrigeration.

Start cautious feeding: The suggested starter formulae are usually milk based, such as starter F-75 diet (containing with 75 kcal/100 mL). The protein content is 0.9 g of protein/100 mL. Feeding should be started with F-75 as soon as possible as frequent small feeds. If child is unable to take orally with a cup and spoon or takes <80% of the target intake, nasogastric feeds should be initiated. Breastfeeding should be continued ad libitum. Older children could be started on cereal based diets (Table 7.12).

One should begin with 80 kcal/kg/day and gradually increase to 100 kcal/kg/day. To fulfill this, one should start with 2 hourly feeds of 11 mL/kg/feed. Night feeds are essential. The volume of feeds are increased gradually while decreasing the frequency of administration. The calories are increased only after the child can accept the increased volume of feeds.

Table 7.12: Starter diets

Diet contents (per 100 mL)	F-75 Starter	F-75 Starter (cereal based) Example: 1	F-75 Starter (cereal based) Example: 2
Cow milk or equivalent (mL) (approximate measure of one katori)	30 (1/3)	30 (1/3)	25 (1/4)
Sugar (g) (approximate measure of one level teaspoon)	9 (1½)	6 (1)	3 (1/2)
Cereal: Powdered puffed rice* (g) (approximate measure of one level teaspoon)	–	2.5 (¾)	6 (2)
Vegetable oil (g) (approximate measure of one level teaspoon)	2 (1/2)	2.5 (1/2)	3 (¾)
Water: Make up to (mL)	100	100	100
Energy (kcal)	75	75	75
Protein (g)	0.9	1.1	1.2
Lactose (g)	1.2	1.2	1.0

*Powdered puffed rice may be replaced by commercial precooked rice preparations (in same amounts).

Wherever feasible, actual weighing of the constituents should be carried out. Household measure should be used only as an alternative, as they may not be standardized.

The above charts give the composition for 100 mL diet. Wherever, there is a facility for refrigeration, 1 liter diet could be prepared by multiplying the requirement of each constituent by 10.

Step 8: Achieve Catch-up Growth with F-100 Diet and RUTF

For catch-up growth, energy and protein intake has to be enhanced further; F-75 diet (F-75 kcal/100 mL) would not be enough. Starter F-75 feeds should be gradually replaced with feeds which have a higher calorie density (100 kcal/100 mL) and have at least 2.5–3.0 g protein/100 mL. These feeds are called F-100 diets or Catch-up diets (Table 7.13).

Once appetite returns, increasing intakes of F-100 should be encouraged. It is recommended that each successive feed is increased by 10 mL until some is left uneaten. The frequency of feeds gradually decreased to 6 feeds/day and the volume increased till the child is being

offered 200 mL/kg/day of F-100 diet. Breastfeeding should be continued *Ad libitum*.

Once the child achieves rapid weight gain, F-100 should be changed to RUTF and gradually to home food.

The daily amount of RUTF to be consumed varies according to body weight as follows: 3–4.9 kg: 105–130 g; 5–6.9 kg: 200–260 g; 7–9.9 kg: 260–400 g and 10–14.9 kg: 400–460 g. This amount is to be given along with plenty of water in 2–3 hourly feeds. The child should continue to receive other foods and breastfeeding during medical nutrition therapy with RUTF.

Home foods should be added as soon as possible to prepare the child for home foods at discharge. They should have comparable energy and protein concentrations once the catchup diets are well tolerated. Khichri, dalia, banana, curd-rice and other culturally acceptable and locally available diets can also be offered liberally.

Special diets for diarrhea: For children with persistent diarrhea, who do not tolerate low lactose diets, lactose free diet can be started. In these diets, carbohydrates (rice, sugar and glucose) can be given in varying proportions according to the patients' individual tolerance to achieve optimal balance between osmolarity and digestibility.

Monitoring progress during treatment: If there is a good weight gain of >10 g/kg/day, the same treatment should be continued till recovery. If there is a moderate weight gain of 5–10 g/kg/day; food intake should be checked and the children should be screened for systemic infection. In case of poor weight gain of <5 g/kg/day possible causes like inadequate feeding, untreated infection, psychological problems and coexisting infections like tuberculosis and HIV should be looked for and managed appropriately.

Table 7.13: Catchup diets

Diet contents (per 100 mL)	F-100 Catch-up	F-100 Catch-up (cereal based)
Cow milk/toned dairy milk (mL) (approximate measure of one katori)	95 (¾)	75 (1/2)
Sugar (g) (approximate measure of one level teaspoon)	5 (1)	2.5 (1/2)
Cereal: Puffed rice (g) (approximate measure of one level teaspoon)	–	7 (2)
Vegetable oil (g) (approximate measure of one level teaspoon)	2 (1/2)	2 (1/2)
Water to make (mL)	100	100
Energy (kcal)	101	100
Protein (g)	2.9	2.9
Lactose (g)	3.8	3

Step 9: Provide Sensory Stimulation and Emotional Support

Delayed mental and behavioral development often occurs in severe malnutrition. In addition to the above management, one should encourage a cheerful, stimulating environment; structured play therapy for at least 15–30 min/day; physical activity as soon as the child is well enough and tender loving care.

Step 10: Prepare for Follow-up

Ideally, 6–8 weeks of hospitalization is required for optimum recovery. SAM children admitted to hospital can be transferred to outpatient care when their medical complications have settled, edema, is resolving and they have a good appetite, they are consuming adequate RUTF, and are clinically well and alert.

The decision to transfer children from inpatient to outpatient care should be determined by their clinical condition and not on the basis of specific anthropometric outcomes such as a specific mid-upper arm circumference or weight-for-height/length.

National guidelines recommend treatment for helminthic infections should be given to all children with SAM before discharge. Give a single oral dose of Albendazole 200 mg for children aged 12–23 months, 400 mg for children aged 24 months or older.

Post-Discharge Care at Home

A child with SAM may be considered to have completed treatment when:

- There is no edema for at least 2 weeks, plus
- Weight-for-height (or length) reaches -2 SD or higher on WHO Growth Standard or mid-upper-arm circumference is more than 12.5 cm

After discharge, the principles of care are the same for supervised home care of uncomplicated SAM (as above). This is a very important phase and full support needs to be extended to the family by involving the frontline workers and community. The treatment of the child is not complete till the weight-for-height and MUAC reaches normal range (see below).

The caregiver should be advised to bring child back for regular follow-up checks, ensure booster immunizations, make sure that vitamin A is given every 6 months, feed frequently with energy and nutrient dense foods and give structured play therapy.

Until the above is reached, the child must be under constant care at hospital and/or home by a frontline health team. Support to the family must be continued during this phase and after discharge from treatment.

Severe Acute Malnutrition: Under 6 Months of Age

Infants less than 6 months of age with SAM and any of the following complicating factors should be admitted for inpatient care:

- a. Any serious clinical condition or medical complication as outlined for infants who are 6 months of age or older with severe acute malnutrition;
- b. Recent weight loss or failure to gain weight;
- c. Ineffective feeding (attachment, positioning and suckling) directly observed for 15–20 min, ideally in a supervised separated area;
- d. Any pitting edema;
- e. Any medical or social issue needing more detailed assessment or intensive support (e.g. disability, depression of the caregiver, or other adverse social circumstances);

Infants less than 6 months of age with SAM should receive the same general medical care as infants with severe acute malnutrition who are 6 months of age or older:

- a. Infants with severe acute malnutrition who are admitted for inpatient care should be given parenteral antibiotics to treat possible sepsis and appropriate treatment for other medical complications such as tuberculosis, HIV, surgical conditions or disability;
- b. Infants with severe acute malnutrition who are not admitted should receive a course of broad-spectrum oral antibiotic, such as amoxicillin, in an appropriately weight adjusted dose.

Feeding approaches for infants who are less than 6 months of age with severe acute malnutrition should prioritize establishing, or re-establishing, effective exclusive breastfeeding by the mother.

Infants who are admitted:

- a. Should be breastfed where possible and the mothers should be supported to breastfeed the infants. If an infant is not breastfed, support should be given to the mother to re-lactate
- b. Should also be provided a supplementary feed: supplementary suckling approaches should, where feasible, be prioritized; for infants with severe acute malnutrition but no edema, expressed breast milk should be given, and, where this is not possible, commercial (generic) infant formula or F-75 or diluted F-100 may be given (prepared F-100 should be further diluted by adding 30% water), either alone or as the supplementary feed together with breast milk; and for infants with severe acute malnutrition and edema, infant formula or F-75 should be given as a supplement to breast milk;
- c. Should not be given undiluted F-100 at any time (owing to the high renal solute load and risk of hypernatremic dehydration); prepared F-100 should be further diluted by adding 30% water.
- d. If there is no realistic prospect of being breastfed, should be given appropriate and adequate replacement feeds such as commercial (generic) infant formula, with relevant support to enable safe preparation and use, including at home when discharged.

- e. Assessment of the physical and mental health status of mothers or caregivers should be promoted and relevant treatment or support provided

Infants less than 6 months of age with SAM and have been admitted to inpatient care can be transferred to outpatient care when:

- All clinical conditions or medical complications, including edema, are resolved, and
- The infant has good appetite, is clinically well and alert, and
- Weight gain on either exclusive breastfeeding or replacement feeding is satisfactory, e.g. above the median of the WHO growth velocity standards or more than 5 g/kg/day for at least 3 successive days, and
- The infant has been checked for immunizations and other routine interventions, and
- The mother or caregiver is linked with needed community-based follow-up and support

For infants who are less than 6 months of age with severe acute malnutrition and who do not require inpatient care, or whose caregivers decline admission for assessment and treatment:

- Counseling and support for optimal infant and young child feeding should be provided, based on general recommendations for feeding infants and young children, including for low-birth-weight infants;
- Weight gain of the infant should be monitored weekly to observe changes;
- If the infant does not gain weight, or loses weight while the mother or caregiver is receiving support for breastfeeding, then he or she should be referred to inpatient care;
- Assessment of the physical and mental health status of mothers or caregivers should be promoted and relevant treatment or support provided.

Preventing Undernutrition

Since childhood undernutrition is multifactorial, it can only be prevented through interventions across sectors. Action is required at the individual and societal level (Panel 2). Health and wellbeing of girls, women and children must be ensured. Underlying social determinants such as poverty, illiteracy, discrimination and social insecurity must be addressed. Convergence of health programs (antenatal care, facility birth, home based newborn care, immunization, IMNCI, etc.) with ICDS initiatives (feeding counseling, supplementary nutrition and preschool education) must converge.

Integrated Child Development Services (ICDS)

The ICDS program seeks to directly reach out to children, below six years, especially from vulnerable groups and remote areas. The Scheme provides an integrated approach for converging basic services through community-based workers and helpers. The services are

Panel 2: Preventing undernutrition in children

Individual Level Action

Mother

- Care of the adolescent girl
- Childbirth after 20 years
- Spacing between pregnancies
- No more than 2 children
- Iron and folic acid to ensure good hemoglobin
- Antenatal checks as per national program
- Additional food and micronutrients (especially iron and folic acid) in pregnancy

Child

- Initiation of breastfeeding within one hour
- Exclusive breastfeeding for first 6 months, continuing till 2 years or more
- Special support to low birth weight babies for breastfeeding and kangaroo mother care
- Complementary feeding introduction at 6 months
- Optimum intake of food that is balanced, energy-dense and of good quality
- Hygiene, handwashing
- Full immunization especially, measles, BCG, rotavirus, *H. influenzae* and pneumococcal
- Prompt treatment of diarrhea with ORS and zinc
- Prompt treatment of pneumonia and other illnesses
- Growth monitoring and periodic checks

Adolescent girls: Future mothers

- Optimum nutrition
- Education in parenting and mothercraft
- Marriage after 18 years of age

Society Level Action

- Safe water and sanitation
- A culture of good nutrition
- Maternity and child care leave to enable women to breastfeed and to take care of infants and children
- Crèches for children of working women
- Promoting breastfeeding at workplace
- Cash support to pregnant and lactating women (as being provided by the government)
- Socio-economic development, high income, equity
- Education of women and men
- Women's empowerment
- Food security at the household level
- Nutrition promoting agriculture

provided at a center called the 'Anganwadi'. A package of six services is provided under the ICDS Scheme:

- Supplementary nutrition for mother and the child. The norms are given in Table 7.14.
- Immunization of pregnant women and infants as per the national program.
- Nonformal preschool education. Stimulating learning.
- Health check-up. This includes health care of children less than six years of age, antenatal care of expectant mothers and postnatal care of nursing mothers. These

Table 7.14: Norms for supplementary nutrition in ICDS

Beneficiaries	Energy kcal	Protein (g)
Children (6 to 72 months)	500	12–15
Severely malnourished children (SAM) (6 to 72 months)	800	20–25
Pregnant women and lactating mothers	600	18–20

Source: <http://icds-wcd.nic.in/icds/icds.aspx>

services are provided by the ANM and medical officers under the RCH programme. The various health services include regular health check-ups, immunization, management of malnutrition, treatment of diarrhea, deworming and distribution of simple medicines.

- e. Referral services. During health check-ups and growth monitoring, sick or malnourished children are referred to the primary health center or its subcenter.
- f. Nutrition and health education. Healthy behaviors and detection and treatment of sickness.

Under the POSHAN Abhiyaan, a flagship mission of the Prime Minister launched in February 2018, a new impetus has been given to nutrition program. The goals for this three-year mission are to:

- Reduce stunting in children (0–6 years) @ 2% per annum
- Reduce under-nutrition (underweight prevalence) in children (0–6 years) @ 2% per annum
- Reduce low birth weight (LBW) @ 2% per annum
- Reduce prevalence of anemia amongst young children (6–59 months) @ 3% per annum

- Reduce prevalence of anemia amongst women and adolescent girls (15–49 years) @3% per annum

Under the POSHAN (PM's Overarching Scheme for Holistic Nutrition) Abhiyaan the focus is on health and nutrition in first 1000 days of life, convergence across sectors (including Swachh Bharat and Health), IT driven tracking of beneficiaries apart from growth monitoring. A major thrust of the mission will be to create an unprecedented Jan Andolan for nutrition and health.

Suggested Reading

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Micronutrients in Health and Disease

Rajni Sharma • Arvind Bagga

Vitamins are organic compounds, required in small amounts, for maintenance of health and normal growth that are not synthesized in the body and must be obtained from the diet. They can be categorized into fat-soluble (A, D, E, K) and water-soluble forms (B complex vitamins, C and folate). The former control protein synthesis at either transcriptional or post-transcriptional level and perform diverse biochemical functions, as hormones (e.g. vitamin D), antioxidants (e.g. vitamin E) and regulators of tissue growth and differentiation (e.g. vitamin A). Several vitamins (e.g. B complex vitamins) function as precursors for enzyme cofactor biomolecules (coenzymes) that act as catalysts and substrates in metabolism. Breast milk is deficient in vitamins D and K and exclusively breastfed infants must be supplemented with these vitamins (Box 8.1).

Certain minerals are essential to support biochemical processes involved in cell structure and function. Important minerals include calcium, chloride, cobalt, copper, iodine, iron, magnesium, manganese, molybdenum, nickel, phosphorus, potassium, selenium, sodium, sulfur and zinc. The amount required varies from >100 mg/day (major minerals including sodium, potassium, chloride, calcium, magnesium and phosphorus) to <100 mg/day (trace minerals including iron, copper, zinc). Ultra-trace minerals are required in miniscule amounts (<1 mg/day). Marginal or severe imbalances in trace elements are risk factors for several diseases. In addition to deficiencies of iron and iodine, features of deficiency of copper, zinc and selenium are recognized.

Box 8.1: Breast milk and vitamins

Breast milk is the complete food for infants. However, breast milk is deficient in vitamins D and K.

Breast milk contains only 30–40 IU/L of vitamin D, whereas the RDA is higher. Exclusively breastfed babies require vitamin D supplementation in the dose of 400 IU/day to prevent rickets.

Vitamin K is produced by the gut microflora. It may take sometime for a newborn gut to be colonized by bacteria and start producing the vitamin. All babies should receive vitamin K at birth to prevent hemorrhagic disease of the newborn.

Intakes of micronutrients recommended by the National Academy of Science 2006 are available at www.nap.edu.

Intakes proposed by the Indian Council of Medical Research in 2010 are listed in Table 6.1 and are also available at [icmr.nic.in/final RDA-2010.pdf](http://icmr.nic.in/final%20RDA-2010.pdf)

FAT-SOLUBLE VITAMINS

Vitamin A

Vitamin A (retinol) is derived from natural plant pigments called carotenoids (provitamin A) that are converted to retinol in the body and stored as retinol palmitate in the liver. Retinol is further converted to the active forms of vitamin A: Retinal and retinoic acid.

Being a fat-soluble vitamin, vitamin A is absorbed as a part of chylomicrons.

Physiological Functions

Retinol is converted to retinal which plays an important role in vision especially night vision. Within the eye, 11-*cis*-retinal, an isomer of retinal, is bound to rhodopsin (rod cells) and iodopsin (cones). As light enters the eye, 11-*cis*-retinal is isomerized to the all-*trans* form. The all-*trans*-retinal dissociates from the opsin in a series of steps called bleaching. This isomerization induces a nervous signal along the optic nerve to the visual center of the brain. Subsequently, the all-*trans*-retinal is recycled and converted to 11-*cis*-retinal form via a series of enzymatic reactions. Deficiency in vitamin A inhibits the reformation of rhodopsin and leads to night blindness. Retinal and its derivative retinoic acid bind to intracellular receptor, regulate gene expression and induce the synthesis of proteins involved in growth and cell differentiation. Retinol is also required for production of glycoproteins and mucus and helps to maintain the integrity of epithelial tissues. Vitamin A deficiency leads to drying of epithelial surfaces and excessive keratin formation of the surface.

Sources

Carotenoids (provitamin A) are found in green and yellow plants including carrots, dark-green leafy vegetables,

squash, oranges and tomatoes. β -carotene is the major carotenoid found in plants. Animal sources such as liver, shark/cod liver oil, egg yolk, whole milk and butter are good sources of preformed vitamin A (retinol). Many processed foods and infant formulas are fortified with preformed vitamin A.

Recommended Daily Allowance

The recommended daily allowance of vitamin A is as follows: (i) infants 300–400 μg ; (ii) children 400–600 μg ; (iii) adolescents 750 μg .

1 μg retinol = 3.3 international units (IU) of vitamin A. Hence, 30 mg retinol = 100,000 IU vitamin A

Vitamin A Deficiency

Mild vitamin A deficiency manifests with follicular hyperkeratosis of the skin that consists of rough skin with raised hyperkeratotic patches resembling goosebumps. Defective dark adaptation is a characteristic early clinical feature, resulting in night blindness. The ocular epithelium becomes dry (xerophthalmia) (Table 8.1) and hyperkeratinized with the appearance of small foam-like silvery lesions on the conjunctiva (Bitot spots) (Fig. 8.1). More severe deficiency leads to hyperkeratinization of the cornea with the appearance of corneal opacity, which can progress to ulceration and infection (keratomalacia) (Fig. 8.2). Loss of mucosal integrity of the respiratory, gastrointestinal tracts and impaired immunity predispose children to severe systemic infections especially measles. In developing countries, vitamin A deficiency is the leading cause of blindness in preschool children.

Malnourished children and those with fat malabsorption (celiac disease and liver disease) are predisposed to vitamin A deficiency.

Laboratory tests show mild leukopenia and serum retinol level of 15 $\mu\text{g}/\text{dL}$ or less (normal 20 to 80 $\mu\text{g}/\text{dL}$).

Treatment of vitamin A deficiency: Specific treatment consists of oral vitamin A at a dose of 50,000 IU, 100,000 IU and 200,000 IU in children aged <6 months, 6–12 months and >1 year, respectively. The same dose is repeated next day and 4 weeks later. Alternatively, parenteral water-soluble preparations are administered in children with persistent vomiting or severe malabsorption (parenteral dose is half the oral dose for children above 6–12 months and 75% in <6 months old). Clouding of the cornea in a child with vitamin A deficiency

Table 8.1: WHO classification of xerophthalmia

Primary signs	Secondary signs
X1A Conjunctival xerosis	XN Night blindness
X1B Bitot's spots	XF Fundal changes
X2 Corneal xerosis	XS Corneal scarring
X3A Corneal ulceration (<1/3 of cornea)	
X3B Corneal ulceration (>1/3 of cornea)	

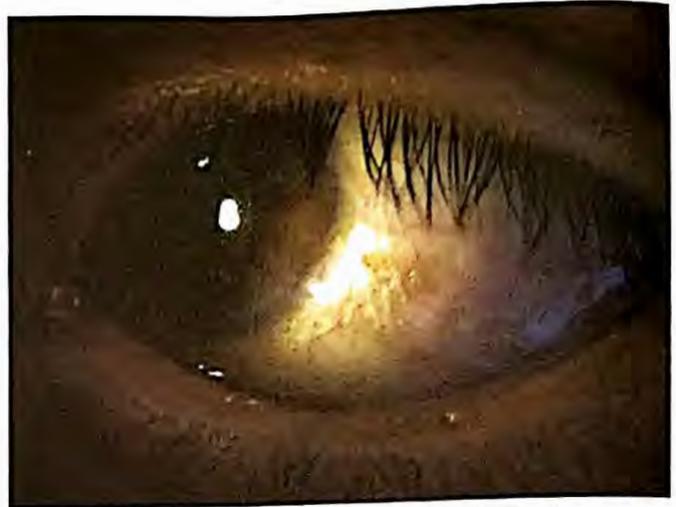


Fig. 8.1: Bitot spot showing foamy frothy sharply demarcated whitish spot on the temporal side of bulbar conjunctiva. This is formed by keratinization of the epithelium and accumulation of mucus, bacteria and debris on the surface, and is a classic sign of vitamin A deficiency (Courtesy: Dr Vanathi, RP Centre, AIIMS)



Fig. 8.2: Bilateral keratomalacia in a child with protein energy malnutrition and severe vitamin A deficiency precipitated by an episode of pneumonia. Note the bilateral corneal opacification and corneal perforation in the left eye.

is an emergency and requires parenteral administration of 50,000 to 100,000 IU (15 to 30 mg retinol). In case of keratomalacia, local treatment with antibiotic drops and ointment and padding of the eye enhances healing.

Prevention: Under the National Vitamin A Prophylaxis Programme, sponsored by the Ministry of Health and Family Welfare, children between 1 and 5 years were previously given oral doses of 200,000 IU vitamin A every six months. Evaluation studies since then revealed inadequate coverage in most states. Currently, vitamin A is given only to children less than three years old since they are at greatest risk and the administration of the first two doses is linked with routine immunization to improve

the coverage. Hence, a dose of 100,000 IU is given with measles vaccine at 9 months and 200,000 IU with the DPT booster at 15–18 months. In endemic areas, 3 more doses are administered at 24, 30 and 36 months. Dietary improvement is necessary to prevent vitamin A deficiency. Children with measles and severe malnutrition should receive vitamin A at 100,000 IU, if <1-year-old and 200,000 IU, if older.

Carotenemia

Beta-carotene is an important precursor of vitamin A in vegetable-based diets; 10 µg β-carotene has the biological potency of 1 µg retinol. Excessive dietary intake of carotene containing foods, most commonly carrots and carrot-containing products, can lead to deposition of carotenoids in keratin and subcutaneous fat. At high plasma levels, yellow pigmentation (carotenemia) shows in superficial skin (face, palms and soles), but not in sclerae. The color returns to normal within 2–6 weeks of discontinuing intake of carrots.

Hypervitaminosis A and Teratogenicity

Vitamin A toxicity occurs ingesting more than 50,000 IU/day of vitamin A for several months in the form of fish liver oil, therapeutic vitamin preparations or, in adolescents, as retinol or retinoic acid for acne. Acute manifestations include pseudotumor cerebri (vomiting, irritability, bulging fontanel, diplopia, headache). Patients with chronic hypervitaminosis may have anorexia, dry skin, alopecia, painful joints and hepatosplenomegaly. Vitamin A is teratogenic, if taken in high doses in early gestation. The WHO recommends that vitamin A in take during pregnancy should not exceed 3000 µg daily or 7500 µg every week.

Vitamin D

Vitamin D, the 'sunshine vitamin', is produced in the upper layers of the skin on exposure to solar ultraviolet B (UVB) radiation. Under normal conditions, endogenous synthesis of vitamin D is sufficient to meet the body's needs. However, when endogenous production is low, due to a variety of factors, diet becomes an important source of the vitamin.

Metabolism and Mechanism of Action

There are two forms of vitamin D: Vitamin D₂ (ergocalciferol, made in plants) and D₃ (cholecalciferol, made in animals). Vitamin D₃ is synthesized from 7-dehydrocholesterol in the dermis after exposure to UVB solar irradiation of wavelength 290–315 nm. It is then bound to vitamin D-binding protein and transported to the liver. Vitamin D can also be derived from the diet from either plant (vitamin D₂) or animal (vitamin D₃) sources. Dietary vitamin D is readily absorbed from the duodenum by an active transport system and incorporated into

chylomicrons and transported to the liver. Being a fat-soluble vitamin, vitamin D absorption is decreased in conditions of fat malabsorption such as chronic pancreatitis, cystic fibrosis, etc.

In the liver, the enzyme 25α-hydroxylase hydroxylates vitamin D₂ and D₃ to form 25-hydroxyvitamin D₂ [25OHD₂ or ergocalcidiol] and 25-hydroxyvitamin D₃ [25OHD₃ or cholecalcidiol], respectively. This biochemical step is substrate dependent and occurs without any negative feedback control. 25OHD (predominantly in the form of cholecalcidiol) is then released into the bloodstream and has a biological half-life of approximately 3 weeks. Due to its long half-life, serum cholecalcidiol level is considered the biochemical marker for vitamin D status in the body.

Cholecalcidiol (25OHD₃) undergoes further hydroxylation in the kidneys by the enzyme 1α-hydroxylase to form 1,25-dihydroxyvitamin D₃ [1,25(OH)₂D₃] or cholecalcitriol. Cholecalcitriol is the active form of vitamin D and affects calcium homeostasis through its action on the intestine, kidney and bones. In the intestine, it increases absorption of calcium by inducing the formation of calcium transport proteins and intracellular calcium-binding protein (calbindin) in the enterocytes. In the kidney, cholecalcitriol enhances calcium resorption in the renal tubules by a similar mechanism. It decreases the activity of renal 1-α-hydroxylase enzyme via feedback inhibition, and stimulates renal 24-hydroxylase enzyme activity (that inactivates both calcidiol and calcitriol). In the bone, calcitriol helps in stimulating osteoclast activity and proper mineralization of bone. Thus, the overall effect of cholecalcitriol in the body is to increase serum levels of calcium.

The activity of renal 1α-hydroxylase enzyme is affected by other factors as well: Both parathyroid hormone and low serum phosphate levels increase the activity of 1-α-hydroxylase, whereas the hormone fibroblast growth factor-23 (FGF-23), produced by bone, decreases its activity (Fig. 8.3).

Sources

The dietary sources of vitamin D include fish and fish oils, egg yolk and some plants. However, natural diet contains very little vitamin D and adequate endogenous production or dietary supplementation is essential to prevent deficiency.

Adequate vitamin D synthesis in the skin depends on various factors including time spent outdoors and the amount of clothing. The dermal pigment melanin decreases the amount of UVB rays that reach the epidermal layers containing the substrate, 7-dehydrocholesterol. Hence, individuals with dark skin require more duration of sun exposure to make the same amount of vitamin D. Moreover, the amount of UVB radiation reaching the skin depends on the time of the day, latitude, season, cloud cover and presence of air pollutants. Excessive exposure to sunlight does not increase vitamin D production as previtamin D₃ is degraded into inert products such as

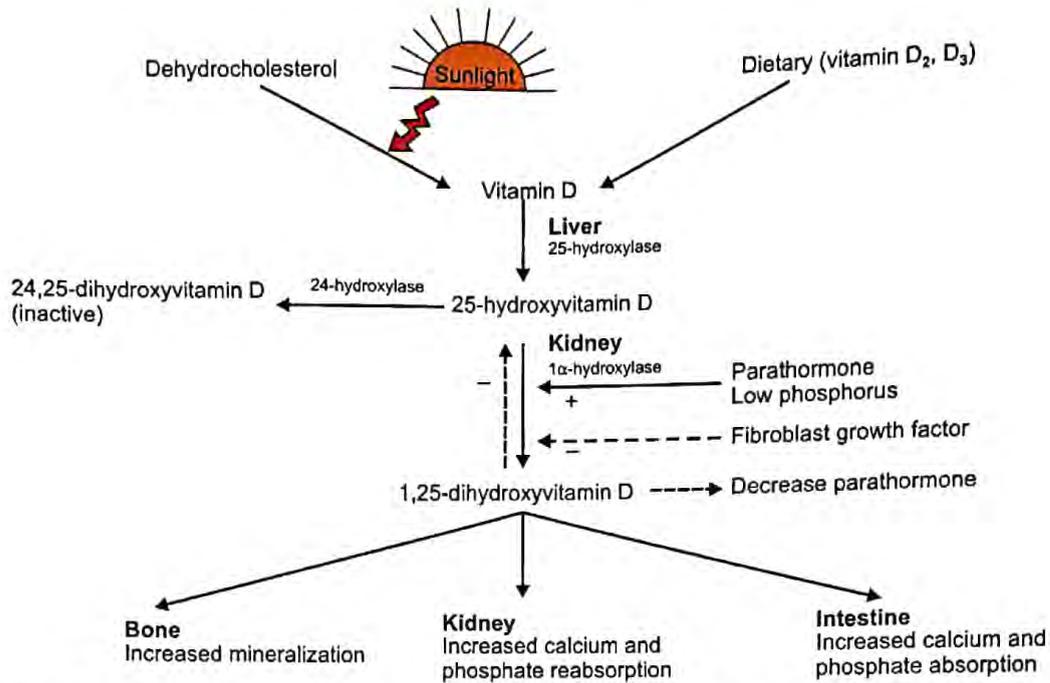


Fig. 8.3: Vitamin D metabolism. Serum levels of fibroblast growth factor-23 are elevated in response to increased serum phosphate and also inhibit the production of parathormone

lumisterol-3 and tachysterol-3, and vitamin D₃ photoisomerizes to suprasterol and inert products.

Vitamin D Requirements

The daily requirement of vitamin D is 10 µg (400 IU) per day in infants and 15 µg (600 IU) per day in children >1 year age. When endogenous production is inadequate, vitamin D needs to be supplied through dietary supplementation.

The risk factors that predispose to vitamin D deficiency include limited exposure to sunlight, full body clothing, dark skin, debilitation, living at high latitudes, disability and predominant indoor living.

Breast milk is a poor source of vitamin D containing only 30–40 IU per liter and exclusively breastfed infants are at high risk of developing vitamin D deficiency and rickets unless supplemented. Therefore, exclusively breastfed babies should receive 400 IU of supplemental vitamin D per day. Formula milk has 400 IU of vitamin D per litre and children getting less than 1 litre formula per day also require supplementation. Pregnant and lactating mothers should receive 600 IU of vitamin D per day in order to meet their daily requirements.

Rickets

Rickets is a disease of growing bone. It is derived from the word 'wrickets' meaning 'twisted' referring to the characteristic bony deformities or 'bow legs' of rickets. The most common cause of rickets is a nutritional deficiency of vitamin D and less commonly, a dietary deficiency of calcium or phosphorus.

Pathophysiology: Vitamin D deficiency leads to hypocalcemia which stimulates the parathyroid gland to secrete parathormone (PTH). Increased PTH levels stimulate osteoclastic activity of bone and help restore the blood calcium levels to normal. However, PTH leads a concomitant loss of phosphate from the kidney leading to low serum phosphate levels.

Under normal conditions of growth, the cartilaginous growth plate undergoes mineralization by enchondral calcification. In this process, the chondrocytes hypertrophy and then undergo apoptosis followed by mineralization. Adequate amount of phosphate is essential for the apoptosis of the chondrocytes. In the absence of adequate phosphate, the chondrocytes continue to hypertrophy and this leads to the characteristic swellings at the growth plates. Mineralization of the bone is also decreased leading to osteomalacia and bending of weight bearing bones.

Osteomalacia is a term used for decreased mineralization of the bony matrix and is seen both in children and adults, whereas rickets is a disease of growing bones. Osteomalacia is different from osteoporosis; the latter refers to a proportionate loss of bone volume, both organic matrix (osteoid) and mineral, which occurs most commonly due to prolonged intake of corticosteroids.

Nutritional Rickets

Vitamin D deficiency is the leading cause of rickets, both in developing and developed countries. Though nutritional rickets had once been virtually eradicated in developed nations by fortification of milk or direct

administration of vitamin D, recent reports suggest that it is becoming increasingly common in exclusively breastfed infants particularly those who not get vitamin supplements. Apart from poor dietary intake and insufficient exposure to sunlight, vitamin D deficiency may result from various malabsorption syndromes, chronic liver disease and use of anticonvulsant drugs. Anticonvulsant drugs and antitubercular drugs (isoniazid, rifampicin) induce hepatic cytochrome P450 oxidase that leads to conversion of 25OHD₃ into its inactive metabolites.

As mentioned, nutritional rickets may also occur secondary to severe dietary deficiency of calcium that can occur with or without concomitant vitamin D deficiency. Dietary deficiency of phosphate is rare due to the widespread availability of phosphate in the diet but may occur in preterm babies who have high phosphate requirements for growth.

Clinical features: The classical features of rickets include swellings of the wrist and ankles and leg deformities in the form of bow-legs (genu varum) or knock-knees (genu valgum) (Fig. 8.4). From head to toe, the following signs may be seen: Frontal bossing, delayed closure of anterior fontanelle, craniotabes (soft skull bones), delayed dentition and beaded appearance of the anterior costochondral junctions (rachitic rosary). A depression (termed Harrison sulcus) may be evident along the lower border of the chest at the site of insertion of the diaphragm which appears due to the pull of the diaphragm on the weakened chest wall. Apart from this, other features of rickets include hypocalcemic seizures, muscle weakness, hypotonia, failure to thrive and irritability (due to bony pains). There

is an increased risk of fracture even with minimal trauma. Pelvic deformities can develop including outlet narrowing which can be troublesome for females at a later age by increasing the risk of obstructed labor.

Evaluation: The initial evaluation of rickets includes serum biochemistry and radiographs of the wrists and/or knee joints. Serum levels of calcium may be normal or low, serum phosphate will be low and alkaline phosphatase high. Radiologic changes are characteristically seen at the metaphysis. The first change is loss of normal zone of provisional calcification adjacent to the metaphysis seen as a blurring or a frayed appearance of the metaphyseal margin (fraying). Cartilage hypertrophy leads to widening of the growth plate giving the appearance of cupping and widening of metaphyseal ends (splaying) (Fig. 8.5). Weight-bearing and stress on uncalcified bone gives rise to bowing of limbs. Eventually, a generalized reduction in bone density is seen (osteopenia).

The diagnosis of vitamin D deficiency is based on low circulating levels of 25OHD₃. Values above 20 ng/mL are considered normal, between 10 and 20 ng/mL are insufficient and below 10 ng/mL are indicative of deficiency (Table 8.2).

Management: Treatment of nutritional rickets requires administration of high doses of vitamin D. Previously, oral bolus doses of vitamin D (also called Stoss therapy) were preferred which consisted of 60,000 IU of vitamin D daily or on alternate days to reach a maximum total dose of 6,00,000 IU. There is now consensus to use lower daily doses of 2000 IU, 3000–6000 IU, and 6000 IU for infants below 12 months, 1–12 years and more than 12 years,



Fig. 8.4: A 5-year-old child with rickets with mild frontal bossing, wide wrists and bow legs



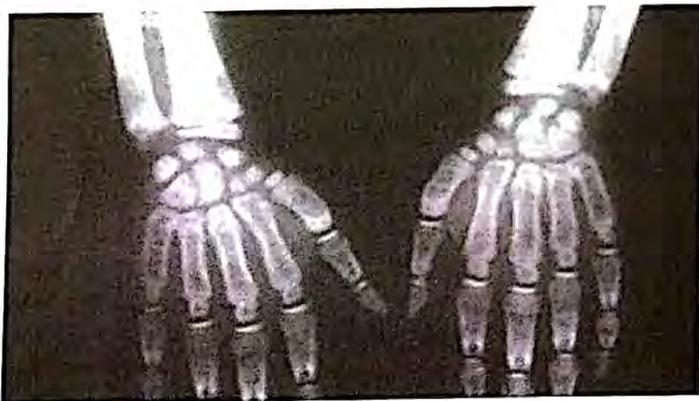
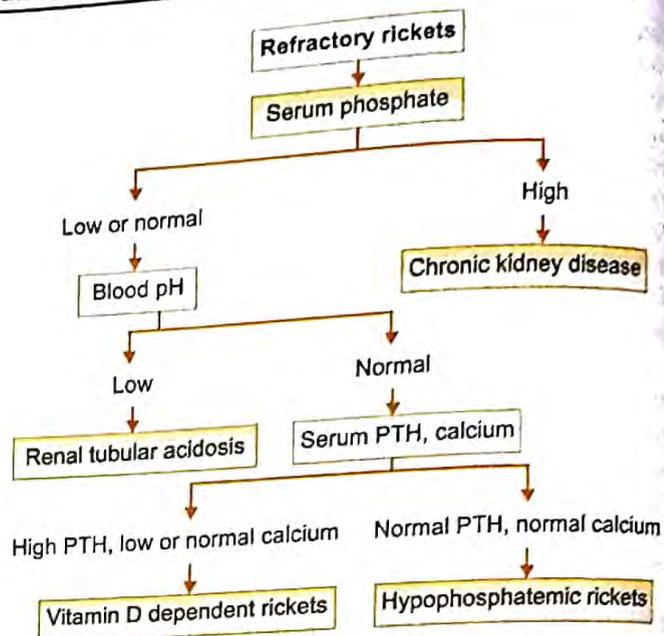
Fig. 8.5: Radiograph of wrist in 4-year-old boy with rickets. Note widening, cupping and fraying at the metaphyseal ends of forearm bones

Table 8.2: Vitamin D levels in serum

	25-hydroxyvitamin D level (ng/mL)
Deficient	Less than 10
Insufficient	10–20
Optimal	20–60
High	60–90
Toxic	Greater than 90

respectively, for a duration of 12 weeks, followed by a maintenance dose of 400–600 IU/day (Table 8.3). Higher doses can be given as oral bolus dose (Stoss therapy) in patients with suspected noncompliance to daily therapy. Oral calcium supplements (30–75 mg/kg/day) should be given to all patients for 2 months. Following adequate therapy, most patients with vitamin D deficiency rickets show radiological evidence of healing (Fig. 8.6) within 4 weeks. Reduction in blood levels of alkaline phosphatase and resolution of clinical signs occur slowly. The X-ray and blood biochemistry should be rechecked after completion of therapy. If radiologic healing cannot be demonstrated, despite adequate therapy, patients should be evaluated for refractory rickets (Fig. 8.7).

Prevention: For prevention of rickets, all infants from birth to 12 months of age should get 400 IU/day, independently of their mode of feeding. Beyond 12 months of age, all children and adults need to meet their nutritional requirement for vitamin D through diet and/or supplementation, which is at least 600 IU/day (15 µg).

**Fig. 8.6:** Healing of the growth plate after vitamin D therapy**Fig. 8.7:** Biochemical evaluation of a child with refractory rickets

Hypervitaminosis D

Excessive vitamin D due to over-dosage can result in hypervitaminosis D (serum levels >100 ng/mL). This can result in hypercalcemia and hypercalciuria increasing the risk of renal stones. Other manifestations of hypercalcemia include anorexia, vomiting, hypertension, renal insufficiency and failure to thrive. Such an “epidemic of hypercalcemia” was reported in England in the 1950s due to high dose vitamin D supplementation (between 2,000 and 3,000 IU/day) given for several months.

Refractory Rickets

Rickets that does not respond to the usual treatment of nutritional rickets is called refractory rickets. The diagnosis is made in patients with no radiological healing after vitamin D therapy. It can be broadly classified into two categories: Defects in vitamin D metabolism and low phosphate disorders. Figure 8.7 outlines the approach to a case of refractory rickets.

Vitamin D Dependent Rickets (VDDR)

These rare autosomal recessively inherited rickets are seen in infants between 3 and 6 months of age, who do not respond to adequate therapy of nutritional rickets.

Table 8.3: Treatment doses of vitamin D for nutritional rickets

Age	Daily dose for 90 days, IU	Single dose, IU	Maintenance daily dose, IU
3 months	2,000	NA	400
3–12 months	2,000	50,000	400
>12 months to 12 years	3,000–6,000	150,000	600
>12 years	6,000	300,000	600

VDDR type I: This condition is characterized by a deficiency of the enzyme, 25-hydroxyvitamin D 1α -hydroxylase. Reduced blood levels of calcium, normal to low phosphate and elevated alkaline phosphatase are characteristics. Blood levels of $25(\text{OH})_2\text{D}_3$ are normal but those of $1,25(\text{OH})_2\text{D}_3$ are markedly decreased despite hypocalcemia.

The clinical features are similar to vitamin D deficiency rickets and include hypotonia, growth failure, motor retardation (poor head control, delayed standing and walking), convulsions due to hypocalcemia, anemia and occasionally respiratory difficulty. Physical examination shows thickening of wrists and ankles, frontal bossing, widely open anterior fontanelle, rickety rosary, bony deformities and positive Trousseau and Chvostek signs. Dentition is delayed and development of tooth enamel impaired.

The treatment of VDDR type I consists of physiological doses of alpha-calcidol or calcitriol (0.25 μg daily). Most subjects require concomitant treatment with calcium with or without phosphate supplements. With appropriate therapy, the serum calcium levels rise and radiological healing occurs within 6 to 8 weeks.

VDDR type II: The features are similar to VDDR type I. There is end organ resistance to $1,25(\text{OH})_2\text{D}_3$. This leads to virtual abolition of actions of $1,25(\text{OH})_2\text{D}_3$, despite its markedly raised levels in circulation (secondary to hypocalcemia and low 24-hydroxylase activity).

Early onset of rickets, a high prevalence of alopecia and ectodermal defects (oligodontia, milia and epidermal cysts) are characteristic. Hypocalcemia, secondary hyperparathyroidism, elevated circulating levels of $1,25(\text{OH})_2\text{D}_3$ and an absence or decreased response to vitamin D analogs are seen. The response to treatment in patients with VDDR type II is not satisfactory. An occasional patient may get clinical and biochemical improvement and radiological healing following long-term administration of large amounts of intravenous or oral calcium.

Familial Hypophosphatemic Rickets

Normal level of serum phosphate is essential for mineralization of the growth cartilage. Some inherited clinical disorders lead to excessive loss of phosphate in the urine with very low serum phosphate levels and can present as refractory rickets. The most common inheritance pattern of these familial hypophosphatemic disorders is an X-linked dominant form with variable penetrance. Rarely, an autosomal recessive inheritance or sporadic forms can also occur.

Pathogenesis: The gene for X-linked hypophosphatemic rickets is termed the *PHEX* gene (phosphate regulating gene with homology to an endopeptidases on the X chromosome) which produces an endopeptidase. This

enzyme is responsible for the breakdown of FGF-23 and enzyme deficiency leads to high FGF-23 levels and excessive renal loss of phosphate. FGF-23 also decreases the activity of renal 1α -hydroxylase. Therefore, the blood levels of $1,25(\text{OH})_2\text{D}_3$ are low despite hypophosphatemia (which normally activates 1α -hydroxylase activity).

Clinical features: Lower limb deformities, such as coxa vara, genu valgum, genu varum and short stature, are common in hypophosphatemic rickets. Abnormalities of maxillofacial region and premature fusion of cranial sutures may lead to deformities of skull. Dental abnormalities are commonly seen including pulp deformities with intraglobular dentin, and frequent dental abscesses. Symptoms of hypocalcemia including tetany and muscle weakness, which are generally seen in disorders of vitamin D metabolism, are absent in hypophosphatemic forms. The mother of affected patient(s) may have bowing of legs and short stature or fasting hypophosphatemia.

Evaluation: The level of serum calcium is normal or slightly low (9–9.5 mg/dL), that of phosphate decreased (1.5–3 mg/dL). Serum alkaline phosphatase level is raised. PTH levels are normal. Blood levels of $1,25(\text{OH})_2\text{D}_3$ are inappropriately low for the level of serum phosphate. Urinary phosphate excretion is increased with decreased tubular reabsorption of phosphate.

Management: Oral phosphate and vitamin D supplements are the mainstay of therapy. Phosphates are provided at a dosage of 30–50 mg/kg (total 1–3 g elemental phosphorus) divided into 5 to 6 equal parts and can be given in the form of Joulie solution or as neutral phosphate effervescent tablets. Joulie's solution contains 30.4 mg of phosphate/mL. Diarrhea is a frequent problem with higher doses.

Vitamin D supplementation is necessary for the healing of rickets. Treatment is started with alpha-calcidol at a dose of 25–50 ng/kg/day (maximum 2 μg /day) until there is biochemical and radiological evidence of healing of rickets. Periodic monitoring of serum and urine levels of calcium and phosphate is essential. A level of serum phosphate greater than 3.0 to 3.2 mg/dL is desirable.

Other Causes of Rickets

Chronic kidney disease: Patients with chronic kidney disease have low $1,25(\text{OH})_2\text{D}_3$ levels due to poor 1α -hydroxylase activity in the kidney. Rickets may occasionally be the presenting manifestation of patients with tubulointerstitial disease. Serum levels of calcium are low and those of urea, creatinine, and PTH are increased. In contrast to other causes of vitamin D deficiency, serum phosphate levels are high. Therapy consists of restricting phosphate intake and providing supplements of calcium and active vitamin D analogs.

Renal tubular acidosis: Proximal or distal renal tubular acidosis (RTA) are important causes of refractory rickets

in children. The conditions are characterized by hyperchloremic (normal anion gap) metabolic acidosis with normal blood levels of urea and creatinine. Patients with proximal RTA have a generalized urinary loss of bicarbonate, phosphate, glucose and amino acids from the proximal tubules. The use of bicarbonate and phosphate supplementation (in proximal RTA) results in healing of rickets.

Oncogenous rickets: Benign mesenchymal tumors may secrete fibroblast growth factor-23 (FGF-23) that results in phosphaturia, hypophosphatemia and refractory rickets. Removal of the tumor reverses the biochemical abnormalities and heals the rickets.

Metaphyseal dysplasia: It is a type of skeletal dysplasia with bony deformities and radiological findings that mimic rickets. Short stature with bowing of legs and waddling gait are prominent. The classic biochemical findings are characteristically absent. Hypercalcemia has occasionally been reported in Jansen metaphyseal chondrodysplasia.

Fluorosis: Endemic fluorosis might present with bony deformities and radiological features mimicking rickets in school-going children. Pain in limbs and spine, mottling of teeth and family history of a similar illness are important features. Osteosclerosis and calcification of ligaments may be found in older children and adults; levels of alkaline phosphatase and PTH are raised. Levels of fluoride are increased in the community drinking water source.

Vitamin E

Vitamin E belongs to a group of compounds called tocopherols that are naturally occurring membrane antioxidants. Tocopherols prevent polyunsaturated fatty acids (PUFAs) from getting oxidized by oxygen-free radicals. The absorption of vitamin E in the gut is enhanced by simultaneous digestion and absorption of dietary lipids and medium chain triglycerides. Bile and pancreatic juices enhance absorption of vitamin E, which is incorporated into chylomicrons and delivered to the liver. From the liver, it is secreted with low density lipoproteins (LDL) and delivered to peripheral tissues. Red blood cells, which contain about 20% of vitamin E in plasma in their membranes, also participate in transport.

Nutritional requirements: Vitamin E requirement of normal infants is approximately 0.4 µg/kg body weight/day. For premature infants, 15 to 20 µg/day is required. The RDA for infants increases from 3 to 6 mg tocopherol from birth to 2 years of age. One mg of tocopherol provides 1.5 IU activity of vitamin E.

Sources: The common sources of vitamin E are vegetable oils (corn, cottonseed, safflower) and margarine. Other sources include leafy vegetables, nuts, milk and eggs; breast milk and colostrum are also rich sources.

Vitamin E Deficiency

Vitamin E deficiency causes muscle weakness, peripheral neuropathy, and hemolytic anemia. Infants particularly preterm babies are born in a state of relative tocopherol deficiency. This is attributed to limited placental transfer of vitamin E, relative dietary deficiency, intestinal malabsorption and rapid growth. The risk of vitamin E deficiency is high in infants fed on formulae high in polyunsaturated fats and low tocopherol content. As the digestive system matures, tocopherol absorption improves and its blood levels rise. A common presentation in preterm babies is with hemolytic anemia. The levels of hemoglobin range between 7 and 9 g/dL. Reticulocytosis and hyperbilirubinemia are accompanied by low levels of vitamin E. Administration of iron exacerbates hemolysis, unless vitamin E is also administered. Parenteral therapy with vitamin E corrects hemolysis.

Older children and adolescents with fat malabsorption, cholestatic liver disease or short bowel syndrome are prone to vitamin E deficiency. Abetalipoproteinemia, caused by the genetic absence of apolipoprotein B, is associated with fat malabsorption, steatorrhea, and undetectable plasma levels of vitamin E. Children with abetalipoproteinemia present with progressive neuropathy and pigmented retinopathy in the first two decades of life. Other manifestations include spinocerebellar ataxia with loss of deep tendon reflexes, loss of vibration and position sense, ophthalmoplegia, muscle weakness, ptosis and dysarthria.

Most malabsorption syndromes respond to large doses of oral vitamin E (15–20 mg/kg/day) with amelioration of deficiency and improvement in neurological symptoms.

Hypervitaminosis E

Relatively large amounts of vitamin E, in range of 400 to 800 mg tocopherol, have been taken daily by adults for months to years without causing any apparent harm. Occasionally, muscle weakness, fatigue, nausea and diarrhea are reported in persons ingesting 800–3200 mg/day. Vitamin E intoxication, at dosages exceeding 1,000 mg/day, results in antagonism to vitamin K action and risk of bleeding.

Vitamin K

Vitamin K exists in 2 forms: Vitamin K₁ (phylloquinone) that present in plants and vitamin K₂ (menaquinone) that is synthesized by intestinal bacteria.

Absorption and metabolism: The absorption of phylloquinone and menaquinone requires bile and pancreatic juice. Dietary vitamin K is absorbed in the jejunum, incorporated into chylomicrons and delivered to the circulation via the lymph. The liver is the primary site of action of vitamin K. The total body pool of vitamin K is small, 80% being in the liver.

Physiological function: The main role of vitamin K is as a cofactor in post-translational carboxylation of glutamic acid to form γ -carboxyglutamates in the liver. Factors II (prothrombin), VII, IX and X are vitamin K-dependent coagulation factors. The function of these proteins is to facilitate the chelation of calcium ions to glutamate and platelet phosphatide, which is essential for the coagulation cascade to operate.

Nutritional requirements: Vitamin K requirements are met by combination of dietary intake and microbiological biosynthesis in the intestines. Vitamin K requirement of newborns is 3 to 5 $\mu\text{g}/\text{day}$, that increases to 10 $\mu\text{g}/\text{day}$ at 2 years and 10 to 30 $\mu\text{g}/\text{day}$ in older children.

Newborn babies, especially preterm babies, are particularly prone to vitamin K deficiency due to a combination of factors; vitamin K does not cross the placenta and they do not have adequate intestinal bacterial flora to synthesize it endogenously. Moreover, breast milk is a poor source of vitamin K containing only 2 $\mu\text{g}/\text{L}$ phyloquinone. Hence, newborns need to be supplemented with vitamin K to prevent manifestations of deficiency including hemorrhage.

Sources: Green leafy vegetables and liver are rich dietary sources of vitamin K. Endogenous synthesis by intestinal flora is usually sufficient to meet daily requirements.

Vitamin K Deficiency

Vitamin K deficiency can occur in patients on chronic antibiotics due to the elimination of intestinal bacterial flora. Malabsorption syndromes such as biliary obstruction, cystic fibrosis, short bowel syndrome and celiac disease are other causes of deficiency.

Hemorrhagic disease of the newborn is a syndrome of severe systemic bleeding and ecchymoses appearing in the first week of life, predominating in breastfed infants. Bleeding can occur from various sites including gastrointestinal tract, nasal, umbilical stump or intracranial. Prothrombin and partial thromboplastin time are prolonged with normal platelet counts. Maternal use of drugs such as primidone, warfarin and phenytoin that antagonize the action of vitamin K can also cause severe hemorrhage in the baby. Routine administration of prophylactic vitamin K is recommended at birth to all healthy newborns at a dose of 0.5–1.0 mg intramuscularly to prevent hemorrhagic disease.

WATER-SOLUBLE VITAMINS

Unlike fat-soluble vitamins, water-soluble vitamins are not stored in the body (except vitamin B₁₂) and their deficiency can develop in a short period of time on deficient diets. Also, toxicity is very rare even in very high doses. They mostly act as co-enzymes in various intracellular metabolic reactions. Table 8.4 outlines the function, sources and clinical features of deficiency of essential B vitamins.

Thiamine (Vitamin B₁)

Biologic action: Thiamine is essential for glucose metabolism and cellular energy generation. Thiamine pyrophosphate, the active form of thiamine, is an important cofactor in the citric acid cycle that is active in the heart and brain. The vitamin is also involved in nucleic acid and fatty acid synthesis.

Requirements: Recommended daily allowance is 0.4 mg/1000 Cal of carbohydrate intake.

Dietary sources: These include human milk, cow milk, unpolished grains, eggs, organ meats (liver, kidney) and legumes. Thiamine is sensitive to heat, sulfites, pasteurization and sterilization.

Deficiency: Thiamine deficiency results in beriberi that affects people who consume diets based on polished rice, when the intake is below 1 mg/day. Three forms of beriberi are described: Dry, wet and infantile. Dry beriberi manifests as a peripheral neuritis with irritability, paralysis of lower limbs, loss of deep tendon jerks, muscle wasting and loss of position sense. Wet beriberi is characterized by congestive heart failure and peripheral edema. Infantile beriberi has a more subtle onset occurring in breastfed infants of thiamine-deficient mothers (who may not have signs of beriberi), or with very low thiamine intake. The clinical picture is dominated by cardiomegaly, cyanosis, dyspnea and aphonia. The disease may result in death after a few weeks, in the infantile form. Wernicke encephalopathy may occur in thiamine deficient infants and children and consists of a triad of mental confusion, ocular abnormalities (ophthalmoplegia and nystagmus), and ataxia. Hemorrhagic lesions may be seen in the thalamus and periventricular gray matter.

Diagnosis: Thiamine deficiency may be suspected in all cases of malnutrition. The diagnosis is confirmed by measurement of 24 hours urinary thiamine excretion, which in children is 40–100 $\mu\text{g}/\text{day}$; values below 15 $\mu\text{g}/\text{day}$ are deficient. Diagnosis of deficiency can also be based on the response of red cell transketolase to the addition of thiamine *in vitro*. Erythrocytes from deficient persons have a greater response to addition of thiamine pyrophosphate than normal controls. An increase in transketolase activity of less than 15% is normal, 15–25% mild deficiency and over 25% severely deficient. Serum lactate and pyruvate levels may be raised.

Treatment: Treatment with thiamine leads to resolution of neurologic and cardiac symptoms within 24–48 hours. Treatment of patients with mild beriberi with thiamine (5 mg/day) is satisfactory. Severely ill children should receive 10 mg intravenously twice daily. In management of fulminant heart disease, higher doses of thiamine with treatment of congestive heart failure are necessary.

Table 8.4: Essential B vitamins: Function, sources, deficiencies and at-risk groups

Vitamin	Function	Sources	Daily requirement	Deficiency	At-risk groups
B ₁ (Thiamine)	Oxidative decarboxylation of pyruvate	Human milk, cow milk, unpolished grains, eggs, organ meats (liver, kidney), legumes	<6 mo: 0.2 mg 6–12 mo: 0.3 mg 1–3 yr: 0.5 mg 4–8 yr: 0.6 mg 9–13 yr: 0.9 mg >14 yr: 1.2 mg	Beriberi: peripheral neuritis, irritability, paralysis, congestive heart failure Wernicke encephalopathy	Groups with diets based on polished rice, alcoholics
B ₂ (Riboflavin)	Part of flavoproteins FMN, FAD	Meat, milk, eggs, cereals and vegetables	<1 yr: 0.3 mg 1–3 yr: 0.5 mg 4–8 yr: 0.6 mg 9–13 yr: 0.9 mg >14 yr: 1.2 mg	Photophobia, glossitis, cheilosis, angular stomatitis, seborrheic dermatitis, corneal vascularization	Malabsorption states, deficient diets
B ₃ (Niacin)	Forms cofactors NAD, NADP	Milk, eggs, cereals and leafy vegetables	<1 yr: 2–4 mg 1–3 yr: 6 mg 4–8 yr: 8 mg 9–13 yr: 12 mg >13 yr: 16 mg	Pellagra	Groups on predominant maize-based diet
B ₆ (Pyridoxine)	Synthesis of amino acids, myelin, neurotransmitters, hemoglobin	Yeast, sunflower seeds, wheat germ, unpolished rice/cereals, soya beans, walnuts	<6 mo: 0.1 mg 6–12 mo: 0.3 mg 1–3 yr: 0.5 mg 4–8 yr: 0.6 mg 9–13 yr: 1 mg >13 yr: 1.3 mg	Peripheral neuropathy, refractory seizures, dermatitis, microcytic anemia	Malabsorption states, isoniazid use
B ₁₂ (Cobalamin)	Regeneration of folate, metabolism of amino acids and myelin	Dairy products, eggs and meat	<6 mo: 0.4 µg 6–12 mo: 0.5 µg 1–3 yr: 0.9 µg 4–8 yr: 1.2 µg 9–13 yr: 1.8 µg >13 yr: 2.4 µg	Subacute combined degeneration of cord, peripheral neuropathy, megaloblastic anemia	Intrinsic factor deficiency, ileal resection, vegan diets exclusively breastfed infants of vegan mothers
Folate	DNA synthesis, cell growth	Leafy vegetables, fruits, fortified cereal products, sunflower seeds	<6 mo: 65 µg 6–12 mo: 80 µg 1–3 yr: 150 µg 4–8 yr: 200 µg 9–13 yr: 300 µg >13 yr: 100 µg	Megaloblastic anemia	Preterm babies, pregnancy, malabsorption states, hemolytic anemia, anticonvulsant therapy

FAD: Flavin adenine dinucleotide, FMN: Flavin mononucleotide, mo: Months, NAD: Nicotinamide adenine dinucleotide, NADP: NAD phosphate

Riboflavin (Vitamin B₂)

Riboflavin is a constituent of two coenzymes involved in oxidation-reduction reactions of cellular respiration: Flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN). A number of redox enzymes, including glutathione reductase and xanthine oxidase, require flavin coenzymes.

Riboflavin requirements: The recommended daily intake is 0.4 mg/1000 Cal for infants and 0.8–1.2 mg/1000 Cal for children.

Dietary sources: Meat, milk, eggs, cereals and vegetables (broccoli, spinach and asparagus) are good sources. Riboflavin is resistant to oxidation and to heat and is not destroyed by pasteurization. Human milk contains 40–70 µg/100 Cal of riboflavin and cow milk 250 µg/100 Cal.

Deficiency: Riboflavin deficiency occurs from inadequate intake or malabsorption. It takes 1–2 months to develop and is associated with other deficiencies.

Features include photophobia, glossitis, cheilosis, angular stomatitis, seborrheic dermatitis (especially around the nasolabial folds) and corneal vascularization.

Diagnosis of deficiency: Diagnosis should be considered with a history of dietary deficiency and clinical manifestations. A reliable indicator of riboflavin status is the daily losses of the vitamin; urinary excretion of less than 10% of intake over 24 hours is indicative of deficiency. Activity of glutathione reductase in erythrocytes gives a functional index of flavin coenzyme activity; cofactor-induced increase of 20% above the basal level indicates deficiency.

Treatment: Children are treated with 3–10 mg of oral riboflavin daily for several weeks; infants respond to 1 mg daily. Therapeutic doses of vitamin help in improving corneal lesions rapidly.

Niacin (Vitamin B₃)

Nicotinic acid and nicotinamide, biologically equivalent vitamins, are both referred to as niacin. This vitamin can be synthesized in the body from tryptophan, however, the conversion ratio is 60:1, requiring large amounts of tryptophan to meet niacin needs.

Sources: Milk, eggs, cereals and leafy vegetables are good sources of tryptophan. Deficiency occurs in areas where maize is the staple food as the niacin in maize is present in bound form and not easily absorbed. The vitamin is resistant to heating. Human milk contains 30 mg/100 cal of niacin compared with 0.12 mg/100 cal in cow milk.

Niacin requirements: Requirements are expressed in terms of *niacin equivalents* (NE). One NE equals 1 mg of niacin or 60 mg of tryptophan. RDA for niacin is related to dietary energy intake; the recommended intake is 6.4 to 8 NE/1000 cal, human milk provides about 8 NE/1000 cal.

Niacin deficiency: Niacin deficiency leads to pellagra which is characterized by three Ds: dermatitis, diarrhea and dementia. The cutaneous lesions consist of a symmetrical pigmented rash in body parts exposed to sunlight especially the neck (Casal necklace). More acute cases may progress to vesiculation, ulceration and secondary infection. Neurologic symptoms include apathy, headache and loss of memory. In most chronic forms, posterolateral cord degeneration and peripheral nerve lesions are seen.

Diagnosis of niacin deficiency: The diagnosis is suspected on history of inadequate diet, isoniazid treatment or chronic alcohol ingestion when typical manifestations are present. Determination of urinary excretion of N¹-methylnicotinamide is most helpful; normal 24 hours excretion is between 4 and 6 mg, values below 3 mg indicate deficiency. In pellagra, these values are usually between 0.5 and 0.8 mg/day.

Treatment of pellagra: The daily dose for treatment is about 10 times the recommended dietary intake (50–300 mg/day). Parenteral therapy is considered when gastrointestinal absorption is deficient. Prevention of pellagra is achieved by an adequate protein diet containing tryptophan and niacin-rich foods.

Pyridoxine (Vitamin B₆)

Rich sources of vitamin B₆ include yeast, sunflower seeds, wheat germ, unpolished rice/cereals, soya beans and walnuts. Primary dietary deficiency is rare but secondary deficiency can occur in malabsorption states and with drugs like isoniazid.

Pyridoxine deficiency may cause peripheral neuropathy, refractory seizures, dermatitis and microcytic anemia. Pyridoxine is given 10–50 mg/day to patients on INH (isoniazid) to prevent peripheral neuropathy and other neurologic effects. For refractory seizure, 100 mg of pyridoxine is injected intramuscularly.

Biotin

Biotin deficiency has been observed in individuals who consume a large number of raw eggs (rich in avidin) for several months. The avidin is not hydrolyzed by gastrointestinal enzymes; it binds biotin and prevents its absorption. Cooking of eggs destroys avidin.

Clinical features of biotin deficiency include anorexia, vomiting, dry scaly dermatitis, glossitis and hypercholesterolemia. Long-term parenteral alimentation without biotin can also lead to deficiency in pediatric and adult patients. Multiple carboxylase deficiency is a genetic disorder affecting the activity of carboxylase synthetase. This condition responds to large doses of biotin. Another genetic defect affects the activity of biotinidase, an enzyme involved in the recycling of biotin.

Dietary sources of biotin include liver, egg yolk, milk, yeast extracts and meat. Recommendations are 0.15 mg biotin in the multivitamin supplements for infants and children. For treatment of biotin deficiency, oral administration of 2–5 mg daily for 2 to 3 weeks is recommended for mild cases. A parenteral biotin dose of 200 µg daily for 2 to 5 days is used in severe cases.

Pantothenic Acid

Pantothenic acid (vitamin B₅) is present in virtually all naturally occurring foods and is also synthesized by microorganisms. Pantothenate is absorbed in the proximal small intestine; in the liver, it becomes a part of coenzyme A, which is essential for metabolism of fatty acid, proteins and carbohydrates. Isolated pantothenate deficiency is rare and includes burning feet, insomnia and gastrointestinal symptoms. The suggested daily intake is 2–3 mg for infants and 3–5 mg for children.

Cobalamin (Vitamin B₁₂)

Cobalamin or vitamin B₁₂ consists of three compounds: methylcobalamin, 5'-deoxyadenosyl cobalamin and cyanocobalamin. The first two are active forms of vitamin B₁₂ in the body while cyanocobalamin is most common commercially available preparation.

Sources: Vitamin B₁₂ is produced by intestinal microorganisms in animals. Humans do not produce vitamin B₁₂ and have to depend on animal sources including dairy products, eggs and meat. Organs such as liver, kidney, heart and muscle meat, clams and oysters are rich sources of vitamin B₁₂.

Absorption and metabolism: Vitamin B₁₂ binds to intrinsic factor, a glycoprotein produced by the gastric parietal cells,

and the complex is absorbed by specific receptor-mediated process in the ileum. Absence of intrinsic factor results in an inability to absorb ingested vitamin B₁₂ known as pernicious anemia. Passive diffusion accounts for a fraction of total absorption, but may be useful in the management of pernicious anemia with megadoses of the vitamin. Cobalamin undergoes enterohepatic recirculation; this process accounts for a long half-life of the vitamin. Vitamin B₁₂ is transported in plasma bound to transcobalamin II. The average total body pool in an adult is enough to sustain daily vitamin B₁₂ needs for several years.

Requirements: The recommended intake of vitamin B₁₂ for infants is 0.3 µg/day. Older children should receive 0.5–1.5 µg/day and adolescents 2.0 µg/day.

Deficiency: Vitamin B₁₂ deficiency can occur in patients with impaired intestinal absorption due to defects in intrinsic factor, or distal ileal disease. True dietary vitamin B₁₂ deficiency occurs in persons who follow vegan diets containing no animal or fish products. Content of vitamin B₁₂ in breast milk is determined by maternal intake. Hence, exclusively breastfed infants of strict vegan mothers can become vitamin B₁₂ deficient over a period of time especially if weaning is not initiated at an appropriate age.

Vitamin B₁₂ status is assessed by measurement of serum cobalamin levels, with values below 150 pg/mL indicative of negative vitamin B₁₂ balance. Plasma levels of methylmalonic acid and homocysteine are increased because of block in vitamin B₁₂-dependent steps of metabolism.

Characteristic features of vitamin B₁₂ deficiency include progressive demyelination, which begins in peripheral nerves and progresses to involve the posterior and lateral columns of the spinal cord and central nervous system (subacute combined degeneration). These lesions are possibly due to a generalized methyl group deficiency in the nervous system and faulty myelin production. Secondary folate deficiency results in megaloblastic anemia, neutrophil hypersegmentation and thrombocytopenia.

Diagnosis of deficiency: The anemia is macrocytic and nucleated RBC showing megaloblastic morphology may be seen in blood. Levels of red cell folate are low; serum LDH levels are elevated.

Treatment: Deficiency is treated with parenteral administrations of vitamin B₁₂ (1 mg). Reticulocytosis is seen within 2–4 days. Patients with neurologic involvement require daily therapy for 2 weeks.

Folic Acid (Pteroylmonoglutamic Acid)

Folic acid is the parent compound of a group of naturally occurring, structurally related compounds known as the folates. Folic acid is essential for normal growth and

maintenance of cells, since it acts as a coenzyme for normal DNA and RNA synthesis. Leafy vegetables such as spinach, turnip greens, lettuces, dried beans and peas, fortified cereal products, sunflower seeds and certain fruits and vegetables are rich sources.

Requirements: The recommended daily allowance of folic acid varies from 25 µg in infancy to 200 µg by adolescence.

Deficiency: Folate is absorbed in the small intestine. Deficiency can occur in malabsorption states such as chronic gastrointestinal infections, short bowel syndrome and celiac disease. Preterm babies are at risk of folate deficiency due to increased tissue demands and lack of adequate stores as maternal transfer occurs in the last trimester of pregnancy. Children with hemolytic anemia have high folate requirements due to increased erythropoiesis predisposing them to deficiency. Anticonvulsant drugs increase the catabolism of folate leading to secondary deficiency.

Deficiency of folate impairs DNA synthesis, limits cell division and affects normal growth and repair of tissues. The tissues that have the fastest rate of cell replacement are affected first. Erythropoiesis is hindered, resulting in megaloblastic anemia.

Maternal deficiency of folate, during pregnancy, is implicated in neural tube defects. Periconceptional folate supplements, begun 1 month before conception and continued for 3 months after, is recommended to reduce the risk.

In patients with megaloblastic anemia, it is imperative to exclude and treat vitamin B₁₂ deficiency before treating with folate. Otherwise the neurological signs of vitamin B₁₂ deficiency may develop and progress irreversibly. Deficiency is corrected using folic acid at a dose of 0.5–1 mg/day orally for 3–4 weeks.

Vitamin C

Vitamin C (L-ascorbic acid or ascorbate) plays many important roles in the body; it is needed for formation of procollagen and maintenance of normal connective tissue, wound healing and bone (osteoid) formation. Vitamin C is a reducing agent required for oxidation-reduction reactions including the hydroxylation of lysine and proline. Additionally, it reduces ferric to ferrous state and helps in iron absorption in the gut. Due to its antioxidant properties, it stabilizes a number of other compounds, including vitamin E and folic acid. Humans, unlike other animals, lack the enzyme (gulonolactone oxidase) required for conversion of glucose to ascorbic acid hence vitamin C is must be obtained from the diet.

Sources: Rich sources of vitamin C include fresh citrus fruits (oranges, grapefruit, lime and gooseberry) and vegetables (cabbage, cauliflower, spinach, cucumber). Much of the vitamin is lost in cooking and storage, but is stable in canned and frozen foods. Human milk is rich

source of vitamin C containing 5 to 15 mg/100 cal and cow milk 0.2–2.0 mg/100 cal. Daily requirements are 30–40 mg for infants and 40–70 mg for children.

Absorption and metabolism: Ascorbic acid is absorbed by an active, sodium-dependent process in the upper small intestine. The vitamin circulates in plasma in its free, anionic form, reaching high concentrations in adrenal and pituitary glands and in leukocytes. Vitamin C appears unchanged in the urine when renal threshold is exceeded.

Deficiency: Children at risk for scurvy include those who are fed boiled or evaporated milk and those with severe dietary restrictions with lack of citrus fruits and fresh vegetables.

Early features include irritability, anorexia, anemia and appearance of petechiae due to increased capillary fragility. Gingival swelling, bleeding gums, generalized tenderness of the limbs (due to subperiosteal bleed), painful joint swellings (hemarthrosis), and peripheral edema are seen. The child may present with inability to move limbs (pseudoparalysis) due to pain and assume a frog-like posture, with semiflexion at hips and knees. Characteristic angular swellings at the costochondral junction, known as scorbutic rosary, with depression of the sternum are often apparent. Scurvy can result in cerebral hemorrhage or hemopericardium and is potentially fatal, if left untreated.

Diagnosis of scurvy: The diagnosis is made by presence of characteristic physical findings and history of inadequate dietary intake of vitamin C. X-rays of long bones show a ground glass appearance with thinning of cortex (pencil thin cortex). An irregular thickened white line appears at the metaphysis (white line of Frankel), representing the zone of well-calcified cartilage. There is a zone of rarefaction proximal to this line, which represents poorly formed trabeculae (Trümmerfeld zone). The lateral part of the rarefaction appears as a triangular defect called Pelken spurs. The epiphyses are surrounded by a thin white line (Wimberger ring sign) (Fig. 8.8).

Therapy for scurvy: Therapy with 100–200 mg of vitamin C orally or parenterally prompts rapid improvement in symptoms and resolution of the radiological signs. Daily intake of 100 mL of orange juice or tomato pulp has the same effect.

MINERALS

Calcium

Calcium is the most abundant mineral in the body and is located primarily (98%) in bone. Calcium is essential for the coagulation cascade, nerve conduction and muscle stimulation. Intestinal absorption of calcium varies inversely with intake and is regulated by $1,25(\text{OH})_2\text{D}_3$, which controls the synthesis of calcium-binding protein at the brush border. In the presence of vitamin D, calcium



Fig. 8.8: X-ray of lower limbs showing features of scurvy: Pencil thin cortex, thickened white line at upper and lower tibial metaphyses (thin arrows), Pelken spurs (thick arrow). The tibial epiphyses is surrounded by a thin white line (Wimberger ring sign) (arrow heads)

absorption can adapt to a wide range of dietary calcium intakes, varying from 10 to 80% of available calcium. Calcium absorption also depends on the interaction of calcium with other dietary constituents, including fiber, phytate, oxalate, fat and lactose.

The main sources of calcium for infants are milk and dairy products, with smaller amounts derived from grains and fruits once solid foods are introduced. Children consuming strict vegetarian diets may develop calcium deficiency, either alone or in combination with vitamin D deficiency. Strict vegetarian diets may provide as little as 250 mg of calcium per day and include generous amounts of substances that inhibit calcium absorption, such as fiber and phytates. Secondary calcium deficiency may develop in association with steatorrhea, chronic malabsorption syndromes, or intestinal or renal abnormalities of calcium metabolism.

The recommended intake of calcium is 200 mg and 260 mg/day for infants aged 0–6 and 6–12 months, respectively. Children aged 1 to 10 years require an intake of 500 to 800 mg/day. During the pubertal growth spurt, calcium requirements are as high as 1000 to 1200 mg/day. Pregnant and lactating women require 400 mg/day. Calcium deficiency may cause tetany characterized by muscle cramps, numbness and tingling in limbs. Rickets and osteoporosis may occur with chronic deficiency.

Magnesium

Magnesium is essential for reactions controlling carbohydrate metabolism, membrane transport and signal

transmission contributing to the action of more than 300 enzymes. Over 80% of the total body magnesium is in bone and skeletal muscle. Rich sources of magnesium include legumes, nuts, bananas and whole grains. Magnesium is efficiently absorbed in the intestine and regulation of its balance depends on renal tubular reabsorption. Primary deficiency is common in children with protein energy malnutrition. Deficiency may also develop secondary to intestinal malabsorption, excessive gastrointestinal losses (fistulae or continuous suction) or renal losses (tubular disease or diuretics). Clinical manifestations of magnesium deficiency include irritability, tetany and hypo- or hyper-reflexia and cardiac arrhythmias in severe cases. Magnesium requirements in the first 6 months range between 40 and 50 mg/day; 60 mg/day for 6–12 months and approximately 200 mg/day for older children.

TRACE ELEMENTS

Eleven 'major' elements constitute 99% of human body weight: Hydrogen, carbon, nitrogen, oxygen, sodium, potassium, chlorine, calcium, phosphorus, sulfur and magnesium. In addition, the body is composed of numerous "trace" elements. The term trace elements comprise an increasing number of compounds with proven or putative essentiality for human nutrition. Each of these contributes less than 0.01% of total body weight. Their major functions are related to enzyme systems where they act either as cofactor for metal-ion-activated enzymes or as specific constituents of metallo-enzymes.

Zinc

Functions: Zinc is the second most common trace element in the body after iron. It is an essential micronutrient with diverse but critical physiological role being part of more than 200 enzymatic reactions. As a component of zinc finger proteins, zinc regulates gene transcription and participates in nucleic acid metabolism, protein synthesis and thereby, cellular growth. Zinc is a major antioxidant being part of the enzyme superoxide dismutase.

Dietary sources: Zinc is derived mainly from animal protein. Liver, oyster, meat, fish, nuts and eggs are a rich source. Diets based on cereals/starch, plants and legumes are associated with zinc deficiency, due to the presence of dietary phytic acid that decreases the bioavailability of zinc.

Absorption and metabolism: Zinc is absorbed throughout the small intestine by a process of facilitated diffusion. In the systemic circulation, the major fraction of plasma zinc is loosely bound to albumin. Almost 90% of total body zinc is localized in bone and skeletal muscle. Zinc status is regulated both at the absorptive step and by intestinal re-excretion. The major excretory route for endogenous zinc is via the intestinal tract; fecal losses are increased in children with intestinal diseases or diarrhea.

Deficiency: Infants, children, adolescents, pregnant and lactating women have increased demand of zinc due to active growth and tissue synthesis. Deficiency is also seen as a part of malnutrition and malabsorption syndromes, caused by low dietary intake or poor absorption due to intestinal disease. Excessive loss of zinc in stools can occur with recurrent or chronic diarrhea. Severe zinc deficiency syndromes can occur in patients on prolonged intravenous feeding.

Poor physical growth is an important feature of zinc depletion in preschool and school-age children. Delayed sexual maturation and hypogonadism is a prominent feature of zinc deficiency in adolescents. Other features include anemia, anorexia, diarrhea, alopecia, dermatitis, impaired immune function, poor wound healing and skeletal abnormalities.

Acrodermatitis enteropathica is an autosomal recessive disorder of severe zinc deficiency, caused by impaired intestinal absorption due to defect in intestinal zinc transporter protein. It presents in early infancy, with vesicobullous, dry, scaly or eczematous skin lesions chiefly in the periorificial (around the mouth and perineum) and acral areas. Alopecia and eye changes, such as conjunctivitis, blepharitis and photophobia, may be present. Chronic diarrhea, growth retardation, stomatitis, loss of taste sense, irritability and delayed wound healing are seen. Catchup growth and resolution of symptoms is noted following oral zinc therapy.

The diagnosis of zinc deficiency is based on the combination of dietary history of chronic low zinc intake or excessive intestinal losses, presence of clinical features compatible with deficiency and low levels of zinc in plasma or hair.

Requirement and treatment of deficiency: Normal requirements for children range between 3.5 and 5.0 mg/day. Acquired zinc deficiency states can be treated with 0.5 to 1.0 mg elemental zinc/kg/day for several weeks or months. Malnourished children have much higher requirements of 2–4 mg/kg/day due to zinc depletion and intestinal disease. One mg of elemental zinc is available from 4.5 mg zinc sulfate or 3 mg zinc acetate.

Copper

Copper is a component of several metallo-enzymes required for oxidative metabolism.

Absorption and metabolism: Most of the ingested copper is absorbed in stomach and small intestine, from where it is transported to the liver and released into the systemic circulation bound to ceruloplasmin, the main transport protein for copper. Copper is mainly stored in the liver and muscle. It is excreted through biliary secretions in the feces; urinary excretion is minimal.

Sources: The richest sources are meats, liver, seafood, nuts and seeds. Additional copper may enter the food chain

through pesticides and contamination of water by pipes and cooking utensils.

Deficiency: Primary dietary deficiency is infrequent. Secondary deficiency may develop in malabsorption syndromes, liver disease, peritoneal dialysis and other conditions causing excessive copper losses. Copper deficiency decreases the life span of the erythrocyte and impairs mobilization of stored iron from liver and bone marrow. Features of deficiency are microcytic, hypochromic anemia unresponsive to iron therapy, depigmentation of hair, neutropenia, neurological problems and osteoporosis.

Copper transport is disrupted in two human diseases: Wilson disease and Menke disease. Both have defects in copper transporting membrane proteins. Menke disease is a rare X-linked fatal disorder of impaired copper absorption presenting in early infancy with kinky hair, skin hypopigmentation, neurological regression and seizures. Laboratory findings include hypocupremia, low plasma ceruloplasmin, neutropenia and anemia.

Selenium

Selenium is a constituent of glutathione peroxidase, an antioxidant in red blood cells and other tissues. Selenium also helps maintain normal immune function and is a part of the enzyme type 1-deiodinase which converts thyroxine to triiodothyronine. Dietary sources include whole grain, meat, egg, seafood, garlic and mushrooms. Endemic selenium deficiency results in Keshan disease, a form of cardiomyopathy in young children seen in some regions of China. In combination with iodine deficiency, lack of selenium can result in myxedematous endemic cretinism, seen in certain parts of Africa. Selenium deficiency may be seen in patients on total parenteral nutrition and manifests with macrocytosis, brown hair and whitening of nails.

Chromium

Glucose intolerance, which complicates malnutrition in young children, has been attributed in part to chromium deficiency. Chromium acts in glucose homeostasis by potentiating insulin action, possibly by facilitating binding to its receptor. Symptoms of chromium deficiency are usually in the setting of total parenteral alimentation and include glucose intolerance, peripheral neuropathy and evidence of disturbed nitrogen and lipid metabolism.

Iodine

Iodine, a micronutrient present in small quantities in the thyroid gland, is essential for the formation of thyroid hormones thyroxine (T_4) and triiodothyronine (T_3). Thyroid hormones play a key role in body growth and brain development, especially in the fetus and first three years of postnatal life.

Iodine is most commonly found in sea water and sea food/plants are rich sources. Iodine is relatively deficient

in soil especially in mountainous regions due to leaching and erosion. The Himalayan belt and Ganges valley are areas of severe iodine deficiency in India.

Recommended daily intake: The recommended iodine intake is around 90 $\mu\text{g}/\text{day}$ from birth to 5 years of age increasing to 120 $\mu\text{g}/\text{day}$ at ages 6–12 years, and 150 $\mu\text{g}/\text{day}$ in adolescents and adults. Pregnant and lactating women require higher amounts (200 $\mu\text{g}/\text{day}$). Iodine is excreted in urine and 24-hour urinary iodine excretion is a useful measurement of iodine sufficiency in a community. Urinary iodine $<100 \mu\text{g}/\text{L}$ indicates iodine insufficiency with values $<20 \mu\text{g}/\text{L}$ pointing to severe deficiency.

Iodine deficiency disorders: Nearly 1.5 billion people in 130 countries around the world live in areas of iodine deficiency and are at risk of developing iodine deficiency disorders (IDD). IDD are the commonest cause of mental retardation in these populations and are responsible for an average lowering of IQ scores by 13.5 points compared to populations living in iodine-sufficient areas. Goitre is the earliest manifestation of iodine deficiency and is an adaptive response to increase thyroid hormone production under the influence of increased TSH levels, but eventually leads to decompensation in the form of hypothyroidism. Goitre rates can be as high as 10–30% in endemic populations suffering from iodine deficiency (Table 8.5).

Iodine deficiency in the fetus: Maternal hypothyroidism due to iodine deficiency leads to an increased risk of abortions and stillbirths. The fetal thyroid gland begins to function from the second half of gestation. Inadequate availability of T_4 due to maternal iodine deficiency adversely affects early brain development in the fetus leading to permanent manifestations of endemic cretinism, including mental retardation, hearing impairment (deaf-mutism), spastic diplegia and squint.

Iodine deficiency in the neonate: Iodine deficiency affects functioning of the thyroid gland leading to neonatal goitre and hypothyroidism. The brain of the human infant at birth has only reached about one-third of its full size and continues to grow rapidly until the end of the second year. The thyroid hormone, dependent on an adequate supply of iodine, is essential for normal brain development at this critical time. Neonatal hypothyroidism persists into infancy and childhood, if the deficiency is not corrected and results in retardation of physical and mental development.

Iodine deficiency in children: Moderate iodine deficiency is associated with abnormalities in psychoneuromotor and intellectual development of children who are clinically euthyroid, but who do not exhibit other features of endemic cretinism (Table 8.5). Some patients may show goiter (Fig. 8.9) (see Chapter 18). Studies in moderately iodine-deficient areas indicate that fine motor skills and

Table 8.5: Spectrum of iodine deficiency disorders (IDD)

Fetus	Abortions, stillbirths Congenital anomalies Endemic cretinism Increased perinatal mortality
Neonate	Neonatal goiter Endemic mental retardation Neonatal hypothyroidism
Child, adolescent	Goiter Impaired mental function Subclinical hypothyroidism Retarded physical development

**Fig. 8.9:** A 14-year-old girl with goiter

visual problem solving improved in school children after iodine repletion.

Therapy: Universal iodization of salt is a successful public health intervention to prevent IDD in populations at risk of deficiency throughout the world. In India, the National Iodine Deficiency Disorders Control Programme (formerly Iodine Deficiency Disorders Control Programme) has established salt iodination plants to ensure an adequate supply of iodized salt in the country. The target iodine content of salt as per the program is 30 and 15 parts per million (ppm) at the manufacturing and distribution levels, respectively.

Iron

Iron deficiency remains a major nutritional problem among infants and young children. The National Family Health Survey (NFHS) IV (2015-16), showed that 56% urban and 59% rural children between 6 and 59 months are anemic. Iron deficiency anemia is associated with impaired performance in mental and physical functions, including physical coordination and capacity, cognitive abilities, and social and emotional development. Health consequences of iron deficiency in young children are serious and often irreversible (Chapter 13).

Suggested Reading

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Newborn Infants

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Newborn infants are unique in their physiology and the health problems that they experience. Neonatal period is characterized by transition to extrauterine life and rapid growth and development. Newborn period, just first 28 days of life, carries the greatest risk of mortality. Despite being less than 2% of total period of under-5 childhood, the newborn period accounts for over half of under-5 child mortality. Good care, therefore, not only improves survival of children but lays foundation of optimal long-term physical and neurocognitive development.

Newborn health is the key to child health and survival. In India (SRS 2012), neonatal deaths account for 56% of under-5 (Fig. 9.1) and 69% of infant deaths. First week deaths (<7 days; early neonatal deaths) alone account for 45% of total under-5 deaths. Preterm birth complications account for 35% of all neonatal deaths and constitute the most important cause of neonatal mortality. Bacterial infections (sepsis, pneumonia and diarrhea) contribute to 21% of neonatal deaths. Other causes of neonatal mortality are birth asphyxia and congenital malformations. Almost three-fourths of all neonatal deaths occur among the low birth weight newborns. Of all the neonatal deaths, about

40% occur within first 24 hours, half within 72 hours and three-fourths within one week of birth. Health of the mother and care during pregnancy and at childbirth has profound influence on neonatal outcome. As noted in Chapter 1, decline in neonatal mortality is critical to achieve national health goals. The stagnant early neonatal mortality is a cause for concern.

Definitions

Neonatal period: From birth to under four weeks (0 to 27 days or 1 to 28 days, depending on whether the first day has been taken as day 0 or day 1 of life) of age. An infant is called a neonate during this phase. First week of life (<7 days or <168 hours) is known as early neonatal period. Late neonatal period extends from 7th to <28th days.

Postneonatal period: Period of infancy from 28 to <365 days (<1 year) of life.

Weeks of gestation refer to completed weeks of gestation, e.g. 36 weeks gestation, refer to range of gestation from 36 weeks 0 day to 36 weeks and 6 days.

Perinatal period: Perinatal period extends from 22nd week of gestation (>154 days or fetal weighing 500 g or more) to less than 7 days of life.

Live birth: A product of conception, irrespective of weight or gestational age, that, after separation from the mother, shows any evidence of life such as breathing, heart-beat, pulsation of umbilical cord or definite movement of voluntary muscles.

Fetal death: A fetal death is a product of conception that, after separation from the mother, does not show any evidence of life.

Stillbirth: Fetal death at a gestational age of 22 weeks or more or weighing 500 g or more at birth.

Term neonate: A neonate born between 37 and 42 weeks (259–293 days) of gestation.

Preterm neonate: A neonate born before 37 weeks (<259 days) of gestation irrespective of the birth weight.

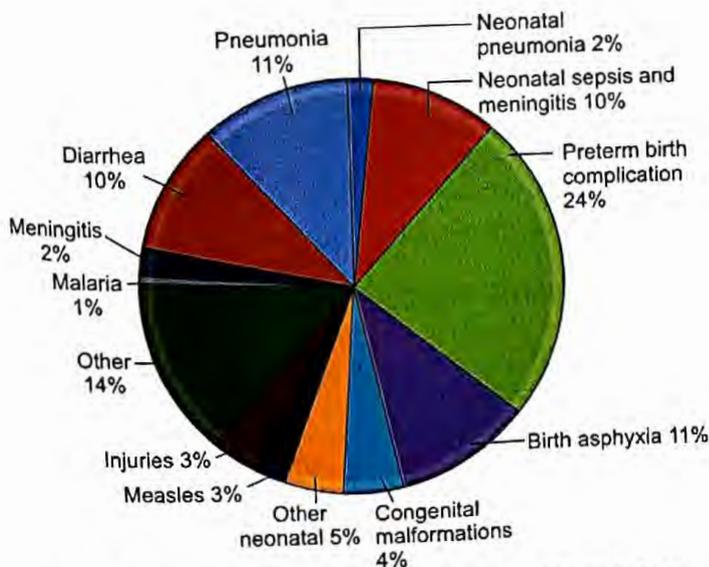


Fig. 9.1: Causes of under-5 deaths at global level (2013)

Online Learning Resource Material

The Newborn Division of Department of Pediatrics, AIIMS, has produced excellent resource material for learning of health professionals. The material is in form of modules, posters, videos and webinars on common newborn issues and is available at: www.newbornwhocc.org.

The online material complements the information provided in this Chapter. The readers are encouraged to visit the website and use the resource to enhance their learning.

Post-term neonate: A neonate born at a gestational age of 42 weeks or more (294 days or more).

Low birth weight (LBW) neonate: A neonate weighing less than 2500 g at birth irrespective of the gestational age.

Very low birth weight (VLBW) neonate: A neonate weighing less than 1500 g at birth irrespective of the gestational age.

Extremely low birth weight (ELBW) neonate: A neonate weighing less than 1000 g at birth irrespective of the gestational age.

Neonatal mortality rate (NMR): Deaths of infants under the first 28 days of life per 1000 live births per year.

Perinatal mortality ratio (PNMR): Number of perinatal deaths (stillbirths plus neonatal deaths before 7 days of life) per 1000 live births. It is designated as a ratio since the numerator is not part of the denominator (for a rate, like in NMR, numerator must be part of the denominator. As that is not the case in PNMR and therefore, it is a ratio and not a rate).

RESUSCITATION OF A NEWBORN

Of the 25 million infants born every year in India, 3–5% experience asphyxia at birth. Asphyxia is characterized by progressive hypoxia, hypercapnia, hypoperfusion and acidosis. It may lead to multiorgan dysfunction that may cause death. Hypoxic-ischemic encephalopathy (HIE) resulting from asphyxia may lead to long-term neuromotor sequelae.

The American Heart Association (AHA) and the American Academy of Pediatrics (AAP) have recently updated the resuscitation guidelines. A summary of the recommendations of AHA-AAP (2015) is provided here.

Pathophysiology of Asphyxia

When an infant is deprived of oxygen, an initial brief period of rapid breathing occurs. If the asphyxia continues, the respiratory movements cease and the infant enters into a period of apnea known as *primary apnea*. During primary apnea, the heart rate begins to fall, neuromuscular tone gradually diminishes but the blood pressure remains normal. In most instances, tactile stimulation during this period will reinitiate respiration.

If the asphyxia continues, the infant develops deep gasping respiration, the heart rate continues to decrease,

the blood pressure begins to fall and the infant becomes flaccid. The breathing becomes weaker until the infant gasps and enters into a period of *secondary apnea*. The infant is now unresponsive to stimulation and does not spontaneously resume respiratory efforts unless resuscitation in the form of positive pressure ventilation (PPV) is initiated.

As a result of fetal hypoxia, the infant may go through the phases of primary and secondary apnea before birth. Hence, apnea at birth may be either primary or secondary apnea. These two are clinically indistinguishable; in both instances, the infant is not breathing and the heart rate may be below 100 beats per minute. Hence, when faced with an apneic infant at birth, one should assume that an apneic infant at birth is experiencing secondary apnea and, therefore, must institute full resuscitation efficiently without wasting too much of time in providing tactile stimulation.

Lung Inflation

During intrauterine life, the lungs do not take part in gas exchange, which is taken care of by the placenta. The lung alveoli in the fetus are filled with fluid secreted by type II alveolar cells. The process of fluid removal starts with the onset of labor. The fluid gets reabsorbed from the alveoli into the perivascular space and then into blood and lymphatic channels. The process of labor may facilitate removal of lung fluid, whereas removal is slowed when labor is absent (as in elective cesarean section).

Removal of lung fluid from the alveoli is facilitated by respiration soon after birth. The first few breaths after birth are effective in expanding the alveoli and replacing the lung fluid with air. Problems in clearing lung fluid may occur in infants whose lungs have not inflated well with the first few breaths, such as those who are apneic at birth or have a weak initial respiratory effort as with prematurity or sedation.

Pulmonary Circulation

Oxygenation depends not only on air reaching the alveoli, but also on pulmonary circulation. During intrauterine life, there is little blood flow to the lungs due to pulmonary vasoconstriction. After birth, pulmonary vasodilatation takes place resulting in fall in pulmonary vascular resistance and increased blood flow in the pulmonary circuit.

The asphyxiated infant has hypoxemia (low-oxygen content of the blood) and acidosis (low pH) resulting in failure of vasodilation of the pulmonary arterioles and failure of closure of ductus arteriosus (persistence of fetal circulation). Due to poor pulmonary blood flow, proper oxygenation of the tissues of the body does not take place as there is inadequate uptake of oxygen in lungs, even if the infant is being properly ventilated.

In mildly asphyxiated babies whose oxygen and pH are only slightly lowered, it may be possible to increase

pulmonary blood flow by quickly restoring ventilation. However, pulmonary perfusion in severely asphyxiated infants may not improve with ventilation alone. The combination of oxygenation and correction of metabolic acidosis would be necessary to open the pulmonary arterioles to improve pulmonary blood flow.

Cardiac Function and Systemic Circulation

Asphyxia causes redistribution of blood flow to preserve blood supply to vital organs. There is vasoconstriction in the bowel, kidney, muscles and skin while the blood flow to the heart and brain is relatively preserved (diving-in reflex).

As asphyxia is prolonged, myocardial function and cardiac output too deteriorate and blood flow to all the organs is further reduced. This sets in the stage for progressive organ damage.

Preparing for Resuscitation

With careful consideration of antepartum and intrapartum risk factors, asphyxia can be anticipated in up to only half of the newborns who will eventually require some form of resuscitation. In others, the need for resuscitation can come as a surprise. Therefore, each delivery should be viewed as an emergency and basic readiness must be ensured to manage asphyxia.

Preparation for delivery should include:

- i. Assessing perinatal risk factors, ensuring availability of at least one person who is capable of undertaking full resuscitation and whose sole responsibility is that of newborn only. In an anticipated need for resuscitation, there may be need of more than one person.
- ii. All resuscitation equipment immediately available and in working order (Table 9.1)
- iii. Ensuring a good teamwork and proper communication between teammates.

Role of Apgar Scores In Resuscitation

The Apgar score is an objective method of evaluating the newborn's condition (Table 9.2). It is generally performed at 1 minute and again at 5 minutes after birth. However, resuscitation must be initiated before the 1-minute score is assigned. Therefore, the Apgar score is not used to guide the resuscitation.

While the Apgar score is not useful for decision making at the beginning of resuscitation, the change of score at

Table 9.1: Neonatal resuscitation supplies and equipment

Suction equipment

Mechanical suction
Suction catheters 10, 12 or 14 F
Meconium aspirator

Bag and mask equipment

Neonatal resuscitation bags (self-inflating)
Face-masks (for both term and preterm babies)
Oxygen with flow meter and tubing

Intubation equipment

Laryngoscope with straight blades no. 0 (preterm) and no. 1 (term)
Extra bulbs and batteries (for laryngoscope)
Endotracheal tubes (internal diameter of 2.5, 3.0, 3.5 and 4.0 mm)

Medications

Epinephrine
Normal saline or Ringer lactate
Naloxone hydrochloride

Miscellaneous

Linen, shoulder roll, gauze
Radiant warmer
Stethoscope
Syringes 1, 2, 5, 10, 20, 50 mL
Feeding tube 6 F
Umbilical catheters 3.5, 5 F
Three way stopcocks
Gloves

sequential time points following birth can reflect how well the baby is responding to resuscitative efforts. Extended Apgar scores should be obtained every 5 minutes for up to 20 minutes, if the 5-minute Apgar score is less than 7.

TABC of Resuscitation

The components of the neonatal resuscitation can be summarized as TABC:

T-Temperature: Provide warmth, dry the baby and remove the wet linen.

A-Airway: Position the infant, clear the airway, if required (by wiping or suction of baby's mouth and nose). If necessary, insert an endotracheal (ET) tube to ensure an open airway.

Table 9.2: Apgar score

Sign	0	1	2
Heart rate	Absent	Slow (<100 beats/min)	Normal (>100 beats/min)
Respiration	Absent	Weak cry	Good strong cry
Muscle tone	Limp	Some flexion	Active movements
Reflex irritability	No response	Grimace	Cough or sneeze
Color	Blue or pale	Body pink, extremities blue	Completely pink

B-Breathing: Tactile stimulation to initiate respirations, positive-pressure breaths using either bag and mask or bag and ET tube as necessary.

C-Circulation: Stimulate and maintain the circulation of blood with chest compressions and medications as indicated.

Resuscitation Algorithm

Figure 9.2 presents the algorithm of neonatal resuscitation. At the time of birth, one should ask three questions about the newborn:

- i. Term gestation?
- ii. Breathing or crying?

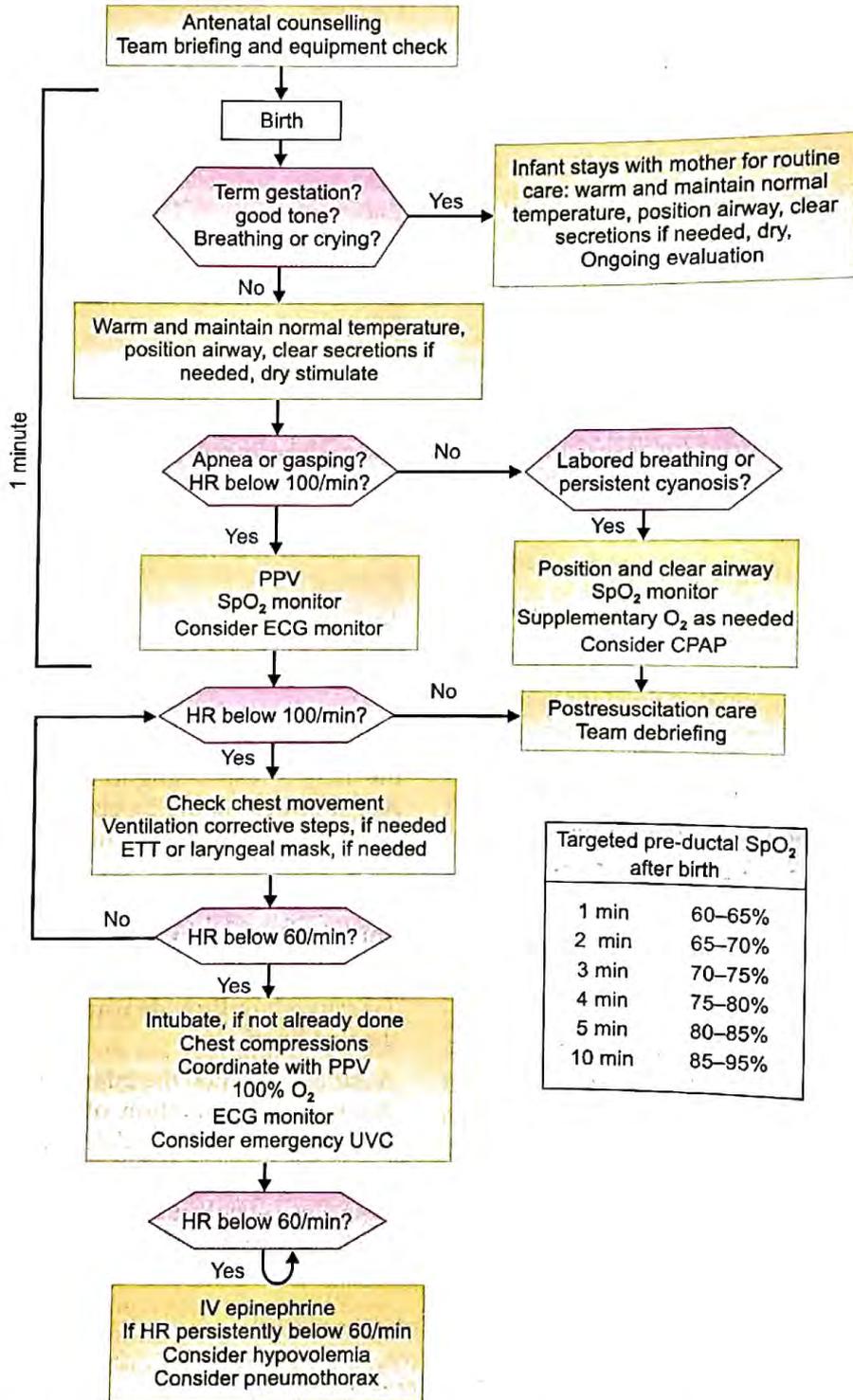


Fig. 9.2: The algorithm of neonatal resuscitation. CPAP continuous positive airway pressure; PPV positive pressure ventilation; SpO₂ saturation of oxygen (Adapted with permission from American Academy of Pediatrics 2015).

iii. Good muscle tone? (flexed posture and active movement of baby denotes good tone)

If answers to all the three questions are 'Yes', the infant stays with mother and receives just "Routine care". Routine care consists of four steps:

- i. Warmth: Provided by putting the baby directly on the mother's chest in skin-to-skin contact.
- ii. Clearing of airway, if required: Position the baby and wipe the baby's mouth and nose using a clean cloth. No need to suction routinely.
- iii. Dry the baby
- iv. Ongoing evaluation for vital parameters. Helping mother in breastfeeding will facilitate easy transition to extrauterine environment.

If answer to *any* of the three questions is "No", the baby requires at least some resuscitation. After cutting the cord, the baby should be subjected to a set of interventions known as *initial steps*.

Initial Steps

Warmth

The baby should be placed under the heat source, preferably a radiant warmer. The baby should not be covered with blankets or towels to ensure full visualization and to permit the radiant heat to reach the baby.

Positioning

The baby should be placed on her back or side with the neck slightly extended. This helps in keeping the airway open and facilitates breathing. Care should be taken to prevent hyperextension or flexion of the neck, since either may interfere with respiration.

To help maintain the correct position, one may place a rolled blanket or towel under the shoulders of the infant elevating her by $\frac{3}{4}$ or 1 inch off the mattress. This 'shoulder roll' is particularly helpful, if the infant has a large occiput resulting from molding, edema or prematurity (Fig. 9.3).

Clear Airway, If Necessary

The appropriate method for clearing the airway will depend on the presence or absence of meconium.



Fig. 9.3: Rolled towel under the shoulders

The secretion can be removed from the airway by wiping the nose and mouth with a clean cloth or by suctioning with a bulb syringe or suction catheter. The mouth is suctioned before nose ('M' before 'N') to ensure the infant does not aspirate, if she should gasp when the nose is suctioned. If the infant has copious secretion from the mouth, the head should be turned to the side. This will allow secretions to collect in the side of mouth, where they can be easily removed.

For suctioning, the size of suction catheter should be 12 or 14 Fr. The suction pressure should be kept around 80 mm Hg (100 cm H₂O) and should not exceed 100 mm Hg (130 cm H₂O). One should not insert the catheter too deep in mouth or nose for suction as it may stimulate posterior pharynx producing vagal response resulting in bradycardia or apnea.

Dry and Stimulate

After suctioning, the baby should be dried adequately using prewarmed linen to prevent heat loss. The wet linen should be removed away from the baby. The act of suctioning and drying itself provides enough stimulation to initiate breathing. If the newborn continues to have poor respiratory efforts, additional tactile stimulation by gently rubbing trunk, back and extremities for several seconds may be provided to stimulate the breathing. However, one should not waste too much of time in providing tactile stimulation.

Management of Infant Born through Meconium-Stained Liquor (MSL)

A baby born through meconium-stained liquor (MSL) may aspirate the meconium into the trachea and lungs. *The procedures like intrapartum suctioning of the mouth and nose before delivery of the shoulders and postnatal tracheal suctioning of non-vigorous babies are no more recommended.*

If a term baby born through MSL is vigorous (breathing well and good tone), the baby is provided initial steps. The gentle suction of mouth and nose may be required to clear airways and the baby is kept with mother with continued observation for development of any respiratory difficulty. If non-vigorous (feeble breathing or low tone), the baby is provided initial steps under radiant warmer and PPV is provided, if required.

Evaluation

After providing initial steps, the baby should be evaluated by assessing respiration, HR and color (or oxygen saturation by pulse oximetry).

Respiration is evaluated by observing the infant's chest movements. HR can be assessed by auscultating the heart or by palpating the umbilical cord pulsation for 6 seconds. The number of beats or pulsation is multiplied by 10 to obtain the HR per minute (e.g. a count of 12 in 6 seconds is an HR of 120 per minute). Color is evaluated by looking

at tongue, mucous membranes and trunk. A blue hue to the lips, tongue and central trunk indicates central cyanosis. Presence of cyanosis in extremities (acrocyanosis) does not have any significance.

- If the baby has good breathing, HR 100/min or more and no cyanosis, then she does not require any additional intervention and the baby should be monitored frequently.
- If the baby has labored breathing or persistent central cyanosis, administration of CPAP in preterm babies and supplemental oxygen in term babies is recommended. Baby should have its oxygen saturation monitored and supplemental oxygen is titrated to achieve the targeted saturations (Fig. 9.2).
- If the baby is apneic, has gasping breathing or heart rate below 100 min, positive pressure ventilation (PPV) is needed.

Supplemental Oxygen

Central cyanosis requires supplemental oxygen, which can be provided by an oxygen mask or oxygen tube held in cupped hand over baby's face or by flow inflating bag and mask. The flow of oxygen should be at least 5 L/minute.

Positive Pressure Ventilation (PPV)

PPV is usually given by using a self-inflating bag and face mask (bag and mask ventilation or BMV). The self-inflating bag is easy to use as it reinflates completely without any external compressed source of gas.

The resuscitation bag (Fig. 9.4) should have a capacity of 240 to 750 mL. The bag is attached to sources of oxygen and air and a blender which provides a desired concentration of supplemental oxygen.

Oxygen should be treated as a drug. Both too little and too much of oxygen are bad for the baby. Even a brief exposure to high concentration of oxygen can have detrimental effect on the baby. Studies have shown that term babies resuscitated with room air compared to 100% oxygen have better survival and long-term outcomes. The evidence in favor or against the use of oxygen in preterm babies is yet lacking.

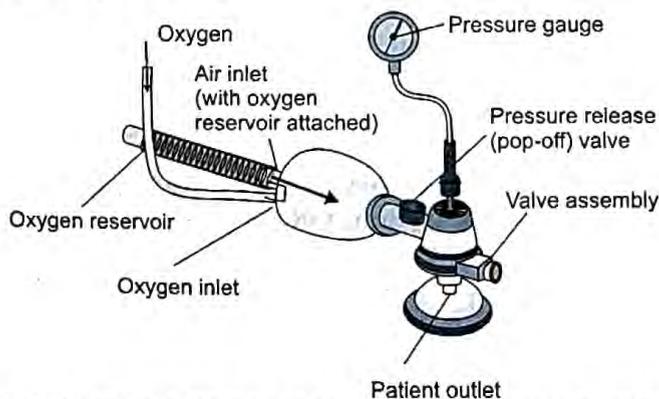


Fig. 9.4: Self-inflating bag (Adapted with permission from AAP 2005)

It is, therefore, recommended that *term babies* should be initiated on room air resuscitation. Ideally, oxygen saturation should be monitored by pulse oximetry and oxygen delivery should be titrated to maintain the oxygen saturation in the targeted range (Fig 9.2). In absence of pulse oximetry, room air should be substituted by 100% oxygen, if the baby fails to improve (improvement in HR and breathing) by 90 seconds.

PPV in *preterm babies* (<35 weeks) is recommended using intermediate concentration of oxygen (21 to 30%). The oxygen concentration should be titrated by continuously monitoring of oxygen saturation by pulse oximetry. BMV is indicated, if:

- The infant is apneic or gasping
- HR is less than 100 beats per minute

In suspected or confirmed diaphragmatic hernia, bag and mask ventilation is contraindicated.

Procedure

The infant's neck should be slightly extended to ensure an open airway. The care provider should be positioned at head end or at the side of baby so as to have an unobstructed view of infant's chest and abdomen. Select an appropriate sized face mask that covers the mouth and nose, but not eyes of the infant (Fig. 9.5). The face mask should be held firmly on face to obtain a good seal. The bag should be compressed using fingers and not by hands.

PPV is the single most effective step in babies who fail to breath at birth. Ensuring adequacy of ventilation is the most important priority in such babies.



Fig. 9.5: Properly fitting mask (Adapted with permission from AAP 2005)

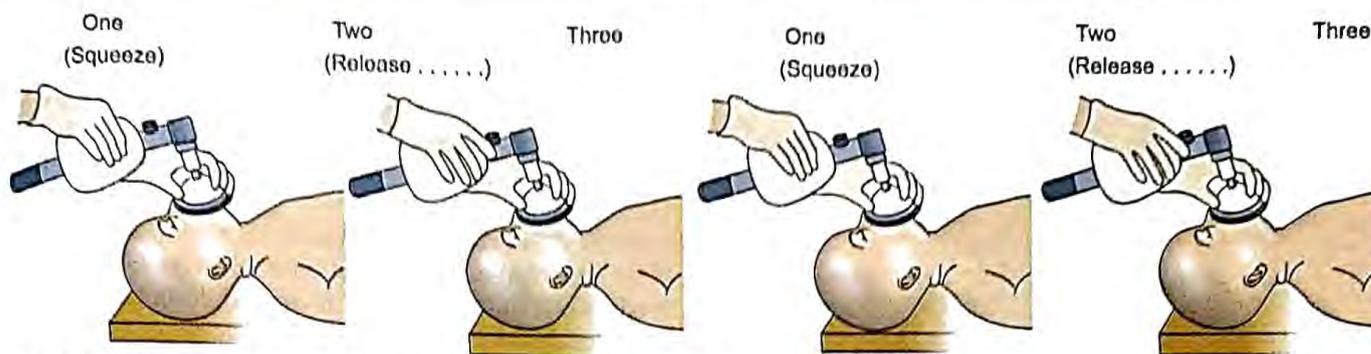


Fig. 9.6: Correct rhythm of providing positive pressure ventilation (Adapted with permission from American Academy of Pediatrics 2005)

If the baby is not responding to PPV by prompt increase in HR, ventilation corrective steps are taken: Observe for an appropriate rise of the chest and auscultate for breath sounds. If chest does not rise and there are no audible breath sounds, the steps outlined in Table 9.3 should be undertaken.

When normal rise of the chest is observed, one should begin ventilating. Ventilation should be carried out at a rate of 40 to 60 breaths per minute, following a 'squeeze, two, three' sequence (Fig. 9.6).

Usual pressure required for the first breath is 30–40 cm H₂O. For subsequent breaths, pressure of 15–20 cm H₂O is adequate. After the infant has received 30 seconds of PPV, evaluate the HR and take a follow-up action as in Fig. 9.2.

Improvement in the infant's condition is judged by increasing HR, spontaneous respiration and improving color. If the infant fails to improve, check adequacy of ventilation in form of visible chest rise. If chest rise is inadequate, one should take necessary action as described earlier.

PPV may cause abdominal distension as the gas escapes into the stomach via esophagus. Distended stomach presses on the diaphragm and compromises the ventilation. Therefore, if ventilation is continued for more than two minutes, an orogastric tube (feeding tube size 6–8 Fr) should be inserted and left open to decompress the abdomen.

Chest Compressions

The heart circulates blood throughout the body delivering oxygen to vital organs. When an infant becomes hypoxic, the HR slows and myocardial contractility decreases. As a result, there is diminished flow of blood and oxygen to the vital organs.

Chest compressions (CC) consist of rhythmic compressions of the sternum that compress the heart against the spine, increase intrathoracic pressure and circulate blood to the vital organs of the body. CC help in mechanically pumping the blood to vital organs of the body. CC must always be accompanied by BMV so that only oxygenated blood is being circulated during CC.

Table 9.3: Ventilation corrective steps (MR SOPA)

Action	Condition
Inadequate seal	Re-apply mask
Blocked airway	Reposition the infant's head
Blocked airway	Clear secretions by suction
Blocked airway	Ventilate with mouth slightly open
Inadequate pressure	Increase pressure slightly
Consider alternate airway	Blocked airway (endotracheal tube)

Chest compressions are indicated, if HR is below 60/min even after 30 seconds of PPV. Once the HR is 60/min or more, chest compressions should be discontinued.

Procedure

The CC are delivered by the thumb technique (Fig. 9.7). With the thumb technique, the two thumbs are used to depress the sternum, with the hands encircling the torso and the fingers supporting the back. The earlier used two-finger technique for CC is no more recommended.

When CC is performed on a neonate, pressure is applied to the lower third of sternum. Care must be taken to avoid applying pressure to xiphoid. To locate the area, one should slide the fingers on the lower edge of thoracic cage and locate xiphisternum. The lower third of the sternum is just above it.

Rate

It is important to ventilate between chest compressions. A positive breath should follow every third chest compression. In one minute, 90 chest compressions and 30 breaths are administered (a total of 120 events). To obtain the proper ratio of 90 compressions and 30 ventilations in 1 minute (3:1), chest should be compressed three times in 1½ seconds, leaving out approximately ½ second for ventilation.

Thumbs or the tips of fingers (depending on the method used) should remain in contact with the chest during compression and release. Do not lift your thumbs or fingers off the chest between compressions.

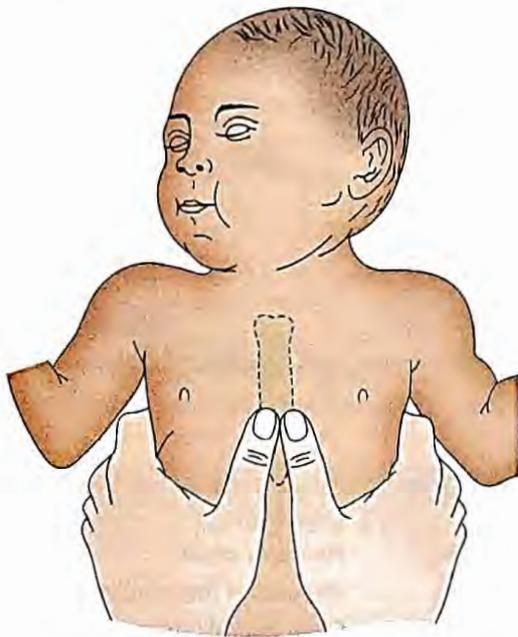


Fig. 9.7: Chest compression with thumb technique (Adapted with permission from AAP 2005)

To determine efficiency of chest compressions, the carotid or femoral pulsation should be checked periodically.

Possible complications of chest compressions include broken ribs, laceration of liver and pneumothorax.

Evaluation

After a period of 30 seconds of chest compressions, the heart rate is checked.

HR below 60. Chest compressions should continue along with bag and mask ventilation. In addition, medications (epinephrine) have to be administered.

HR 60 or above. Chest compressions should be discontinued. BMV should be continued until the heart rate is above 100 beats per minute and the infant is breathing spontaneously.

Endotracheal Intubation

Endotracheal (ET) intubation is required only in a small proportion of asphyxiated neonates. Intubation is a relatively difficult skill to learn and it requires frequent practice to maintain the skill.

Indications

The indications of ET intubation are: (i) when tracheal suction is required (in non-vigorous babies born through MSL), (ii) when prolonged BMV is required, (iii) when BMV is ineffective, and (iv) when diaphragmatic hernia is suspected. The other conditions where ET intubation may be considered are: before starting chest compressions and for administering epinephrine.

Endotracheal Tube (ET)

ET should be of uniform diameter throughout the length of the tube (and not tapered near the tip) and have vocal cord guide at the tip and centimeter markings. ET size depends on the weight or gestation of the baby (Table 9.4).

Most ET currently manufactured for neonates have a black line near the tip of the tube which is called a vocal cord guide. Such tubes are meant to be inserted so that the vocal cord guide is placed at the level of the vocal cords. This helps position the tip of ET above the bifurcation of trachea.

For intubation, a neonatal laryngoscope, with straight blades of sizes '0' (for preterm babies) and '1' (term babies) is required. Before intubating, the appropriate blade is attached to the handle of laryngoscope and the light is turned on.

Procedure

The infant's head should be in midline and the neck kept slightly extended. The laryngoscope is held in the left hand between the thumb and the first three fingers, with the blade pointing away from oneself. Standing at the head end of the infant, the blade is introduced in the mouth and advanced to just beyond the base of the tongue so that its tip rests in the vallecula. The blade is lifted as shown in Fig. 9.8 and landmarks looked for; the epiglottis and glottis should come into view. The glottic opening is surrounded by vocal cords on the sides. Once the glottis and vocal cords are visualized, the ET is introduced from the right side of the mouth and its tip inserted into the

Table 9.4: Appropriate endotracheal tube size

Inner diameter of tube (mm)	Weight (g)	Gestational age (weeks)
2.5	<1000	<28
3.0	1000–2000	28–34
3.5	2000–3000	34–38
4.0	>3000	>38

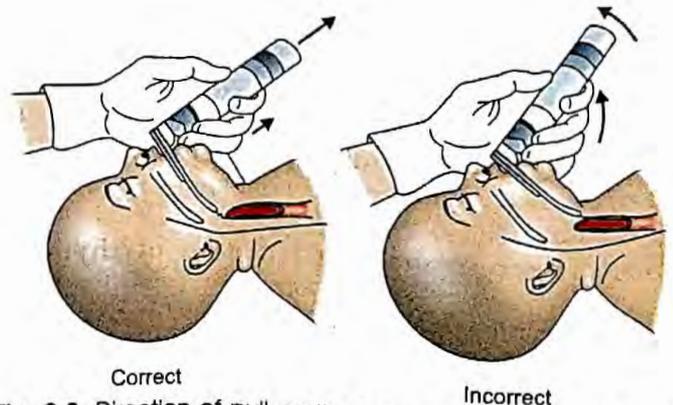


Fig. 9.8: Direction of pull on the laryngoscope (Adapted with permission from AAP 2005)

Table 9.5: Medications: Indication, dosage and effects

Medication (concentration)	Indication	Effects	Concentration administered	Dose of the prepared solution	Route
Epinephrine (1:1000)	HR <60/min after 30 sec of effective PPV and chest compressions	Inotropic; chronotropic; peripheral vasoconstrictor	1:10000	0.1–0.3 mL/kg	IV; through umbilical vein (endotracheal route, if no IV access)
Normal saline, Ringer lactate	Acute bleeding with hypovolemia	Increased intravascular volume improves perfusion		10 mL/kg	Umbilical vein
Naloxone (0.4 mg/mL) of narcotic use within 4 hr of birth	Respiratory depression with maternal history	Narcotic antagonist	0.4 mg/mL	0.25 mL/kg (0.1 mg/kg)	IV preferred; delayed onset of action with intramuscular use; administer only after restoring ventilation

Sodium bicarbonate is administered, only if prolonged asphyxia is associated with metabolic acidosis despite use of epinephrine and volume expanders. IV: Intravenous; PPV: Positive pressure ventilation

glottis until the vocal cord guide is at the level of the glottis, thus positioning it half way between the vocal cords and carina.

Medications

The majority of infants requiring resuscitation will have a response to prompt and effective ventilation with 100% oxygen. Only a few require medications.

Medications used in resuscitation include epinephrine and volume expanders (Table 9.5). Sodium bicarbonate and naloxone are indicated only for special circumstances. There is no role of atropine, dexamethasone, calcium, mannitol and dextrose for newborn resuscitation in the delivery room.

Route of administration: Since veins in scalp or extremities are difficult to access during resuscitation, umbilical vein is the preferred route. No intracardiac injection is recommended.

For umbilical vein catheterization, 3.5 Fr or 5 Fr umbilical catheter is inserted into the umbilical vein such that its tip is just inside the skin surface and there is free flow of blood. Direct injection into the umbilical cord is undesirable.

Epinephrine may be injected directly into the tracheo-bronchial tree through ET. Since absorption is erratic, this method is to be used, only if venous access cannot be obtained. The drug is injected by a syringe or a feeding tube (5 Fr) into the endotracheal tube, flushed with 0.5 mL of normal saline and dispersed into the lungs by PPV.

Indications

Use of adrenaline is indicated, if HR remains below 60 despite adequate ventilation and chest compressions for 30 seconds.

Suggested Reading

- Textbook of Neonatal Resuscitation.; 7th ed. American Academy of Pediatrics and American Heart Association, 2015

LEVEL OF NEWBORN CARE

Level-1 units: Provide care to normal term newborns and stable newborns of 35 to 36 weeks gestation. These units stabilize small and sick infants and transfer them to higher level facilities.

Level-2 units (special care nursery): Look after babies born at or after 32 weeks of gestation or weighing 1500 gm or more at birth or those with moderate sickness. These units can provide CPAP and ventilation for brief periods. They can serve as step-down units for level-3 and level-4 care.

Level-3 units (intensive care units): Provide care to babies less than 32 weeks and 1500 gm and ones with critical illnesses. These units can offer full range of respiratory support.

Level-4 care includes full range of advanced subspecialties including options of cardiac surgery.

The Indian health system defines level of care in following manners:

Newborn care corner (NBCC): All birthing facilities must have NBCC to provide resuscitation (care at birth) and care to well babies. These units identify and refer at risk and sick neonates to higher facilities.

Newborn stabilization units (NBSU): In addition to NBCC services, these units provide sick newborn care to babies above 1800 gm.

Special newborn care units (SNCU): In addition to services provided by NBCC and NBSU, these units provide care to babies <1800 gm and limited ventilation facilities.

CARE OF NORMAL NEWBORN BABIES

Care at Birth

Standard precautions and asepsis at birth: The personnel attending the delivery must exercise all the universal/standard precautions in all cases. All fluid from the baby/mother should be treated as potentially infectious. Gloves, masks and gowns should be worn when resuscitating the

newborn. The protective eyewear or face shields should be worn during procedures that are likely to generate droplets of blood or other body fluids.

Observe 'five cleans' to prevent sepsis at birth:

- i. *Clean hands:* Hand-hygiene and wear sterile gloves
- ii. *Clean surface:* Use clean and sterile towel to dry and cover the baby
- iii. *Clean blade:* The umbilical cord to be cut with a clean and sterile blade/scissors
- iv. *Clean tie:* The cord should be clamped with a clean and sterile clamp or tie
- v. Nothing to be applied on the cord. Keep it dry.

Prevention and management of hypothermia: Immediately after birth, the newborn is at high risk of hypothermia. This early hypothermia may have a detrimental effect on the health of the infant. Special care should be taken to prevent and manage hypothermia. The temperature of delivery room should be 25°C and it should be free from draft of air. The baby should be received in a pre-warmed sterile linen sheet at birth. The infant should be dried thoroughly including the head and face, and any wet linen should not be allowed to remain in contact with the infant. The infant may be placed on the mother's abdomen immediately after the birth for early skin-to-skin (STS) contact. This will not only maintain the newborn's temperature, but also promote early breastfeeding and decreases the pain and bleeding in the mother. The baby should be observed during the transition period and appropriately clothed including caps and socks.

Delayed clamping of umbilical cord: Umbilical cord clamping must be delayed for at least 30 seconds (in term as well as preterm babies) in order to allow transfer of additional amount of blood from placenta to the infant. This delayed cord clamping in term babies is associated with improved hematologic status, iron status and clinical anemia at 2 to 6 months. In preterm infants, delayed cord clamping is associated with reduced IVH and other morbidities. However, if the baby is asphyxiated at birth, cord should be clamped immediately after birth and resuscitation is initiated without any delay.

Cleaning of baby: The baby should be dried and cleaned at birth with a clean and sterile cloth. The cleaning should be gentle and should only wipe out the blood and the meconium and not be vigorous enough to remove the vernix caseosa (whitish greasy material on the skin). The vernix protects skin of the infant and helps maintain temperature. This gets absorbed on its own after sometime.

Clamping of the cord: The umbilical cord should be clamped at 2–3 cm away from the abdomen using a commercially available clamp, a clean and autoclaved thread or a sterile rubber band (Fig. 9.9). The stump should be kept away from the genitals to avoid contamination. The cord should be inspected every 15–30 minutes during initial a few hours after birth for early detection of any oozing.



Fig. 9.9: Correct application of the umbilical clamp

Placement of identity band: Each infant must have an identity band containing name of the mother, hospital registration number, gender and birth weight.

Care of Baby in Initial a Few Hours after Birth

Recording of weight. The baby should be weighed after stabilization and when the temperature is documented to be normal. A sterile preheated sheet (or a single use paper towel) should be placed on weighing machine with 10 g sensitivity. Electronic weighing scales are ideal. Zeroing of the machine should be performed. The baby is then gently placed on the weighing machine and the weight is recorded.

First examination: The baby should be thoroughly examined at birth from head to toe and the findings should be recorded in neonatal record sheet. Examine midline structures for malformations (e.g. cleft lip, neck masses, chest abnormality, omphalocele, meningocele, cloacal abnormality). Special attention should be given to identify and document the patent anal opening. There is no need for routine passage of catheter in the stomach, nostrils and the rectum for detection of esophageal atresia, choanal atresia and anorectal malformation, respectively. The baby should be examined for presence of birth injuries. The axillary temperature of the baby should be recorded before the baby is shifted out from the birthing place.

Initiation of breastfeeding: Breastfeeding should be initiated within one hour of birth. The health provider irrespective of the mode of delivery. Breastfeeding counseling alone without proactive support is unlikely to result in high rates of successful breast-feeding. Extra support is needed in primipara mothers and small babies.

Vitamin K: It should be administered to all the babies (0.5 mg for babies less than 1000 g and 1 mg for babies more than 1000 g). It is preferable to administer vitamin K₁ preparation, however, if not available, vitamin K₃ may

be administered. Vitamin K₃ can cause hemolysis in G6PD deficient babies.

Communication with the family: Before leaving the birth place, the health professional should communicate with the mother and the family members. The following facts should be clearly told to the family: (i) gender of the baby, (ii) birth weight, (iii) well-being of the baby, (iv) need for initiation of breastfeeding within one hour and need for continued observation for any problem.

Rooming in: Normal newborn should not be separated from the mother. In the initial a few hours of life, the baby is very active and co-bedding of the baby with mother facilitates early breastfeeding and bonding. Studies have shown that any separation during initial hours may have a detrimental effect on successful breastfeeding.

Care of Baby beyond a Few Hours after Birth

Care of the cord: The umbilical stump should be kept dry and devoid of any application. The nappy of the baby should be folded well below the stump to avoid any contamination.

Exclusive breastfeeding: A proactive and a systematic approach should be followed to initiate, support and maintain breastfeeding. The various advantages of the breastfeeding should be discussed with the mother to motivate her. Availability of dedicated lactation nurse or counsel or significantly improves the chances of successful breastfeeding.

Position of sleep: Evidence has linked prone position to the occurrence of sudden infant death syndrome (SIDS). All healthy term newborns should be put to sleep on their back (supine position).

Traditional practices that should be discouraged: The application of kajal or surma in the eyes, putting oil in the ear or applying cow-dung on cord must be strongly discouraged.

Timing of discharge in a normal newborn. A normal baby should stay in the health facility for at least 24 hours and preferably for 48 hours. Smaller babies or those with feeding problems or sickness should remain in hospital as required.

The following criteria should be met in all the babies prior to discharge:

- The routine formal examination of the newborn has been performed and documented.
- The newborn is breastfeeding properly. The adequacy of feeds can be determined by:
 - Passage of urine 6 to 8 times every 24 hours
 - Baby sleeping well for 2–3 hours after feeds.
- The newborn has received the immunization as per schedule.
- The mother is confident and trained to take care of the neonate.

- The newborn is not having significant jaundice or any other illness requiring closer observation by a health provider.
- The mother has been counseled regarding routine newborn care and her queries are answered.
- Follow-up advice should be communicated to the mother. Babies, particularly born to primigravida mothers should be called for follow-up visit at 48 hours of discharge, if discharged before 72 hours.
- Parents have been explained the following 'danger signs' when they need to bring the baby to the hospital:
 - i. Difficulty in feeding or poor feeding
 - ii. Convulsion
 - iii. Lethargy (movement only when stimulated)
 - iv. Fast breathing (RR >60/min)
 - v. Severe chest indrawing
 - vi. Temperature of more than 37.5°C or below 35.5°C
- A date for follow-up has been assigned. A normal newborn with adequacy of breastfeeding and no significant jaundice by 72 hours of age can be seen at 6 weeks of age. In presence of any high-risk factor (e.g. low birth weight, prematurity significant jaundice, or feeding not established), the baby should be seen within 2–3 days of discharge.

Common Parental Concerns

- **Weight loss in first week:** Normally, babies lose 8–10% of birth weight in the first week of life which is regained by 7–10 days age. Subsequently, there should be a gain of 20 to 40 g per day.
- **Crying during micturition:** The sensation of a full bladder is uncomfortable to many babies who cry before passing urine and they quieten as soon as the act of micturition starts. Crying during passage of urine as opposed to before the act of micturition should alert clinician to the possibility of urinary tract infection.
- **Bathing:** During the first week, till cord falls off, only sponging is recommended which can be given after the first 24 hours of life. Later, bathing every 2–3 days is quite sufficient. A draught-free warm room, warm water and quick completion of bath ensure that the baby does not get cold during bathing. The head constitutes a large surface area of the baby; therefore, it should be washed last and dried first. Bathing time can be used to inspect baby's cord, eyes and skin for any discharge, rash or redness.
- **Cosmetics:** Babies have a sensitive skin and use of cosmetics should be minimized. A low alkalinity, mild, non-perfumed/non-medicated soap should be used. Any oil except mustard oil can be used. Sprinkling talcum powder on babies can result in its inhalation and should be avoided. Avoid products containing boric acid (present in most prickly heat preparations).
- **Regurgitation (possetting):** Babies commonly regurgitate small amount of curdled milk soon after feeding. This

behavior is normal as long as the baby gains weight and passes urine 6–8 times a day.

- **Frequent stools:** During the first few days of life, the stool color in breastfed neonates changes from black-green to yellow by the end of first week. In between, the stools appear loose ('transitional stools'). The stool frequency may increase at this time. It is attributed to the enhanced gastrocolic reflex which results in the passage of small stools just after feeding. If the baby remains well hydrated, has no signs of sepsis, feeds well, passes urine 6–8 times per day and gains weight, there is no cause for concern.
- **Breast engorgement:** Under the effect of transplacentally transmitted hormones, the breasts in boys and girls may get hypertrophied and secrete milk like fluid. It resolves spontaneously in a few days. Engorged breasts should not be squeezed or massaged as it could lead to soreness and infection.
- **Rashes and skin peeling:** Papular lesions on erythematous base can be seen in many babies; dispersed over the trunk and face, on day two or three of life. These lesions, called erythema toxicum, are eosinophil-laden sterile lesions. They resolve spontaneously and require no treatment (Fig. 9.10a). Pyodermas, on the other hand, are pus-filled lesions occurring in response to local infection of the skin, commonly occurring in skin creases (Fig. 9.10b). If boils are <10 in number and there are no signs of sepsis, local cleaning with antiseptic solution and application of 1.0% gentian violet is sufficient. Further investigation and treatment for sepsis is indicated, if there are >10 lesions, signs of sepsis or non-resolution after topical treatment.

Skin peeling is another normal skin finding noted especially in post-term and IUGR babies. Oil massaging can decrease the flaking and no other intervention is required.

- **Diaper rash:** There is redness, inflammation and excoriation of skin in diaper area due to maceration by stools and urine. The problem is more frequent with plastic nappies. The treatment consists of keeping the area dry, avoiding rubbing of the skin for cleaning and application of a soothing cream. Use of cotton diaper is less often associated with this rash.

EVALUATION OF NEWBORN

Most neonates are born healthy, normal and free from disease. Some (approximately 10%) need observation in nursery.

Newborn examination yields different information at different times. Hence, newborns should be examined in detail at following time points: (i) soon after birth, (ii) at 24 hours of birth, (iii) before discharge from hospital, and again (iv) at follow-up visit.

Immediately after birth, the Apgar scores are assigned at 1 and 5 minutes (Table 9.2). If the score is less than 7, it

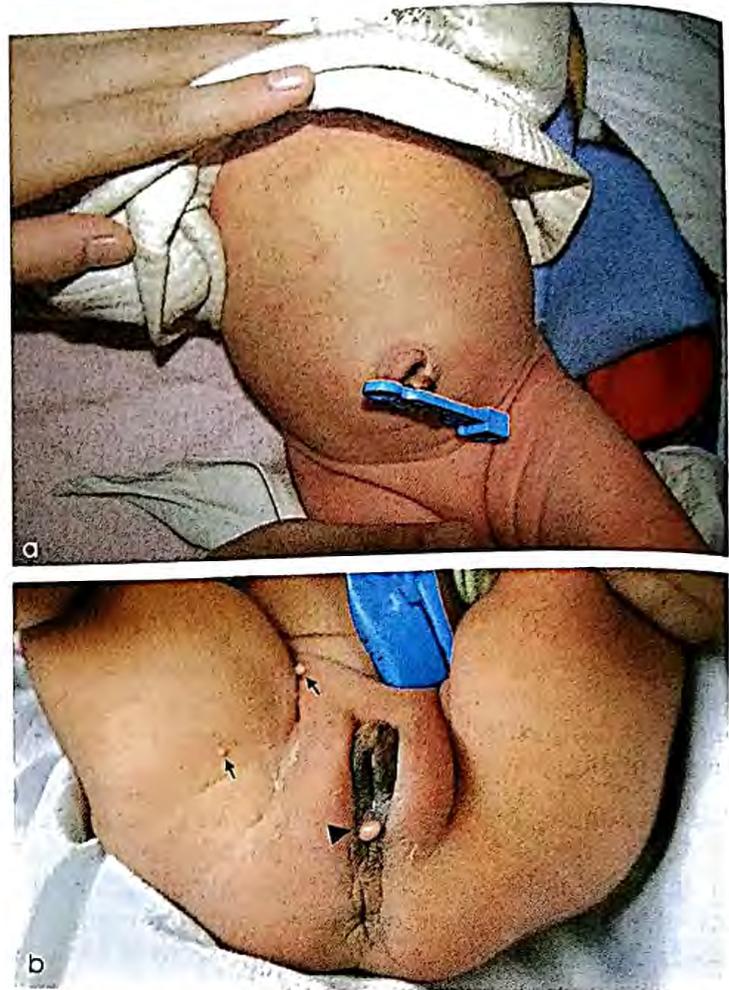


Fig. 9.10: (a) Erythema toxicum; (b) Hymenal tag (arrow head) and pustules (arrows)

is assigned every 5 minutes until 20 minutes or till two successive score are 7 or greater. These scores rapidly assess the cardiopulmonary status. Apgar scores may be falsely low in infants born very preterm and those with maternal drug intake, sepsis, congenital heart disease and central nervous system malformations. Low Apgar scores are poor predictor of long-term neurodevelopmental outcome.

If systemic examination reveals an abnormal finding, laboratory evaluation may be warranted. Table 9.6 provides a scheme for the comprehensive history and examination of the newborn.

General Observation

The least disturbing examination should be done first; this gives an opportunity to assess the state of alertness, posture, spontaneous activity, color, any obvious respiratory distress or malformation. The newborns should be examined when they are in light sleep or awake but quiet (happens after 1–1.5 hour of feeding).

A newborn with hypotonia has an extended posture as in a baby with hypoxic encephalopathy. A clear note of the color of the baby, including cyanosis, pallor, jaundice

Table 9.6: Newborn history and examination: Format for case presentation

History	
General	Mother's name and age, parity, last menstrual period, expected date of delivery
Past obstetric history	Past pregnancies: When, gestation, fetal or neonatal problems, current status of children
Antenatal	Number of antenatal visits, tests (hemoglobin; urine albumin, sugar; ultrasound; blood group, VDRL, HIV), tetanus toxoid immunization, supplements (iron, folic acid, calcium, iodine)
Obstetric or medical complications	Obstetric complications (toxemia, urinary tract infections, twins/triplets, placenta previa, accidental hemorrhage); fetal problems (IUGR, hydrops, Rh isoimmunization); medical problems (diabetes, hypertension); investigations, medications, course
Labor	Presentation, onset of labor (spontaneous/induced), rupture of membranes (spontaneous/artificial), liquor (clear/meconium stained); duration of first and second stage of labor; fetal heart rate (tachycardia, bradycardia, irregular)
Delivery	Place of delivery, vaginal (spontaneous/forceps/vacuum), cesarean (indication, elective/emergency); local/general anesthesia; duration of third stage; postpartum hemorrhage
Immediate care at birth	Resuscitation; time of first breath and cry; Apgar score; cord care; passage of urine/stool
Feeding history	Breastfeeding (when initiated, frequency, adequacy); other feeds
Postnatal problems	Feeding problems, jaundice, eye discharge, fever; current problems
Family history	History of perinatal illness in other siblings
Past medical problems	History of past medical problems, if any
Personal/social history	Socioeconomic status, family support
General examination	
Immediately after birth	Weight, gestation, congenital anomalies, sex assigning, Apgar scores, examination of umbilical vessel, and placenta
Appearance	Overall appearance: Well or sick looking; alert/unconscious
Vital signs	Temperature, cold stress; respiratory rate, retractions, grunt/stridor; heart rate, palpable femoral arteries; blood pressure, capillary refill time; cry; apneic spells
Anthropometry	Weight, length, head circumference, chest circumference
Gestation	Assessment by physical criteria; more detailed assessment by expanded New Ballard examination
Classification by intrauterine growth	Appropriate/small/large for gestational age; symmetric or asymmetric small for gestational age; signs of IUGR
Congenital anomalies	Head to toe examination for malformations
Birth trauma	Signs of trauma; cephalohematoma
Common signs	Cyanosis, jaundice, pallor, bleed, pustules, edema, depressed fontanel
Special signs	Caput; eye discharge; umbilical stump; discharge or redness; jitteriness; eye discharge; oral thrush; development peculiarities (toxic erythema, Epstein pearls, breast engorgement, vaginal bleeding, capillary hemangioma, mongolian spot)
Feeding	Observe feeding on breast (check positioning and attachment)
Reflexes	Moro, grasp, rooting
Systemic examination	
Chest	Shape; respiratory rate; retractions; air entry; adventitious sounds
Cardiovascular system	Apical impulse, heart sounds, murmur
Abdomen	Distension, wall edema, tenderness, palpable liver/spleen/kidneys, any other lump, ascites, hernial sites, gonads, genitalia
Musculoskeletal system	Deformities; tests for developmental dysplasia of hip; club foot
Central nervous system	State of consciousness; vision, pupils, eye movements; facial sensation; hearing; sucking and swallowing; muscle tone and posture; power; tendon reflexes

IUGR: Intrauterine growth retardation

and plethora should be made. One should also look at the spontaneous movements shown by the baby.

Vital Signs

In a sick baby, assessment of vital parameters takes priority over all other examination. Temperature is measured in

the apex of the baby's axilla by holding the thermometer. The finding of hypothermia (temperature of less than 36.5°C) in neonate has very important connotations. Neonates have a normal respiratory rate of 40–60 breaths/minute. The HR is faster in preterm babies compared to term babies. The normal HR range is 110–160 beats per

minute. Bradycardia (rate $<100/\text{min}$) may be associated with heart disease while tachycardia (rate $>160/\text{min}$) may be due to sepsis, anemia, fever or congestive cardiac failure. Capillary refill time is assessed by applying firm pressure on the sternum area for 5 seconds than releasing and observing the time taken to refill. The refill time is prolonged (more than 3 sec) because of poor peripheral circulation as in the shock or hypothermia.

Assessment of Size and Growth

Depending on the weight, the neonates are termed as low birth weight (LBW, less than 2500 g), very low birth weight (VLBW, less than 1500 g) or extremely low birth weight (ELBW, less than 1000 g). The aberrant growth pattern is assessed by plotting the weight against the gestational age on a standard intrauterine growth curve (which is different from postnatal growth curves for assessing growth after birth), as shown in Fig. 9.11. A neonate whose weight falls between the 10th and 90th percentile is considered as appropriate for gestational age (AGA); if the weight falls below 10th percentile, the neonate is classified as small for gestational age (SGA); the neonate is classified as large for gestational age (LGA), if the weight falls at 90th percentile or above for gestational age. The SGA babies have grown suboptimally during intrauterine period (intrauterine growth restriction, IUGR). These babies have thin slender look, loose folds of wrinkled skin, and monkey like facies.

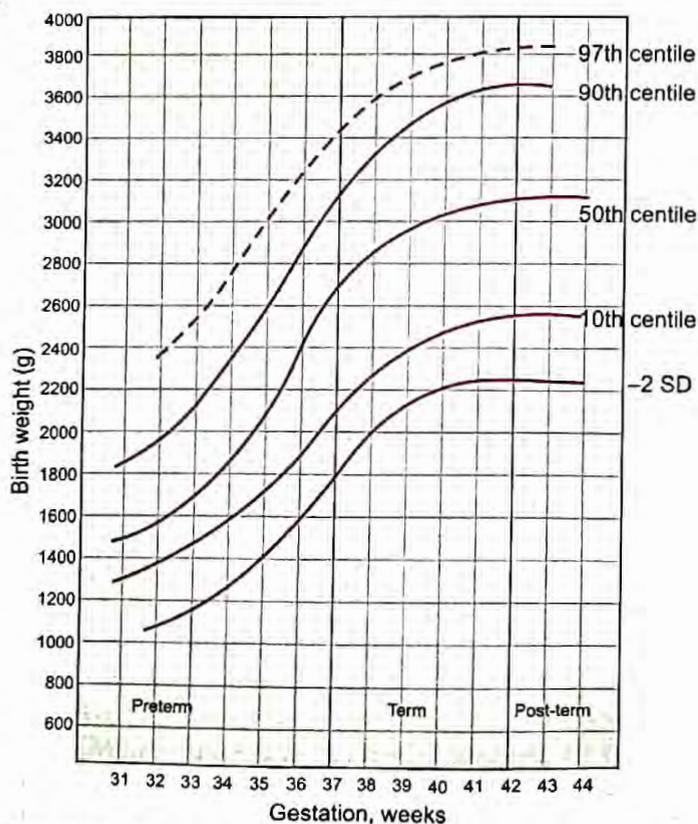


Fig. 9.11: Intrauterine growth curves. SD standard deviation

Anthropometry

The weight is measured in grams (g). The average birth weight of an Indian baby is 2.9 kg. Length is measured in centimeters using an infantometer. The newborn baby at birth is about 50 cm long. Head circumference (HC) is measured by placing a soft non-stretchable tape around the head just above the eyebrows and finding the largest circumference over the occiput. HC is 33–37 cm at birth in term babies. A large head may be due to macrocephaly, the causes include hydrocephalus and cerebral parenchymal diseases. Chest circumference is about 3 cm lesser than head circumference and if the difference is more than 3 cm it is an indication of IUGR. The Ponderal Index (PI) is calculated by multiplying the weight in grams by hundred and then dividing by cube of length in cm. This parameter is usually less than 2 in IUGR babies and 2 or more in AGA babies.

Assessment of Gestational Age

Based on gestation, neonates can be classified as preterm (<37 weeks), post-term (>42 weeks) or term (37–41 completed weeks).

The detailed evaluation requires examination of physical features and neurological maturity (Fig. 9.12). The scoring system commonly used is the Expanded New Ballard Scores (ENBS), which has an accuracy of 1 week.

Regional General Examination

Skin and hair: The skin is examined with regard to thickness, transparency and edema, rashes and lesions like hemangioma. Jaundice is detected by pressing on the skin so that the yellow color of subcutaneous tissue due to bilirubin deposition is highlighted. The skin may exhibit minor clinical problems that are innocuous and self-limiting. Ecchymoses or petechiae may relate to birth trauma, especially if present on head and neck region.

Head and fontanel: The size and shape of the head along with sutures and fontanelles should be examined carefully. The overriding of sutures is due to molding, which happen during the process of vaginal birth. The most common findings after birth are caput succedaneum and cephalohematoma. These should be differentiated as shown in Table 9.7. A full and tense fontanelle is abnormal in a quiet neonate. Large fontanelles and split sutures can be associated with increased intracranial pressure and hypothyroidism.

Neck, face, eyes and ears: Newborns have short necks. The neck is examined for masses such as enlarged thyroid gland, sternomastoid tumor and cystic hygroma. Facial nerve paresis may occur due to birth injury; this is identified by the presence of asymmetric facies while the baby is crying with open eyes and the inability to move the lips. This should be differentiated from the absence of depressor anguli oris in which asymmetric crying facies is observed; however, in this condition, the eyes remain



Fig. 9.12: Salient difference in physical characteristics of preterm and term neonates: (a) Well-curved pinna, cartilage reaching up to periphery; (b) Flat and soft pinna, cartilage not reaching up to periphery; (c) Well-pigmented and pendulous scrotal sacs, with fully descended testes; (d) Light pigmentation and not yet descended testes; (e) Deep transverse creases on the soles; (f) Faint marks on the sole, no deep creases; (g) Well-formed breast bud (>5 mm); (h) Poorly developed breast bud; (i) Silky hair, where individual strands can be made out; (j) Fuzzy hair; (k) Labia majora covering clitoris and labia minora; and (l) Prominent labia minora and clitoris

Table 9.7: Differences between caput succedaneum and cephalohematoma

Characteristic	Caput succedaneum	Cephalohematoma
Incidence	Common	Less common
Location	Subcutaneous plane	Over parietal bones, between skull and periosteum
Time of presentation	Maximum size and firmness at birth	Increasing size for 12–24 hours and then stable
Time course	Softens progressively from birth and resolves within 2–3 days	Takes 3–6 weeks to resolve
Characteristic findings	Diffuse; crosses suture line	Does not cross suture line; has distinct margins
Association	None	Linear skull fracture (5–25%); hyperbilirubinemia

tightly shut while crying (Fig. 9.13). Nose is looked for its size, shape, secretions, patency and flaring. The flaring of the nostrils indicates an increase in respiratory efforts regardless of the cause.

The alveolar ridge may have natal teeth or retention cysts (also called Epstein pearls) that disappear in a few weeks. It is very important to examine the palate for cleft.

Subconjunctival hemorrhages are common after vaginal delivery and resolve spontaneously. The cornea should be clear. Pupils should be equal in size, reactive to light and symmetrical.

Gross hearing is often assessed by looking for blink on response to noise. More formal hearing screening for all newborns is now recommended. Accessory auricles and preauricular tags are common finding that may be associated with renal anomalies.



a



b

Fig. 9.13: (a) Absent depressor anguli oris muscle. Note asymmetry of face on crying, presence of nasolabial folds and closed eyes. (b) newborn with right-sided lower motor nerve facial palsy secondary to forceps application. Note absence of nasolabial fold

Umbilicus, anus and spine: Inspect the number of vessels in the umbilical cord. A single umbilical artery may be found in 0.7% of live births; this may be associated with renal and gastrointestinal tract anomalies.

One should palpate the base of the umbilical cord for a hernia (Fig. 9.14). The spine should be palpated with a finger to exclude spina bifida, masses and any scoliosis. The anal opening should be examined for its patency and position. Presence of a sinus in the lumbosacral area may mark underlying neural tube defect (Fig. 9.15).

Genitalia (male and female): The genital area is examined by the hips abducted in the supine position. The urethra and clitoris are examined for patency and cliteromegaly, respectively. A hymenal tag may be present in a female baby (innocuous finding).



Fig. 9.14: Umbilical hernia



Fig. 9.15: Sinus in lower back may signify underlying neural tube defect

Extremities: One should make sure that the arms and limbs are fully movable with no evidence of dislocation or asymmetry of movements. The fingers are counted and any abnormality noted like nail hypoplasia, syndactyly, polydactyly, oligodactyly or unequal limbs. A calcaneovalgus deformity is usually self-correcting within the next few months but equinovarus is much more sinister and should be brought to the notice of an orthopedic specialist (Fig. 9.16).

Systemic Examination

Chest

The anteroposterior diameter of the neonate's chest is roughly same as the transverse diameter. Respiratory distress is indicated by nasal flaring, grunting, tachypnea and intercostal and subcostal retractions. Such distress may indicate pneumonia, respiratory distress syndrome (RDS), delayed reabsorption of lung fluid or any other cardiorespiratory cause.



a



Fig. 9.16: (a) Congenital talipes equinovarus deformity; (b) A newborn delivered by extended breech. Note lower limbs with extended knees and flexed hips

Cardiovascular System

An infant with heart disease manifests with tachypnea, cyanosis or both. The position of apical impulse may give idea regarding presence of conditions like congenital diaphragmatic hernia (CDH) and pneumothorax. Presence of a cardiac murmur requires complete evaluation of a neonate. Bilateral femoral artery pulsation may be absent in the coarctation of aorta.

Abdomen

Inspection of abdomen may reveal unusual flatness or scaphoid shape of abdomen that may be associated with CDH. Visible gastric or bowel patterns may indicate ileus or other obstruction. Normally, 1–2 cm of liver, tip of the spleen and the lower pole of the left kidney may be palpated.

Musculoskeletal System

The common alterations are deformations caused by adverse mechanical factors in utero. Most positional deformities are mild and resolve in time. The hips are to

be examined to detect hip problems before permanent damage occurs by one year of age. Developmental dysplasia of hips (DDH) occurs in 1 of 800 live births, more commonly in girls, those with a family history and delivered by breech.

Neurological Examination

This consists of the assessment of the level of alertness and examination of cranial nerves, motor and sensory system and neonatal reflexes.

Cranial nerves: Neonates respond to cotton soaked in peppermint by 32 weeks of gestation. By 26 weeks, the infant consistently blinks in response to light and by term gestation, fixation and following (tested using fluffy red yarn ball) is well established.

By 28 weeks, the infant startles or blinks to loud noise. Sucking and swallowing are important aspects that should be examined as they give insight into the proper functioning of the V, VII, IX, X and XII cranial nerves.

The act of sucking requires the coordinated action of breathing, sucking and swallowing. Suck-swallow coordination so as to accept *paladai* feeding is present by 32 weeks. Suck-swallow and breathing coordination occurs by 34 weeks when baby can breastfeed. However, perfect coordination of suck-swallow and breathing develops only by 38 weeks of gestation.

Motor examination: By 28 weeks, there is minimal resistance to passive manipulation of all the limbs and a distinct flexor tone is appreciated in lower extremities by 32 weeks. By 36 weeks, flexor tone is palpable in both the lower and upper extremities.

Primary neonatal reflexes: Moro reflex is best elicited by the sudden dropping of the baby's head in relation to trunk; the response consists of opening of the hands and extension and abduction of the upper extremities, followed by anterior flexion (embracing) of upper extremities with an audible cry (Fig. 9.17). The hand-opening is present by 28 weeks, extension and abduction by 32 weeks and anterior flexion by 37 weeks. Moro reflex disappears by 3–6 months in normal infants. The most common cause of depressed or absent Moro reflex is a generalized disturbance of the central nervous system. An asymmetrical Moro reflex is indicative of root plexus injury.

The palmar grasp is clearly present at 28 weeks of gestation and is strong by 32 weeks. This allows the lifting of the baby at 37 weeks of gestation. This becomes less consistent on development of voluntary grasping by 4 months. The tonic neck response is another important response elicited by rotation of the head, that causes extension of the upper extremity on the side to which the face is rotated and flexion of the upper extremity on the side of the occiput. This disappears by 4 months.



Fig. 9.17: Moro reflex: (a) Abduction and extension of arms is followed by; (b) Adduction and flexion component; (c) Asymmetric Moro reflex in brachial plexus injury (Erb's palsy on the right side—the upper limb does not move)

THERMAL PROTECTION

Newborn babies are prone to hypothermia as they have poor heat regulating mechanisms. The babies have larger surface area to their body weight, thin and permeable skin and lower subcutaneous fat. The head constitutes a significant portion of the newborn's surface area and can contribute significantly to overall heat loss. The babies have limited heat-generating mechanisms including brown fat. After birth, the babies are exposed to outside environment, which generally has a lower temperature.

Sources of Heat Loss

Heat loss in a newborn occurs through four ways:

- i. *Radiation* to surrounding environment not in direct contact with baby
- ii. *Convection* to air flowing in surrounding
- iii. *Conduction* to substances in direct contact with baby
- iv. *Evaporation* of amniotic fluid and moisture from baby's skin to atmosphere

Sources of Heat Production

When exposed to cold environment, the neonate tries to generate heat by increasing physical activity (crying,

increased body movements) and by mounting a sympathetic surge that causes cutaneous vasoconstriction and generating heat by non-shivering thermogenesis in the brown fat. Brown fat is richly vascularized, sympathetically innervated fat collections located in the axillae, groin and nape of the neck, interscapular area and perirenal area. Release of norepinephrine uncouples beta-oxidation in fat that results in heat production. Blood passing through brown fat gets heated up to keep baby warm. Preterm and small for gestational age infants have scanty brown fat stores.

Response to hypothermia: Hypothermia-induced peripheral vasoconstriction leads to increased metabolism with excess oxygen consumption and glucose utilization. Switch to anaerobic metabolism in hypothermia causes metabolic acidosis (Fig. 9.18). The acidosis induces pulmonary vasoconstriction and pulmonary hypertension further worsening the hypoxemia. When body temperature drops below 32°C, hemoglobin cannot release oxygen resulting in tissue hypoxia. The occurrence of hypoxemia, bradycardia, hypoglycemia and metabolic acidosis as a result of hypothermia contribute towards increased mortality.

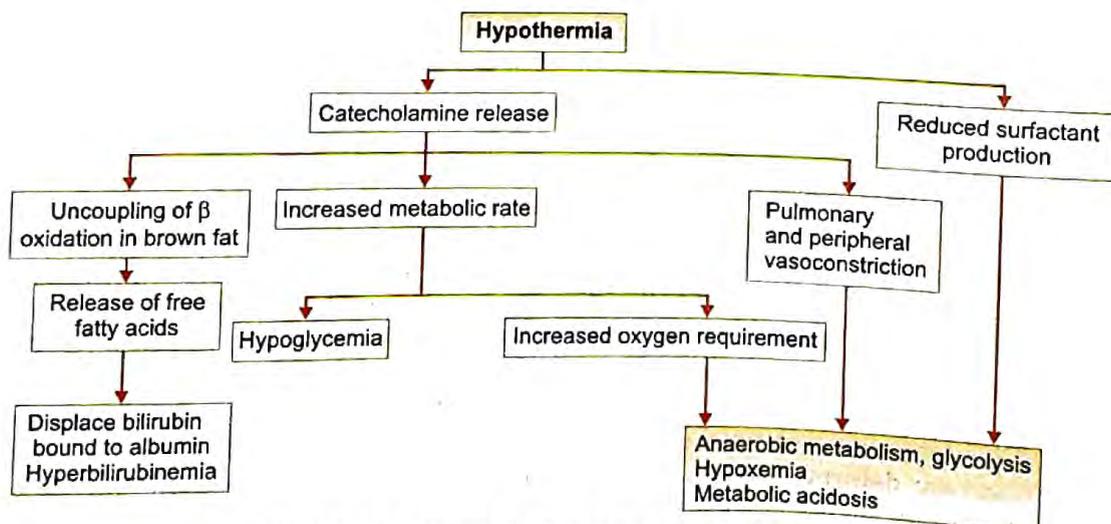


Fig. 9.18: Response to cold stress in sick neonate

Hyperthermia: An immature thermoregulating mechanism and reduced ability to sweat predispose newborns to hyperthermia. Factors like overclothing, high environmental temperature in summers, poor feeding and dehydration are the common factors that can lead to hyperthermia.

Definitions

Thermoneutral environment: Thermoneutral zone refers to a narrow range of environmental temperature in which a baby has the lowest basal metabolic rate and oxygen utilization and the baby has normal body temperature. The thermoneutral zone is different for babies of different gestation and postnatal age. It is higher for lower gestation babies, lower for clothed babies, naked babies and during initial a few days of life.

Based on axillary temperature, the disorders can be categorized as follows:

Normal body temperature: 36.5°C to 37.5°C

Hypothermia: Less than 36.5°C

- Cold stress (or mild hypothermia): 36.0 to 36.4°C
- Moderate hypothermia: 32 to 35.9°C
- Severe hypothermia: <32°C

Hyperthermia: Greater than 37.5°C

Measurement of Temperature

Ideally, a low-reading thermometer (up to 30°C) be used for temperature measurement in neonates to correctly identify severity of hypothermia. One can get a reasonable idea regarding body temperature of a baby by touching the baby's hands and feet and abdomen by back of examiner's hand. If everything appears warm, baby has normal temperature. Warm abdomen but cold feet and hands indicate mild to moderate hypothermia. Cold feet and hands as well as the abdomen would indicate that the baby has severe hypothermia.

Frequency of Measurement

The frequency of temperature measurement can be once daily for healthy babies who are otherwise well, two to three times daily for healthy small babies (2 to 2.5 kg), four times daily for very small babies (<2 kg) and every two hours for sick babies. Mother should be encouraged to assess body temperature of the neonate by touching the baby.

Disorders of Body Temperature

Hypothermia may happen as a result of exposure to a cold environment such as low ambient temperature, cold surface, or cold air, or the baby is wet or not clothed adequately. Hyperthermia may result, if the infant is exposed to warm environment such as in summers, direct sun exposure, or overheating in the incubator or radiant warmer. Hypothermia as well as hyperthermia can also indicate underlying serious illness.

Hypothermia

Prevention

- The birthing room should have ambient temperature of at least 25°C and should be free from drafts of air (keep windows and doors closed).
- After delivery, the baby should be dried immediately, put in skin-to-skin contact on mother's abdomen and covered by warm and dry linen. The wet towel should be discarded. The baby should be capped and dressed adequately (Fig. 9.19).
- Kangaroo mother care (KMC) is an effective way to keep LBW baby warm.
- Frequent breastfeeding is critical to provide energy to keep the baby warm.
- Bathing and weighing are postponed. Term babies can be sponged after 24 hours of life in summer months. Bathing should be postponed during winters and in sick or LBW babies until the umbilical cord falls off (end of first week). Dressing the baby in multiple layers of warm and light clothes provides better thermal protection than a single layer of heavy woolen clothing.
- Mother and baby should be kept on the same bed (co-bedding/rooming in).
- Warm transportation: This is the weakest link in the warm chain with greatest possibility of severe and undetected hypothermia.
- Training/awareness of healthcare providers: Unless persons involved in the care of newborns realize the implications of hypothermia, it cannot be detected or managed effectively.

Incubators and radiant warmers: These equipment are used to assist sick and small neonates maintain their normal body temperature (Fig. 9.20). Incubator is a transparent acrylic cabin which has warm air circulating around the baby to keep him warm. There is an inbuilt feedback system (servo-control) that controls ambient



Fig. 9.19: A well-clothed baby

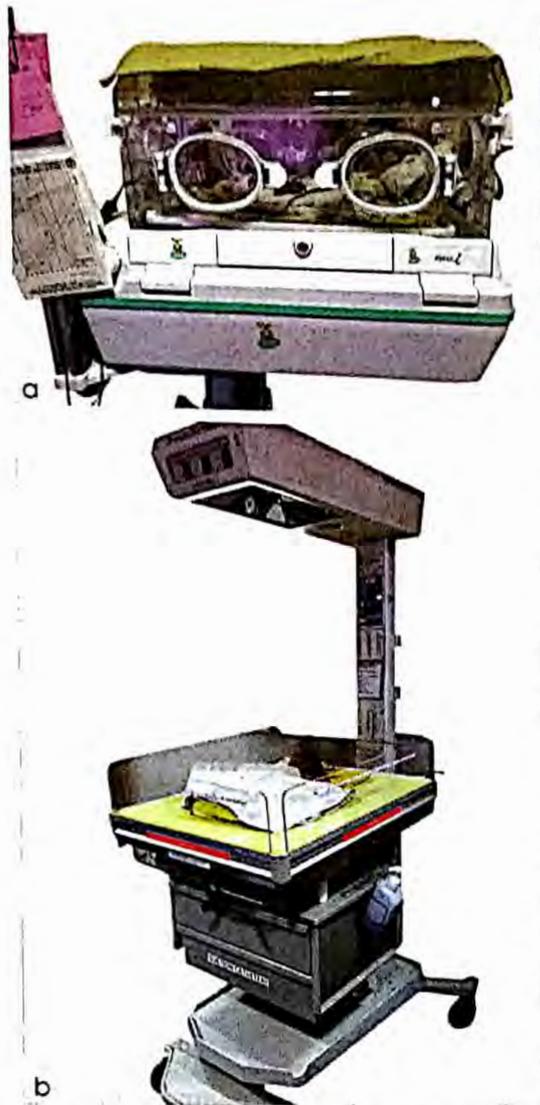


Fig. 9.20: (a) An Incubator; and (b) Radiant warmer. Note that incubator is covered with cloth to prevent excessive light or noise for adequate comfort of the baby

temperature inside incubator by altering heater output based on baby's temperature and thereby maintains the temperature of baby in the normal range.

A radiant warmer is an open system (as compared to incubator which is a closed cabinet) and the neonate lies on a crib. There is overhead radiant warmer that modulates its heater output based on baby's temperature sensed by a skin probe.

Radiant warmers and incubators should be used in the servo-control mode with the abdominal skin temperature maintained at 36.5°C to 37°C.

Signs and Symptoms

Peripheral vasoconstriction results in acrocyanosis, cool extremities and delayed peripheral capillary refill time (CRT). The baby becomes restless and then lethargic. Chronic or recurrent episodes of hypothermia result in poor weight gain. Cardiovascular manifestations may

occur in the form of bradycardia, hypotension, raised pulmonary artery pressure with resultant hypoxemia, tachypnea and distress. Presence of lethargy, poor reflexes, decreased oral acceptance and apnea denotes neurological depression. Abdomen distension, vomiting and feeding intolerance make enteral intake difficult. Acidosis, hypoglycemia, oliguria, azotemia and generalized bleeding can occur in severe cases. Babies who have chronic cold stress do not gain adequate weight.

Management

Methods for temperature maintenance include skin-to-skin contact, warm room, radiant warmers, incubators and increasing ambient temperature by use of hot air blowers, or a 200 watt bulb.

Cold Stress or Moderate Hypothermia

- Remove the baby from the source that may be causing hypothermia such as cold environment, cold clothes, cold air or wet clothing.
- Initiate skin-to-skin contact, if possible. If not possible, dress the baby in warm clothing and keep him in a warm room. Alternately, a radiant warmer or incubator may be used.
- Monitor temperature frequently. If the temperature of baby is not rising, check if adequate amount of heat being provided. Sepsis should be suspected unresponsive hypothermia.
- Ensure frequent feeding to prevent hypoglycemia. Monitor vitals.

Severe Hypothermia

- Remove all wet clothing and place baby in an incubator (air temperature 35–36°C), preheated radiant warmer or thermostatically controlled heated mattress set at 37–38°C. Alternately, one may use a room heater.
- Once baby's temperature reaches 34°C, the rewarming process should be slowed down.
- Temperature is measured every hour for 3 hours. If rise of temperature has been by 0.5°C per hour, then heating is continued 2 hourly until normal body temperature is attained and thereafter 3 hourly for 12 hours. If rise of temperature is not adequate, one should check the heating technique.
- Provide oxygen, empirical antibiotics, saline bolus if shock, IV dextrose and vitamin K. Monitor vitals.

Suggested Reading

- Guidelines for perinatal care. Second Edition, American Academy of Pediatrics and American College of Obstetricians and Gynecologists, 1998
- Thermal protection of the newborn: A practical guide. WHO/FHW/MSM/97.2

BREASTFEEDING

Breast milk is an ideal food for neonates. It is the best gift that a mother can give to her baby. It contains all the nutrients for normal growth and development of a baby from the time of birth to the first 6 months of life. Ensuring exclusive breastfeeding for 6 months has a potential to reduce under-5 mortality rate by 13%, by far the most effective intervention that is known to reduce newborn and child deaths.

To accrue the maximum benefits, the breastfeeding must be exclusive (only breast milk; nothing other than breast milk except vitamin drops, if indicated), initiated within an hour of birth and continued through first 6 months after birth.

Benefits of Breast Milk

Nutritional superiority: Breast milk contains all the nutrients a baby needs for normal growth and development, in an optimum proportion and in a form that is easily digested and absorbed.

Carbohydrates: Lactose is in a high concentration (6–7 g/dL) in breast milk. The galactose is necessary for formation of galactocerebrosides. Lactose helps in absorption of calcium and enhances the growth of lactobacilli, the good bacteria, in the intestine.

Proteins: The protein content of breast milk is low (0.9–1.1 g/dL) compared to animal milk. Most of the protein is in form of lactalbumin and lactoglobulin (60%), which is easily digested. Human milk contains amino acids like taurine and cysteine which are necessary for neuro-transmission and neuromodulation. These are lacking in cow milk and formula.

Fats: Breast milk is rich in polyunsaturated fatty acids, necessary for the myelination of the nervous system. It also contains omega 2 and omega 6 (very long chain) fatty acids, which are important for the formation of prostaglandins and cholesterol.

Vitamins and minerals: The quantity and bioavailability of vitamins and minerals is sufficient to the needs of the baby in the first 6 months of life.

Water and electrolytes: Breast milk has a water content of 88% and hence a breastfed baby does not require any additional water in the first few months of life even during summer months.

Immunological superiority: Breast milk contains a number of protective factors which include immunoglobulin—mainly secretory IgA, macrophages, lymphocytes, lactoferrin, lysozyme, bifidus factor and interferon among others. A breastfed baby is 14 times less likely to die of diarrhea and almost four times less likely to die of respiratory infection.

Other benefits: Breast milk contains a number of growth factor, enzymes and hormones. The epidermal growth

factor in breast milk enhances maturation of the intestinal cells and reduces the risk of allergy in later life. Enzymes like lipases increase the digestion of fats in the milk.

Protection against other illness: Breastfed babies have a lower risk of allergy, ear infections and orthodontic problems. They have a lower risk of diabetes, heart disease and lymphoma in later life.

Mental growth: Babies who are breastfed are better bonded to their mothers. Studies have shown that babies who were breastfed had a higher IQ than those babies who were given other forms of milk.

Benefits to mother: Breastfeeding soon after birth helps uterine involution, reducing chances of postpartum hemorrhage. It provides protection against pregnancy due to lactational amenorrhea. If the mother has been exclusively breastfeeding her baby and has not resumed menses, then there is no need for any other contraception during initial 6 months after delivery.

Breastfeeding is most convenient and time saving. It reduces the risk of cancer of breast and ovary. Breastfeeding is the most effective way of shedding extra weight that mother has gained during pregnancy.

Breast Anatomy

The breast is made up of glandular tissue, supporting tissue and fat (Fig. 9.21). The glandular tissue consists of small clusters of sac-like spaces which produce milk. Each sac is lined by network of myoepithelial cells that propel the milk into lactiferous ducts towards nipple. Before reaching the nipple, the ducts widen to form lactiferous sinuses which store milk. The lactiferous sinuses lie beneath the junction of areola and rest of breast.

The areola and nipples are extremely sensitive as they are supplied by a rich network of nerve endings. On the areola, there are small swellings of glands which produce

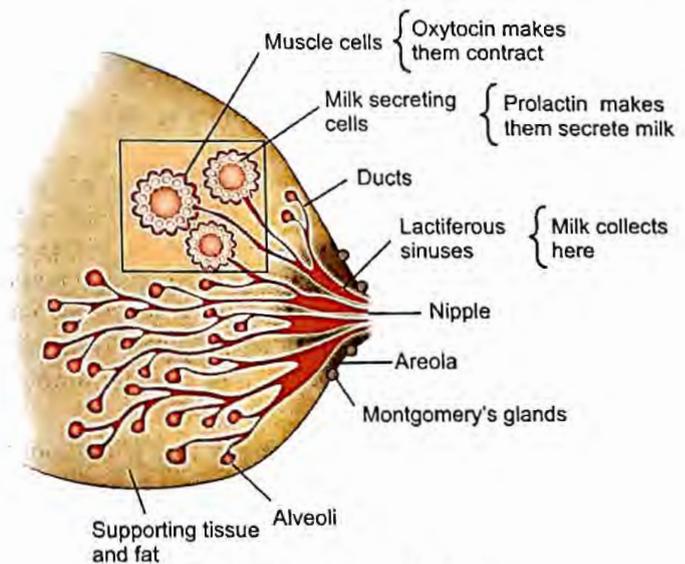


Fig. 9.21: Anatomy of breast

an oily fluid to keep the nipple skin soft. Since the lactiferous sinuses lie beneath the areola, a baby must suck at the nipple and areola. The gum line of the baby should rest at the junction of areola and rest of breast tissue in order to express milk stored in lactiferous sinuses.

Physiology

Lactogenesis is a complex phenomenon involving many hormones and reflexes. Two hormones are most important, prolactin and oxytocin.

Prolactin reflex (milk secretion reflex): Prolactin produced by the anterior pituitary gland is responsible for milk secretion by the alveolar epithelial cells (Fig. 9.22a). When the baby sucks, the nerve ending in the nipple carry impulse to the anterior pituitary which in turn release prolactin and that acts on the alveolar glands in the breast to stimulate milk secretion.

This cycle from stimulation to secretion is called the prolactin reflex or the milk secretion reflex. The more the baby sucks at the breast, the greater is the milk production. The earlier the baby is put to the breast, the sooner this reflex is initiated. The greater the demand more is the production. It is, therefore, important for mothers to feed early, frequently and empty out the breasts completely at each feeding session. Since prolactin is produced during night-time, breastfeeding during night is very important for maintenance of this reflex.

Oxytocin reflex (milk ejection reflex): Oxytocin is a hormone produced by the posterior pituitary. It is responsible for ejection of the milk from the glands into the lactiferous sinuses. This hormone is produced in response to stimulation to the nerve endings in the nipple by suckling as well as by the thought, sight, or sound of the baby (Fig. 9.22 b and c). Since this reflex is affected by the mother's emotions, a relaxed, confident attitude helps the milk ejection reflex. On the other hand, tension and lack of confidence hinder the milk flow.

Factors which reduce milk production are:

- Using dummies, pacifiers and bottles not only interfere with breastfeeding but also predispose the baby to diarrhea.
- Giving supplements such as sugar water, gripe water, honey, breast milk substitutes or formula, either as prelacteal (before initiation of breastfeeding) or supplemental (concurrent to breastfeeding) feeds. Studies have reported that even 1 or 2 supplemental feeds reduce the chances of successful breastfeeding.
- Painful breast conditions like sore or cracked nipples and engorged breast.
- Lack of night feeding, as the prolactin reflex is not adequately stimulated.
- Inadequate emptying of breast such as when baby is sick or small and the mother does not manually express breast milk or when baby is fed less frequently.

Prolactin
Secreted after feed to
produce next feed

Prolactin
in blood

Baby
suckling

Sensory
impulses
from nipple

Prolactin: Secreted more
at night; suppresses
ovulation

Oxytocin reflex
Works before or during
feed to make milk flow

Oxytocin
in blood

Baby
suckling

Sensory
impulses
from nipple

Oxytocin makes uterus contract

Oxytocin reflex

Thinks lovingly of baby
Sound and sight of baby
instills confidence

These help reflex

Worry
Stress
Pain
Doubt
These hinder reflex

Fig. 9.22: (a) Prolactin; (b) Oxytocin reflex; and (c) Factors which help and hinder oxytocin reflex

Reflexes in the Baby

A baby is born with certain reflexes which help the baby to feed. These include rooting, suckling and swallowing reflexes.

The rooting reflex: When cheek or the side of the mouth is touched, the baby opens her mouth and searches for the nipple. This is called rooting reflex. This reflex helps the baby to find the nipple and in proper attachment to the breast.

The suckling reflex: When baby's palate is touched with nipple, the baby starts sucking movements. This reflex is very strong immediately after birth. The suckling reflex consists of:

- Drawing in the nipple and areola to form an elongated teat inside the mouth.
- Pressing the stretched nipple and areola with the jaw and tongue against the palate.
- Drawing milk from the lactiferous sinuses by wave-like peristaltic movement of the tongue underneath the areola and the nipple and compressing them against the palate above.

To suckle effectively, the baby has to attach (latch) well. Obtaining good attachment at breast is a skill, which both the mother and the baby have to learn.

The method of suckling at the breast and bottle is entirely different. Suckling on a bottle filled with milk is a passive process and the baby has to control the flow of milk into the mouth with her tongue. While breastfeeding requires active efforts by the baby. A bottlefed baby develops nipple confusion and refuses to feed on the breast. Single session of bottle-feeding lessens the chances of successful breastfeeding. Bottle-feeding of babies is fraught with risk of serious infections and consequent ill-health.

The swallowing reflex: When the mouth is filled with milk, the baby reflexly swallows the milk. It requires a couple of suckles before baby can get enough milk to trigger swallowing reflex. It requires coordination with breathing. The suckle-swallow-breathe cycle lasts for about one second.

Composition of Breast Milk

The composition of breast milk varies at different time points of lactation to suit the needs of the baby. Milk of a mother who has delivered a preterm baby is different from milk of a mother delivered a term baby.

- i. **Colostrum** is the milk secreted during the initial 3–4 days after delivery. It is small in quantity, yellow and thick and contains large amount of antibodies and immunocompetent cells and vitamins A, D, E and K.
- ii. **Transitional milk** is the milk secreted after 3–4 days until two weeks. The immunoglobulin and protein content decreases while the fat and sugar content increases.
- iii. **Mature milk** follows transitional milk. It is thinner and watery but contains all the nutrients essential for optimal growth of the baby.

iv. **Preterm milk** is the milk of a mother who delivers before 37 weeks. It contains more proteins, sodium, iron, immunoglobulins and calories as per the requirement of preterm baby.

v. **Foremilk** is the milk secreted at the start of a feed. It is watery and is rich in proteins, sugar, vitamins, minerals and water that quenches the baby's thirst.

vi. **Hindmilk** comes later towards the end of feed and is richer in fat that provides more energy and gives a sense of satiety. Thus, the composition of milk also varies during the phase of feeding. For optimum growth, the baby needs both fore- as well as hind-milk. Therefore, the baby should be allowed to empty out one breast completely before switching over to the other.

Technique of Breastfeeding

Mothers require substantial assistance to learn the technique of breastfeeding. With correct technique, breastfeeding is natural and a pleasurable experience for the mother. However, a variety of breastfeeding problems do occur in large proportion of mothers that require counseling and support from the health providers for their prevention and appropriate treatment.

Positioning

Position of the mother: The mother can assume any position that is comfortable to her and the baby. She can sit or lie down. Her back should be well supported and she should not be leaning on her baby (Fig. 9.23).

Position of baby: Make sure that baby is wrapped properly in a cloth

- i. Baby's whole body is supported not just neck or shoulders.
- ii. Baby's head and body are in one line without any twist in the neck.
- iii. Baby's body turned towards the mother (abdomens of the baby and the mother touching each other).
- iv. Baby's nose is at the level of the nipple.

Attachment (Latching)

After proper positioning, the baby's cheek is touched and that initiates rooting reflex. Allow the baby to open his mouth widely and at that point, the baby should be latched onto the breast ensuring that the nipple and most of the areola are within baby's mouth (Fig. 9.24). It is important that the baby is brought on the mother's breast and mother should not lean onto baby.

Signs of Good Attachment

- i. The baby's mouth is wide open.
- ii. Most of the nipple and areola in the mouth, only upper areola visible, not the lower one.
- iii. The baby's chin touches the breast.
- iv. The baby's lower lip is everted.



Fig. 9.23: Different postures of feeding



Fig. 9.24: Good attachment

Effective Suckling

- Baby suckles slowly and pauses in between to swallow (suck, suck, suck.. and swallow). One may see throat cartilage and muscles moving and hear the gulping sounds of milk being swallowed.
- Baby's cheeks are full and not hollow or retracting during sucking.

Problems in Breastfeeding

Inverted nipples: Flat or short nipples which become prominent easily on pulling out do not pose difficulty in breastfeeding. However, truly inverted or retracted nipples make latching difficult. As the baby is not able to take nipple and areola in the mouth properly, sucking on the nipples makes them sore and excoriated. Treatment is started after birth of the baby. The nipple is manually everted, stretched and rolled out several times a day. A plastic syringe is used to draw out to correct the problem (Fig. 9.25).

Sore nipple: Nipples become sore when baby suckles on the nipple rather than areola because of incorrect attachment. As the baby is unable to express milk, he sucks vigorously in frustration and bites the nipple causing soreness. Frequent washing with soap and water and pulling the baby off the breast while he is still sucking may also result in sore nipple. Treatment consists of correct positioning and latching of the baby to the breast. A

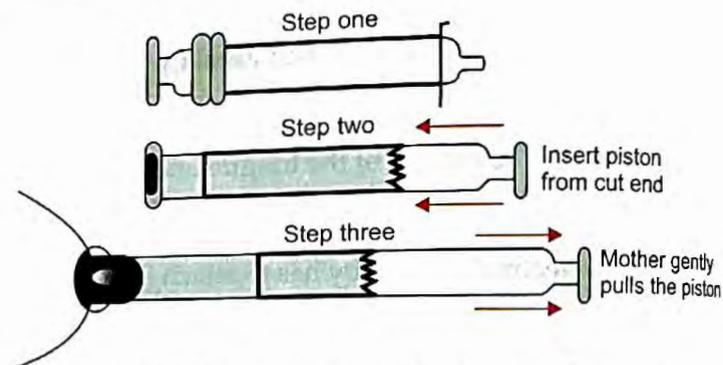


Fig. 9.25: Syringe treatment for inverted/flat nipple

mother would be able to feed the baby despite sore nipple, if the baby is attached properly. Hindmilk should be applied to the nipple after a feed and the nipple should be aired and allowed to heal in between feeds. She should be advised not to wash nipple each time before/after feeding. She can clean breast and nipple once daily at time of bathing. There is no need to apply any cream or ointment to the sore nipples.

Breast engorgement: The milk production increases by the second and third day after delivery. If feeding is delayed or infrequent, or the baby is not well positioned at the breast, the milk accumulates in the alveoli. As milk production increases, the amount of milk in the breast exceeds the capacity of the alveoli to store it comfortably. Such a breast becomes swollen, hard, warm and painful and is termed as an 'engorged breast' (Fig. 9.26).



Fig. 9.26: Engorged breast. Note tense and shiny skin; nipple shows excoriation

Breast engorgement can be prevented by early and frequent feeds and correct attachment of the baby to the breast. Treatment consists of local warm water packs, breast massage and analgesics to relieve the pain. Milk should be gently expressed to soften the breast.

Breast abscess: If a congested engorged breast, cracked nipple, blocked duct or mastitis are not treated in the early stages, breast abscess formation can occur. The mother has high grade fever and a raised blood count. She must be treated with analgesics and antibiotics. The abscess may require incision and drainage. Breastfeeding must be continued.

Not enough milk: First make sure that the perception of "not enough milk" is correct. If baby is satisfied and sleeping for 2–3 hours after breastfeeding, passing urine at least 6–8 times in 24 hours and gaining weight, the mother is producing enough milk. There could be a number of reasons for insufficient milk such as incorrect method of breastfeeding, supplementary or bottle-feeding, no night breastfeeding, engorgement of breast, any illness, painful condition, maternal stress or insufficient sleep. Try to identify the possible reason and take appropriate actions. Advise mother to take sufficient rest and drink adequate fluids. Feed the baby on demand. Let the baby feed as long as possible on each breast. Advise the mother to keep the baby with her.

Expressed Breast Milk (EBM)

If a mother is not in a position to feed her baby (e.g. ill mother, preterm baby, working mother, etc.), she should express her milk in a clean wide-mouthed container and this milk should be fed to her baby. EBM can be stored at room temperature for 6–8 hours, in a refrigerator for 24 hours and a freezer at -20°C for 3 months.

Method of Milk Expression

Ask the mother to wash her hands thoroughly with soap and water before she expresses. She should make herself comfortable. Gently massage the breast (Fig. 9.27). Hold the container under her nipple and areola. Place her thumb on top of the breast at least 4 cm from the tip of the nipple and the first finger on the undersurface of the breast opposite the thumb. Compress and release the breast tissue between her fingers and thumb a few times.

If the milk does not appear, she should reposition her thumb and finger closer to the nipple and compress and release the breast as before. Compress and release all the way around the breast. Express milk from both breasts.

To maintain adequate lactation, mother should express milk at least 8 to 10 times in 24 hours.

CARE OF LOW BIRTH WEIGHT BABIES

Low birth weight (LBW; birth weight less than 2500 g) babies have higher morbidity and mortality. LBW results from either preterm birth (before 37 completed weeks of

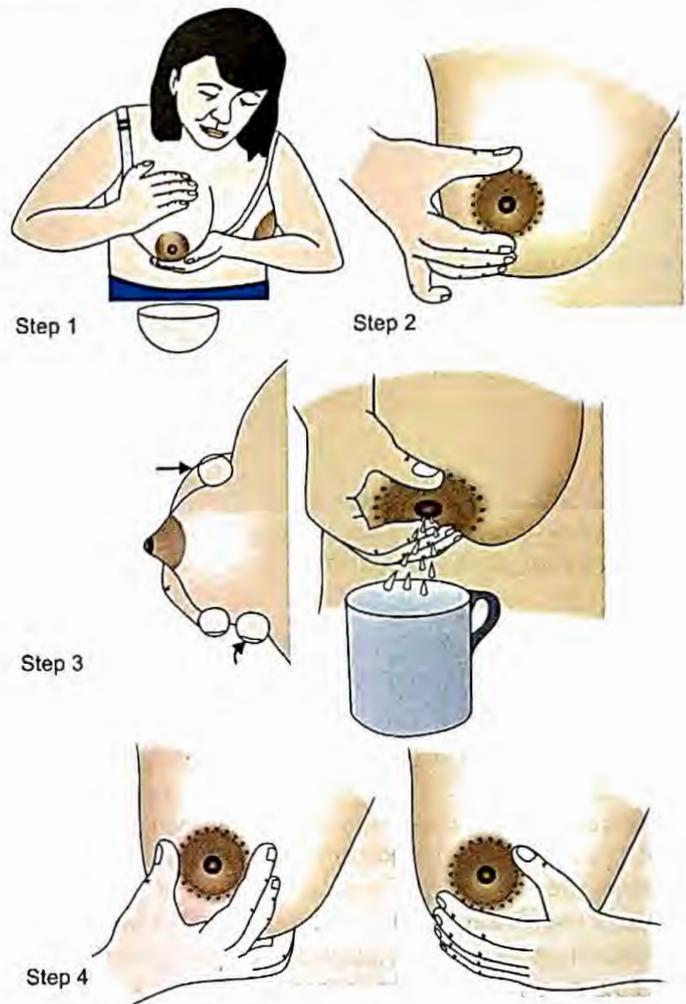


Fig. 9.27: Four steps of breast milk expression. Step 1: Massage the breasts gently toward the nipples; Step 2: Place the thumb and index finger opposite each other just outside the dark circle around the nipple; Step 3: Press back toward the chest, then gently squeeze to release milk; Step 4: Repeat step 3 in different positions around the areola

gestation) or due to intrauterine growth restriction (IUGR) or both.

IUGR is similar to malnutrition and may be present in both term and preterm infants. Neonates affected by IUGR are usually undernourished and have loose skin folds on the face and in the gluteal region (Fig. 9.28), absence of subcutaneous fat and peeling of skin. Problems faced by a preterm and IUGR neonate are different, although the management principles are common to both (Table 9.8).

IUGR results when the fetus does not grow as per the normal fetal growth trajectory. Fetal growth restriction results from one or more adverse factors that affect the normal growth pattern of the fetuses. There are two types of IUGR babies:

- **Symmetric IUGR:** When insult on the fetal growth occurs early. The size of the head, body weight and length are equally reduced. Causes include genetic and chromosomal disorders or TORCH infections.



Fig. 9.28: Baby with intrauterine growth retardation showing many loose folds of skin

Table 9.8: Major problems in preterm babies and those with intrauterine growth retardation (IUGR)

Preterm babies

Hypothermia
 Perinatal asphyxia
 Respiratory (hyaline membrane disease, pulmonary hemorrhage, pneumothorax, bronchopulmonary dysplasia, pneumonia)
 Bacterial sepsis
 Apnea of prematurity
 Metabolic (hypoglycemia, hypocalcemia)
 Hematologic (anemia, hyperbilirubinemia)
 Feeding problems and poor weight gain

Babies with IUGR

Perinatal asphyxia
 Meconium aspiration
 Hypothermia
 Hypoglycemia
 Feed intolerance
 Polycythemia
 Poor weight gain

- **Asymmetric IUGR:** The insult on the fetal growth occurs during late gestation producing a brain sparing effect. Head circumference is relatively preserved compared to length and weight. Causes include placental insufficiency, pregnancy-induced hypertension or maternal medical diseases.

Small for gestational age (SGA): It is a statistical definition and denotes weight of infant being less than 2 standard deviation or less than the 10th percentile of the population norms (plotted on intrauterine growth chart). For the practical purpose, SGA and IUGR are considered synonymous.

Issues in LBW Care

Besides the usual morbidities affecting neonates irrespective of weight and gestation, LBW may have additional problems requiring special care.

Resuscitation

Problems

- Compromised intrauterine environment with higher chances of perinatal asphyxia.
- Preterm babies have immature lungs that may be more difficult to ventilate.
- Immature blood vessels in the brain are prone to hemorrhage.
- Thin skin and a large surface area, which contribute to rapid heat loss.
- Increased risk of hypovolemic shock caused by small blood volume.

Management

- Adequate preparation for higher need for resuscitation
- Gentle resuscitation using small bags for positive pressure ventilation, use of CPAP
- Take extra care to avoid hypothermia

Temperature Control

Problems

- Higher surface area to body weight ratio
- Low glycogen stores
- Low subcutaneous fat

Management

- Frequent monitoring and educating parents
- Special attention to maintenance of the warm chain
- Kangaroo mother care

Fluids and Feeding

These have been discussed under the section on feeding.

Infection

Problems

- Immature defenses
- Greater probability of invasive interventions like mechanical ventilation, umbilical vessel catheterization.

Management

- Strict adherence to asepsis, hand hygiene
- Minimal handling of babies
- High index of suspicion of sepsis, rationale use of antibiotics
- Decreasing exposure to adults/other children with communicable diseases particularly respiratory.

Metabolic Derangements

Problems

- Low hepatic glycogen stores with rapid depletion in stress places these infants at increased risk of hypoglycemia.

- Immature glucose homeostatic mechanisms in premature babies can also lead to decreased inability to utilize glucose and resultant hyperglycemia, especially during stressful periods like infection.
- Early onset hypocalcemia: Presenting within 3 days of life and is usually asymptomatic, detected on investigation. It is especially seen in premature babies, infants of diabetic mothers and those with birth asphyxia.
- Late onset hypocalcemia presents as classical neonatal tetany, jitteriness and seizures. Feeds with higher phosphate load such as cow milk and some formulae, result in hyperphosphatemia with subsequent hypocalcemia.

KANGAROO MOTHER CARE

Kangaroo mother care (KMC) refers to care of preterm or low birth weight infants by placing the infant in skin-to-skin contact with the mother or any other caregiver. Initially conceived as an alternative to conventional warmer care for LBW infants, KMC has now become standard of care either as an alternative to or an adjunct to technology-based care.

KMC was first suggested in 1978 by Dr Edgar Rey in Bogotá, Colombia. The term kangaroo care is derived from practical similarities to marsupial caregiving, i.e. the infant is kept warm in the maternal pouch and close to the breasts for unlimited feeding.

The key features of KMC include:

- Started early after birth and ideally provided continuously and for prolonged period
- Exclusive breastfeeding
- Initiated in the birthing facility/hospital, the baby is discharged early and the KMC continued at home

Adequate support is provided to the mothers to provide KMC at home. Other caregivers also provide KMC to the baby so as give break to mothers. Most published experience and research concerning KMC comes from health facilities,

Evidence shows that KMC:

- Is as good as incubator care in terms of safety and thermal protection

- Improves breastfeeding rate
- Reduces various severe morbidities
- Contributes to the humanization of neonatal care and to better bonding between mother
- Can safely be considered a modern method of care in any setting, even where expensive technology and adequate care are available.

Criteria for Eligibility

Baby

KMC is indicated in all stable LBW babies (Fig. 9.29). However, sick babies should be cared under radiant warmer initially and KMC should be started once the baby is hemodynamically stable. Short KMC sessions can be initiated during recovery with ongoing medical treatment (IV fluids, oxygen therapy). KMC can be provided while the baby is being fed via orogastric tube or on oxygen therapy.

Mother

All mothers can provide KMC, irrespective of age, parity, education, culture and religion. The mother should be free from serious illness to be able to provide KMC. She should maintain good hygiene.

Initiation of KMC

Counseling: When baby is ready for KMC, arrange a time that is convenient to the mother and her baby. The first few sessions are important and require extended interaction. Demonstrate her the KMC procedure in a caring, gentle manner and with patience. Encourage her to bring her mother/mother-in-law, husband or any other member of the family. It helps in building positive attitude of the family and ensuring family support to the mother.

Mother's clothing: KMC can be provided using any front-open, light dress as per the local culture. KMC works well with blouse and sari, gown or shawl (Fig. 9.30). Suitable apparel that can retain the baby for extended period of time can be adapted locally.

Baby's clothing: Baby is dressed with cap, socks, nappy and front open sleeveless shirt.

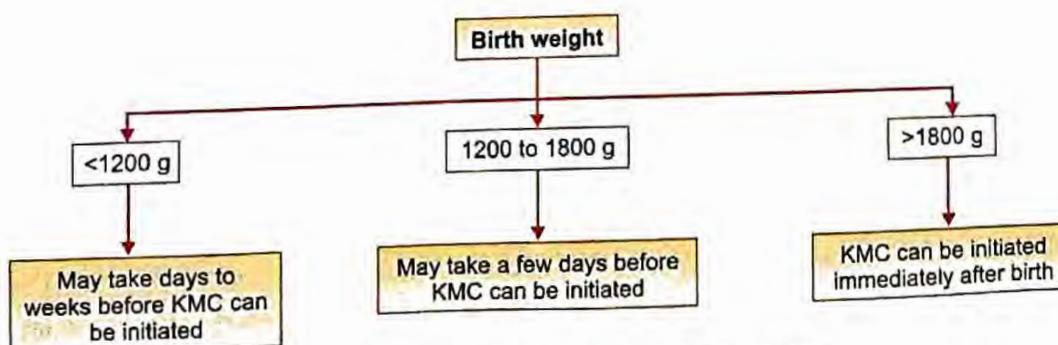


Fig. 9.29: Kangaroo mother care (KMC) protocol



Fig. 9.30: (a) Mother and (b) Father practicing KMC in front open gown and shawl; (c) AIIMS KMC jacket; (d) Mother performing KMC using AIIMS KMC jacket, (e) A mother providing KMC to her twin babies. One baby is receiving oxygen by open tube; and (f) KMC being practiced in a ventilated baby

Procedure

Kangaroo positioning: The baby should be placed between the mother's breasts in an upright position (Fig. 9.31). The head should be turned to one side and in a slightly extended position. This slightly extended head position keeps the airway open and allows eye-to-eye contact between the mother and her baby. The hips should be flexed and abducted in a 'frog' position; the arms should also be flexed. Baby's abdomen should be at the level of the mother's epigastrium. Mother's breathing stimulates the baby, thus reducing the occurrence of apnea. Support the baby's bottom with a sling or binder.

Monitoring: Babies receiving KMC should be monitored carefully, especially during the initial stages. The baby's neck position is neither too flexed nor too extended, breathing is regular, color is pink and baby is maintaining temperature.

Feeding: The mother should be explained how to breastfeed while the baby is in KMC position. Holding the baby near the breast stimulates milk production. She may express milk while the baby is still in KMC position. The baby could be fed with *paladai*, spoon or tube, depending on the condition of the baby.

Privacy: The staff must respect mother's sensitivities in this regard and ensure culturally acceptable privacy standards in the nursery and the wards where KMC is practiced.

Duration: Skin-to-skin contact should start gradually in the nursery, with a smooth transition from conventional care to continuous KMC (Fig. 9.32). Sessions that last less than one hour should be avoided because frequent handling may be stressful for the baby. The length of skin-to-skin contact should be gradually increased up to 24 hours a day, interrupted only for changing diapers.



Fig. 9.31: Kangaroo positioning



Fig. 9.32: Kangaroo mother care being provided to extremely low birth weight babies

When the baby does not require intensive care, she should be transferred to the postnatal ward where KMC should be continued.

The mother can sleep with baby in KMC position in reclined or semirecumbent position about 30° from horizontal. This can be done with an adjustable bed or with pillows on an ordinary bed. A comfortable chair with an adjustable back may be used for resting during the day.

When to Stop KMC

KMC is continued till the baby finds it comfortable and cosy. KMC is unnecessary once the baby attains a weight of 2500 g and a gestation of 37 weeks. A baby who, upon being put in the kangaroo position, tends to wriggle out, pulls limbs out, or cries or fusses is no longer in need of KMC.

FLUID AND ELECTROLYTE MANAGEMENT

Transition from fetal to extrauterine life is accompanied by remarkable changes in body fluid composition. Neonates are born with an excess of total body water (TBW) primarily in the extracellular fluid (ECF) compartment. This excess of TBW is normally lost by diuresis during first week of life. Term neonates lose about 7–10% of body weight during first 3 to 5 days of life. Preterm neonates have proportionately higher TBW and, therefore, may lose up to 10–15% of birth weight during first week of life.

The heart, kidneys, the skin and the neuroendocrine system regulate fluid and electrolyte balance in neonates. In neonates, kidneys have a limited capacity to concentrate or dilute urine due to lower glomerular filtration rate and reduced proximal and distal tubular sodium reabsorption. In addition to water loss by the kidneys and gastrointestinal system, additional water losses occur due to evaporation from the skin and respiratory tract (insensible water loss; IWL). IWL is higher in preterm infants owing to thin skin. Fever, increased respiratory rate, radiant warmers and phototherapy increase IWL.

Guidelines for Fluid Therapy

Healthy babies of 1200 g or more should be started on enteral feeding with breast milk. A baby of 1800 g or more would be able to breastfeed directly while a smaller baby may require expressed breast milk fed by suitable alternate route.

Intravenous (IV) fluid therapy: IV fluids are indicated when baby is either small or sick. Babies less than <28 weeks should be started on IV fluids routinely. Sick babies (irrespective of weight or gestation) such as those with respiratory distress, significant asphyxia, feed intolerance, hemodynamic instability, gastrointestinal malformations (like tracheoesophageal fistula, intestinal atresia, etc.) or any other severe illness precluding oral feeding should be given IV fluids. Peripheral intravenous line is the most common route used to provide fluids. Fluid requirement is calculated based on birth weight, day of life and the current fluid balance.

Babies with birth weight >1500 g: Infants on IV fluids require to excrete a solute load of about 15 mOsm/kg/day in the urine. To excrete this solute load at a urine osmolarity of 300 mOsm/L, the infant would have to pass a minimum of 50 mL/kg/day of urine. Allowing for an additional IWL of 20 mL/kg, the initial fluids should be 60–80 mL/kg/day (Table 9.9). The initial fluids should

be 10% dextrose with no electrolytes in order to maintain a glucose infusion rate of 4–6 mg/kg/min. As the infant grows and receives enteral feeds, the solute load presented to the kidneys increases and the infant requires more fluid to excrete the solute load. Water is also required for fecal losses and for growth purposes. Therefore, the fluid requirements increase by 15 to 20 mL/kg/day till a maximum of 150 mL/kg/day by the 7th day. Sodium and potassium should be added to IV fluids after 48 hours.

Babies with birth weight <1500 g: The urine output in these babies is similar to a baby of 1500 g or more. However, the fluid requirement is higher due to increased IWL. These babies need 80 mL/kg/day of 10% dextrose on day 1 of life (Table 9.9). The babies should ideally be dressed including provision of caps and socks to reduce the IWL under the radiant warmer. As the skin matures, the IWL progressively decreases and fluid requirement becomes similar to bigger babies. Fluids need to be increased at 10–15 mL/kg/day up to a maximum of 150 mL/kg/day by 5th to 7th day. Sodium and potassium should be added to IV fluids after 48 hours.

Problems with IV fluid therapy include local and systemic infection, phlebitis, fluid overload and extravasation. Because IV fluid therapy is a major risk factor for nosocomial infection, all asepsis precautions must be followed during insertion of IV cannula or administering fluids. Oral feeds should be started at the earliest possible opportunity when clinical condition of neonate improves and IV fluid should be stopped when oral feeds constitute about two-thirds of daily fluid requirement. IV sites should be inspected frequently to timely detect extravasation.

Calculation of fluids for a 1250 g baby:

- Day 1: 100 mL (80 mL/kg) to be infused at 4.2 mL/hr
- Day 2: 120 mL (95 mL/kg) to be infused at 5.0 mL/hr

Monitoring of Fluid and Electrolyte Status

Fluid therapy should be monitored every 12 to 24 hours in a baby on IV fluids using following parameters:

Body weight: Serial weight measurements can be used as a guide to estimate the fluid deficit in newborns. Term neonates lose 1–3% of their birth weight daily with a cumulative loss of 5–10% in the first week of life. Preterm neonates lose 2–3% of their birth weight daily with a cumulative loss of 10–15% in the first week of life. Failure to lose weight in the first week of life may be an indicator of excessive fluid administration. However, excessive weight loss (>3% in 24 hours) in the first 5–7 days or later

Table 9.9: Daily fluid requirements during first week of life (mL/kg/day)

Birth weight	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7 and onwards
<1500 g	80	95	110	120	130	140	150
≥1500 g	60	75	90	105	120	135	150

would be non-physiological and would merit correction with fluid therapy.

Clinical examination: The usual physical signs of dehydration are unreliable in neonates. Infants with 10% (100 mL/kg) dehydration may have sunken eyes and fontanel, cold and clammy skin, poor skin turgor and oliguria. Infants with 15% (150 mL/kg) or more dehydration would have signs of shock (hypotension, tachycardia and weak pulses).

Urine output: A well-hydrated baby would pass urine at 1 to 3 mL/kg/hr.

Suggested Reading

- Chawla D, Agarwal R, Deorari AK, Paul VK. Fluid and electrolyte management in term and preterm neonates. *Indian J Pediatr.* 2008;75:255–9.

Feeding of LBW Babies

Nutritional management influences immediate survival as well as subsequent growth and development of LBW infants. Early nutrition could also influence the long-term neurodevelopmental outcomes.

Term infants with normal birth weight require some assistance for feeding in the immediate postnatal period, but they are able to feed directly from mothers' breast. In contrast, feeding in LBW infants has following limitations:

- Over one-third of LBW infants are born at preterm with inadequate feeding skills. They might not be able to breastfeed efficiently and require alternate methods of feeding such as spoon or gastric tube feeding.
- Many LBW babies have significant illnesses during first few days of life interfering enteral feeding.
- Preterm infants have higher fluid requirements in the first few days of life due to higher insensible water loss.
- Since intrauterine accretion of many nutrients occurs mainly in third trimester, preterm infants (particularly those born before 32 weeks of gestation) have lower body stores of these nutrients at birth, which necessitates supplementation in the postnatal period.
- Because of the gut immaturity, they are more likely to experience feed intolerance necessitating adequate monitoring and treatment.

Methods

Direct and exclusive breastfeeding is the goal of feeding all LBW infants. However, because of the various limitations, not all LBW infants would be able to accept breastfeeding at least during the initial a few days after birth. These infants have to be fed by either spoon/*paladai* or gastric tube (gavage) feeding. The babies not able to receive any enteral feeding at all require intravenous (IV) fluids.

The appropriate method of feeding in an LBW infant is decided by following factors:

- Whether the infant is sick or not; and
- Feeding ability of the infant

Level of Sickness

It is essential to categorize LBW infants into two major groups, sick and healthy, before deciding the initial method of feeding.

Sick infants: This group constitutes infants experiencing various significant illnesses such as respiratory distress requiring assisted ventilation, shock, seizures, etc. These infants generally require IV fluids. Enteral feeds are initiated as soon as they reasonably recover from the illness and are hemodynamically stable. The choice of feeding method depends on the infants' gestation and clinical condition.

The enteral feeding is important for sick neonates and not be delayed without a valid reason. The infants with respiratory distress receiving mechanical ventilation can be fed enterally once the acute phase is over. Similarly, sepsis (unless associated with shock/sclerema/NEC) is not a contraindication for enteral feeding.

Healthy LBW infants: Enteral feeding should be initiated immediately after birth in healthy LBW infants with the appropriate feeding method determined by their oral feeding skills and gestation.

Ability to Feed

Breastfeeding requires effective sucking, swallowing and a proper coordination between suck/swallow and breathing. These complex skills mature with increasing gestation. A robust sucking pattern is not present until 32–34 weeks gestation. A coordination between sucking, swallowing and breathing does not mature until 34 weeks of gestation and it fully matures by 37 to 38 weeks of gestation. The maturation of oral feeding skills and the choice of initial feeding method at different gestational ages are summarized in Table 9.10.

Not all infants born at a particular gestation would have same feeding skills. Hence, the feeding method in an infant is individualized based on the feeding skills (Fig. 9.33).

Stable LBW infants, irrespective of their initial feeding method, should be offered direct breastfeeding. This helps in faster acquisition of feeding skills of smaller preterm infants and improves milk production in their mothers (non-nutritive sucking). Figure 9.34 shows the method of *paladai* and gastric tube (gavage) feeding.

Progression of Oral Feeds

All LBW infants, irrespective of their gestation and birth weight, should ultimately be able to feed directly from the mothers' breast. For preterm LBW infants, the progression to direct and exclusive breastfeeding is summarized in Fig. 9.35.

Table 9.10: Maturation of oral feeding skills and the choice of initial feeding method in LBW infants

Gestational age, weeks	Maturation of feeding skills	Initial feeding method
<28 weeks	Inadequate sucking efforts	Intravenous fluids
28–31 weeks	Lack of propulsive gut motility Sucking bursts develop	Orogastric or nasogastric tube feeding with occasional spoon or <i>paladai</i> feeding
32–34 weeks	Lack of coordination between suck/ swallow and breathing Slightly mature sucking pattern	Feeding by spoon or <i>paladai</i>
>34 weeks	Coordination between breathing and swallowing begins Mature sucking pattern Coordination between breathing and swallowing	Breastfeeding

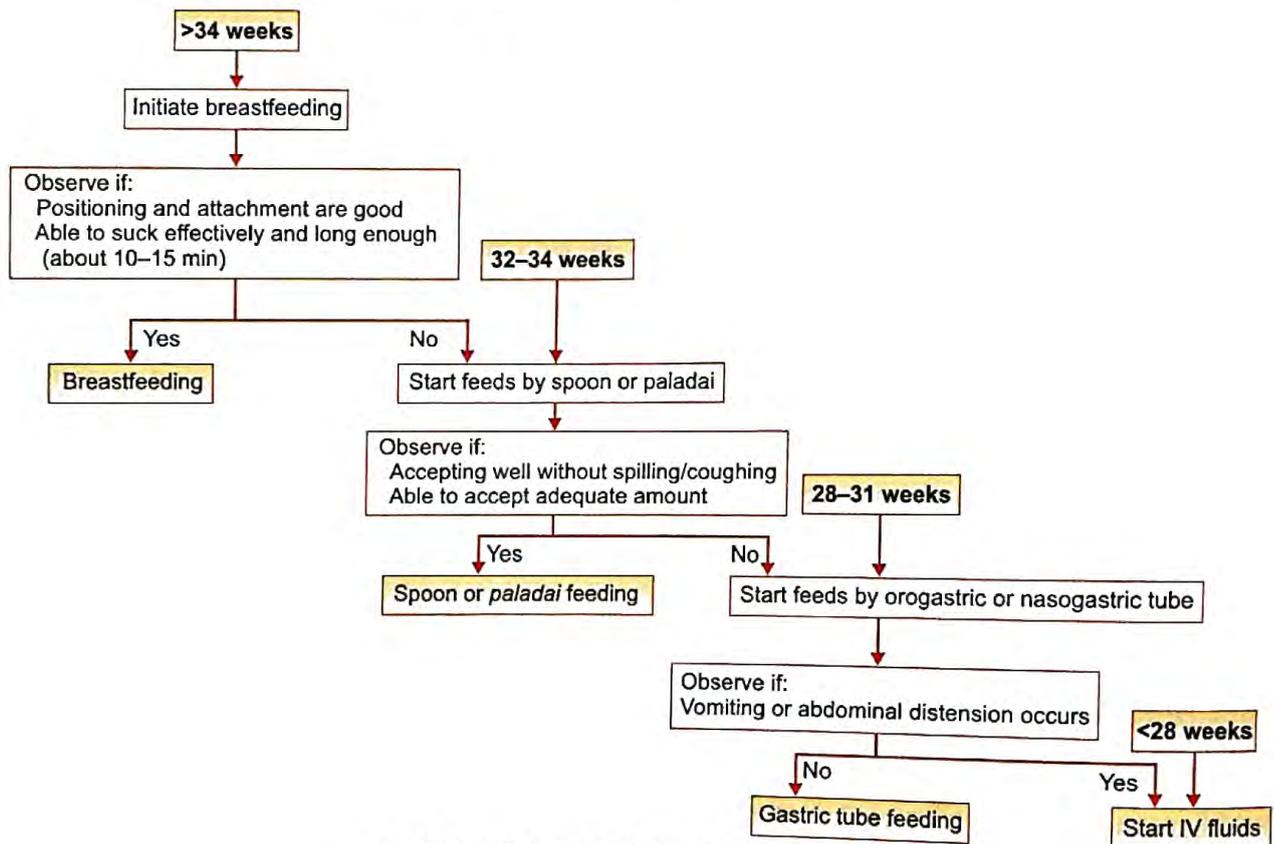


Fig. 9.33: Choosing initial methods of feeding



Fig. 9.34: (a) *Paladai* feeding; (b) Gavage feeding

Term LBW infants started on IV fluids (because of their sickness) can be put on the breast once they are hemodynamically stable.

Choice of Milk

All LBW infants, irrespective of their initial feeding method should receive only breast milk. This can be ensured by giving expressed breast milk (mothers' own milk) for those infants fed by *paladai* or gastric tube.

Expressed breast milk (EBM): All mothers should be counseled and supported in expressing breast milk for feeding their preterm infants. Expression should ideally be initiated within hours of delivery so that the infant gets colostrum. Thereafter, it should be done 2–4 hourly for ensuring good lactation in the mother. Expressed breast

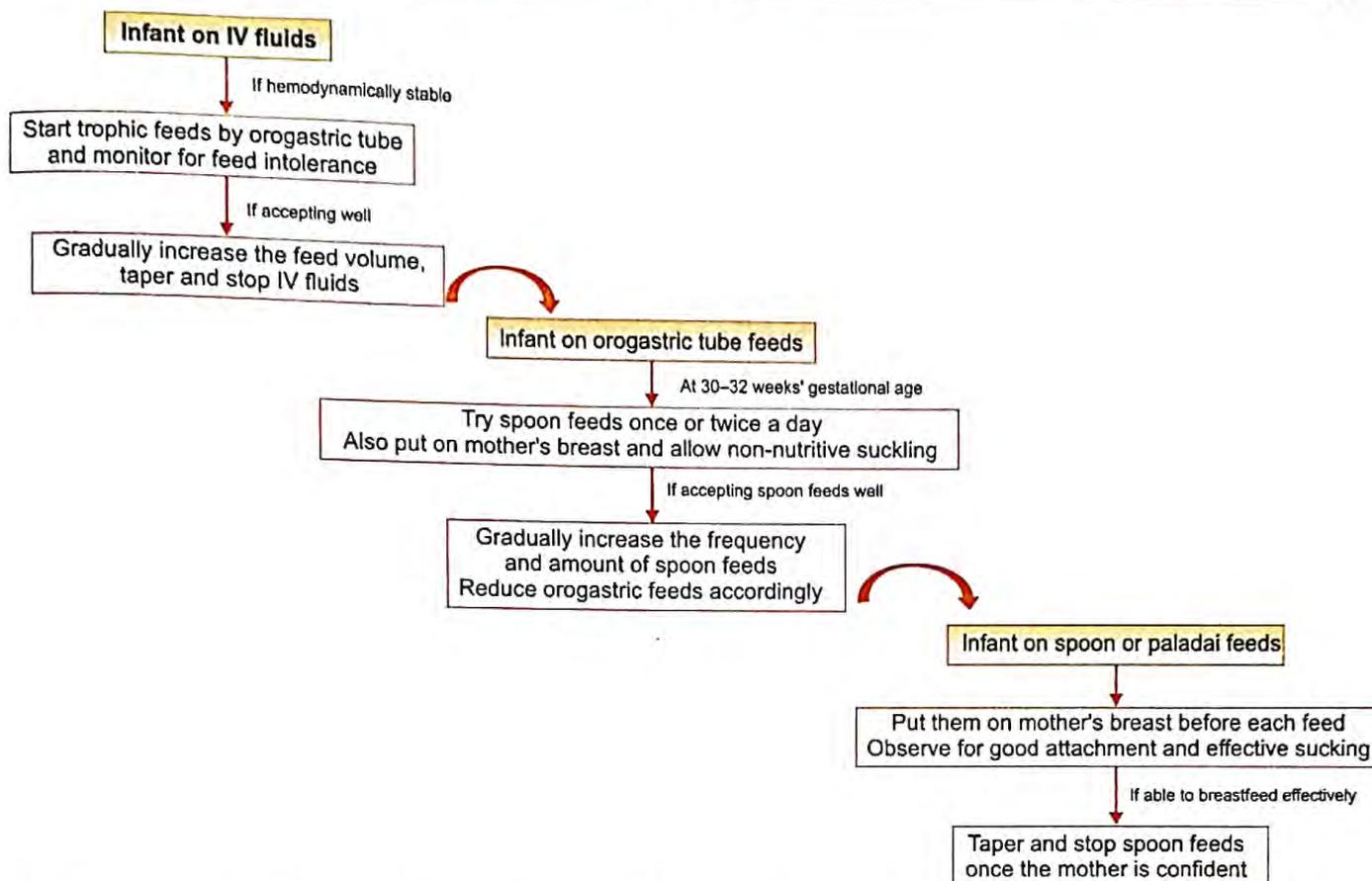


Fig. 9.35: Progression of oral feeding in preterm LBW infants. Term and near-term sick Infants started on intravenous (IV) fluids can be initiated on breastfeeding once they are hemodynamically stable

milk can be stored for about 6 hours at room temperature and for 24 hours in domestic refrigerator (2° to 8°C).

The steps of breast milk expression are given in Fig. 9.27.

Sick mothers/contraindication to breastfeeding: In these rare circumstances, the options available are:

- i. Formula feeds:
 - a. Preterm formula in VLBW infants, and
 - b. Term formula in infants weighing 1500 g or more at birth
- ii. Animal milk, e.g. undiluted cow milk

Once the mother's condition becomes stable (or the contraindication to breastfeeding no longer exists), these infants should be started on exclusive breastfeeding.

How Much to Feed?

Infants who are breastfed: Infants who are able to suckle effectively at the breast should be breastfed on demand. Small babies (<2000 g) may not be relied on demand feeding and be fed every 2–3 hours.

Infants who are fed by spoon/paladai or by intragastric tube: The daily fluid requirements of neonates have been discussed in the section of fluids and electrolytes. VLBW infants (<1500 g) need about 80 mL/kg fluids on the first day of life. It needs to be increased by 10–15 mL/kg/day to a maximum of 160 mL/kg/day by the end of the first week of life. LBW infants >1500 g are usually given about 60 mL/kg fluids on the first day of life and fluid intake is increased by about 15–20 mL/kg/day to a maximum of 160 mL/kg/day by the end of the first week of life. The volume for an individual feed can be determined by dividing total fluid to be given divided by number of feeds planned in 24 hours.

Nutritional Supplementation

Birth weight of 1500–2499 g: These infants are more likely to be born at term or near term gestation (>34 weeks). They need vitamin D and iron (Table 9.11).

Birth weight <1500 g: Those infants who are usually born before 32–34 weeks gestation have inadequate body stores

Table 9.11: Nutritional supplements for infants with birth weight between 1500 g and 2499 g

Nutrients	Method of supplementation	Dose	Duration
Vitamin D	Multivitamin drops or syrup	400 IU/day	2 weeks to 1 year of age
Iron	Iron drops or syrup	2 mg/kg/day (maximum 15 mg)	6–8 weeks to 1 year of age

of most of the nutrients. Since EBM has inadequate amounts of protein, energy, calcium, phosphorus, trace elements (iron, zinc) and vitamins D, E and K, it is often not able to meet the daily requirement of these infants. Hence, these infants need multinutrient supplementation till they reach term gestation (40 weeks, i.e. until the expected date of delivery). These nutrients can be provided by fortification of expressed breast milk with human milk fortifiers (HMF). Fortification increases the nutrient content of the milk without compromising its other beneficial effects. As HMF does not provide adequate iron, the same has to be given separately in form of drops. Fortification or supplementation of minerals and vitamins should be continued only till term gestation (40 weeks) in VLBW infants. After 40 weeks, only vitamin D and iron needs to be supplemented (similar to infants with birth weights of >1500 g).

Growth Monitoring of LBW Infants

Regular growth monitoring helps in assessing the nutritional status and adequacy of feeding in LBW infants; it also identifies those infants with inadequate weight gain.

All LBW infants should be weighed daily until the time of discharge. Length and head circumference should be recorded weekly.

Both term and preterm LBW infants tend to lose weight (about 10% and 15%, respectively) in the first 7 days of life; they regain their birth weight by 10–14 days. Thereafter, the weight gain should be at least 15–20 g/kg/day till a weight of 2–2.5 kg is reached. After this, a gain of 20 to 40 g/day is considered appropriate.

Growth charts: Using a growth chart is a simple and effective way to monitor the growth. Serial plotting of weight and other anthropometric indicators in the growth chart allows the individual infant's growth to be compared with a reference standard. It helps in early identification of growth faltering in these infants.

Management of Inadequate Weight Gain

Inadequate weight gain is a common problem in LBW infants. It may result in failure to thrive and wasting in the first year of life. The common causes are summarized in Table 9.12.

Management of inadequate weight gain consists of the following steps:

- i. Proper counseling of mothers and ensuring adequate support for breastfeeding
- ii. Explaining the frequency and timing of both breastfeeding and spoon or *paladai* feeds including night feeds: Infrequent feeding is a common cause of inadequate weight gain.
- iii. Giving EBM by spoon or *paladai* feeds after breastfeeding also helps in preterm infants who tire out easily while sucking from the breast.

Table 9.12: Causes of inadequate weight gain

Inadequate Intake

Breastfed infants

Incorrect feeding method (improper positioning or attachment)*

Less frequent breastfeeding, not feeding in the night hours*

Infants on spoon or *paladai* feeds

Incorrect method of feeding* (e.g. excess spilling)

Incorrect measurement or calculation

Infrequent feeding*

Not fortifying the milk in VLBW infants

Increased demands

Hypothermia or cold stress*

Chronic illnesses, bronchopulmonary dysplasia

Medications such as corticosteroids

*Common causes

- iv. Proper demonstration of the correct method of expression of milk and *paladai* feeding: It is important to observe how the mother gives *paladai* feeds; the technique and amount of spillage should be noted. This should be followed by a practical demonstration of the proper procedure.
- v. Ensuring optimum thermal protection

Jaundice

Problems

- Larger RBC volume for body weight
- Immaturity of hepatic enzymes and hepatic excretory capacity
- Immature blood–brain barrier—increased risk for bilirubin encephalopathy

Management: This has been discussed in section on jaundice.

Hematological Abnormality

Problems

Polycythemia: Placental insufficiency with intrauterine hypoxia leads to stimulation of erythropoiesis and resultant polycythemia, especially seen in IUGR babies. Polycythemia (>65% hematocrit) produces hyperviscosity with decreased organ perfusion. Manifestations include jitteriness, respiratory distress, cardiac failure, feeding intolerance, hypoglycemia, hypocalcemia and hyperbilirubinemia.

Anemia: Accelerated destruction of fetal RBCs, low reticulocyte count and inadequate response of the bone marrow to erythropoietin cause anemia of prematurity. Low iron stores, higher incidence of sepsis and frequent blood sampling in LBW babies further predisposes to risk of severe anemia.

Management

- **Treatment of polycythemia:** Symptomatic infants or those with hematocrit >75% require partial exchange transfusion. For others, management includes increasing the fluid intake.
- **Anemia:**
 - All LBW babies should be started on 2–3 mg/kg of iron from 2 months till 2 years of age.
 - Blood sampling should be minimized.
 - Transfusions may be given as per institution protocol.

Immature Organ Systems In Preterm Infants

Respiratory distress syndrome: This has been described in detail later.

Intraventricular hemorrhage: Preterms have a fragile highly vascular collection of vessels near the lateral ventricle of brain. Respiratory distress, mechanical ventilation or vigorous resuscitation can cause rupture of these vessels leading to adverse neurological sequelae. Preventive measures include giving antenatal steroids, minimal and gentle handling, avoiding rapid changes in intravascular volume such as rapid boluses or infusion of hyperosmolar solutions, and avoiding high pressures during ventilation.

Retinopathy of prematurity (ROP): Growth of retinal vessels occurs from the optic disc to the periphery from 18 weeks of gestation till term. Injury to these developing vessels in retina during postnatal (especially high oxygen saturation, sepsis, blood transfusions) may induce their pathological proliferation resulting in ROP. In some babies, ROP can cause vision loss, if left untreated. This complication can be decreased with rational use of oxygen, maintaining SpO₂ value between 85 and 95% and regular screening and for early detection and treatment. Advanced stages of ROP require peripheral retinal ablation by laser or cryotherapy.

Hearing damage: Preterm infants are at higher risk of hearing loss. Rational usage of ototoxic drugs, preventing hypoxia, optimally treating jaundice and routine screening for early detection can minimize this complication.

Prolonged Hospital Stay

LBW babies need longer stay in the hospital which could be quite substantial in very small or sick babies. It results in their separation from parents at birth and often incurs high expenses. It is an emotionally and financially trying time for all families. Keeping parents involved in decision-making process and providing them adequate support helps greatly in management of the baby and taking care of the family.

Criteria for Discharge

- The clothed baby is able to maintain normal body temperature without the need for radiant warmer or incubator.
- The baby is gaining weight consistently for a few days. Weight, length and head circumference should be recorded at discharge and plotted on a growth chart, which can be used on follow-up to determine, if growth is adequate.
- Baby should be feeding well either on breast or using alternate methods. The mother is adequately trained in feeding of the baby.
- Absence of significant morbidity and the baby is not needing any treatment such as IV antibiotics. If baby is being discharged on oral medication, then parents should be well educated regarding method of administration of drugs.
- Screening tests are performed before discharge or on follow-up, e.g. those for ROP detection in infants <32 weeks and auditory brainstem evoked response (ABER).
- Nutrition supplements including multivitamins, iron, calcium and vitamin D are started.
- Immunization with BCG, Hep B and OPV is given.
- All danger signs are explained to the parents with information is given when and where to report in case of development of a danger sign.

The following are the danger signs:

 - Difficulty in feeding
 - Reduced activity
 - The baby is too cold or too warm
 - Fast breathing or chest indrawing
 - Abnormal movements
 - Yellow palms or soles
- Follow-up within 3–7 days of discharge to ensure the baby has been adapted well to home environment.

INFECTIONS IN THE NEONATES

Neonates can acquire infection from a wide range of micro-organisms including bacteria, virus and protozoa. Bacteria-mediated infection constitutes a common morbidity and accounts for nearly one-third of total neonatal deaths. Infections can be superficial and systemic.

Superficial Infections

Omphalitis: Any redness or induration around the umbilicus or pus drainage from it should alert the clinician to omphalitis. Omphalitis starts as a local infection of the umbilicus, usually from unclean handling or application of unclean substances to the cord. It can spread to cause life-threatening systemic sepsis.

- **Local infection:** When the redness extends to less than 1 cm of surrounding area and there is absence of any sign of sepsis. Local cleaning with antiseptic solution,

followed by application of 0.5% gentian violet four times a day till redness subsides would take care.

- **Severe infection:** When area of redness extends beyond 1 cm of surrounding tissue or there are signs of sepsis local therapy plus systemic antibiotic should be started as in management of septicemia.

Oral thrush: White patchy lesions on the oral mucosa and tongue can occur in healthy newborns. True oral thrush lesions are difficult to wipe off and leave hemorrhagic points when removed. Local nystatin or clotrimazole application four times a day after feed is recommended.

Conjunctivitis: Infection should be differentiated from sticky eyes and blocked nasolacrimal duct. Sticky eyes generally manifests as mucoid discharge without any signs of inflammation and requires cleaning with saline. Conjunctivitis manifests as purulent discharge and signs of inflammation and requires local instillation of antibiotics. Gonococcal conjunctivitis can result in blindness and requires timely systemic antibiotics therapy.

Systemic Infections (Neonatal Sepsis)

When pathogenic organisms gain access into the bloodstream, it can result into neonatal sepsis, which may be generalized and/or localized to the lungs (pneumonia), the meninges (meningitis) or bones and joints (osteomyelitis/arthritis). Systemic bacterial infections are known by the generic term neonatal sepsis (NNS), which incorporates generalized sepsis, pneumonia, meningitis and bone-joint infections.

Etiology

Escherichia coli, *Staphylococcus aureus* and *Klebsiella sp.* are the predominant organisms. Organisms like *Acinetobacter*, *Pseudomonas* and coagulase negative staphylococci are also important pathogens in healthcare associated infections.

Early Versus Late Sepsis

Early-onset sepsis (EOS) (up to 72 hours after birth) infections are caused by organisms prevalent in the maternal genital tract or in the delivery area. EOS occurs in presence of perinatal risk factors namely spontaneous onset of preterm labor, prolonged rupture of membranes, foul smelling liquor, multiple per vaginal examinations, maternal fever, and difficult or prolonged labor. EOS frequently manifests as pneumonia and less commonly as septicemia or meningitis.

Late-onset sepsis (LOS) (72 hours or later) infections are caused by the organisms thriving in the external environment of the home or the hospital. The infection is often transmitted through the hands of the care-providers. The presentation is that of generalized sepsis, pneumonia or meningitis. The predisposing factors include LBW, lack of breastfeeding, poor cord care, superficial infections (pyoderma, umbilical sepsis), aspiration of feeds and

disruption of skin integrity with needle pricks and use of intravenous fluids.

Clinical Features

NNS often manifests with vague and ill-defined symptoms and, therefore, requires high index of suspicion for early diagnosis. An early but non-specific manifestation is alteration in the established feeding behavior. The baby, who had been active and sucking normally, refuses to suck and becomes lethargic, or unresponsive. Poor cry, hypothermia, abdominal distension, vomiting and apneic spells are other common manifestations. Diarrhea is uncommon. Fast breathing, chest retractions and grunt indicate pneumonia. Most cases of meningitis do not have any distinct clinical picture per se, making it mandatory to suspect meningitis in all cases suspected of sepsis. Shock, bleeding, sclerema and renal failure are indicators of overwhelming sepsis.

Diagnosis of sepsis is fraught with poor specificity. A host of conditions like hypothermia, hyperthermia, hypoglycemia, hypoxia, late metabolic acidosis, congestive heart failure and even simple conditions like nasal block may mimic sepsis. A careful clinical examination and relevant investigations are necessary to differentiate these conditions from NNS and avoid unnecessary antibiotics therapy. Babies who are clinically stable can be observed, without admission and intravenous antibiotics, while providing good supportive care (Fig. 9.36).

Investigations

No investigation is required to start treatment in a sick baby who has high probability of sepsis (Fig. 9.36). Blood culture provides definitive diagnosis of NNS and should be taken before starting antimicrobial therapy. After cleaning the skin (with alcohol, povidone iodine and again alcohol), a specimen of 0.5 to 1.0 mL of blood can be taken in a small culture media bottle containing 5 to 10 mL of the liquid broth.

A panel of tests (sepsis screen) consisting of total leukocyte count (TLC; $<5000/\text{mm}^3$), absolute neutrophil count (ANC; $<1800/\text{mm}^3$), immature to total neutrophil ratio (I/T ratio; more than 20%), CRP (more than 1 mg/dL) and micro-ESR (15 mm or more in the first hour) constitute a useful sepsis screen for clinically doubtful cases. Sepsis screen is considered positive, if two of these parameters are positive.

Lumbar puncture should be performed in all cases suspected of NNS except in asymptomatic babies being investigated for maternal risk factors. Table 9.13 provides gestation specific cut offs for values of various parameters in cerebrospinal fluid.

Treatment

Institution of prompt treatment is essential for ensuring optimum outcome of neonates with sepsis who often reach the health care facilities late and in a critical condition.

	Scenario 1	Scenario 2	Scenario 3	Scenario 4
Age of baby	72 hours or less	72 hours or less	72 hours or less	>72 hours
Perinatal risk factors	Yes	Yes	No	Not relevant
Sepsis symptoms in baby	No	Yes	Yes	Yes
Management	<ul style="list-style-type: none"> • Extreme risk factors¹ <ul style="list-style-type: none"> – Initiate antibiotics • Other risk factors² <ul style="list-style-type: none"> – Monitor the baby – Start antibiotics, if baby develops signs of sepsis or hemodynamic instability – No need for sepsis screen 	<ul style="list-style-type: none"> • Start antibiotics • No need for sepsis screen 	<ul style="list-style-type: none"> • If baby is too sick³ <ul style="list-style-type: none"> – Initiate antibiotics • If baby is not too sick⁴ <ul style="list-style-type: none"> – Perform sepsis screen – Give antibiotics, if sepsis screen is positive – If the sepsis screen is negative: look for alternate cause for symptoms and follow the baby closely 	
	<ul style="list-style-type: none"> • Perform blood culture before starting antibiotics in all cases • Perform lumbar puncture: <ul style="list-style-type: none"> – Before starting antibiotics in symptomatic babies – If culture is positive in asymptomatic babies 			
<p>¹Chorioamnionitis, foul smelling liquor or rupture of membrane >72 hours</p> <p>²Spontaneous preterm labor, rupture of membranes (24 to 71 hours) or unclean per vaginal examination</p> <p>³Presence of shock, bleeding tendency, respiratory failure requiring ventilation, seizures in absence of asphyxia, severe hypothermia, cellulitis, etc.</p> <p>⁴Single episode of apnea, occasional vomiting, transient temperature instability, some reduced activity, mild tachypnea</p>				

Fig. 9.36: Approach to neonate suspected of sepsis

Table 9.13: Normal CSF examination in neonates, mean (range)

Test	Term	Preterm
Cells		
Leukocytes	7 (0–32)	9 (0–29)
Polymorphonuclear cells	61%	57%
Protein (mg/dL)	90 (20–170)	115 (65–150)
Glucose (mg/dL)	52 (34–119)	50 (24–63)

Supportive care and antibiotics are the two equally important components of treatment. Antibiotics take at least 12 to 24 hours to show any effect, optimum supportive care improves the outcomes in sick septic babies.

Supportive care: Good supportive care requires meticulous attention to various aspects:

- Provide warmth; ensure normal temperature (36.5°–37.5°C).
- Start oxygen by hood or mask, if the baby is cyanosed or grunting. Provide bag and mask ventilation, if breathing is inadequate. Instilling normal saline drops in nostrils may help clear the nasal block.
- Assess peripheral perfusion by palpating peripheral pulses, capillary refill time (normally <2–3 seconds) and skin color. Serial measurement of urine output is helpful for this purpose. Infuse normal saline or Ringer lactate 10 mL/kg

over 5–10 minutes, if perfusion is poor. Repeat the same 1–2 times over the next 30–45 minutes, if perfusion continues to be poor. Dopamine and dobutamine may be required to maintain normal perfusion.

- Insert intravenous line. If hypoglycemia is suspected, infuse glucose (10%) 2 mL/kg stat. Do not use glucose boluses routinely. Provide maintenance fluid, electrolytes and glucose (4–6 mg/kg/min). Add potassium to IV fluids once normal flow of urine has been documented.
- Ensuring optimal nutrition is extremely helpful in sick babies. Enteral feeds should be initiated early, if there is no abdominal distension and baby is hemodynamically stable. Feed mother's milk.

Specific care: Antimicrobial therapy constitutes the mainstay of treatment of sepsis. In a seriously sick neonate suspected of sepsis, appropriate antibiotics therapy should be initiated without any delay after obtaining blood samples for culture.

Empiric therapy when etiologic agent is not known: The empiric therapy of NNS should cover the major causative pathogens while awaiting reports of culture studies.

Since the antimicrobial spectrum and susceptibility profile is different in different settings, there cannot be a universal policy of empiric regimen. Antibiotics are often

Table 9.14: Choice of initial antibiotic therapy

<i>Clinical situation</i>	<i>Septicemia and pneumonia</i>	<i>Meningitis</i>
Community acquired; resistant strains unlikely	Ampicillin or penicillin and gentamicin (first line)	Cefotaxime and gentamicin
Hospital acquired or when there is a low to moderate probability of resistant strains	Ampicillin or cloxacillin and amikacin (second line)	Cefotaxime and amikacin
Hospital acquired sepsis or when there is a high probability of resistant strains	Cefotaxime and amikacin (third line)	Cefotaxime and amikacin

Therapy might be modified based on culture report

used in neonates on the slightest suspicion of sepsis because of the grave and fulminant nature of neonatal sepsis. But unbridled overuse of antibiotics is associated with the serious risk of emergence of resistant strains of pathogens. Most newborn units in the country are facing the problem of overwhelming antimicrobial resistance to practically all antibiotics. Rational use of antibiotics is, therefore, the responsibility of every physician.

Each treating unit should adopt a suitable policy. Based on changes in the spectrum of etiologic agents and the antibiotics sensitivity pattern, the choice of antibiotics must be periodically reviewed and modified. Table 9.14 provides possible regimen of empiric antibiotics.

Therapy after an etiologic agent is known: Antimicrobial therapy can be made specific once a positive culture and sensitivity report is available. However, this would be known only after 2–3 days. Even in best institutions, only approximately one-fourth of babies suspected of sepsis have positive blood culture.

Mode of Administration and Dosage

Antibiotics should preferably be administered parenterally. In a baby with septicemia or pneumonia (but not meningitis), who has received intravenous ampicillin and gentamicin initially and is clinically well after 3 days, the physician may consider an individual basis switching over to oral amoxycillin along with single-dose intramuscular gentamicin therapy for the rest of the course.

Monitoring

Intensive care and monitoring is the key determinant of improved survival of neonates. The elements of monitoring in sepsis are not different from those in other life-threatening conditions. Proper monitoring of sick babies enables care providers detection of complications at the earliest. The periodicity of documenting the various parameters should be individualized.

Prognosis

The outcome depends upon weight and maturity of the infant, type of etiologic agent, its antibiotic sensitivity pattern; and adequacy of specific and supportive therapy. The early-onset septicemia carries higher risk of adverse

outcomes. The reported mortality rates in neonatal sepsis in various studies from India ranges between 45 and 58%.

Necrotizing Enterocolitis

Necrotizing enterocolitis (NEC) occurs among smaller premature infants, often those less than 32 weeks. The clinical picture mimics neonatal septicemia because of the presence of abdominal distension, apnea, bradycardia, instability of temperature, cyanosis and lethargy.

Management

Oral feeding should be withheld. A nasogastric tube is inserted to relieve distension and to aspirate stomach contents. Fluids and electrolytes in adequate quantities should be administered. Parenteral nutrition may be administered. The baby is given antibiotics after taking suitable cultures. Shock is managed by replacement of fluids and use of vasopressor agents. Plasma and platelet transfusion may be necessary to prevent bleeding tendency.

Suggested Reading

- Sankar MJ, Agarwal R, Deorari AK, Paul VK. Sepsis in the newborn. *Indian J Pediatr.* 2008 Mar; 75:261–6.

PERINATAL ASPHYXIA

Perinatal asphyxia is an insult to the fetus or newborn due to a lack of oxygen (hypoxia) and/or a lack of perfusion (ischemia) to various organs. It is often associated with tissue lactic acidosis and hypercarbia.

There is no universally accepted definition of perinatal asphyxia. The American Academy of Pediatrics Committee on Fetus and Newborn has suggested essential criteria (Table 9.15) for defining perinatal asphyxia.

In the absence of such quantification, it is better to use the term 'neonatal depression', which refers to a condition of the infant in the immediate postnatal period (approximately 1st hr) without making any association with objective evidence.

National Neonatology Forum of India (NNF) and WHO use an Apgar of 0–3 and 4–7, at 1 min, to define severe and moderate birth asphyxia, respectively (1985). For the community settings, NNF defines asphyxia as absence of cry at 1 min and severe asphyxia as absent or inadequate breathing at 5 minutes.

Table 9.15: Essential criteria for perinatal asphyxia

Prolonged metabolic or mixed acidemia (pH <7.0) on an umbilical arterial blood sample
 Persistence of Apgar score of 0–3 for >5 minutes
 Neurological manifestations, e.g. seizures, coma, hypotonia or hypoxic ischemic encephalopathy (HIE) in the immediate neonatal period
 Evidence of multiorgan dysfunction in the immediate neonatal period

Neuropathology

These differ according to gestation (Table 9.16) and are of the following main types:

Term

Selective neuronal necrosis involves cerebral cortex, hippocampus, basal ganglia, cerebellum and anterior horn cells of spinal cord. Seen predominantly in term infants and depending on site, this manifests clinically as diminished consciousness, seizures and abnormalities of feeding, breathing, etc. Parasagittal area is a watershed area for many arteries and is vulnerable to ischemia resulting in proximal limb weakness (upper >lower) that later may develop into spastic quadriparesis. Status marmoratus is a variant of selective neuronal necrosis involving basal ganglia and thalamus, having long-term sequelae such as choreoathetosis, spastic quadriparesis and retardation.

Preterm

Selective neuronal necrosis is rare in preterms; diencephalic neuronal necrosis restricted to thalamus and brainstem with or without hypothalamus and lateral geniculate body is seen. Hypoxia and acidosis followed by hyperoxia demonstrates a unique pattern of injury involving pontine nucleus and subiculum of the hippocampus.

Periventricular leukomalacia (PVL) results from hypoxic-ischemic insult leading to coagulative necrosis and infarction of periventricular white matter that is the watershed area between various arteries. Long-term sequelae of PVL include spastic diplegia and quadriplegia (lower limbs >upper limbs) and visual impairment.

Table 9.16: Neurological patterns of hypoxic-ischemic encephalopathy**Premature newborns**

Selective subcortical neuronal necrosis
 Periventricular leukomalacia
 Focal and multifocal ischemic necrosis
 Periventricular hemorrhage or infarction

Term newborns

Selective cortical neuronal necrosis
 Status marmoratus of basal ganglia and thalamus
 Parasagittal cerebral injury
 Focal and multifocal ischemic cerebral necrosis

Diagnosis and Approach

Hypoxia is an evolving process that starts at the onset of the insult and continues after resuscitation and thereafter manifests in form of sequelae. Management thus depends on which point in this evolution it is detected; with the preventive approach beginning in the prenatal period and then continuing in the form of a long follow-up much after the stabilization of the initial condition.

A wide-spectrum of clinical manifestations is seen depending on the severity of injury. These manifestations change over time and are clinically noted in babies of gestational age more than 36 weeks by classification on the basis of Levene stages of HIE (Table 9.17).

HIE staging helps predict evolution of the disease and long-term outcome. Babies with stage 1 have uniformly good prognosis. Adverse neurological outcomes are present in 20% of babies with stage 2 HIE. In stage 3 HIE, half of the neonates die and remaining half tend to have poor neuro-development outcomes.

Post-Resuscitation Management of an Asphyxiated Baby (Fig. 9.37)

- i. **Temperature:** Maintain normal temperature of the baby and avoid hyperthermia. In resourceful setting, moderate induced hypothermia (core temperature of 33° to 34°C) reduces the death or severe neuro-developmental handicap. However, the efficacy and safety of therapeutic hypothermia has not been proved in resource restricted setting (in absence of intensive care).

Table 9.17: Levene classification for hypoxic-ischemic encephalopathy

Feature	Mild	Moderate	Severe
Consciousness	Irritability	Lethargy	Comatose
Tone	Hypotonia	Marked hypotonia	Severe hypotonia
Seizures	No	Yes	Prolonged
Sucking/respiration	Poor suck	Unable to suck	Unable to sustain spontaneous respiration

Modified from: Levene MI. The asphyxiated newborn infant. In: Levene MI, Lilford RJ, ed. Fetal and Neonatal Neurology and Neurosurgery. Churchill Livingstone, Edinburgh 1995;405–26

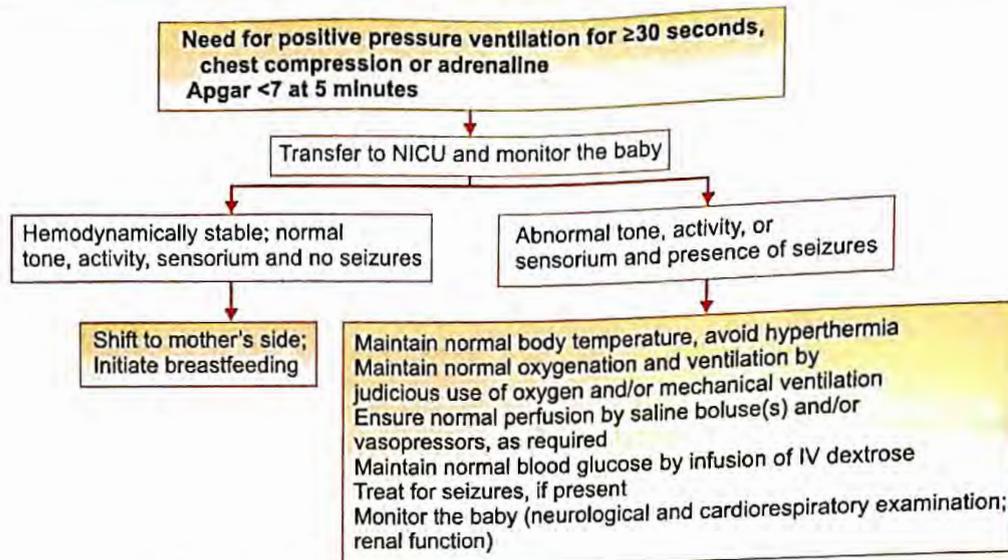


Fig. 9.37: Postresuscitation management of an asphyxiated baby

ii. **Oxygen:** Both hypoxia and hyperoxia can damage neurons. Oxygen saturations are maintained between 90 to 95%. CO_2 concentration in ventilated babies should be maintained between 40 and 50 mm Hg as hypocarbia as well as hypercarbia are detrimental to brain.

iii. **Perfusion:** Cerebral perfusion in asphyxiated babies is in 'pressure passive' state means there is loss of auto-regulation and blood supply to the brain is entirely dependant on BP; it decreases when BP falls and increases when BP rises. Therefore, to maintain normal perfusion pressure, a systemic mean arterial pressure of 45–50 mm Hg (term), 35–40 (1–2 kg weight) and 30–35 mm Hg (<1 kg weight) is required. Judicious use of fluid boluses and use of vasopressors help maintain BP.

iv. **Glucose:** Levels between 75 and 100 mg/dL are recommended. Hyperglycemia enhances cerebral edema and compromises perfusion, while hypoglycemia potentiates excitotoxic damage. Hypoglycemia is commonly seen in asphyxiated infants and the infant must be regularly monitored.

v. **Metabolic profile:** Hypocalcemia and electrolyte disturbances should be regularly looked for until stabilization of baby and corrected as indicated.

vi. **Seizures:** 20–50% of infants with HIE develop seizures during day 1 or 2. Seizures are commonly subtle or focal or multifocal. Metabolic disturbances such as hypoglycemia, hypocalcemia and hyponatremia must be ruled out. Seizures should be treated with anti-epileptic drugs (AEDs) such as phenobarbitone and phenytoin. The seizures may be intractable initially but usually tend to burn out by 48 hours. Subtle seizures lasting for brief duration need not be treated.

Once the baby is seizure-free for 3–4 days, AEDs are stopped in the same order as they were started, except phenobarbitone. Phenobarbitone is stopped at discharge,

if neurological examination is normal and baby is feeding well on breast.

Prognosis

The following features predict a poor outcome:

- Lack of spontaneous respiratory effort within 20–30 minutes of birth is associated with almost uniform mortality
- HIE stage 3
- Abnormal neurological findings persisting beyond the first 7–10 days of life
- Oliguria (<1 mL/kg/day) during the first 36 hours

Thus all these babies should have regular follow-up with monitoring of neurodevelopmental milestones to detect any deficits early and to intervene effectively.

Suggested Reading

- Agarwal R, Jain A, Deorari AK, Paul VK. Post-resuscitation management of asphyxiated neonates. *Indian J Pediatr* 2008;75:175–80.

RESPIRATORY DISTRESS

Respiratory distress in the neonate is a common problem and it can be a serious neonatal emergency. Respiratory distress is defined as presence of tachypnea (RR >60/min) with lower chest retractions, grunting and cyanosis. It can be due to respiratory (Table 9.18) and non-respiratory causes (Table 9.19). Early recognition and prompt treatment is essential to improve the outcomes.

Approach

Respiratory distress in a neonate can be recognized by the presence of varying combinations of tachypnea (RR >60/min), chest retractions, grunting, flaring of alae nasi and cyanosis. The gestation, age at onset, severity of distress and presence of associated clinical features help

Table 9.18: Pulmonary causes of respiratory distress

Cause	Time of onset	Remarks
Respiratory distress syndrome	First 6 hours of life	Common in preterm neonates
Meconium aspiration syndrome	First few hours of life	Common in term, post-term and small for date babies; history of meconium-stained liquor
Pneumonia	Any age	Often bacterial
Transient tachypnea of newborn	First 6 hours after birth	Tachypnea with minimal distress; lasts for 48–72 hours
Pneumothorax	Any age	Sudden deterioration; usually during assisted ventilation
Tracheoesophageal fistula, diaphragmatic hernia	Any age	May show associated malformations; polyhydramnios in esophageal atresia

Table 9.19: Non-pulmonary causes of rapid breathing

Cardiac	Congestive heart failure; congenital heart disease
Metabolic	Hypothermia, hypoglycemia, metabolic acidosis
Central nervous system	Asphyxia, cerebral edema, hemorrhage
Chest wall	Asphyxiating thoracic dystrophy, Werdnig-Hoffman disease

in arriving at diagnosis. It should be noted that chest retractions are mild or absent in respiratory distress due to non-respiratory causes.

Respiratory causes: Conditions listed in Tables 9.18 and 9.19 can occur both in preterm and term babies. However, if a preterm baby has respiratory distress within the first few hours of life, the most likely cause is respiratory distress syndrome (RDS). Similarly, if a term baby born to a mother with meconium-stained liquor develops respiratory distress within the first 24 hours, the most likely cause is meconium aspiration syndrome (MAS). A term baby with uncomplicated birth developing tachypnea in the first few hours of birth is likely to have transient tachypnea of newborn. Presence of suprasternal recessions with or without stridor indicates upper airway obstruction.

Cardiac disease: Cardiac etiology for respiratory distress should be suspected, if a neonate with distress has cyanosis or hepatomegaly. Congenital heart disease and cardio-myopathies or rhythm disorders can present as congestive cardiac failure in the neonatal period. Transposition of great vessels (TGV) and hypoplastic left heart syndrome usually present on day one with progressive distress. Most other cardiac conditions present after the first week of life. A preterm neonate having a systolic murmur with tachypnea and hepatomegaly is likely to have patent ductus arteriosus (PDA).

Neurological causes: Neonates with birth asphyxia, cerebral hemorrhage, or meningitis can present with tachypnea and respiratory distress. These neonates are usually lethargic with poor neonatal reflexes.

Respiratory Distress Syndrome (RDS)

RDS is common in preterm babies less than 34 weeks of gestation. The overall incidence is 10–15% but can be as high as 80% in neonates <28 weeks. In addition to prematurity, asphyxia, acidosis, maternal diabetes and cesarean section can increase the risk of RDS.

Etiopathogenesis

In RDS, the basic abnormality is surfactant deficiency. Surfactant is a lipoprotein-containing phospholipids like phosphatidylcholine and phosphatidylglycerol and proteins. Surfactant is produced by type II alveolar cells of lungs and helps reduce surface tension in the alveoli. In the absence of surfactant, surface tension increases and alveoli tend to collapse during expiration. During inspiration, more negative pressure is needed to keep alveoli patent. There is inadequate oxygenation and increased work of breathing. Hypoxemia and acidosis result in pulmonary vasoconstriction and right to left shunting across the foramen ovale. This worsens the hypoxemia and the neonate eventually goes into respiratory failure. Ischemic damage to the alveoli causes transudation of proteins into the alveoli that forms hyaline membrane. Surfactant production starts around 20 weeks of life and peaks at 35 weeks gestation. Therefore, any neonate less than 35 weeks is prone to develop RDS.

Clinical Features

Respiratory distress usually occurs within the first 6 hours of life. Clinical features include tachypnea, retractions, grunting, cyanosis and decreased air entry. Diagnosis can be confirmed by chest X-ray. Radiological features include reticulogranular pattern, ground glass opacity, low lung volume, air bronchogram (Fig. 9.38) and white out lungs in severe disease.

Management

Mild to moderate RDS can be managed with continuous positive airway pressure (CPAP). CPAP is a noninvasive modality of support where a continuous distending pressure (5–7 cm H₂O) is applied at nostril level to keep the alveoli open in a spontaneously breathing baby



Fig. 9.38: Moderate to severe respiratory distress syndrome. Note homogenous opacification of lungs obscuring heart borders and presence of air bronchogram (arrows)

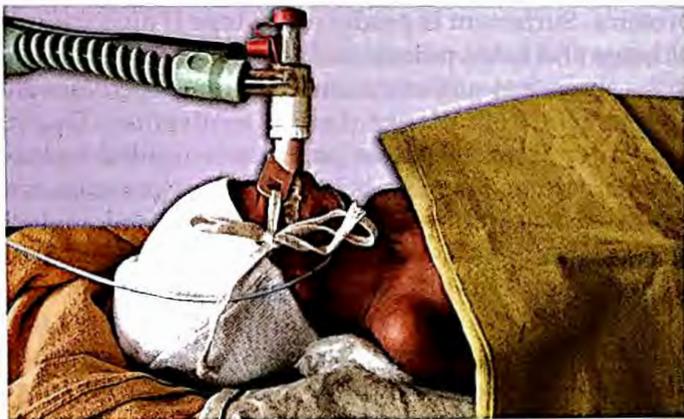


Fig. 9.39: Continuous positive airway pressure being provided to a preterm baby

(Fig. 9.39). This is an excellent modality of respiratory support which minimizes lung injury and other complications such as air leak and sepsis. Preterm babies developing severe RDS often require mechanical ventilation. Preterm babies are at risk of lung injury by excessive pressure and high oxygen. High saturations of oxygen (above 95%) can produce retinopathy of prematurity (ROP) which can blind the infant.

Since surfactant deficiency is the basis of RDS, exogenous surfactant is recommended as the treatment of choice for moderate to severe RDS.

Prevention of RDS

Administration of antenatal steroids to mothers in preterm labor (<35 weeks) has been a major breakthrough in management of preterm infants. Antenatal steroids

reduces RDS, intraventricular hemorrhage and mortality in preterm neonates (Table 9.20).

Meconium Aspiration Syndrome (MAS)

Meconium staining of amniotic fluid (MSAF) occurs in 10–14% of pregnancies. Neonates born through MSAF can aspirate the meconium into the lungs and develop respiratory distress (meconium aspiration syndrome; MAS). Aspirated meconium can block the large and small airways causing areas of atelectasis and emphysema which can progress to develop air leak syndromes like pneumothorax.

Clinical Features and Course

MAS usually occurs in term or post-term babies and small for gestational age babies. Infants usually develop

Table 9.20: Antenatal corticosteroids (ACS) use for preterm labor

Indications

1. Gestation 24 to 34 weeks

AND

1. True preterm labor, OR

2. Following conditions that lead to imminent delivery:

- Antepartum hemorrhage
- Preterm premature rupture of membranes
- Severe pre-eclampsia

Contraindications

- Frank chorioamnionitis as suggested by (1) history of fever and lower abdominal pain, (2) on examination: foul smelling vaginal discharge, tachycardia and uterine tenderness and (3) fetal tachycardia
- Maternal diabetes, pre-eclampsia and hypertension are NOT contraindications

Regimen

- Injection Dexamethasone 6 mg intramuscularly. A total of 4 doses at interval of 12 hours. Appropriate preparation of betamethasone can also be given but is not available in India.
- ACS exerts maximal benefits when delivery happens 24 hours after the last dose and up to 7 days thereafter. Partial effect is evident within a few hours before birth as well as after 7 days.
- Oral preparations of ACS are not useful.
- Repeated courses are not indicated

Benefits

Reduction in

- Respiratory distress syndrome (RDS)
- Intraventricular hemorrhage (IVH)
- Necrotizing enterocolitis (NEC)
- Neonatal mortality
- *Other benefits:* Reduced incidence of PDA, reduction in systemic infections, decreased need for respiratory support and, therefore, reduced length of hospital stay, low rate of intensive care admissions and finally reduced cost of care. Not associated with any significant short-term maternal or fetal adverse effects. No increased risk of maternal infection.

respiratory distress in the first few hours of life that often deteriorates in subsequent 24–48 hours. If untreated, distress can progress to respiratory failure. Complications include pneumothorax, other air leak syndromes (pneumopericardium, pneumomediastinum) and persistent pulmonary hypertension.

Management

Clinical course in these babies can be complicated by severe pulmonary hypertension. A good supportive care in terms of maintenance of normal body temperature, blood glucose and calcium levels, ensuring analgesia and avoiding unnecessary fiddling pay good dividends. Oxygenation and ventilation is maintained by judicious use of oxygen, mechanical ventilation and inhaled nitric oxide (to reduce pulmonary artery hypertension). With ventilatory support, 60–70% neonates survive, but in the absence of ventilatory support, mortality is high in severe disease.

Pneumonia

Pneumonia is a common cause of respiratory distress in both term and preterm babies and is caused by pathogens similar to those of neonatal sepsis such as *E. coli*, *S. aureus* and *K. pneumoniae*. Neonatal pneumonia may be due to aspiration or occasionally due to viral or fungal infection. Though group B streptococcal pneumonia is common in the West, it is uncommonly reported in India.

The neonate has features suggestive of sepsis in addition to respiratory distress. Chest X-ray shows pneumonia, blood counts are raised and blood culture may be positive. Treatment includes supportive care and specific antibiotic therapy. Ampicillin or cloxacillin with gentamicin is usually used. If the pneumonia is due to hospital-acquired infection, antibiotics like cephalosporins with amikacin may have to be used.

Transient Tachypnea of Newborn (TTN)

Transient tachypnea of the newborn is a benign self-limiting disease occurring usually in term neonates and is due to delayed clearance of lung fluid. These babies have tachypnea with minimal or no respiratory distress. Diagnosis is that of exclusion (of other serious disorders such as RDS, pneumonia). Chest X-ray may show hyper-expanded lung fields, prominent vascular marking and prominent interlobar fissure (Fig. 9.40). Oxygen treatment is often adequate. Prognosis is excellent.

Surgical Problems

Tracheoesophageal fistula (TEF) should be suspected in any neonate with excessive frothing. Diagnosis can be confirmed by a plain X-ray with a red rubber catheter (not infant feeding tube, it is soft and gets coiled up) inserted in stomach. Presence of gastric bubble suggests concomitant TEF.

Diaphragmatic hernia should be suspected in any neonates who has severe respiratory distress and has a

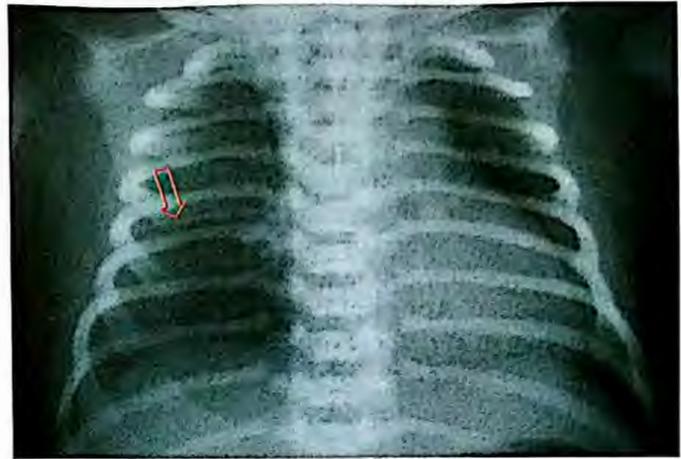


Fig. 9.40: Transient tachypnea of newborn. Note hyperinflated lungs, prominent bronchovascular markings and horizontal fissure (arrow)

scaphoid abdomen. This condition can be detected during antenatal ultrasonography. Chest X-ray shows presence of bowel loops in the thoracic cavity.

Pneumothorax

Presence of air in the pleural cavity (pneumothorax) is most common in babies with meconium aspiration syndrome and those being ventilated (Fig. 9.41). Transillumination of the chest can help in diagnosis. Needle aspiration or chest tube drainage is a life-saving procedure in this situation.

Apnea

Apnea is defined as cessation of respiration for 20 seconds with or without bradycardia and cyanosis or for shorter periods, if it is associated with cyanosis or bradycardia. Apnea is a common problem in preterm neonates. It could be central, obstructive or mixed.



Fig. 9.41: Tension pneumothorax on right side displacing the mediastinum and pushing down the diaphragm

Apnea of prematurity occurs in preterm neonates between the second to fifth days of life and is because of the immaturity of the developing brain. Central apnea can also occur because of pathological causes like sepsis, metabolic problems (hypoglycemia, hypocalcemia), temperature instability, respiratory distress, anemia and polycythemia. Obstructive apnea can occur because of block to the airway by secretion or improper neck positioning.

Treatment is supportive and involves correction of underlying cause. Apnea of prematurity is treated with aminophylline or caffeine. Prognosis is good in apnea of prematurity. In other cases, it depends on the underlying cause.

JAUNDICE

Jaundice is an important problem in the first week of life. High bilirubin levels may be toxic to the developing central nervous system and may cause neurological impairment even in term newborns. Nearly 60% of term newborns become visibly jaundiced in the first week of life. In most cases, it is benign and no intervention is required. Approximately, 5–10% of them have clinically significant jaundice requiring use of phototherapy or other therapeutic options.

Physiological Versus Pathological Jaundice

Physiological jaundice represents physiological immaturity of the neonates to handle increased bilirubin production. Visible jaundice usually appears between 24–72 hours of age. Total serum bilirubin (TSB) level usually peaks by 3 days of age and then falls in term neonates. TSB levels are below the designated cut-offs for phototherapy. It does not require any treatment.

Pathological jaundice is referred to as an elevation of TSB levels to the extent where treatment of jaundice is more likely to result into benefit than harm. There is no clear-cut demarcation between pathological and physiological jaundice. TSB levels have been arbitrarily defined as pathological, if it exceeds 5 mg/dL on first day, 10 mg/dL on second day, or 15 mg/dL thereafter in term babies. Such jaundice warrants investigation for the cause and therapeutic intervention such as phototherapy. Appearance of jaundice within 24 hours, TSB levels above the expected normal range, presence of clinical jaundice beyond 3 weeks and conjugated bilirubin (dark urine staining the nappy) would be categorized under this category.

Presence of any of the following signs indicates pathological jaundice:

- Clinical jaundice detected before 24 hours of age
- Rise in serum bilirubin by more than 5 mg/dL/day
- Serum bilirubin more than 15 mg/dL
- Clinical jaundice persisting beyond 14 days of life
- Clay-/white-colored stool and/or dark urine staining the clothes yellow
- Direct bilirubin >2 mg/dL at any time

Breastfeeding Jaundice

Exclusively breastfed infants have a different pattern of physiological jaundice as compared to artificially fed babies. Jaundice in breastfed babies usually appears between 24 and 72 hours of age, peaks by 5–15 days of life and disappears by the third week of life. One-third of all breastfed babies are detected to have mild clinical jaundice in the third week of life, which may persist into the 2nd to 3rd month of life in a few babies. This increased frequency of jaundice in breastfed babies is not related to characteristics of breast milk but rather to inadequate breastfeeding (breastfeeding jaundice). Ensuring optimum breastfeeding would help decrease this kind of jaundice.

Breast Milk Jaundice

Approximately 2–4% of exclusively breastfed term babies have jaundice in excess of 10 mg/dL beyond 3rd–4th weeks of life. These babies should be investigated for prolonged jaundice. A diagnosis of breast milk jaundice should be considered, if this is unconjugated (not staining nappies); and other causes for prolongation such as inadequate feeding, continuing hemolysis, extravasated blood, G6PD deficiency and hypothyroidism have been ruled out. Mothers should be advised to continue breastfeeding at frequent intervals and TSB levels usually decline over a period of time. Some babies may require phototherapy. Breastfeeding should not be stopped either for diagnosis or treatment of breast milk jaundice.

Clinical Estimation

Originally described by Kramer, dermal staining of bilirubin may be used as a clinical guide to the level of jaundice. Dermal staining in newborn progresses in a cephalocaudal direction. The newborn should be examined in good daylight. The skin of forehead, chest, abdomen, thighs, legs, palms and soles should be blanched with digital pressure and the underlying color of skin and subcutaneous tissue should be noted.

Serum levels of total bilirubin are approximately 4–6 mg/dL (zone 1), 6–8 mg/dL (zone 2), 8–12 mg/dL (zone 3), 12–14 mg/dL (zone 4) and >15 mg/dL (zone 5) (Fig. 9.42). Yellow staining of palms and soles is a danger sign and requires urgent serum bilirubin estimation and further management. In general, the estimation of bilirubin levels by dermal zones is unreliable particularly at higher TSB levels, after phototherapy and when it is carried out by an inexperienced observer. Total serum bilirubin can be assessed non-invasively by a transcutaneous handheld device.

Measurement of Bilirubin Levels

Newborns detected to have yellow discoloration of the skin beyond the legs, or when their clinically assessed TSB levels approach phototherapy range, should have lab confirmation of total serum bilirubin. TSB assessment has a marked interlaboratory variability.

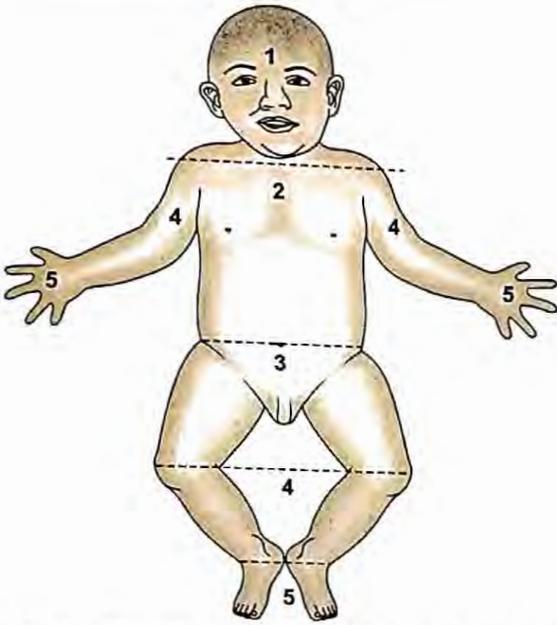


Fig. 9.42: Dermal zones for estimation of total serum bilirubin levels

Causes

Important causes of jaundice in neonates include:

- i. *Hemolytic*: Rh incompatibility, ABO incompatibility, G6PD deficiency, thalassemias, hereditary spherocytosis
- ii. *Non-hemolytic*: Prematurity, extravasated blood, inadequate feeding, polycythemia, idiopathic, breast milk jaundice

Causes are usually classified based on the time of onset of jaundice.

Appearing within 24 hours of age:

- Hemolytic disease of newborn: Rh, ABO and minor group incompatibility
- Infections: Intrauterine viral, bacterial; malaria G6PD deficiency

Appearing between 24 and 72 hours of life:

- Physiological
- Sepsis
- Polycythemia
- *Concealed hemorrhages*: Cephalohematoma, subarachnoid bleed, IVH
- Increased enterohepatic circulation

Appearing after 72 hours:

- Sepsis
- Neonatal hepatitis
- Extrahepatic biliary atresia
- Breast milk jaundice
- Metabolic disorders

Remember that the age of appearance may overlap and the above mentioned grouping is only a general classification.

Risk factors for development of severe hyperbilirubinemia include:

- i. Jaundice observed in the first 24 hours
- ii. Blood group incompatibility with positive direct antiglobulin test, other known hemolytic disease (e.g. G6PD deficiency)
- iii. Gestational age 35–36 weeks
- iv. Previous sibling received phototherapy
- v. Cephalohematoma or significant bruising
- vi. Inadequate breastfeeding, with excessive weight loss
- vii. East Asian race

Approach to a Jaundiced Neonate

All the neonates should be visually inspected for jaundice every 12 hours during initial 3 to 5 days of life (Fig. 9.43). Transcutaneous bilirubin (TcB) can be used as an aid for initial screening of infants. Visual assessment (when performed properly) and TcB have reasonable sensitivity for initial assessment of jaundice.

As a first step, serious jaundice should be ruled out. Phototherapy should be initiated, if the infant meets the criteria for serious jaundice. Total serum bilirubin should be determined subsequently in these infants to determine further course of action.

Management

Investigations

The aim of performing investigations is to confirm the level of jaundice, identify the cause and follow response to treatment.

First line

- Total serum bilirubin (and its fractions, if jaundice is prolonged or there is yellow staining of nappies): All cases with suspected pathological levels either clinically or by transcutaneous measurements need confirmation by blood test.
- Blood groups of mother and baby (if the mother is 'O' or Rh negative): Detects any incompatibility
- Peripheral smear: Evidence of hemolysis

Second line

- *Direct Coombs test*: Detects presence of antibody coating on fetal RBC
- *Hematocrit*: Decreased in hemolysis
- *Reticulocyte count*: Increased in hemolysis
- G6PD levels
- *Others*: Sepsis screen; thyroid function test; urine for reducing substances to rule out galactosemia; specific enzyme/genetic studies for Crigler-Najjar, Gilbert and other genetic enzyme deficiencies

Physiological Jaundice

The parents should be explained about the benign nature of jaundice. The mother should be encouraged to

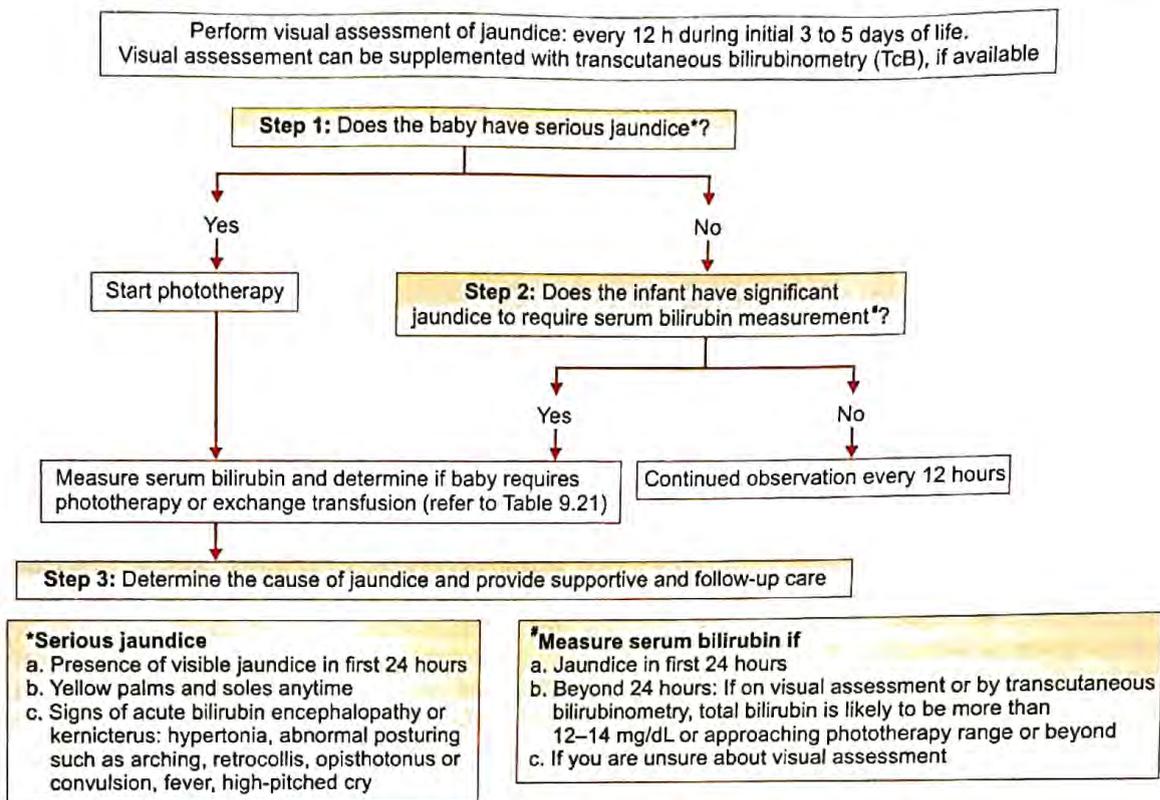


Fig. 9.43: Approach to an infant with jaundice

breastfeed frequently and exclusively. Mother should be told to bring the baby to the hospital, if the baby looks deep yellow or palms and soles have yellow staining. There is no use to expose the baby to direct sunlight to reduce hyperbilirubinemia.

Any newborn discharged prior to 72 hours of life should be evaluated again in the next 48 hours for assessment of adequacy of breastfeeding and progression of jaundice.

Pathological Jaundice

Term and near term neonates: The American Academy of Pediatrics (AAP) has laid down criteria for managing babies with elevated serum bilirubin (Figs 9.44 for phototherapy and 9.45 for exchange transfusion). Both the Figs have age in hours on the X-axis and TSB levels on Y-axis. There are three curves on each Fig. representing three risk categories of babies defined by gestation and other risk factors. Risk factors refer to hemolysis, asphyxia, acidosis, low albumin level, G6PD deficiency, hypothermia and sickness.

Preterm neonates: Table 9.21 provides cutoffs for exchange transfusion and phototherapy in preterm neonates below 35 weeks of gestation.

Prolonged Jaundice (Beyond 3 Weeks)

This is defined as persistence of significant jaundice (10 mg/dL) beyond three weeks in a term baby. The common causes include inadequate feeding, breast milk

jaundice, extravasated blood (cephalohematoma), ongoing hemolytic disease, G6PD deficiency and hypothyroidism. One should rule out cholestasis by noting the urine and stool color and checking the level of direct bilirubin. If the baby has dark urine or significant jaundice, investigations should be initiated to rule out:

- Cholestasis (stool color, urine color, direct and indirect bilirubin levels)
- Ongoing hemolysis, G6PD screen
- Hypothyroidism
- Urinary tract infection

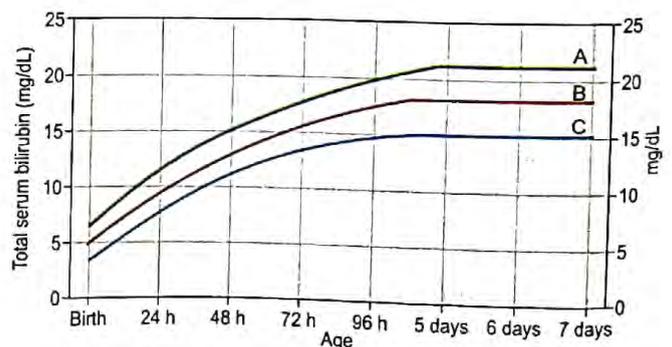


Fig. 9.44: Guidelines for phototherapy in infants of 35 weeks' gestation or more. (A) Infants at lower risk (>38 weeks and well); (B) Infants at medium risk (>38 weeks + risk factors or 35–37 6/7 week and well) and (C) Infants at higher risk (35–37 6/7 week + risk factors)

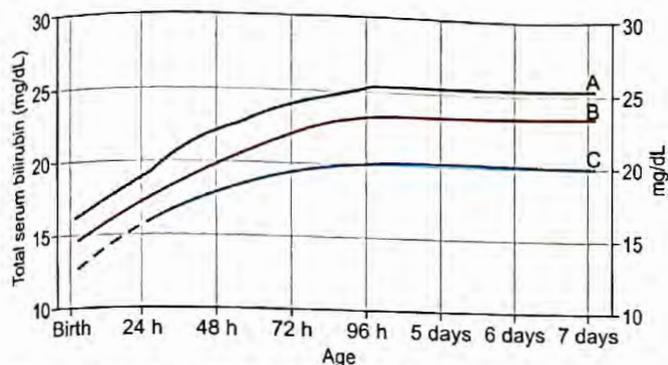


Fig. 9.45: Guidelines for exchange transfusion in infants 35 weeks' gestation or more. (A) Infants at lower risk (>38 weeks and well); (B) Infants at medium risk (>38 weeks + risk factors or 35–37 6/7 week and well) and (C) Infants at higher risk (35–37 6/7 week + risk factors) (Adapted from AAP 2004)

Table 9.21: Suggested TSB cut-offs for phototherapy and exchange transfusion in preterm infants <35 weeks

Gestation (completed weeks)	Phototherapy	Exchange transfusion
<28	5–6	11–14
28 to 29	6–8	12–14
30 to 31	8–10	13–16
32 to 33	10–12	15–18
34	12–14	17–19

Use postmenstrual age (for phototherapy for example, when a 29 week infant is 7 days old, use the TSB level for 30 weeks).

(Adapted with permission from Maisels et al, Jour Perinatol, 2012)

Phototherapy

Phototherapy remains the mainstay of treating hyperbilirubinemia in neonates. Phototherapy is highly effective and carries an excellent safety track record of over 50 years. It acts by converting insoluble bilirubin (unconjugated) into soluble isomers that can be excreted in urine and feces. Many review articles have provided detailed discussion on phototherapy-related issues. The bilirubin molecule isomerizes to harmless forms under blue-green light (460–490 nm); and the light sources having high irradiance in this particular wavelength range are more effective than the others.

For phototherapy to be effective, bilirubin needs to be present in skin so there is no role for prophylactic phototherapy. Phototherapy acts by several ways:

- **Configurational isomerization:** Here the Z-isomers of bilirubin are converted into E-isomers. The reaction is instantaneous upon exposure to light but reversible as bilirubin reaches into the bile duct. After exposure of 8–12 hours of phototherapy, this constitutes about 25% of TSB, which is nontoxic. Since this is excreted slowly from body, this is not a major mechanism for decrease in TSB.
- **Structural isomerization:** This is an irreversible reaction where the bilirubin is converted into lumirubin. The

reaction is directly proportional to dose of phototherapy. This product forms 2–6% of TSB which is rapidly excreted from body thus is mainly responsible for phototherapy-induced decline in TSB.

- **Photo oxidation:** This is a minor reaction, where photo-products are excreted in urine.

Types of phototherapy lights: The phototherapy units available in the market have a variety of light sources that include fluorescent lamps of different colors (cool white, blue, green, blue-green or turquoise) and shapes (straight or U-shaped commonly referred as compact fluorescent lamps, i.e. CFL), halogen bulbs, high intensity light-emitting diodes (LED) and fibroptic light sources.

With the easy availability and low cost in India, CFL phototherapy is being most commonly used device. Often, CFL devices have four blue and two white (for examination purpose) CFLs but this combination can be replaced with 6-blue CFLs in order to increase the irradiance output.

In last couple of years, blue LED is making inroads in neonatal practice and has been found to equally effective. LED has advantage of long life (up to 50,000 hours) and is capable of delivering higher irradiance than CFL lamps.

Maximizing the efficacy of phototherapy: The irradiance of phototherapy lights should be periodically measured and a minimum level of 30 microW/cm²/nm in the wavelength range of 460 to 490 nm must be ensured. The lamps should be changed, if the lamps are flickering or ends are blackened, if irradiance falls below the specified level or as per the recommendation of manufacturers.

Expose maximal surface area of the baby (Fig. 9.46). Avoid blocking the lights by any equipment (e.g. radiant warmer), a large diaper or eye patch, a cap or hat, tape, dressing or electrode, etc. Ensure good hydration and nutrition of the baby. Make sure that light falls on the baby perpendicularly, if the baby is in incubator. Minimize interruption of phototherapy during feeding sessions or procedures.



Fig. 9.46: A jaundiced baby receiving phototherapy with two overhead units and billblanket pad (arrow)

Administering phototherapy: Make sure that ambient room temperature is optimum 25° to 28°C to prevent hypothermia or hyperthermia in the baby. Remove all clothes of the baby except the diaper. Cover the baby's eyes with an eye patch, ensuring that it does not block baby's nostrils. Place the naked baby under the lights in a cot or bassinet, if weight is more than 2 kg or in an incubator or radiant warmer, if the baby is small (<2 kg). Keep the distance between baby and light 30 to 45 cm (or as per manufacturer recommendation).

Ensure optimum breastfeeding: Baby can be taken out for breastfeeding sessions and the eye patch can be removed for better mother–infant interaction. However, minimize interruption to enhance effectiveness of phototherapy. There is no need to supplement or replace breast milk with any other types of feed or fluid (e.g. breast milk substitute, water, sugar water, etc.).

Monitoring and stopping phototherapy: Monitor temperature of the baby every 2 to 4 hours. Measure TSB level every 12 to 24 hours.

Discontinue phototherapy once two TSB values 12 hours apart fall below current age-specific cut offs. The infant should be monitored clinically for rebound bilirubin rise within 24 hours after stopping phototherapy for babies with hemolytic disorders.

Exchange Transfusion

Double volume exchange transfusion (DVET) should be performed, if the TSB levels reach to age specific cut-off for exchange transfusion (Fig. 9.45 and Table 9.21) or the infant shows signs of bilirubin encephalopathy irrespective of TSB levels.

Indications for DVET at birth in infants with Rh isoimmunization include:

- i. Cord bilirubin is 5 mg/dL or more
- ii. Cord Hb is 10 g/dL or less

At birth, if a baby shows signs of hydrops or cardiac decompensation in presence of low PCV (<35%), partial exchange transfusion with 50 mL/kg of packed red blood cells should be done to quickly restore oxygen carrying capacity of blood.

The ET should be performed by pull and push technique using umbilical venous route. Umbilical catheter should be inserted just enough to get free flow of blood.

Follow-up

Babies with serum bilirubin >20 mg/dL and those who require exchange transfusion should be kept under follow-up in the high-risk clinic. Hearing assessment (BERA) should be done at 3 months of age. With prompt treatment, even very elevated serum bilirubin levels within the range of 25 to 29 mg/dL are not likely to result in long-term adverse effects on neurodevelopment.

Prevention

- Antenatal investigation should include maternal blood grouping. Rh positive baby born to an Rh negative mother is at higher risk for hyperbilirubinemia and requires greater monitoring. Anti-D (RhoGam) injection after first obstetrical event ensures decreased risk of sensitization in future pregnancies.
- Ensuring adequate breastfeeding
- Parent education regarding danger signs should include yellowish discoloration below knees and elbows or persistent jaundice beyond 15 days as reason for immediate check-up by health personnel.
- High-risk babies, such as ones with large cephalohematoma or family history of jaundice, should be followed up after 2–3 days of discharge.

CONGENITAL MALFORMATIONS

Tracheoesophageal Fistula (TEF)

Upper part of esophagus is developed from retropharyngeal segment and the lower part from pregastric segment of the first part of the primitive gut. At four weeks of gestation, the laryngotracheal groove is formed. Later, two longitudinal furrows develop to separate the respiratory primordium from the esophagus. Deviation or altered cellular growth in this septum results in formation of tracheoesophageal fistulae. Incidence is 1 in 4000 live births. In the most common variety (over 80% of cases), the upper part of the esophagus ends blindly and the lower part is connected to the trachea by a fistula.

Clinical Features

The presence of maternal polyhydramnios and single umbilical artery should alert the health provider to look for atresia of the upper digestive tract. Association of congenital anomalies of vertebrae, anorectal region, heart, kidneys or limbs should also arouse suspicion. The newborn baby has excessive drooling soon after birth with frothing (Fig. 9.47). There is choking and cyanosis on feeding. Overflow of milk and saliva from esophagus and regurgitation of secretion through the fistulous tract (when present) into the lungs results in aspiration pneumonia.

Diagnosis

A stiff red rubber catheter cannot be passed into stomach as it gets arrested at a distance of 7–10 cm from the mouth (Fig. 9.47). A skiagram may be obtained after instilling 1–2 mL of air through the catheter. It is not advisable to use barium as a contrast material since it may be aspirated in lungs.

On X-ray, an air bubble is seen in the stomach, if there is communication between the lower part of the esophagus and trachea, which occurs in the commonest variety of tracheoesophageal fistula. In other variety, wherein there is no communication of esophagus and trachea, there will be no gas in stomach.



Fig. 9.47: Esophageal atresia with tracheoesophageal fistula. Note the radiopaque catheter at T4 level (arrow). There is a double gas bubble sign indicating presence of concomitant duodenal atresia.

Management

The baby should be nursed supine or in an upright position and esophageal pouch should be gently sucked every 5 minutes, or continuously using a slow suction device. Intravenous fluids should be administered and infection, if any, should be treated. Surgical repair should be undertaken as early as possible.

Anorectal Malformation

A variety of anorectal anomalies have been described (Fig. 9.48b). These may be anatomically classified as high, intermediate or low. The position is determined by the relation of terminal part of bowel to the puborectalis sling. High or intermediate lesions are more common in males. An X-ray film of the abdomen is obtained 12–24 hours after birth, with the baby being kept in an inverted position. A lateral picture of the pelvis should be obtained to define whether the rectal pouch is above or below a line drawn from the pubis to the coccyx.

Treatment is surgical. Prognosis is better with low defects. About 80 to 90% of patients become continent after surgery for low defects. More than two-thirds of patients are incontinent after surgery of high defects.



Fig. 9.48: Various congenital malformations: (a) Congenital hydrocephalus; (b) Anorectal malformation; (c) Tuft of hair overlying with underlying neural tube defect; (d) Meningocele

Neural Tube Defects

Anencephaly: Anencephaly is due to a defect in the development of neural axis and is not compatible with life.

Encephalocele: In encephalocele, the brain and/or its coverings herniate through a defect in the skull.

Congenital hydrocephalus: Congenital hydrocephalus results from impaired CSF circulation or absorption in basal cisterns. This usually follows intrauterine infections such as toxoplasmosis, but may also be the result of a congenital malformation of the aqueduct, Dandy-Walker syndrome (posterior fossa cyst and a defect of cerebellar vermis), Arnold-Chiari malformation (displacement of brainstem and cerebellum in the spinal canal).

Diagnosis should be suspected, if the head is too large or sutures and fontanels are wide open or if the head circumference increases rapidly (more than 1 cm in a fortnight during the first 3 months) (Fig. 9.48). CT or MRI scan should be done to confirm the diagnosis.

Myelomeningocele: It presents as membranous protrusion at the lumbosacral region and contains meninges, cerebrospinal fluid, nerve roots and a dysplastic spinal cord. The defect is open and not covered by skin. In contrast, meningocele is covered with skin (Fig. 9.48). There may be no associated neurological deficit, but severe motor and sensory deficit are common and urinary and fecal incontinence are usually present.

Folic acid 4 mg per day should be prescribed to the women in periconceptional period to prevent recurrence.

Cleft Lip and Cleft Palate

Cleft lip is recognized readily (Fig. 9.49), but a careful inspection of the oral cavity is necessary to identify cleft palate. A cleft of the soft palate can be easily missed unless the baby is examined carefully. Ventricular septal defect is a common associated anomaly with cleft palate.

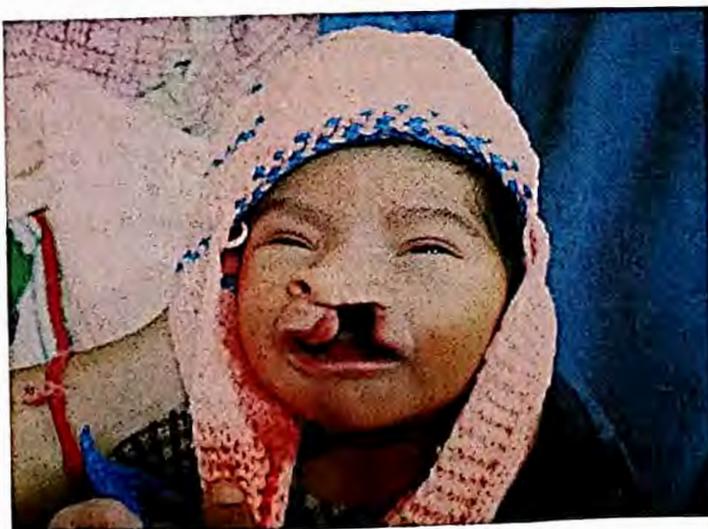


Fig. 9.49: Unilateral cleft lip and cleft palate



Fig. 9.50: Diaphragmatic hernia: Chest X-ray showing multiple air-filled cysts in left hemithorax, shift of mediastinum to the right and the absence of outline of the left diaphragm

Feeding is difficult in cases of cleft palate. For the first few days, gavage feeding or spoon-feeding may be done. Bottle-feeding may be tried with a soft nipple with rubber flange, which close the cleft and help the baby in sucking. If this is not successful, palatal prosthesis may be used.

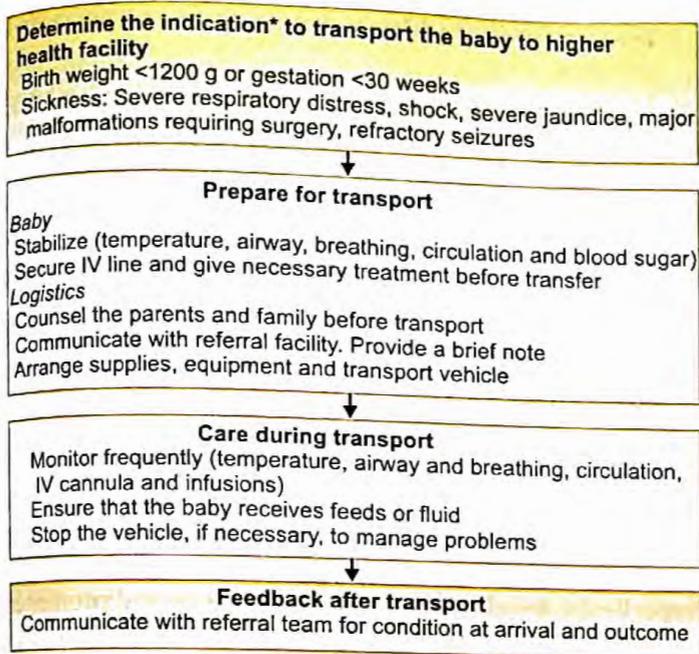
Diaphragmatic Hernia

Diaphragmatic hernia occurs because of failure of closure of the pleuroperitoneal membrane. This allows intestinal loops to ascend to the thorax that compress the developing lung and can result in pulmonary hypoplasia (Fig. 9.50). These babies can present at any time after birth. At birth, a baby may be suspected to have diaphragmatic hernia, if there is respiratory distress and a scaphoid abdomen. Bag and mask ventilation should be avoided in these babies. Surgical repair after stabilization is the treatment of choice.

TRANSPORT OF NEONATES

Transport is an important component of sick newborn care. It requires careful attention to vital parameters, temperature and blood glucose levels as well as coordination with the receiving hospital (Fig. 9.51).

If the birth of an at-risk neonate is anticipated, the mother should be transported (*in utero* transport) to a facility with optimum maternal and neonatal care before delivery (*in utero* transfer). However, if referral of a neonate is unavoidable, efforts should be made to do the best possible job.



* Indications may vary as per the facility

Fig. 9.51: Transport of sick neonates

FOLLOW-UP OF HIGH-RISK NEONATES

Improved perinatal and neonatal care has resulted in improved survival of many sick and small neonates who are at-risk for long-term morbidities such as growth failure, developmental delay and visual/hearing problems. A proper and appropriate follow-up program would help in prevention, early detection and appropriate management of these problems, thereby ensuring disability and morbidity free survival.

Who Needs Follow-up Care?

Table 9.22 lists the cohort of high-risk infants who require followup services.

What should be Done at Follow-up?

- i. *Assessment of feeding and dietary counseling:* Parents should be asked about the infants' diet and offered dietary counseling at each visit. Breastfeeding frequency and adequacy should be assessed. The amount, dilution and mode of feeding should be

Table 9.22: Common newborn conditions requiring high-risk follow-up care

Birth weight <1500 g and/or gestation <32 weeks
<i>Perinatal asphyxia:</i> Apgar score ≤ 3 at 5 min and/or hypoxic-ischemic encephalopathy
Mechanical ventilation for >24 hours
<i>Metabolic problems:</i> Symptomatic hypoglycemia and hypocalcemia
<i>Infections:</i> Meningitis and/or culture positive sepsis
Hyperbilirubinemia >20 mg/dL or requirement of exchange transfusion

noted, if supplemental feeding is given. It is also important to record the duration of exclusive breastfeeding. If mentation can be considered. Complementary feeding should be started at 6 months corrected age. Initially, semisolids should be advised in accordance with the local cultural practices.

- ii. *Growth monitoring:* Growth (including weight, head circumference, midarm circumference and length) should be monitored and plotted on an appropriate growth chart at each visit.
- iii. *Developmental assessment:* Assessment of developmental milestones should be done according to the corrected age. The milestones should be assessed in four domains—gross motor, fine motor, language and personal-social. Infants who lag behind in any domain should undergo a formal developmental evaluation. Age appropriate stimulation should be provided to these babies.
- iv. *Immunization:* Immunization should be ensured according to chronological age.
- v. *Ongoing problems:* Ongoing morbidities, such as diarrhea, pneumonia, occur more frequently in these babies and should require appropriate treatment.
- vi. *Neurological assessment:* Muscle tone should be assessed, any asymmetry between the extremities should also be recorded. Any history of seizures or involuntary movements should also be recorded.
- vii. *Hearing and vision evaluation:* High-risk infants have higher incidence of moderate to profound hearing loss (2.5–5% versus 1%). Since clinical screening is often unreliable, brainstem auditory evoked responses (BAER/BERA) should be performed between 40 weeks PMA and 3 months postnatal age. Vision of the baby should be checked at 9 months.

METABOLIC DISORDERS

Hypoglycemia

Hypoglycemia is defined as a blood glucose value of less than 40 mg/dL (plasma glucose less than 45 mg/dL).

Screening for hypoglycemia is recommended in high risk situations (Table 9.23). These babies should be screened for hypoglycemia at 2, 6, 12, 24, 48 and 72 hours after birth with reagent strips (dextrostix). Babies showing blood sugar value of less than 40 mg/dL on reagent strip should be treated for hypoglycemia but should have confirmation of hypoglycemia by a lab test as reagent

Table 9.23: Common causes of hypoglycemia

<i>Inadequate substrate:</i> Small for gestational age (weight for gestation <3rd percentile), gestation <35 weeks, birth weight <2000 g
<i>Relative hyperinsulinemia:</i> Infants of diabetic mother, large for date baby (weight for gestation >97th percentile).
<i>Sickness:</i> Hypothermia, sepsis, asphyxia

strips have high false positive rates. Appropriate for gestational age babies who are breastfeeding adequately do not require any screening for hypoglycemia.

Clinical Features

Clinically, the hypoglycemia may be asymptomatic or may manifest with a range of clinical features like stupor, tremors, apathy, cyanosis, convulsions, apneic spells, tachypnea, weak and high-pitched cry, lethargy, difficulty in feeding, eye rolling, episodes of sweating, sudden pallor, hypothermia and rarely, cardiac arrest.

Management of Hypoglycemia

Prevention of hypoglycemia: All high-risk babies should receive proper breastfeeding, counseling and support. Adequacy of breastfeeding should be assessed and small babies not able to suck effectively on the breast, should receive expressed breast milk by alternate methods.

Asymptomatic babies: If the blood sugar is more than 20 mg/dL in an asymptomatic baby, a trial of oral feeds is given and blood sugar be tested after 30–45 minutes. If repeat blood sugars values are above 40 mg/dL, frequent feeding is ensured with 6 hourly monitoring of blood sugar for 48 hours. However, if blood sugar values persist below 40 mg/dL, baby should receive IV glucose infusion.

If the initial blood sugar value is less than 20 mg/dL, then intravenous glucose infusion is started.

Symptomatic babies: A bolus of 2 mL/kg of 10% dextrose should be given, followed immediately by glucose infusion at an initial rate of 6 mg/kg/min. Blood sugar is checked after 30–45 minutes and then 6 hourly. Repeat hypoglycemic episodes may be treated by increasing the glucose infusion rate by 2 mg/kg/min until a maximum of 12 mg/kg/min. If two or more consecutive values are >50 mg/dL after 24 hours of parenteral therapy, the infusion can be tapered off at the rate of 2 mg/kg/min every 6 hours, with glucose monitoring. Tapering has to be accompanied by concomitant increase in oral feeds.

Drug Therapy and Breastfeeding

Though most drugs given to mother get transferred into human milk, the amount is not significant and does not pose any risk to the baby. The clinician should evaluate each medication carefully, examine published data on the drug and advise the mother carefully about the use of medications while breastfeeding.

EFFECT OF MATERNAL CONDITIONS ON FETUS AND NEONATES

Diabetes Mellitus

Diabetes is one of the most common endocrine disorders affecting women during pregnancy. The following complications are likely to occur during pregnancy of a diabetic mother.

- i. Fetus may die suddenly during the last trimester of pregnancy
- ii. Macrosomia or large size of the body (Fig. 9.52) and its attending risks during delivery such as birth trauma, asphyxia and increased possibilities of cesarean section
- iii. Higher risk of congenital anomalies. (Infants of mothers with diabetes are 20 times more at risk to develop cardiovascular defects.)
- iv. Neonatal respiratory distress
- v. Metabolic problems such as hypoglycemia and hypocalcemia
- vi. Polycythemia, increased viscosity of blood and hyperbilirubinemia

Pathogenesis

Maternal hyperglycemia leads to fetal hyperglycemia and that in turn leads to fetal hyperinsulinemia (Pederson hypothesis). Insulin is an anabolic hormone and promotes growth. Excess maternal glucose and amino acids provide the substrate for increased synthesis of protein, lipids and glycogen in the fetus. Large fetal size is mostly due to the accumulation of fat.



Fig. 9.52: (a) Infant of diabetic mother. Note the large size of the baby with broad shoulders and torso and a relatively smaller head; (b) Hairy pinna of the baby

Management

The infant should be screened for malformations and injuries. Frequent breastfeeding should be encouraged. The neonate should be monitored for blood glucose levels during first three days of life. The other morbidities, such as respiratory distress, hyperbilirubinemia should be treated appropriately.

Hypothyroidism

Hypothyroidism during pregnancy, if treated adequately, does not affect pregnancy outcomes; however, inadequate treatment of the mother predisposes the fetus to adverse neurodevelopment. Neonate should be screened for hypothyroidism using either cord blood or on blood sample taken after 72 hours of birth.

Tuberculosis

If the mother has active pulmonary tuberculosis that has been treated for less than 2 months before birth or the diagnosis of tuberculosis was made after birth, the baby

is at risk to acquire infection from the mother. Such babies should not be separated from the mother. Exclusive breastfeeding is encouraged. The infant should be given isoniazid prophylaxis (5 mg/kg/day) and is evaluated at 6 weeks of age. If there is any evidence of tubercular infection in the baby (clinically or radiologically), the infant should be started on antitubercular therapy. If the infant does not have any evidence of tuberculosis at 6 weeks, the isoniazid therapy continued for 6 months and the infant given BCG vaccine after 2 weeks of cessation of therapy.

Hepatitis B Infection

Women who have hepatitis B infection (active or carrier stage) can transmit the infection to their babies. Such babies should receive hepatitis B vaccine within 12 hours of birth, which can prevent perinatal transmission of hepatitis B virus significantly. Hepatitis B immunoglobulins (HBIG; 100 IU, IM) can be given to enhance the protection but it is costly and there are availability issues.

Immunization and Immunodeficiency

Aditi Sinha • Surjit Singh

IMMUNITY

The immune system has two major components: Innate and adaptive. Innate immunity is primitive, nonspecific, has no memory and provides the first line of defense against infections. Adaptive immunity is highly evolved, specific, has memory and is characterized by rapid immune response when exposed to the same microorganism.

Innate Immune System

The complement system consists of multiple proteins circulating as inactive precursors. Once triggered, these proteins activate each other sequentially to generate active components. There are three pathways of activation of the complement cascade. The classical pathway is triggered by activation of C1q by antibody-antigen complexes or polyanions (heparin, protamine, nucleic acids from apoptotic cells). The alternative pathway is continuously active at low levels due to spontaneous C3 lysis, and amplified by binding of complement components to pathogen (bacterial lipopolysaccharides, endotoxin, yeast cell wall). The lectin pathway is activated by binding of mannose binding lectin to mannose residues on pathogen cell surface. Activation of the classical pathway results in low levels of C4, C2 and C3; activation of alternative pathway is characterized by reduced levels of C3 with normal levels of C4 and C2. Activation of C3 by either pathway results in formation of the membrane attack complex, which binds to the surface of bacteria, fungi and viruses leading to their lysis. C3b component can opsonize immune complexes or foreign cell surface; anaphylatoxins (C3a, C4a, C5a) bind to receptors on mast cells and basophils, resulting in their degranulation and release of histamine and intracellular enzymes. C3a and C5a induce adherence of monocytes, macrophages and neutrophils to vascular endothelial cells causing extravasation and chemotaxis.

Cellular components of innate immunity consist of polymorphonuclear leukocytes, macrophages and natural killer (NK) cells. These ingest extracellular material by phagocytosis.

Adaptive Immune System

Adaptive immune responses develop through synergy between lymphocytes and antigen-presenting cells following specific antigenic challenge, show tremendous diversity and exhibit immunological memory. The components of adaptive immune system are lymphocytes, macrophages and antigen-presenting cells.

Lymphocytes constitute 20–40% of white cells in peripheral blood and are classified and identified using flow cytometry as B (CD19, CD20 positive), T (CD3 positive) and NK (CD 16, CD56 positive) cells. T cell antigen receptor (TCR), which is associated with CD3 to form the TCR-CD3 complex that remains unchanged during cell division. TCR recognizes antigen only when it is bound to MHC molecules on surface of antigen-presenting cells. Mature T lymphocytes are categorized into CD4 positive T helper (Th) cells, and CD8 positive T cytotoxic (Tc) cells based on membrane glycoprotein. The normal ratio of CD4+ and CD8+ cells in peripheral blood is 2:1. CD4+ cells recognize antigen only if bound to class II MHC molecules, whereas CD8+ cells recognize antigen bound to class I MHC molecules. Th cells differentiate into Th1, Th2 and Th17 cells under influence of cytokines. Th1 immune response supports inflammation and activates Tc cells and macrophages (in tuberculoid leprosy and rheumatoid arthritis), whereas Th2 responses induce antibody-mediated immunity (lepromatous leprosy, allergic disorders). Th17 cells contribute to host defense against extracellular bacteria and fungi and have a role in development of allergy and autoimmunity. Tc cells are important in eliminating intracellular pathogens like viruses, and in organ transplant rejection.

PRIMARY IMMUNODEFICIENCY DISORDERS

A small but significant proportion of children evaluated for frequent infections have immunodeficiency. Immunodeficiency disorders can be secondary or primary, the former being far more common. Infection with the human immunodeficiency virus (HIV) is the commonest cause of secondary immunodeficiency. Table 10.1 lists

Table 10.1: Causes of secondary immunodeficiency

Human immunodeficiency virus infection
Following measles
Severe malnutrition
Nephrotic syndrome
Lymphoreticular malignancies
Severe burns
<i>Drugs:</i> Glucocorticoids, cyclophosphamide, azathioprine, diphenylhydantoin
Severe, chronic infections

clinically important causes of secondary immunodeficiency.

Primary immunodeficiency disorders can affect any of the major components of immune system, including T and/or B lymphocytes, antibody production, phagocyte number or function and complement components. The condition should be suspected in patients presenting with ≥ 2 of the following 10 warning signs: (i) ≥ 4 new infections in a year; (ii) ≥ 2 serious sinus infections in a year; (iii) ≥ 2 cases of pneumonia in a year; (iv) ≥ 2 months of antibiotics without effect; (v) failure of an infant to gain weight or grow normally; (vi) recurrent deep skin infections or organ abscesses; (vii) persistent oral thrush, or candidiasis elsewhere beyond infancy; (viii) need for IV antibiotics to clear infections; (ix) ≥ 2 deep-seated infections (e.g. meningitis, cellulitis); and (x) family history of immunodeficiency.

Tables 10.2 and 10.3 outline the workup and clinical findings in various disorders. Conditions that mimic immunodeficiency (e.g. gastroesophageal reflux, Kartagener syndrome, cystic fibrosis) should be excluded.

Cellular and/or Combined Immunodeficiency

Severe combined immunodeficiency (SCID): Children with SCID present in early infancy with severe infections due to viruses, fungi (e.g. *Pneumocystis jirovecii*) or intracellular pathogens (e.g. *Mycobacteria*). Tonsillar tissue is usually absent and lymph nodes are not palpable. Left untreated, such babies do not live for more than a few months. Profound lymphopenia is characteristic. The most common form of SCID is X-linked and is caused by mutations in the common gamma chain [of interleukin 2 (γ)]; approximately one-fourth cases have adenosine deaminase deficiency. SCID due to purine nucleoside phosphorylase deficiency may present later in childhood with milder features.

DiGeorge anomaly: This disorder arises from defects in embryogenesis of third and fourth pharyngeal pouches. It is characterized clinically by an unusual facies (hypertelorism, antimongoloid slant, low set ears, micrognathia, short philtrum, bifid uvula), hypocalcemic tetany, aortic arch anomalies and absent thymus. In addition, 20–30% patients show a variable T cell defect,

Table 10.2: Work-up for suspected immunodeficiency

Screening investigations

Total and differential leukocyte counts, leukocyte morphology, platelet count and size
HIV serology; X-ray chest

Specific investigations

Quantitative immunoglobulins: IgG, and subclasses: IgA; IgM; IgE

Blood group isoheamagglutinins (for functional IgM)

Anti-diphtheria and anti-tetanus antibodies (functional IgG)

CD3, CD4, CD8, CD19, CD16, CD56 by flow cytometry

CD18, flow cytometry (leukocyte adhesion defect)

Bruton tyrosine kinase protein; Wiskott-Aldrich syndrome (WAS) protein

Mitogen stimulation tests (e.g. response to phytohemagglutinin)

Nitroblue tetrazolium dye reduction test, and dihydrorhodamine assay on flow cytometry, CGD

CH50, and AH50 assays and levels of complement component

Mannan binding lectin assay

Enzyme assays, e.g. adenosine deaminase, purine nucleoside phosphorylase

Delayed skin tests (*Candida*, Tetanus toxoid)

AH50: Alternate pathway complement hemolytic assay; CD: Cluster differentiation; CGD: Chronic granulomatous disease; CH50: Total hemolytic complement assay; HIV: Human immunodeficiency virus

ranging from mildly increased susceptibility to infections to severe disease requiring thymic or hematopoietic stem cell transplant.

Wiskott-Aldrich syndrome (WAS): This X-linked recessive disorder is caused by mutations at Xp11.22–23, encoding the WAS protein in the cytoplasm of lymphocytes and platelets. Eczema begins in early infancy and may mimic atopic dermatitis. Thrombocytopenia is associated with small-sized platelets. Due to impaired responses to polysaccharide antigens, patients are susceptible to infections with pneumococci, meningococci and *Haemophilus influenzae*. The clinical phenotype varies; some children have a fulminant course with repeated severe infections (WAS spectrum), while others present later, predominantly with bleeding manifestations (X-linked thrombocytopenia spectrum). The risk of lymphoreticular malignancies is increased. There is severe IgM deficiency in addition to defective T cell signaling, secondary to deficient expression of CD43 in lymphocytes.

Ataxia-telangiectasia: This autosomal recessive disorder is characterized by progressive ataxia (beginning during infancy), telangiectasia (initially on bulbar conjunctiva), sinopulmonary infections, chromosomal breakage and increased sensitivity to ionizing radiation. The gene is localized to chromosome 11q22–23; its product regulates the cell cycle. The degree of immunodeficiency is less profound than in Wiskott-Aldrich syndrome. Serum IgA, IgG2 subclass and IgE levels are usually reduced;

Table 10.3: Clinical clues to the diagnosis of primary immunodeficiency

Type of infection	Age at presentation	Associated findings	Likely etiology
Pneumonia or diarrhea; cryptosporidiosis; disseminated BCG infection	First few months of life	Failure to thrive; rash; atrophic tonsils and lymph nodes	Severe combined immunodeficiency
Pneumonia; pyogenic infections (<i>S. pneumoniae</i> , <i>H. influenzae</i>)	4–6 months	Only boys affected; failure to thrive	X-linked agammaglobulinemia
Diarrhea, sinopulmonary infections; often pyogenic (<i>S. pneumoniae</i> , <i>H. influenzae</i>)	Later childhood (>5–10 years)	Hepatosplenomegaly; lymphadenopathy	Common variable immunodeficiency
Recurrent staphylococcal cold abscesses, pneumonia (often with pneumatocele)	Any age	Coarse facial features, eczematous rash	Hyper-IgE syndrome
Recurrent or persistent giardiasis	Any age	Autoimmune diseases	IgA deficiency
Recurrent staphylococcal infections of lungs, skin or bone; persistent fungal (<i>Aspergillus</i>) pneumonia; liver abscess	Usually early childhood	Lymphadenopathy; draining nodes; hepatosplenomegaly	Chronic granulomatous disease
Pyogenic bacteria (<i>S. pneumoniae</i> , <i>H. influenzae</i>)	4–6 months		Deficiency in early complement components
Recurrent <i>Neisseria</i> infections, e.g. meningitis			Deficiency in late complement (C5–C9) components
Recurrent infections	Early infancy	Boys; atypical eczema; thrombocytopenia	Wiskott-Aldrich syndrome
Recurrent bacterial infections, e.g. pneumonia		Progressive ataxia; proceres telangiectasia	Ataxia-telangiectasia

lymphocyte proliferative responses are decreased and the number of $\gamma\delta$ -positive T cells is increased.

Hyper-IgM syndrome: This syndrome can result from multiple causes, the most common being a CD40 ligand defect. Affected children have a profound immunodeficiency characterized by low levels of IgG but normal or raised IgM. There is increased susceptibility to infections with *Pneumocystis jirovecii*. Some patients may have associated autoimmune disorders.

Humoral Immunodeficiency

X-linked (Bruton) agammaglobulinemia: This X-linked recessive disorder is caused by mutation in the gene for tyrosine kinase (Bruton tyrosine kinase, Btk). Affected boys present in second half of infancy with pyogenic infections; later presentation is also described. Tonsils and lymph nodes are usually atrophic. B cells (CD19+) are absent in peripheral blood but T cells (CD3+) are normal in number and function.

Common variable immunodeficiency: This term refers to heterogeneous conditions characterized by hypogammaglobulinemia and variable defects in T cell number and function. Presentation is later in childhood and, unlike X-linked agammaglobulinemia, affected children show marked lymphadenopathy and hepatosplenomegaly. B cell number (CD19) is usually normal. Low levels of lymphocyte proliferation following mitogen stimulation may be demonstrated. Mutations in the following genes

may be responsible: Inducible costimulator (*ICOS*); *CD19*; *CD20*; *CD81*; B cell-activating factor of tumor necrosis factor family receptor (*BAFF-R*), tumor necrosis factor receptor superfamily member 13B or transmembrane activator (*TNFRSF13B*, *TACI*) or *TNFRSF13C*. Autoimmune disorders (leukopenia, thrombocytopenia, hemolytic anemia and arthritis) are associated. Patients require monitoring for lymphoreticular malignancies.

IgA deficiency: This is one of the most common causes of primary immunodeficiency. Affected individuals usually do not have a clinically significant immunodeficiency and may remain entirely asymptomatic or have recurrent mild respiratory infections, especially if IgG subclass deficiency is also present. These patients may occasionally evolve to common variable immunodeficiency later.

IgG subclass deficiency: IgG1 provides protection against bacterial pathogens (e.g. diphtheria, tetanus), IgG2 protects against capsular polysaccharide antigens (e.g. pneumococcus, *Haemophilus influenzae*), IgG3 has antiviral properties, while IgG4 has antiparasitic activity. Children with deficiency of one of the subclasses may have normal, or sometimes even elevated, total IgG levels.

Transient hypogammaglobulinemia of infancy: Infants show physiological hypogammaglobulinemia between 3 and 6 months of age, when transplacentally acquired maternal IgG has been catabolized, and immunoglobulin production has not begun. In some infants, the physiological

hypogammaglobulinemia is prolonged to 18–24 months, resulting in transient hypogammaglobulinemia of infancy. Serum IgG levels in infancy and early childhood should be interpreted in context of age-related nomograms. Unlike X-linked agammaglobulinemia, B cell numbers are normal. These children recover over time and long-term prognosis is excellent.

Disorders of Nonspecific Immunity

Cellular Immunodeficiency

Chronic granulomatous disease refers to disorders with reduced activity of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase leading to impaired generation of superoxide radical. The disease is X-linked in ~50% patients, secondary to mutations in the gene encoding gp91-phox; others have autosomal recessive inheritance with mutations in the gene encoding p47-phox, p67-phox or p22-phox. Children present with recurrent life-threatening infections, starting in early infancy. Infections are chiefly caused by catalase-positive bacteria (*Staphylococcus aureus*, *Serratia*) and fungi (*Aspergillus*). Findings include persistent pneumonia, prominent lymphadenitis, multiple liver abscesses and osteomyelitis of small bones of hands and feet. The diagnosis is suggested by screening on nitroblue tetrazolium dye reduction test (NBT) and confirmed by dihydrorhodamine assay on flow cytometry.

Miscellaneous

Complement component deficiency: Individuals with deficiencies of the early complement components (C2–C4) may present with recurrent bacterial infections, while those with deficiency of the later components (C5–C9) have predilection for *Neisseria* infections. Systemic lupus erythematosus may occur in those with C2/C4 or C1q deficiency. Deficiency of C1 esterase inhibitor is associated with hereditary angioneurotic edema, characterized by onset of recurrent non-itchy swellings in the body.

Hyper-IgE syndrome: Mutations in *STAT 3* gene result in recurrent 'cold' staphylococcal abscesses, pneumonia with pneumatoceles, retained primary dentition and markedly elevated serum IgE concentration (>2000 IU/mL). Inheritance is usually autosomal dominant.

Treatment of Primary Immunodeficiency Disorders

Hematopoietic stem cell transplantation is the treatment of choice for most forms of significant cellular immunodeficiency (e.g. SCID, Wiskott-Aldrich syndrome, hyper-IgM syndrome). The procedure should be done in early infancy. Children with X-linked agammaglobulinemia, IgG2 subclass deficiency and common variable immunodeficiency require administration of *intravenous immunoglobulin (IVIg)* every 3–4 weeks. Though expensive, therapy with IVIg results in satisfactory quality of life. Patients with IgA deficiency do not require any specific therapy. *Prophylactic therapy with antimicrobials* (usually

cotrimoxazole) is required for some children with IgG1 and IgG3 subclass deficiency.

Long-term cotrimoxazole and itraconazole prophylaxis has improved the management of *chronic granulomatous disease*. *Interferon-γ* is used for treatment of life-threatening infections. *Hematopoietic stem cell transplantation* is increasingly used in patients with the disease.

Plasma infusions may be useful in patients with complement deficiencies. In C1 esterase inhibitor deficiency, prophylactic therapy with *tranexamic acid*, *danazol* or *stanazolol* result in significant improvement. Injections of *synthetic C1 esterase inhibitor* are required, if there is laryngeal involvement with airway compromise. *Gene therapy* has been successfully used in patients with X-linked SCID, chronic granulomatous disease and Wiskott-Aldrich syndrome.

Intravenous Immunoglobulin

Intravenous immunoglobulin (IVIg) is pooled normal intact polyspecific IgG derived from plasma of healthy donors, subjected to strict screening procedures. Each batch of IVIg represents a donor pool of several thousand individuals such that the repertoire of antibodies is representative of the population. Most preparations contain >90% monomeric IgG with only small amounts of IgA and IgM. The IgG subclass distribution depends on the manufacturing process; some IVIg preparations do not contain adequate quantities of IgG3.

IVIg is therapy of choice for Kawasaki disease, idiopathic thrombocytopenic purpura and autoimmune demyelinating polyradiculoneuropathy, dose being 2 g/kg given in single or divided doses. IVIg is also replacement therapy in various forms of hypogammaglobulinemia, the dose being 0.4–0.6 g/kg every 3–4 weeks. Use of IVIg is considered in severe myasthenia, lupus crisis, autoimmune neutropenia, neonatal alloimmune and autoimmune thrombocytopenia, dermatomyositis not responding to steroid therapy, and certain vasculitides. IVIg has been used for prophylaxis and treatment of neonatal sepsis in low birth weight babies, with equivocal results.

Administration of IVIg may be associated with adverse effects, including anaphylactoid and anaphylactic (IgE-mediated) reactions. IVIg infusion must be started slowly and the child monitored closely; infusion rate is slowed or discontinued, if the child develops chills or rigors. The risk of acute kidney injury is negligible with current iso-osmolar preparations. Long-term risks include transmission of hepatitis C infection.

Suggested Reading

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- Singh S. Approach to a patient with suspected primary immunodeficiency disorder. *API Textbook of Medicine*, 10th edn. Eds. Munjal YP, Sharma SK. Jaypee Brothers, New Delhi, 2015, pp. 249–55.

Table 10.5: Comparison of subunit polysaccharide and conjugate vaccines

Characteristic	Polysaccharide vaccine	Conjugated vaccine
Component	Carbohydrate present in bacterial cell surface (capsule)	Polysaccharide attached to carrier protein that is recognized by host as foreign antigen
Immune cells stimulated; response elicited	B cells; humoral immunity, thymic independent	B and T cells; humoral and cellular immunity; thymic dependent
Antibodies type and titer	Chiefly IgM; low titer	Both IgM and IgG; high titer
Duration of protection	Brief	Longer and consistent
Age at which effective	Poor efficacy <2 years of age	Effective in infancy or older age
Booster response	Poor	Satisfactory



Fig. 10.1: Routes of vaccination. (a) Oral: Poliovirus (attenuated), rotavirus; (b) Intranasal: Influenza virus (live-attenuated); (c) Intradermal: BCG, inactivated poliovirus (fractionated dose) and rabies; (d) Subcutaneous: Measles, mumps, rubella, varicella, yellow fever, Japanese encephalitis, meningococcal and pneumococcal polysaccharide, and inactivated poliovirus; (e) Intramuscular: Most vaccines, including hepatitis A and B; diphtheria, tetanus and pertussis, *H. Influenzae b*, pneumococcal polysaccharide, inactivated polio and influenza

discoloration, particulate matter and inability to suspend the lyophilized powder.

Vaccination Schedules and Immunization Programs

The choice of vaccines in national immunization schedules is based on considerations of disease burden, vaccine availability and cost-effectiveness, and program coverage and sustainability. The *Expanded Programme of Immunization (EPI)*, introduced by the World Health Organization (1974), was the first global immunization initiative. Adopted by India in 1978, the EPI focused on vaccinating

young children with BCG, diphtheria and tetanus toxoids and whole cell pertussis (DTP or DTWP) and OPV vaccines, and chiefly covered urban areas. The *Universal Immunization Programme (UIP, 1985)* improved nationwide coverage of immunization and also included measles vaccine. The *Pulse Polio Immunization Programme (1995)* enabled polio control. UIP has remained a key component of the Child Survival and Safe Motherhood Programme (1992), the Reproductive and Child Health Programme (1997) and National Rural Health Mission (NHRM, 2005). Efforts of UIP are supported by Child Vaccine Initiative

Box 10.1: Principles of Immunization

- Different live (oral, parenteral, intranasal) vaccines may be given simultaneously, or at an interval of 4 weeks.
- Different types of inactivated or subunit vaccines may be administered simultaneously or at any interval between their doses. A minimum interval of 4 weeks between two doses of the same vaccine is necessary to ensure adequate immune responses. An exception is the rabies vaccine.
- There is no minimum recommended time interval between two types of vaccines. Hence, a live and an inactivated vaccine can be administered simultaneously or at any interval of time.
- When necessary, two vaccines can be given in the same limb at a single visit, preferring the anterolateral thigh for simultaneous IM injections; vaccines are administered at least 1-inch apart.
- A delay or lapse in the administration of a dose does not require the schedule to be repeated; the missed dose is administered and the course resumed at the point it was interrupted.
- Vaccines should not be mixed in a syringe unless approved by the manufacturer.
- Patients should be observed for allergic reactions for 15–20 minutes after receiving immunization.
- Immunization is not contraindicated in minor illness, prematurity, allergies, malnutrition, exposure to infection and antibiotic therapy.
- Live vaccines are contraindicated in inherited or acquired immunodeficiency and during therapy with immunosuppressive drugs, but may be given after a short (<2 weeks) course of low dose steroids.
- Immunoglobulins interfere with the immune response to certain live vaccines like mumps, measles and rubella, but not OPV, yellow fever or oral typhoid vaccines.
- Hepatitis B, tetanus toxoid and rabies vaccine may be given concurrently with corresponding immunoglobulin.
- Active immunization should follow exposure to rabies, measles, varicella, tetanus and hepatitis B.

and Global Alliance for Vaccines and Immunization (GAVI). Figure 10.2 and Table 10.6 depict milestones in the national immunization program and current national schedule.

Mission Indradhanush: Despite the UIP being operational for three decades, recent surveys indicated that only 65% of infants received full immunization coverage. In 2014, the Government of India launched 'Mission Indradhanush' to strengthen UIP and achieve full immunization coverage rapidly (Box 10.2). The mission derives its name from the seven diseases prevented through these vaccines (BCG, OPV, pentavalent and TT vaccines) and focuses on complete immunization of all children less than 2-year-old and on pregnant women.

Immunization Schedule of the Indian Academy of Pediatrics (IAP)

The IAP Advisory Committee on Vaccines and Immunization Practices (ACVIP) endorses the National Immunization

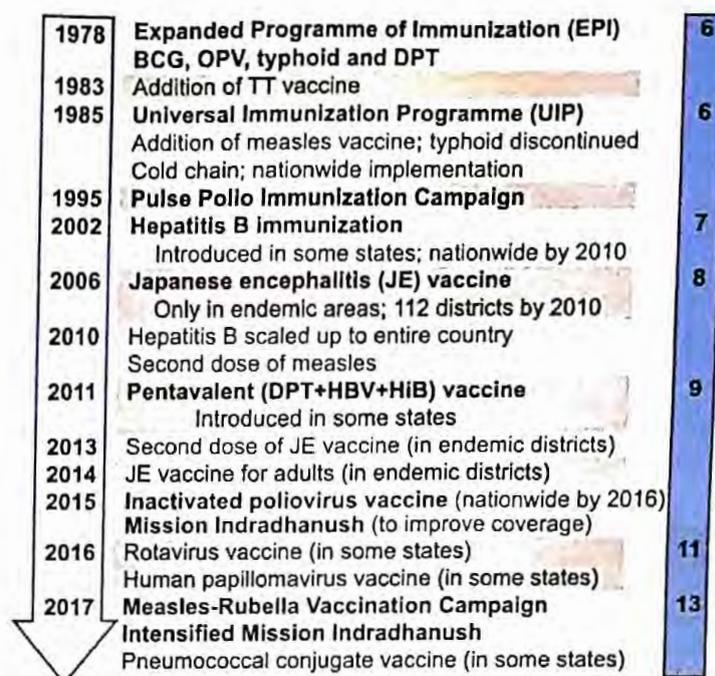


Fig. 10.2: Milestones in the National Immunization Programme. The program that started with four vaccines against six infectious illnesses now provides coverage against 13 childhood infections.

Programme, but recommends certain additional vaccines based on regional burden of vaccine preventable diseases and the availability, safety and efficacy of various vaccines (Table 10.7). Figure 10.3 compares the national programs and recommendations of the IAP.

COMMONLY USED VACCINES

The following section describes vaccines recommended in the national immunization program or Indian Academy of Pediatrics for normal children and certain high-risk groups.

BCG Vaccine

Bacillus Calmette–Guérin (BCG) vaccine contains bacilli derived from subcultures of live-attenuated *M. bovis* Calmette–Guérin strain. The vaccine used in India is the Copenhagen (Danish 1331) strain produced at Guindy (Tamil Nadu) and available as lyophilized powder in vacuum-sealed dark multidose vials. When reconstituted with sterile normal saline, each dose (0.1 mL) contains 0.1–0.4 million live viable bacilli. This heat and light sensitive vaccine is stable in lyophilized form at 2–8°C for one year, but loses potency rapidly when reconstituted.

BCG vaccine primarily induces cell-mediated immunity. Meta-analyses estimate that the vaccine has low protective efficacy against primary infection (~40%), pulmonary infection (8–79%) and all forms (~50%) of tuberculosis. However, it enables satisfactory (>50%) protection against severe forms of tuberculosis (miliary tuberculosis, tubercular meningitis) and reduces the risk of mortality. As childhood tuberculosis accounts for 15–

Table 10.6: Immunization schedule in India before and after phased introduction of new vaccines

Age	Schedule in 2010	Schedule in 2017
At birth	BCG, OPV-0, HBV-0	BCG, bOPV-0, HBV-0
6 weeks	OPV-1, DTP-1, HBV-1	bOPV-1, Pentavalent-1, Rota-1*, fIPV-1, PCV-1*
10 weeks	OPV-2, DTP-2, HBV-2	bOPV-2, Pentavalent-2, Rota-2*
14 weeks	OPV-3, DTP-3, HBV-3	bOPV-3, Pentavalent-3, Rota-3*, fIPV-2, PCV-2*
9 months	Measles-1, JE-1*	MR-1*, JE-1*, PCV-3*
16–24 months	Measles-2, DTP-B1, OPV-B	DTP-B1, bOPV-B, JE-2*, MR-2*
5–6 years	DTP-B2	DTP-B2
11–13 years	-	HPV-1, HPV-2*

B: Booster; BCG: Bacillus Calmette–Guerin; bOPV: Bivalent oral poliovirus; DTP: diphtheria, pertussis, tetanus; fIPV: Fractionated inactivated poliovirus; HBV: Hepatitis B virus; HPV: Human papillomavirus; JE: Japanese encephalitis; MR: Measles, rubella; PCV: Pneumococcal conjugate vaccine; Pentavalent: DTP+HBV+ *Haemophilus Influenzae* b; Rota: Rotavirus

*Where implemented

Box 10.2: Mission Indradhanush

Launched: December 2014

Objective: Fully immunize >90% of infants by 2020

Strategy: Special immunization drives; intense efforts in focus areas

Focus: 201 districts in 28 states that have the majority of partially immunized or unimmunized children

Coverage: 528 districts in 35 states and union territories

Personnel: 3As (Anganwadi workers, accredited social health activists, auxiliary nurse midwives)

Achievements: By August 2017, annual increment in immunization coverage increased from 1% in 2014 to 6.7% in 2015

Intensified Mission Indradhanush

Launched: October 2017

Objective: Fully immunize >90% newborns by December 2018

Implementation: Week-long immunization drives from 7th of each month

Additional: (i) Need based interventions; (ii) strengthen involvement of relevant non-health departments; (iii) enhanced accountability; (iv) vaccination on demand to children ≤ 5 years

Coverage: Left out and drop out sites in selected 173 districts and urban areas in 17 cities (i) with low routine immunization coverage (urban slums; nomadic sites; areas with vaccine preventable disease outbreaks); (ii) without ANMs; (iii) population per subcenter higher than norm; (iv) ≥ 3 consecutive missed routine immunization sessions



Be Wise!

Get your child fully immunized

20% cases and is disseminated, vaccine administration in infancy prevents serious morbidity. Since maternal antibodies do not interfere with cellular immune responses, BCG is given at birth ensuring compliance and early protection.

Conventionally, BCG vaccine is administered at insertion of the deltoid on the left shoulder to allow easy identification of its scar (Box 10.3). Intradermal injection using a 26 G needle raises a 5–7 mm wheal. Bacilli multiply to form a papule by one week that enlarges to 4–8 mm, ulcerates by 5–6 weeks and heals by scarring by 6–12 weeks. Inadvertent subcutaneous injection causes persistent ulceration and ipsilateral axillary or cervical lymphadenopathy. Children with severe immunodeficiency may develop disseminated BCG disease 6–12 months after vaccination. Although immunity wanes, repeat doses of BCG are not useful. Proposed tuberculosis vaccines, including DNA subunit, viral vector and recombinant vaccines carrying *M. tuberculosis* antigen(s), and live vaccines with recombinant or mutant bacilli, are being studied.

Poliomyelitis Vaccines

Vaccination is an important strategy for preventing paralytic poliomyelitis, caused by poliovirus serotypes 1–3, chiefly in young children. Two types of vaccines are available: Live-attenuated oral poliovirus vaccine (OPV), and inactivated poliovirus vaccine (IPV).

Oral Polio Vaccine (OPV)

OPV contains live vaccine (Sabin polioviruses) attenuated by repeated passage in monkey kidney cell cultures and stabilized with magnesium chloride. When administered orally, the vaccine viruses infect the intestinal mucosa and multiply in mucosal cells. Mucosal immunity protects from paralytic poliomyelitis by reducing the chances of infection when wild-type poliovirus is encountered; wild virus is excreted for shorter periods and in fewer numbers, reducing feco-oral transmission and interrupting wild virus circulation. Multiple OPV doses are essential to ensure appropriate response, which is affected by interference by maternal antibodies, competition by other

Table 10.7: Immunization schedule recommended by the Indian Academy of Pediatrics

Age	Schedule*
At birth	BCG, bOPV-0*, HBV-1
6 weeks	IPV-1*, HBV-2*, DTP-1, Hib-1, Rota-1, PCV-1
10 weeks	IPV-2*, DTP-2, Hib-2, Rota-2, PCV-2
14 weeks	IPV-3*, DTP-3, Hib-3, Rota-3, PCV-3
6 months	bOPV-1*, HBV-3*
9 months	bOPV-2*, MMR-1, Typhoid (conjugate), JE-1 ^s
12 months	IPV-B1*, Hib-B1, PCV-B1, HAV-1*
15 months	DTP-B1, MMR-2, Varicella-1, JE-2 ^s
18 months	HAV-2*
2–3 years	Typhoid (conjugate)-B
4–6 years	bOPV-3*, DTP-B2, MMR-3, Varicella-2
11–12 year	Tdap; HPV-1 & HPV-2*

B: Booster; BCG: Bacillus Calmette–Guerin; bOPV: Bivalent oral poliovirus; DTP: Diphtheria pertussis, tetanus; HAV: Hepatitis A virus; HBV: Hepatitis B virus; Hib: *Haemophilus influenzae* b; HPV: Human papillomavirus; IPV: Inactivated poliovirus; JE: Japanese encephalitis; MMR: Mumps, measles, rubella; PCV: Pneumococcal conjugate; Rota: Rotavirus
 *Preferred schedule detailed under respective vaccines, particularly where indicated by;
 †Influenza vaccine recommended annually and vaccination in high-risk groups not shown
^sOnly in endemic areas

enteroviruses, concomitant diarrhea and interruptions in the vaccine cold chain. Vaccine 'take' and seroconversion

Box 10.3: Bacillus Calmette–Guérin (BCG) vaccine

Dose, route	0.1 mL; intradermal
Site	Left upper arm at insertion of deltoid
Schedule	
National program	At birth; catch up till 1-yr (if missed)
IAP 2016	At birth; catch up till 5-yr
Adverse reactions	Local ulceration; discharging sinus; axillary lymphadenitis If immunodeficient, disseminated infection, osteomyelitis; scrofuloderma
Contraindication	Cellular immunodeficiency; symptomatic HIV
Storage	2–8°C; sensitive to heat and light; discard reconstituted vaccine after 4 hr

rates are lower in developing compared to developed countries.

Each dose (2 drops) of trivalent OPV contained 10⁵–10⁶ median cell culture infectious doses of each serotype 1, 2 and 3. Type-specific immunity was associated with highest seroconversion rates for OPV type 2, leading to eradication of wild type OPV2 in 1999. Since this serotype inhibits take of OPV1 and OPV3, and most cases of vaccine-derived poliomyelitis (VDPV) are due to OPV2, as part of Polio Eradication and Endgame Strategic Plan 2013–18, trivalent vaccine has been replaced by bivalent OPV (bOPV); OPV2 use was globally discontinued in April 2016.

Vaccine	Age	Birth	6 wk	10 wk	14 wk	6 mo	9 mo	12 mo	15–18 mo	2 yr	4–6 yr	10–13 yr	15–18 yr
BCG		1											
Oral polio virus		OPV0	OPV1	OPV2	OPV3				OPV B1		OPV B2		
Injectable polio vaccine		OPV0	IPV 1		IPV2 or IPV3	IPV12; OPV1	OPV2	IPV B1			OPV3		
Alternative IAP schedule		OPV0	IPV1	IPV2	IPV3	OPV1	OPV2	IPV B1			OPV3		
DPT			1	2	3				B1		B2	B3	
Hepatitis B		0	1	2	3 or 2	3							
Hemophilus influenza			1	2	3				B1				
TT												1	2
Measles or Measles rubella							1		2		3		
MMR							1		2		3		
Pneumococcal conjugate			1	2	3			B1					
Rotavirus			1	2	3								
Japanese B encephalitis							1	1	2				
Human papilloma virus												1, 2	1, 2 & 3
Typhoid conjugate C or polysaccharide P							C1			C2/P1	P2		
Varicella									1		2		
Influenza												Annually	
Hepatitis A vaccine								1	2				
Rabies												At any age, 3 doses one week apart	

KEY

Schedule	Recommended age	Catch up immunization
Universal Immunization Program only	Blue font	
Indian Academy of Pediatrics only	Yellow font	
Both Schedules	Green font	
Only in selected areas in UIP	Red font	

BCG Bacillus Calmette–Guerin; DTP diphtheria, pertussis, tetanus; IPV inactivated poliovirus; MMR mumps, measles, rubella; OPV oral poliovirus; TT tetanus toxoid

*Boosters (B) as either whole cell or acellular vaccine; B3 as tetanus with reduced diphtheria and reduced pertussis (Tdap)

Fig. 10.3: Vaccinations scheduled in Universal Immunization Program and Indian Academy of Pediatrics (2016). Details are under respective vaccines

Since OPV is very sensitive to temperature, its potency is monitored using vaccine vial monitor (VVM), a heat sensitive patch on the vial label (section on Cold Chain). To decrease chances of vaccine failure, at least three doses are required 4–8 weeks apart. The administration of 'zero' dose at birth enhances seroconversion. Breastfeeding and mild diarrhea are not contraindications for OPV administration. Children with immunodeficiency and pregnant women should not receive the vaccine; its use is also avoided in household contacts of these patients.

In the past, OPV vaccine was given simultaneously with DTP vaccines at 6, 10 and 14 weeks, followed by two booster doses with DTP boosters at 15–18 months and 5 years. Since 1995, children below 5 years also received the vaccine during the (sub-) national immunization days and supplementary immunization activities in the Pulse Polio campaign, wherein simultaneous administration of OPV to all young children in the community interfered with feco-oral transmission of the circulating wild poliovirus. Together with surveillance and targeting of migrant populations and high-risk areas, wild poliovirus was eradicated from India; the last wild polio case (serotype 1) reported from Howrah in January 2011.

While OPV is preferred for eradication of poliomyelitis, the virus may regain neurovirulence, resulting in vaccine-associated paralytic poliomyelitis (VAPP) in 1 of 1.5 million OPV recipients, chiefly with OPV3 (recipients) or OPV2 (contacts). Further, outbreaks of paralytic poliomyelitis may be caused by a virulent strain of poliovirus formed by mutation of OPV, chiefly OPV2, called the circulating vaccine-derived poliovirus (cVDPV). Similar to the wild virus, cVDPV spreads rapidly through the community to cause outbreaks, especially in areas with low or declining rates of OPV coverage.

Inactivated Polio Vaccine (IPV)

IPV is a suspension of formaldehyde killed (salk) poliovirus grown in monkey kidney, human diploid or Vero cell culture. The vaccine primarily induces humoral immune response, but pharyngeal and possibly, intestinal mucosal antibodies are also induced. Vaccine potency is measured by its 'D' antigen content. Each dose of currently used third generation or enhanced potency IPV (eIPV) vaccines contains 40D, 8D and 32D units of types 1, 2 and 3 polioviruses, respectively, grown in Vero cell culture and purified before inactivation. IPV is highly immunogenic; with seroconversion in 90–99% of infants over 8 weeks old administered 2–3 doses 4–8 weeks apart. Vaccination beginning at 6 weeks carries risk of interference with maternal antibodies. Despite low titers of secretory IgA and weak induction of herd immunity, IPV has excellent efficacy in preventing poliomyelitis. IPV administration has the advantage of not causing VAPP. Hence, following a phase of sequential or combined OPV-IPV use, countries with sustained eradication of circulating wild poliovirus have switched to exclusive use of IPV.

Recommendations on Vaccination Against Poliovirus In India

Since February 2014, WHO no longer recommends an OPV only schedule. This is because IPV, apart from protecting from wild type poliovirus also protects against poliomyelitis caused by cVDPV2 (bOPV used for routine immunization; population immunity for OPV2 is declining). Most countries practice a sequential IPV-OPV schedule, which has the advantage that the risk of OPV-induced VAPP is minimized by prior administration of IPV, while ensuring adequate mucosal immunity to interrupt wild poliovirus circulation. WHO recommends that all countries using only OPV should add at least one dose of IPV to the national schedule. The primary series consisting of three OPV doses plus one IPV dose can be initiated from the age of 6 weeks, with minimum interval of 4 weeks between OPV doses. If one dose of IPV is used, it is given at 14 weeks of age when maternal antibodies have diminished and immunogenicity is higher, one of the major objectives of the Polio Eradication and Endgame Strategic Plan 2013–2018 (see below) is to introduce at least one dose of IPV into routine immunization schedules, strengthen routine immunization and withdraw OPV in a phased manner, starting with OPV2.

Evidence suggests that VDPV and wild type OPV may surface 4 years and 10 years, respectively, after global cessation of OPV. Even after global OPV withdrawal, national schedules should continue to provide at least two doses of IPV in their immunization schedule, administered either as full or fractional doses, for at least 10 years after OPV withdrawal. While efforts are ongoing to prioritize IPV supply for use, experts suggest continuation of a 2-dose fractional (fIPV) dose schedule, which ensures that all eligible infants receive IPV. This strategy is dose sparing (one-fifth the IM dose) and results in better immunogenicity than a single intramuscular dose of IPV. Two fractional doses or two full IPV doses are required to achieve $\geq 90\%$ seroconversion, with the first dose given ≥ 14 weeks and an interval ≥ 4 months between the first and second doses. Administering fIPV during routine immunization visits at 6–14 weeks achieves high vaccine coverage and acceptability.

IPV was, therefore, introduced in India in 2015–16 with two fractional (fIPV) intradermal doses at 6 and 14 weeks (Box 10.4). Children continue to receive bOPV on all national immunization days and during supplementary immunization activities. Patients that miss immunization at 6 weeks receive a full intramuscular dose of IPV at 14 weeks. The IAP accepts the above schedule as 'moderately effective' against OPV2. It prefers the more immunogenic three-dose schedule, or two intramuscular doses beginning at 8 weeks and given 8 weeks apart (Box 10.4; also footnote). IPV is the vaccine of choice in patients with immunodeficiency including symptomatic HIV, and in siblings and close contacts of such patients. These children should not receive OPV and receive an additional booster dose of IPV at 5 years. Both schedules

Box 10.4: Bivalent oral poliovirus (bOPV) and inactivated poliovirus (IPV) vaccines

	<i>Bivalent oral poliovirus vaccine</i>	<i>Inactivated poliovirus vaccine</i>
Dose, route	Two drops; oral	0.5 mL, IM or SC; 0.1 mL, intradermal
Schedule		
National program (OPV and IPV)	Dose at birth or <2 weeks (zero dose); 3 doses at 6, 10 and 14 weeks; two booster doses at 15–18 months and 5 years	0.1 mL, intradermal (fractional dose) at 6 and 14 weeks; or one full IM dose at 14 weeks
IAP 2016 (OPV and IPV)*	At birth, 6 months, 9 months and 5 years	3 doses of IPV at 6, 10 and 14 weeks; or 2 doses at 8 and 16 weeks (primary) and one dose at 15–18 months (booster)
Catch up	Up to 5 years; Three doses 4 weeks apart	Up to 5 years; 3 doses at 0, 2 and 6 months
Adverse reactions	Vaccine-derived poliovirus; vaccine-associated paralytic poliomyelitis	Local pain, swelling
Contraindications	Inherited or acquired immunodeficiency; symptomatic HIV	Known allergy
Storage	2–8°C; sensitive to heat; use vaccine vial monitor	2–8°C; sensitive to light and heat; use vaccine vial monitor

*IAP recommends above as ideal, but no child should go unimmunized at any time point when polio vaccine is indicated, and should receive OPV if IPV cannot be given due to shortage/non-availability.

UIP intradermal (ID) fractionated dose IPV schedule is moderately effective; one intramuscular (IM) dose is given ≥8 weeks after second ID-IPV dose; if one dose of ID-IPV was given, two IM doses are given at 8 week intervals.

retain the birth dose of OPV; this dose is necessary in areas with continued risk of wild virus transmission, and is unlikely to cause VAPP in presence of maternally transmitted antibodies.

Polio Eradication and Endgame Strategic Plan 2013–2018

This is a comprehensive strategy to deliver a polio-free world, developed by the Global Polio Eradication Initiative in consultation with health authorities, experts and other stakeholders. The plan addresses the eradication of all polio disease, caused by wild or circulating vaccine-derived poliovirus. Its objectives are: (i) Detect and interrupt all poliovirus transmission; (ii) strengthen immunization systems and withdraw OPV; (iii) contain poliovirus and certify interruption of transmission; and (iv) plan post-polio legacy (Fig. 10.4). A midterm review suggests that certain activities require focus, including: (i) strengthening disease surveillance; (ii) improving quality of immunization campaigns; (iii) building capacity to respond to outbreaks. A post-certification strategy is being developed to maintain a polio-free world. Its goals are: (i) Contain poliovirus sources by ensuring that they are properly controlled or removed; (ii) protect populations by withdrawing OPV and immunizing with IPV against possible re-emergence of any poliovirus; and (iii) detect and respond promptly to any poliovirus reintroduction.

Diphtheria, Pertussis and Tetanus Vaccine

Diphtheria vaccine contains diphtheria toxin (DT) inactivated by formalin and adsorbed on aluminum

hydroxide, the adjuvant. This is the most commonly used vaccine. The quantity of toxoid in the vaccine, expressed as limit of flocculation (Lf) content is 20–30 Lf of DT, 5–25 Lf of tetanus toxoid (TT) and >4 IU of whole cell killed pertussis.

Maternal antibodies protect the infant against disease and interfere with immune responses to DPT vaccination, particularly against pertussis. Protection requires that vaccination is begun within a few weeks of life and multiple doses are given. Primary immunization with 3 doses of the vaccine, given 4–8 weeks apart, induces satisfactory immune response to DT and TT in 95–100% infants. Protective efficacy against pertussis is lower, at ~70–90%, and wanes over 6–12 years. Immunization does not eliminate *C. diphtheriae* from the skin or nasopharynx. Booster doses are required to sustain a protective antibody titer of 0.1 IU/mL and protect from disease in the first decade of life. Natural infections and immunization against pertussis induce immunity lasting 4–12 years, making boosters necessary to prevent infection in adolescence. Box 10.5 indicates the schedule for administration of DTwP or DTaP, containing DT, TT and acellular pertussis.

DTwP vaccine is commonly associated with local (pain and redness) and systemic (fever) reactions, chiefly attributed to the pertussis component. The incidence of these adverse effects increases with the number of doses administered; hence the vaccine should not be used beyond 5 doses or beyond 7 years of age. DTP is also incriminated in rarely inducing of serious neurological complications, though conclusive evidence is lacking

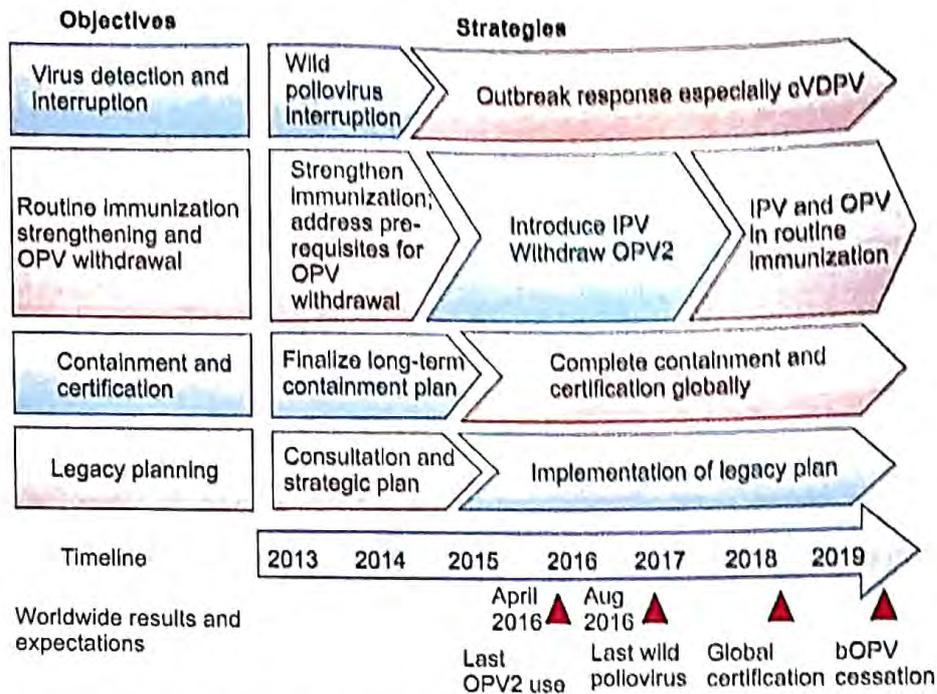


Fig. 10.4: Polio Eradication and Endgame Strategic Plan 2013–18. There are four major objectives with corresponding areas of work. The bottom panel outlines the timeline of wild type and vaccine-derived poliovirus elimination

(Box 10.5). The vaccine is contraindicated in children with progressive neurological disease; children with stable neurological diseases (e.g. developmental delay, cerebral palsy and idiopathic epilepsy) may receive the vaccine. Absolute contraindications to administration of the vaccine and adverse events that require precaution are listed in Box 10.5, if an event listed as precaution recurs with a subsequent dose, further doses are contraindicated. Individuals in which DTP is contraindicated should

complete the immunization schedule with DT that contains the same doses of DT and TT as DTP, but is devoid of the pertussis component. DT is recommended up to the age of 7 years, beyond which Td must be used.

Acellular Pertussis Vaccine (DTaP)

The suspicion that the active pertussis toxin and endotoxin cause the adverse events associated with DTwP led to the

Box 10.5: Diphtheria toxoid, tetanus toxoid and killed whole cell pertussis (DTwP) or acellular pertussis (DTaP) vaccine

<i>Dose, route</i>	0.5 mL; intramuscular
<i>Site</i>	Anterolateral aspect of mid-thigh (gluteal region: sciatic nerve injury; inadequate response)
<i>Schedule</i>	
National program	DTwP at 6, 10 and 14 weeks (primary); at 15–18 months and 5 years (boosters)
IAP 2016 (see footnote)	DTwP for primary and DTaP or DTwP for booster in schedule as above; Tdap/Td at 10–12 years; Td every 10 years
Catch up (IAP 2016)	<7 years: DTwP (preferred) or DTaP at 0, 1 and 6 months 7–10 years: Tdap at 0 month; Td at 1 and 6 months >11 years: One dose of Tdap; one dose of Td every 10 years
<i>Adverse reactions</i>	Common: Local pain, swelling, fever (DTwP>DTaP) Rare: Hypotonic hyporesponsive episodes, inconsolable cry; fever >40.5°C; seizures; encephalopathy (DTwP=DTaP)
<i>Contraindications</i>	(i) Progressive neurological disease (administer DT or dT instead); (ii) anaphylaxis after previous dose; (iii) encephalopathy within 7 days of previous dose
<i>Precautions</i>	Previous dose associated with (i) fever >40.5°C within 48 hours; (ii) hypotonic hyporesponsive episode <48 hours; (iii) persistent inconsolable crying for >3 hours, <48 hours; (iv) seizures <72 hours
<i>Storage</i>	2–8°C; sensitive to light

IAP recommendations:

DTwP should be used in primary immunization; DTaP vaccine should be used only in children with severe adverse effects after previous dose of DTwP or children with neurologic disorders; Either DTwP or DTaP may be used for booster doses; DTaP used should have ≥3 or more pertussis components; Tdap should not replace the second booster of DTwP or DTaP

development of various types of purified acellular pertussis vaccines, or DTaP. These vaccines contain inactivated pertussis toxin and one or more additional pertussis antigens, like filamentous hemagglutinin (FHA), pertactin, fimbrial protein and a nonfimbrial protein. Approved vaccines have at least three pathogenic pertussis antigens, at least 4 IU of inactivated pertussis toxin and 6.7–25 Lf of DT. While the efficacy of these vaccines is similar to DTwP, the risk of systemic and local side effects is lower. The DTaP vaccine is not included in the National Program due to its prohibitive cost. The IAP previously recommended that the vaccine be offered to all children who can afford, in view of the advantage of fewer side effects, or following an adverse effect with DTwP. Since recent studies suggest that the efficacy of DTaP vaccines, when used for primary immunization, is lower (46–92%) than with DTwP (61–89%) particularly for pertussis, the IAP thus recommends that only DTwP (and not DTaP) be used for primary immunization. Boosters at 16–24 months and at 5 years may be with either DTwP or DTaP (Box 10.5). Contraindications for DTaP vaccine are similar and the vaccine should not be given, if a previous dose of DTwP or DTaP was associated with a contraindication; these children should complete immunization with DT instead of DTwP or DTaP.

Reduced Antigen Acellular Pertussis Vaccine (Tdap) and Reduced Antigen Diphtheria Toxoid Vaccine (Td)

As natural immunity to diphtheria and pertussis is acquired through apparent or inapparent infections (Chapter 11), a large proportion of adults especially in developed countries, are susceptible through lack of natural boosting and waning of immunity. In nonendemic countries, revaccination against diphtheria every 10 years may be necessary to sustain immunity among adults, particularly healthcare workers. Vaccines useful in such situations include diphtheria and tetanus toxoids (DT) and combinations with reduced toxoid content (Td, Tdap). While standard dose DT is recommended for primary immunization against diphtheria because of its superior immunogenicity and minimal reactogenicity, the reactogenicity of the vaccine increases with age. If given beyond 7 years of age, primary immunization or booster doses should be in the form of Tdap or Td, which contain smaller amounts of diphtheria toxoid (2 Lf) and acellular pertussis vaccine than DTP, and is adequately immunogenic even in adults. To promote immunity against diphtheria, this vaccine may be used whenever TT is indicated in children above 7 years of age.

Similarly, Tdap offers the prospect of reducing pertussis incidence in adults and adolescents, and also reduces the risk of their transmitting disease to young children. Its reduced antigen content causes less severe adverse effects while being sufficient to induce protective response in previously immunized (booster effect). The available Tdap

vaccines in India contain 5 Lf of tetanus toxoid, 2 Lf of diphtheria toxoid and three acellular pertussis components (pertussis toxoid 8 µg, filamentous hemagglutinin 8 µg and pertactin 2.5 µg). Contraindications to Tdap are the same as those listed for DTaP or DTwP. Tdap may also be used as replacement for Td/tetanus toxoid (TT) booster in children above 10 years and adults of any age, if they have not received Tdap in the past and 5 years have elapsed since the receipt of previous TT/Td vaccine.

Tetanus Vaccine

Extensive routine immunization of pregnant women has led to decline in the incidence of neonatal tetanus. Immunizing pregnant women with two doses, with the second dose administered at least 4 weeks prior to delivery, provides passive immunity to the baby due to the transplacental passage of IgG antibodies. Tetanus toxin is inactivated by formalin and adsorbed onto aluminum salts to enhance immunogenicity. Each dose of the vaccine contains 5 Lf of toxoid. The vaccine is heat stable and remains potent for a few weeks even at 37°C. The efficacy of TT vaccine varies between 80 and 100%. While antitoxin level of 0.01 IU/mL is considered protective, the level of protection available also depends on the toxin load. Since tetanus may occur at any age, primary immunization should begin in early infancy. Tetanus toxoid is given with DT and pertussis vaccine in DTP. DT, Td and TT may be used as boosters at 10 and 16 years of age and for wound prophylaxis (Table 10.8). Children who have not received primary immunization, should receive 2 doses of TT 1 month apart.

Measles-containing Vaccines

Measles vaccine, derived from the Edmonston-Zagreb strain, is available as a monovalent preparation, or in combination with rubella (MR), mumps (MMR) and varicella (MMR-V). Both cellular and humoral responses are elicited. Since infants are protected by maternal antibodies till 6–9 months of age, administering the vaccine at 9 months in endemic countries balances the need for early protection with the ability to ensure seroconversion. However, interference by maternal antibodies causes primary vaccine failure in 15%, making a second dose necessary at 15 months. During outbreaks, the vaccine may be given even earlier (~6 months) with a repeat dose at 12–15 months. Each vaccine dose contains at least 1000 infective units of the attenuated virus. Measles vaccine loses potency rapidly after reconstitution; unused vaccine should be discarded after 4–6 hours since contamination may lead to staphylococcal sepsis and toxic shock syndrome.

The two doses of measles vaccine at 9–12 and 15–24 months (Box 10.6) in the national immunization program are being replaced by the MR vaccine in a phased manner. This follows the nationwide 'measles rubella' program (launched February 2017) in which one dose of the vaccine

Table 10.8 Tetanus prophylaxis following wound

Past doses of TT	Clean minor wound		All other wounds	
	TT	Tetanus immunoglobulin	TT	Tetanus immunoglobulin
Unknown: <3 doses or immunodeficient	Yes	No	Yes	Yes
≥3 doses	No*	No	No**	No

Give tetanus toxoid (TT) if more than *10 years or **5 years have elapsed since last dose

is given to all children 9 months to 15 years of age, irrespective of their immunization status. Recognizing the significant morbidity associated with mumps infections, the IAP recommends MMR instead of MR at 9- and 16-24 months. IAP also recommends a third dose of MMR at 4-6 years, chiefly in order to boost anamnestic response.

Post-exposure prophylaxis with immunoglobulin is considered for immunocompromised contacts and 6-12-month-old infants within 6 days of exposure (see Passive Immunization). Unimmunized immunocompetent contacts older than 12 months should receive measles or MMR vaccine within 72 hours of exposure.

Measles Mumps Rubella (MMR) Vaccine

While childhood mumps is often subclinical or causes benign parotitis, infections in adolescents and adults may be associated with oophoritis or meningitis. Rubella is a benign illness with rash and transient arthritis; vaccination aims at preventing congenital rubella syndrome with fetal growth retardation, heart disease, hearing defects, microcephaly and hepatosplenomegaly. Most developed countries use MMR rather than measles vaccine for primary immunization.

The rubella component is the RA 27/3 strain and the mumps component contains the live-attenuated Jeryl-Lynn strain, both grown in human diploid or chick embryo cell cultures. Each dose contains 1000, 5000 and 1000 TCID₅₀ of live-attenuated measles, mumps and rubella viruses, respectively. Mucosal and systemic humoral and cellular responses are elicited following vaccination. Seroconversion rates following a single dose are 86-100%

for mumps and >95% for rubella. While prolonged immunity is seen, rubella and mumps infections are reported beyond 5 years, confirming the need for a booster dose at 4-6 years. The vaccine is safe, but should be avoided in pregnancy and immunodeficiency. Adverse effects are mild (Box 10.6).

The vaccine is dispensed as a lyophilized preparation that should be used within 4 hours of reconstitution. Haphazard use of MMR vaccine without ensuring optimal (>80%) immunization coverage may result in an epidemiological shift of disease with more cases in adulthood and a paradoxical increase in congenital rubella syndrome. The latter was observed in Greece in 1990s following incomplete MMR coverage in the 1970s.

Hepatitis B Vaccine

Hepatitis B virus (HBV) vaccine contains the surface antigen HBsAg, produced by recombinant DNA technology in yeast, adsorbed on aluminum salt as adjuvant. While immunization at birth, 1 and 6 months has better immunological efficacy than the regime advised in the National Program (Box 10.7), the latter integrates HBV vaccination into the existing schedule without increasing visits and ensures compliance. Since immunization at birth prevents horizontal transmission, vaccination must begin at birth, if the mother's HBsAg status is not known. If the mother is known to be HBsAg positive, the child should receive the vaccine within a few hours of birth, and hepatitis B immunoglobulin (HBIG) within the first 24 hours at separate sites (see Passive Immunization). Subsequently, any of the schedules

Box 10.6: Measles-containing vaccines

Dose, route	0.5 mL; subcutaneous
Site	Right upper arm (at insertion of deltoid) or anterolateral thigh
Schedule	
National program	At 9-12 and 15-24 months, as measles or measles rubella vaccine
IAP 2016	At 9-12 months, 15-18 months and 4-6 years; preferably as MMR; avoid MMR-V <2 years
Catch up	Complete schedule with >4 weeks gap between doses; can use MMR-V >2 years
Adverse reactions	Local pain, tenderness; febrile seizures (especially with MMR-V in <2-yr-old) Measles vaccine: Fever or transient macular rash (after 7-12 days) MMR vaccine: Transient rash, arthralgia, aseptic meningitis, lymphadenopathy
Contraindications	Immunosuppression; malignancy; immunodeficiency (symptomatic HIV); recent infusion of immunoglobulin-containing blood product
Storage	2-8°C; sensitive to heat and light; use within 4-6 hours of reconstitution

MMR-V: Measles, mumps, rubella, varicella

Box 10.7: Hepatitis B vaccine

Dose, route	0.5 mL (10 µg); 1 mL in immunosuppressed children, malignancy or hemodialysis and adults; intramuscular
Site	Anterolateral thigh or deltoid; avoid gluteal region
Schedule	
National program	At birth, 6 weeks, 10 weeks and 14 weeks
IAP 2016	Preferred schedule: Gap between first two doses is ≥4 weeks; doses 2 and 3 is ≥8 weeks; and first and final doses is ≥16 weeks; final dose ≥6 months of age*
Catch up	Three doses at 0, 1 and 6 months; preferred gap between first two doses is ≥4 weeks, and doses 2 and 3 is ≥8 weeks
Adverse reactions	Local soreness; fever; fatigue
Contraindication	Anaphylaxis after previous dose
Storage	2–8°C; do not freeze

*Following are also acceptable: Birth, 1 and 6 months; birth, 6 and 14 weeks; birth, 6, 10 and 14 weeks

incorporating a birth dose of the vaccine can be used. If HBIG is not administered, the baby should be immunized in an accelerated schedule at 0, 1 and 2 months, and an additional dose at 9–12 months. Combined passive and active immunization with use of HBIG and HBV vaccine results in 90% reduced risk of HBV transmission in patients with needle stick injuries, sexual exposure or use of blood product not screened for HBV.

Seroconversion rates exceed 95% after three HBV doses: Antibody titer >10 mIU/mL is protective. Vaccination usually induces long-term immunity, and booster doses are not routinely recommended. Double dose of vaccine and boosters may be required in patients with chronic kidney disease or immunodeficiency, in whom titers may wane.

Hemophilus Vaccine

Haemophilus influenzae b (Hib) causes invasive infections such as pneumonia, meningitis and bacteremia, especially in children <2-year-old. Vaccination prevents 33% of pneumonia and 90% meningitis related to Hib. The chief antigen is Hib capsular polysaccharide, polyribosylribitol phosphate (PRP), which is conjugated to tetanus toxoid (PRP-T), mutant diphtheria toxin CRM-197 (Hib-OC) or meningococcal outer membrane protein (PRP-OMP). Both monovalent and combination (with DTP and hepatitis B or IPV) vaccines are safe and immunogenic, with efficacy of 85–95%. The vaccination schedule depends on age of the child at immunization (Box 10.8). A booster is required in the second year to sustain protection. As Hib infections chiefly affect preschool children, IAP recommends that the vaccine be given to all children up to the age of 5 years; older children need vaccination, only if planned for splenectomy or if having sickle cell disease. Hib vaccine

Box 10.8: *Haemophilus influenzae* b vaccine

Dose, route	0.5 mL, intramuscular
Site	Anterolateral thigh
Schedule	
National program	Pentavalent vaccine with DTP and hepatitis B; three doses given at 6, 10 and 14 weeks
IAP 2016	As above; 3 doses at ≥6 weeks given ≥4 weeks apart; one booster at 15–18 months
Catch up	At 6–12 months: Two doses ≥8 weeks apart; one booster at 15–18 months At 12–15 months: One dose and one booster at 15–18 months 15–60 months: One dose; not recommended >5-year-old except, if hypo/asplenia
Adverse reactions	Fever, rash, local pain or redness
Contraindication	Hypersensitivity to previous dose
Storage	2–8°C

is now part of the Universal Immunization Program, introduced as a pentavalent vaccine (DTP, HBV and HibPRP-T vaccines) in 2015.

Pneumococcal Vaccine

S. pneumoniae causes 15–50% of community-acquired pneumonia, 30–50% of acute otitis media and 50% of deaths due to pneumonia. Pneumococcal pneumonia is the leading single cause of vaccine-preventable deaths, globally and in India. Twenty of 90 known serotypes account for 80% of invasive pneumococcal disease, and 13 serotypes cause 75% of invasive disease in young children. Children below two years of age are particularly susceptible to invasive pneumococcal disease. Children at high risk of disease, regardless of age, include: (i) primary immunodeficiency, HIV, immunosuppressive therapy and organ transplant recipients; (ii) sickle cell disease, asplenia or hyposplenia; (iii) chronic cardiac, liver or pulmonary disease; (iv) chronic kidney disease and nephrotic syndrome; (v) diabetes mellitus; and (vi) children with cerebrospinal fistula or cochlear implants.

Two kinds of vaccines are available. Unconjugated polysaccharide vaccine has 25 µg capsular polysaccharide of each of the 23 serotypes termed PPV23. Since polysaccharides stimulate B cells independent of T cells, the vaccine is poorly immunogenic <2 years and immunological memory is low. This vaccine does not reduce nasopharyngeal pneumococcal carriage or provide herd immunity. Its efficacy in preventing invasive pneumococcal disease in high-risk categories is <70%; more than 2 doses are not recommended.

The pneumococcal conjugate vaccine has the polysaccharide of 13 most commonly pathogenic serotypes linked to a diphtheria carrier protein (PCV13); another is

a 10-valent conjugate vaccine (PCV10) combined with non-typeable *H. influenzae* vaccine. Apart from robust immune response and immunological memory, conjugated vaccines reduce nasopharyngeal bacterial carriage resulting in significant *herd effect*. The protective efficacy is 95–99% for invasive pneumococcal disease covered by included serotypes.

Since pneumococcal infections cause significant morbidity and mortality in children <2 years of age, IAP recommends using the conjugate vaccine (Box 10.9). Since the risk of invasive infections decreases with age, vaccination beyond 5 years is not necessary except in high-risk categories; the latter should additionally receive the polysaccharide vaccine. An additional dose of the vaccine may be given in high-risk categories 3–5 years later. Given its public health importance, pneumococcal vaccination was launched in three states in May 2017. Vaccination will be extended to the entire country in a phased manner.

Rotavirus Vaccine

Rotavirus is the chief cause of diarrhea in infants and toddlers, accounting for 6–45% of diarrhea-related hospitalization in Indian children. Natural infection does not protect against reinfection or severe disease. The first licensed vaccine (Rotashield), a live oral tetravalent vaccine, was withdrawn following an association with intussusception. Two live-attenuated oral vaccines are currently used worldwide (Box 10.10). Rotarix is a monovalent vaccine containing at least 10^6 median cell culture infective doses of rotavirus strain G1P8 attenuated in Vero cell culture. RotaTeq is a pentavalent vaccine with 2–116 million infectious units each of the 5 strains [G1-4 and P8] reassorted between bovine and human WC3 rotaviruses, and attenuated by Vero cell culture. Both vaccines have 85–98% efficacy against severe rotaviral gastroenteritis. Rotavac is an indigenous monovalent human-bovine recombinant live-attenuated vaccine based

on G9P11 or 116E strain, manufactured in India. The vaccine has 49–54% efficacy against rotaviral diarrhea in the first 2 years of life; it is inexpensive and safe with a low risk of intussusception.

All three rotavirus vaccines may be given with OPV without compromising efficacy of either vaccine. Vaccination is avoided during acute gastroenteritis, as it might compromise vaccine take. While none of the vaccines increases the risk of intussusception, caution is necessary in infants at risk of intussusception, e.g. those with chronic gastrointestinal disease and gut malformations. Immunization should be completed by 8 months of age. Studies suggest that vaccine efficacy may be lower in countries with high infection rates and competition for intestinal infection by other pathogens. The vaccine has reasonable potential for preventing diarrhea related morbidity and mortality in developing countries. Given its importance, rotavirus vaccination was introduced in the UIP in 2016 in selected districts in four states (Andhra Pradesh, Himachal Pradesh, Haryana and Odisha) using the Rotavac vaccine.

Human Papillomavirus (HPV) Vaccine

Cervical cancer, the second most common cancer in women, is almost always due to infection with oncogenic HPV belonging to 20 of 100 known serotypes. Serotypes 16 and 18 cause majority of invasive cervical cancer; oncogenic serotypes also cause anal, vulvar, vaginal, penile and oropharyngeal cancer. Nononcogenic serotypes 6 and 11 cause 90% of anogenital warts.

HPV vaccines contain self-assembling virus like particles containing recombinant L1, a major capsid protein. These vaccines protect against 90% of infections with included serotypes, but do not provide cross protection against other strains. The quadrivalent vaccine Gardasil (HPV4) protects against strains 6, 11, 16 and 18, while bivalent Cervarix (HPV2) targets HPV 16 and 18.

Box 10.9: Pneumococcal vaccines

Type	<i>Pneumococcal conjugate (PCV13, PCV10)</i>	<i>Pneumococcal polysaccharide (PPV23)</i>
Dose, route	0.5 mL; intramuscular	0.5 mL; intramuscular or subcutaneous
Site	Anterolateral thigh or deltoid	Deltoid
Schedule		
National program	Some states: Three doses at 6 weeks, 14 weeks and 9 months	Not recommended
IAP 2016	Three doses after ≥6 weeks age; given ≥4 weeks apart; one booster at 15–18 months	High-risk category*; One dose ≥8 weeks after primary course with conjugate vaccine; repeat 5 years later, if risk persists
Catch up	At 7–11 months: Two doses >4 weeks apart; one booster at 15–18 months At 12–23 months: Two doses >8 weeks apart At 24–59 months: One dose >60 months: One dose, if high risk*	
Adverse reactions	Fever, local pain, soreness, malaise	Pain, redness
Contraindication	Anaphylaxis after previous dose	—
Storage	2–8°C; do not freeze	2–8°C

*For details, see text above

Box 10.10: Oral rotavirus vaccines

	Rotarix (RV1)	RotaTeq (RV5)	Rotavac
Dose	1 mL (lyophilized); 1.5 mL (liquid)	2 mL (liquid)	5 drops
Schedule			
National program	Not included	Not included	Selected states: 3 doses at 6, 10 and 14 weeks*
IAP 2016	2 doses at 10 and 14 weeks (preferred to 6 and 10 weeks)*	3 doses at 6, 10 and 14 weeks*	3 doses at 6, 10 and 14 weeks
Adverse reactions	Fever, diarrhea, vomiting; Intussusception is rare		
Contraindication	Past history of Intussusception; severe immunodeficiency		
Precaution	Postpone vaccination during ongoing diarrhea or moderate illness		
Storage	2–8°C; protect from heat; use within 4 hr of reconstitution or opening		

*Administer ≥4 weeks apart beginning at ≥6 weeks of age (≥10 weeks for Rotarix); completing by 8 months of age

Both vaccines prevent cervical *in situ* neoplasia grade 2 and 3, and adenocarcinoma *in situ*. Gardasil also prevents serotype-related genital warts and vaginal and vulvar intraepithelial neoplasia. Both vaccines are most immunogenic at 9–14 years of age and protection persists for at least 5 years. The ideal age at vaccination and need of booster doses, if any, is not determined.

Governments of Delhi and Punjab have initiated school-based programs for girls aged 11–13 years old since 2016. Elsewhere, IAP recommends that the vaccine should be offered to all girls prior to sexual debut (Box 10.11). Immunization carries the risk of complacency regarding routine screening for cancer; which together with incomplete immunization coverage might paradoxically raise cervical cancer-related mortality. There are no serious adverse events of HPV vaccine.

Japanese B Encephalitis Vaccine

Japanese encephalitis (JE) is an important cause of viral encephalitis in India and is associated with high fatality. Vaccination as a control measure is recommended for all children and adults residing in highly endemic areas and for individuals visiting endemic areas for longer than 4 weeks. Previously available vaccines, discontinued in 2005, included inactivated mouse brain-derived vaccine (Nakayama or Beijing-1 strains) and primary hamster kidney cell culture vaccine (Beijing-3 strain). Three of the four second generation vaccines are licensed for use in India (Box 10.12).

The live-attenuated cell culture vaccine is used in the national program in hyperendemic districts of Uttar Pradesh, West Bengal, Assam and Karnataka. It is based on SA-14-14-2, a genetically stable neuro-attenuated JE strain that is unlikely to show neurovirulence (Box 10.12). While a single dose has protective efficacy of 85–99%, two doses are recommended to provide complete and sustained protection. In endemic districts, a strategy of mass immunization followed by routine vaccination is practised. The purified formalin inactivated SA-14-14-2 is a whole virus vaccine derived from Vero cell culture. The vaccine

Box 10.11: Human papillomavirus vaccine

Dose, route	0.5 mL, intramuscular
Site	Upper arm (deltoid)
Schedule	
National program	In some states: Two doses 6–12 months apart in girls 11–13 years
WHO; IAP 2016	Girls 9–14 years old: 2 doses of HPV4; or HPV2 ≥6 months apart Girls ≥15 years, immunocompromised: 3 doses [HPV4: 0, 2 and 6 months; or HPV2: 0, 1 and 6 months]
Catch up	Up to 45 years (IAP); preferably before initiation of sexual activity
Adverse reactions	Local pain, swelling, erythema; fever Syncope (due to injection, not vaccine)
Contraindication	Anaphylaxis after previous dose
Storage	2–8°C; protect from light

is highly immunogenic in children, with seroconversion >90% with two doses. The risk of adverse effects is lower than live-attenuated vaccine. The inactivated purified Vero cell derived vaccine (based on Kolar strain) is safe and effective, with seroconversion in 93–98%.

Typhoid Vaccine

Typhoid vaccine is currently not part of the national program, but is recommended by IAP for families who can afford (Box 10.13). The whole cell-inactivated typhoid vaccine containing heat-killed phenol-preserved or acetone-inactivated whole cell *S. typhi* and *S. paratyphi A* and *B* is no longer used. Two doses of the vaccine, administered SC 4 weeks apart, induced humoral antibodies that were 50–80% effective in preventing typhoid. Adverse effects (chiefly fever, local pain and headache) were common (10–35%) and revaccination was required every 2–3 years.

An oral vaccine, not marketed in India, contains 2–6 million live-attenuated lyophilized bacteria of Ty21a mutant strain of *S. typhi*. The mutation is genetically stable and unlikely to revert to virulent form. The vaccine is

Box 10.12: Japanese B encephalitis vaccine

	Live-attenuated cell culture derived SA-14-14-2	Inactivated cell culture derived SA-14-14-2 [Jecv®; IC51]	Inactivated Vero cell culture derived Kolar [Jenvac®; 82156XY]
Dose, route	0.5 mL; subcutaneous	1–3 yr: 0.25 mL; >3 yr: 0.5 mL; intramuscular	0.5 mL; intramuscular
Site	Anterolateral thigh, upper arm	Anterolateral thigh, upper arm	Anterolateral thigh, upper arm
Schedule			
National program	Only endemic areas; two doses at 9- and 16–18 months	Not used	Not used
IAP 2016	Recommended in endemic areas; not available in private sector	Recommended in endemic areas ≥1 yr-old; two doses 4 weeks apart; need for booster unclear	Recommended in endemic areas ≥1-yr-old; two doses 4 weeks apart; need for booster unclear
Catch up	Up to 18 years; one dose to non-immune adults	Up to 18 years	Up to 18 years
Adverse reactions	Fever, malaise; hypersensitivity rare	Less common: Fever, pain, malaise	Uncommon

supplied as an enteric coated capsule that induces intestinal mucosal immunity, with an efficacy of 50–60% within 7 days of completing the schedule. To avoid bacterial inactivation by gastric acidity, capsules are swallowed intact, making the vaccine unsuitable for young children. Antibiotics are avoided for 3 days before to 7 days after vaccination to avoid interference with response. Vaccination is repeated every 3 years.

The Vi capsular polysaccharide vaccine contains the purified Vi capsular antigen of *S. typhi* strain Ty2. Children older than 2 years, administered one vaccine dose, develop anti-Vi IgG antibodies with protective efficacy of 50–75%. Since polysaccharide vaccines lack memory responses, revaccination is essential every 3 years (Box 10.13). Two typhoid conjugate vaccines are approved for use in India and recommended by IAP for children >9 months old. Here, the Vi antigen is coupled to a carrier protein such as tetanus toxoid (PedaTyph® and Typbar-TCV®); vaccines

coupled to diphtheria toxoid or its mutant toxin CRM197 are not licensed in India. Conjugate vaccines are preferred to polysaccharide vaccine, since they generate strong anamnestic response and show prolonged immunological memory.

Varicella Vaccine

Varicella is a benign self-limiting illness, but complications are common in adults and in immunocompromised patients. Each dose of varicella vaccine has at least 1000 plaque-forming units of the live virus of Oka strain attenuated in human diploid cell culture. Both cellular and humoral immune responses are elicited, providing 95–99% protective efficacy. Following one dose, seroconversion is seen in 95% young children and 80% of those >12 years; two doses seroconvert 90% of the latter. If breakthrough infection occurs, it is usually a mild afebrile illness with a few lesions and predominance of papules over vesicles.

Box 10.13: Typhoid vaccines

	Vi capsular polysaccharide	Typhoid conjugate*	Live-attenuated Ty21a
Dose; route	0.5 mL; SC or IM	0.5 mL; IM	Oral; capsule
Site	Anterolateral thigh or deltoid	Anterolateral thigh or deltoid	Oral
Schedule			
National program	Not included	Not included	Not included
IAP 2016	(If conjugate vaccine not available) One dose at ≥2 years; repeat every 3 years	(Preferred) One dose at 9–12 months; one booster at 2 years	Not available; 3 doses in children who can't swallow (>6 years)
Catch up	One dose beyond 2 years	One dose, up to 18 years	Any age
Adverse reactions	Local pain, swelling, redness; fever	Local pain, swelling, redness; fever	Abdominal discomfort, fever
Contraindication	Anaphylaxis after previous dose	Anaphylaxis after previous dose	Immunodeficiency
Storage	2–8°C; do not freeze	2–8°C	2–8°C

*Ensure gap of 4 weeks between this and any measles containing vaccine

Varicella vaccine is not included in the National Immunization Program because the illness is not a public health priority, the vaccine is expensive, and high rates of immunization coverage are necessary to prevent an epidemiological shift to affect older individuals, causing severe disease. The IAP recommends the vaccine for children if it is afforded (Box 10.14). Two doses are recommended to reduce the risk of breakthrough infections with waning immunity. Internationally available monovalent preparations (Varilrix® and Variped®) and its combination with MMR (MMR-V, Priorix-Tetra®) show similar immunogenicity and efficacy. Other monovalent preparations (Nexipox®, Biovac-V® and Varivax®) are also immunogenic, but information on their efficacy is limited. Since MMR-V is associated with higher rate of adverse events (fever, rash, seizures) in patients 12–23 months old than MMR and varicella administered separately, the IAP cautions against the use of MMR-V in this age group; older patients may safely receive MMR-V.

Vaccination is indicated for the following high-risk groups: (i) chronic cardiac or lung disease; (ii) asymptomatic HIV infection with CD4 >15%; (iii) leukemia in remission and off chemotherapy >3 months; (iv) anticipated prolonged immunosuppression (before transplantation; periods off immunosuppression in nephrotic syndrome); (v) prolonged aspirin therapy (discontinue aspirin for 6 weeks after). Vaccination should also be considered for unimmunized household contacts of immunocompromised patients, and adolescents and adults without history of varicella, particularly in institutional settings (school, hospital or army). When recommended for post-exposure prophylaxis (within 72 hours of contact), its protective efficacy is ~70%.

Influenza Vaccine

Influenza virus has three antigenic types (A to C) and several subtypes based on the surface antigens hemagglutinin, and neuraminidase. Mutations due to antigenic drifts and shifts result in frequent changes in circulating strains. Influenza viruses (A, B) cause global flu epidemics with severe disease in young children, the

elderly and immunocompromised, and those with chronic illnesses. Since available vaccines elicit a strain-specific humoral response with protective efficacy of 30–90%, their composition is annually reviewed by the WHO for changes in component antigens.

Inactivated influenza vaccines: These tri- or quadrivalent vaccines, containing two influenza A and one or two influenza B strains, are derived from viruses grown in chick embryos or cell culture. Whole virus vaccines, associated with significant adverse effects, are no longer used. Current vaccines are either split product, produced from detergent-treated purified viruses, or surface antigen subunit vaccines, containing purified hemagglutinin and neuraminidase. These are highly immunogenic and associated with minimal adverse events. Newer virosome adjuvated vaccines stimulate strong antibody responses and activate Th1/Th2 and cytotoxic T cells. Inactivated vaccine is recommended in high-risk groups (Box 10.15).

Live-attenuated intranasal vaccine: These trivalent or quadrivalent vaccines are developed by repeated passage of viruses at low temperature, to form a temperature sensitive variant that grows well at 25°C but does not replicate at 37–39°C. The vaccine is recommended for healthy children older than 2 years, and is more immunogenic than the inactivated vaccines. Live vaccines are avoided in high-risk categories. Healthy children, >2-year-old, may receive either the live or inactivated vaccine. Following reports of unsatisfactory efficacy of the former, the WHO has recommended the use of only inactivated vaccines during 2016–2018.

Rabies Vaccine

India is endemic for rabies, accounting for 50% of global deaths. Nerve tissue vaccines are not recommended due to poor efficacy and high incidence of adverse effects. Tissue/cell culture vaccines are available as lyophilized preparations that are reconstituted to provide at least 2.5 IU per intramuscular dose, and include: (i) Purified duck embryo vaccine (Vaxirab); (ii) purified chick embryo cell vaccine (Rabipur, Vaxirab-N); (iii) human diploid cell vaccine (Rabivax); and (iv) purified Vero cell vaccine

Box 10.14: Varicella vaccine

Dose, route	0.5 mL, subcutaneously
Site	Anterolateral thigh or upper arm
Schedule	
National program	Not included
IAP 2016	All children, especially high-risk categories*: Two doses >3 months apart; preferably at 15–18 months (minimum 12 months)** and 4–6 years
Catch up	Complete two dose series with ≥3 months between doses (≥1 month if >12-year-old)**
Adverse reactions	Fever, rash, local pain or redness; mild rash after 2–3 weeks (5%)
Contraindications	Anaphylaxis after previous dose; lymphopenia; immunodeficiency; active leukemia or lymphoma; during immunosuppressive therapy
Storage	Freeze dried lyophilized; 2–8°C; protect from light; use within 30 minutes of reconstitution

*See text; **Avoid MMR-V if 12–23 months old or >12-year-old

Box 10.15: Influenza vaccines

	Inactivated vaccine	Live attenuated vaccine
Dose, route	<3 yr: 0.25 mL; ≥3 years: 0.5 mL; intramuscular	0.25 ml in each nostril
Site	Anterolateral thigh or upper arm	Intranasal using <i>Accuapray</i>
Schedule		
National program	Not included	Not included
WHO IAP 2016	Only in high-risk categories *First time vaccination: Two doses >4 weeks apart at 0.5–9 years; 1-dose if >9 years Annual revaccination with one dose, before rainy season	Healthy children aged 2–18 years First time vaccination: 1–2** doses >4 weeks apart at 2–9 years; 1-dose if >9 years Annual revaccination with one dose, before rainy season
Adverse reactions	Mild (10–35%): Local pain, fever, nausea Severe (rare): Anaphylaxis	Runny nose, headache, wheeze, myalgia, fever, sore throat, vomiting
Contraindication	Anaphylaxis after previous dose; <6 months old; use with caution if suspected egg allergy or Guillain-Barre syndrome	Severe allergy after any influenza vaccine; high risk categories*
Storage	2–8°C; do not freeze	2–8°C; do not freeze

*High-risk groups: (i) age 6–24 months; (ii) chronic cardiac or lung disease; (iii) asthma or wheeze during 2–4 years age; asthma requiring oral corticosteroid therapy; (iv) immunodeficiency; (v) sickle cell disease; (vi) diabetes mellitus; (vii) systemic lupus; and (viii) aspirin therapy.

**Annual WHO recommendation

(Indirab, Verorab, Abhayrab, Verovax-R). These vaccines have comparable efficacy and, since they lack myelin basic protein, are relatively safe.

Post-exposure prophylaxis: An animal bite/wound is characterized as follows: Category I: Animal touch or lick on intact skin; Category II: Minor scratches or abrasions without bleeding, licks on broken skin or nibbling of uncovered skin; and Category III: Single or multiple transdermal bites, abrasions that bleed, scratches or contamination of mucous membranes with saliva/licks. Individuals with category II or III wounds need wound management and rabies vaccine (Box 10.16). Patients with wound category III, and immunocompromised patients with wound category II, should also receive rabies immunoglobulin. *Patients who have received pre- or post-exposure prophylaxis with rabies vaccine in the past do not require immunoglobulin.*

Wound management includes immediate irrigation with running water for 10 minutes, thorough cleaning with soap and water, and application of povidone iodine, 70% alcohol or tincture iodine. Tetanus toxoid and antibiotics are administered as indicated. Wound suturing is avoided; if necessary, it is performed after administering immunoglobulin.

Rabies immunoglobulin provides passive immunity by neutralizing rabies viruses; dose is 20 U/kg for human immunoglobulin (ImogenRab, KamRab, BeriRab-P; maximum 1500 U) and 40 U/kg for equine preparations (anti-rabies serum, Equirab, Vinrig; maximum 3000 U). This is infiltrated in and around the wound as soon as possible and not later than day 7 of injury. For large or multiple wounds, immunoglobulin is diluted with normal saline to infiltrate the entire wounded region. Any

remaining immunoglobulin is administered intramuscularly at a site away from vaccination site, usually the deltoid or anterolateral thigh. Local tenderness and stiffness and fever are common. Currently available equine immunoglobulins are potent and overall safe, but adverse effects are common and usually require prior skin testing. While preferred, human immunoglobulin is expensive and not available readily.

Vaccination is usually planned using the *Essen* or *WHO schedule*, in which 5 doses are given on days 0, 3, 7, 14 and 28; an additional dose on day 90 is advised in immunocompromised or severely malnourished individuals. The Updated Thai Red Cross Schedule involves administering two intradermal doses each on days 0, 3, 7 and 30. Abbreviated and effective alternate schedules include: Zagreb (two IM doses on day 0; one dose each on days 7 and 14); abbreviated multisite (similar to Zagreb, except that last dose is on day 21), reduced four dose (IM dose on 0, 3, 7 and 14 days), and eight site (8 intradermal doses on day 0, four doses on day 7, and one each on day 28 and 90). Following re-exposure, patients who have previously completed pre-exposure prophylaxis should receive two doses on days 0 and 3.

Pre-exposure prophylaxis: This is offered to individuals at high risk of rabies, such as laboratory staff handling virus or infected material, care providers to patients with rabies, veterinarians, animal handlers and catchers, taxidermists, wildlife workers, wardens, quarantine officers, municipal workers, postmen and travelers to endemic areas. Three IM doses are given on days 0, 7 and 21 or 28. A booster dose is required after 1-yr and every 5 years thereafter; boosters are required annually, if using the intradermal schedule. Antibody titers are

Box 10.16: Rabies vaccine

Type	Modern tissue culture vaccine
Dose, route	Intramuscular: 1 mL (0.5 mL for purified Vero cell vaccine), or Intradermal*: 0.2 mL (0.1 mL for purified Vero cell vaccine)
Site	Deltoid or anterolateral thigh; never gluteal region
Schedule	
National program	Not recommended
WHO and IAP 2016	Pre-exposure: Preferably all children; days 0, 7 and 21/28 Post-exposure: After animal bites (see text)
Adverse reactions	Common: Local pain, swelling, induration (more with intradermal) Uncommon: Fever, malaise, abdominal pain, headache; hypersensitivity (seen with diploid cell vaccine)
Storage	2–8°C; use within 6 hours of reconstitution

*Licensed in India only for specific purified chick embryo or Vero cell vaccines, in centers with adequate training and frequent use of the vaccine

monitored 6–12 monthly and boosters given to maintain titer >0.5 U/mL.

Hepatitis A Vaccine

India is endemic for hepatitis A; 50% children are seropositive by 5 years of age, following infection usually with minor manifestations. Disease severity, complications and mortality are higher in adolescents, adults and children with underlying chronic liver disease. Two types of vaccines are available. Formalin inactivated viral vaccines usually have aluminium hydroxide or a virosome adjuvant. The vaccine is available either singly or in combination with hepatitis B. Two doses, administered 6–12 months apart, provide protective efficacy of 95%, if administered at >1 year age; maternal antibody may interfere with immune responses in infancy (Box 10.17). Two live vaccines are based on H2 and L-A-1 strains of hepatitis A virus, attenuated through repeated cell culture and grown on human diploid lung fibroblasts. A single dose of the vaccine is immunogenic and safe (Box 10.17).

While hepatitis A vaccination is not a public health priority, improving hygiene has resulted in increased age at infection, and serious infections including fulminant hepatic failure may occur. Hence, IAP recommends its

administration to all children. High-risk categories in which vaccination must be considered include: (i) patients with chronic liver disease; (ii) seronegative travelers to endemic areas; (iii) children attending crèches and daycare; (iv) seronegative adolescents; and (v) liver and kidney transplant recipients. The vaccine is effective as postexposure prophylaxis, if administered to unimmunized household or institutional contacts of symptomatic patients within 10 days of exposure.

Meningococcal Vaccine

Neisseria meningitidis accounts for 30–40% cases of bacterial meningitis in children, with high case fatality. Invasive infections are caused by serogroups A, B, C, Y and W135. While serogroup A (and sometimes C) cause epidemics, endemic disease in India is due to sero-group B. Two types of vaccines are available. Unconjugated vaccines contain group specific capsular polysaccharides, which are T cell independent, do not induce immunological memory and are poorly immunogenic below 2 years of age. These are available as bivalent (containing groups A and C) and tetravalent (groups A, C, Y and W135) vaccines. Conjugate vaccines are preferred over polysaccharide vaccines due to higher immunogenicity,

Box 10.17: Hepatitis A vaccine

	Inactivated vaccine	Live-attenuated vaccine
Dose, route	0.5 mL (720 U); intramuscular	0.5 mL; intramuscular
Site	Deltoid	Deltoid
Schedule		
National program	Not included	Not included
WHO; IAP 2016	>1 year: Two doses 6 months apart 1–10 years: As above >10 years: First confirm seronegative; adult dose (1440 U; 1 mL) for >13-year-old	>1 year: One dose of H2 strain As for inactivated vaccine
Catch up		
Adverse reactions	Local pain, headache, malaise	Soreness, erythema, fever, malaise
Contraindication	Anaphylaxis after previous dose	Hypersensitivity to egg protein; immunodeficiency, chemotherapy or radiotherapy
Storage	2–8°C; protect from light Use within 30 minutes of reconstitution	2–8°C; do not freeze Use within 30 minutes of reconstitution

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prolonged efficacy and potential for herd effect, especially in childhood. Two types of polysaccharide-protein conjugate vaccines are available in India (Box 10.18). The quadrivalent conjugated vaccine (groups A, C, Y and W135; Menactra®) uses diphtheria toxin as carrier protein, while the monovalent (serogroup A) vaccine uses tetanus toxoid as carrier protein.

Yellow Fever Vaccine

The yellow fever vaccine is a live-attenuated vaccine of either 17D-204 or 17DD strain that is effective against all known strains of yellow fever. Neutralizing antibodies develop in 90% vaccinees by 10 days and in 100% by 3 weeks, and persist for three decades. A single dose should be administered at least 10 days before planned travel to endemic areas (Africa; South or Central America). Adverse effects are common (Box 10.19); administration in young infants and pregnant women is avoided.

Combination Vaccines

A combination vaccine consists of multiple immunogens physically combined in a single preparation, including antigens or serotypes of the same pathogen (trivalent polio vaccine) or different pathogens (pentavalent or DTP

vaccines). This is distinct from simultaneous administration of multiple separate vaccines at the same time at separate sites. The immune system of an infant can respond to a large number of antigens simultaneously, and the efficacy of most vaccines is not altered by concurrent administration. With the requirement of vaccination against several infections, a child needs to be administered more than 20 antigens in the first 2 years. Combining vaccines have several benefits. Fewer injections at each visit and fewer visits increase compliance. The immunization program also benefits from decreased expenditure on packaging, storage and transportation and enhanced immunization coverage.

Development of combination vaccines is challenging. The antigens should be compatible and not interfere with each other's immunological 'take' (relevant for live viral vaccines) and be indicated at the same time. Some antigens may require an adjuvant to be present in the combination. The total volume of the vaccine should not be excessive and the product should be stable for at least a year. Their efficacy is evaluated and cost benefit analyses are done before licensing. Common combination vaccines include pentavalent, DTwP, DTaP, DT, dT, OPV, IPV, MMR, MR and influenza (Table 10.9).

Box 10.18: Meningococcal vaccine

	<i>Polysaccharide</i>	<i>Quadrivalent conjugate</i>
<i>Dose, route</i>	0.5 mL, subcutaneous or IM	0.5 mL, IM
<i>Site</i>	Anterolateral thigh or upper arm	Anterolateral thigh or upper arm
<i>Schedule</i>		
National program	Not included	Not included
IAP 2016	High-risk categories*; >2-year-old (>3 months old in outbreaks): One dose; repeat after 3–5 years, if required	High-risk categories*; >2 years old: One dose 9–23 months old (in USA, not licensed in India: Two doses 3 months apart)
<i>Adverse reactions</i>	Fever, local pain or redness	Local pain, swelling or redness; Guillain-Barre syndrome (rare)
<i>Contraindication</i>	Anaphylaxis after previous dose	May interfere with pneumococcal vaccine; separate administration by 4 weeks
<i>Storage</i>	2–8°C; protect from light Use within 30 minutes of reconstitution	2–8°C; do not freeze

*See text

Box 10.19: Yellow fever vaccine

<i>Dose, route</i>	0.5 mL, subcutaneous
<i>Site</i>	Anterolateral thigh or upper arm
<i>Schedule</i>	
National program	Not included
IAP 2016; WHO	Single dose ≥10 days before travel to endemic areas; revaccinate after 10 years
<i>Adverse reactions</i>	Mild (20–30%): Fever, headache and myalgia Severe (3–18/million doses): Hypersensitivity reactions; neurotropic, viscerotropic disease
<i>Contraindication</i>	Age <6 months; symptomatic HIV or CD4 <15%; radiation or chemotherapy; anaphylaxis after previous dose
<i>Precaution</i>	Age 6–9 months or >60 years; pregnancy and lactation; asymptomatic HIV or CD4 ≥15%; family history of vaccine-associated adverse effects
<i>Storage</i>	2–8°C; use within 30 minutes of reconstitution

Table 10.9: Combination vaccines for use in children and infants

Vaccine	Examples
DTwP-HB-Hib	Pentavalent vaccine; Pentavac PFS [®] , Comvac-5 [®] , ComBE Five [®] , Shan-5 [®] May combine in same syringe, e.g. Qvac [®] + HibPro [®] , Hiberix [®] + Tritanrix [®]
DTwP	Tripvac [®] , Triple antigen [®] , Comvac3 [®]
DTaP-HB-Hib	Easy-5 [®]
DTaP-Hib-IPV	Pentaxim [®]
DTaP	Infanrix [®] , Boostrix [®] , Tripacel [®]
Tdap	Boostrix [®] , Adacel [®]
DTwP-HB	Shantetra [®] , Q-VAC [®] , Tritanrix-HB [®] , Tripvac-HB [®] , Comvac-4-HB [®]
DTaP-Hib	May combine Tripacel [®] + ActHib [®] , Infanrix [®] + Hiberix [®]
DTwP-Hib	Easy-4 [®] , Quadrovox [®] , Shan-4 [®] , Tetract Hib [®] ; Triple antigen [®] + HibPro [®]
HepA-HepB	Twinrix [®]
MMR-V	Priorix tetra [®] , Proquad [®]
Meningococcal	A, C, Y and 135 (Mencevax ACWY [®]); A, C, Y and 135 DT conjugate (Menactra [®])
Pneumococcal	10 or 13-valent (Pneumovax [®]), 23-valent (Pneumo23 [®]), polyvalent polysaccharide (Pneumovax [®])

aP: Acellular pertussis; ap: Acellular pertussis reduced dose; D/DT: diphtheria toxoid; d/dT: Diphtheria toxoid reduced dose; HB: Hepatitis B; HepA: Hepatitis A; Hib: *Haemophilus influenzae* b; MMR: Measles, mumps, rubella; T/TT: Tetanus toxoid; V: Varicella; wP: Whole cell pertussis

Adverse Events following Vaccination

Untoward events after vaccination are categorized as follows:

- i. *Vaccine induced*: Event caused or precipitated by an active component of vaccine, e.g. anaphylaxis after measles vaccine, vaccine associated paralytic poliomyelitis, BCG related adenitis, pertussis encephalopathy
- ii. *Vaccine potentiated*: Event precipitated by vaccination but may have occurred without vaccination, e.g. first febrile seizure
- iii. *Injection reaction*: Event from anxiety, pain due to the injection (rather than the vaccine), e.g. syncope after vaccination
- iv. *Program error*: Event due to error in vaccine preparation, handling or administration, e.g. toxic shock syndrome due to contaminated measles vaccine, abscess at injection site; and
- iv. *Coincidental*: Temporally linked, by chance or due to unrelated illness, e.g. gastroenteritis after MMR injection.

Minor reactions are common, and include fever, irritability, malaise and pain, and swelling or redness at the injection site. These are self-limiting or settle following cold compresses and paracetamol. Strategies to reduce pain and anxiety include:

- i. Antipyretics

- ii. Distraction techniques (playing music, pretending to blow away the pain, deep breathing)
- iii. Breastfeeding or ingestion of sweet liquids during vaccination
- iv. Stroking skin near injection site
- v. Administering IM injections rapidly without aspiration; and
- iv. Topical analgesia (5% lidocaine or prilocaine emulsion or spray).

Older children are less anxious, if the procedure is explained, and by vaccinating in sitting rather than lying down position.

Immediate allergic reactions are rare and difficult to predict. Severe reactions (anaphylaxis) are usually caused by vaccine constituents, rather than by microbial contamination. While anaphylaxis is rare (1 per million doses) and may follow any vaccination, yellow fever, MMR and tetanus vaccines are most commonly implicated. Each patient must be observed for at least 15 minutes after vaccination. *Anaphylaxis might need to be differentiated from vasovagal reaction.* Components implicated in allergic reactions include:

- i. *Egg protein*: Yellow fever, measles, MMR, rabies PCEV, influenza (killed injectable and live-attenuated) vaccines
- ii. *Gelatin*: Influenza, measles, MMR, rabies, varicella, yellow fever and zoster vaccines
- iii. Latex in the vaccine vial stopper or syringe plunger
- iv. *Casein*: DTaP vaccine
- v. *Saccharomyces cerevisiae*: Hepatitis B, HPV vaccines.

Trace amounts of neomycin may cause allergic reactions. Thiomersal, aluminum and phenoxyethanol, added as preservatives, may cause delayed type hypersensitivity or contact dermatitis. The use of thiomersal, an organomercury compound with bacteriostatic properties, is being minimized due to risks of mercury toxicity.

Reportable events are:

- i. Anaphylaxis or anaphylactic shock ≤7 days
- ii. Adverse effects listed as contraindications to vaccination
- iii. Any serious or unusual event; and
- iv. Any sequelae of reportable events.

Vaccine-specific events include:

- i. *Oral polio*: Paralytic polio or vaccine strain polio within 1–6 months of vaccine administration
- ii. *Measles*: Thrombocytopenic purpura within 7–30 days; measles infection in an immunodeficient recipient ≤6 months
- iii. *Measles, mumps and/or rubella*: Encephalopathy or encephalitis <15 days
- iv. *Tetanus*: Brachial neuritis ≤28 days
- v. *Pertussis*: Encephalopathy or encephalitis ≤7 days
- vi. *Rotavirus*: Intussusception ≤30 days; and
- vii. *Rubella*: Chronic arthritis <6 weeks.

Table 10.12: Vaccination of previously unimmunized child

Visit	At evaluation	After 1 month	After 2 months	After 6 months
Age <7 years	BCG Oral polio virus DTwP/DTaP Hepatitis B	Oral polio virus DTwP/DTaP Hepatitis B	Oral poliovirus MMR (preferred)/ measles Typhoid	DTwP/DTaP Hepatitis B
Age >7 years	Tdap Hepatitis B	dT Hepatitis B	MMR Typhoid	dT (if <11 years) Hepatitis B

Table 10.13: Passive immunization

Infection	Target population	Dose
Normal human immunoglobulin		
Hepatitis A	Institutional outbreak; unimmunized contact of infected individual; travel to endemic area	0.02 mL/kg (3.2 mg/kg); repeat every 4 months, if travel is prolonged
Measles	Immunocompromised person; infant exposed to infection <6 days back	0.5 mL/kg (immunocompromised); 0.25 mL/kg (infant)
Specific (hyperimmune globulin)		
Hepatitis B	Newborn of HBsAg positive mother; percutaneous or mucosal exposure; sexual contact	0.06 mL/kg (32–48 IU/kg; maximum 2000 IU) within 7 days (preferably 48 hr) of exposure
Varicella	Newborn of infected mother with lesions noted <6 days of birth; infant <1-year-old; immunocompromised child exposed to infection <6 days back	12.5 (5–25) U/kg (maximum 625 units)
Rabies	Bite by rabid animal	20 units/kg
Tetanus	Wound/exposure in unimmunized or incompletely immunized individual; treatment of tetanus	250 units for prevention; 3000–6000 units for therapy
Antisera, antitoxin		
Diphtheria antitoxin	Susceptible contact	500–1000 units
Anti-tetanus serum (horse)	Wound/exposure in unimmunized or incompletely immunized	1500 units subcutaneous or IM
Rabies antiserum	Bite by potentially rabid animal	40 IU/kg

Lapsed immunization: Table 10.12 suggests schedules for children who have missed routine immunization. For vaccines with multiple doses, the entire schedule need not be repeated and only limited doses are given. The vaccination schedule for adolescents is discussed in Chapter 5.

Passive Immunization

Passive immunity is resistance based on antibodies, preformed in another host. Thus, preformed antibodies to varicella and hepatitis B can be injected during the incubation period to limit viral multiplication (Table 10.13). Normal human immunoglobulin serves the same purpose, if specific immunoglobulin is not available, e.g. to protect from hepatitis A or measles.

Suggested Reading

- AAP Red Book. Available at www.aapredbook.org/site/resources.

- CDC The Pink Book. <https://www.cdc.gov/vaccines/pubs/pinkbook/index.html>
- GOI. Immunization Handbook for Medical Officers. New Delhi: Department of Health and Family Welfare; 2016
- Guide to introducing Inactivated Poliomyelitis Vaccine based on the Polio Eradication & Endgame Strategic Plan 2013-2018. Available at http://www.who.int/immunization/diseases/poliomyelitis/endgame_objective2/inactivated_polio_vaccine/
- Indian Academy of Pediatrics, Advisory Committee on Vaccines and Immunization Practices (ACVIP). IAP recommended immunization schedule for children aged 0 through 18 years, 2016, and updates on immunization. Available at <http://www.acvip.org/files/IAP-immunization-schedule-2016-IP-2016-Epub.pdf>
- Mission Indradhanush. Available at <http://www.missionindradhanush.in/>
- National Immunization Schedule for infants, children and pregnant women. Available at <https://mohfw.gov.in/sites/default/files/245453521061489663873.pdf>

Infections and Infestations

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FEVER

Fever is a controlled increase in body temperature over the normal values for an individual. The normal body temperature in children is higher as compared to adults, and varies between 36.1 and 37.8°C (97–100°F) on rectal measurement. There is a normal diurnal variation in the body temperature; it is lowest between midnight and 6 am and maximum between 5 and 7 pm.

Measurement

The core body temperature can be measured at several sites including the oral cavity, axilla, rectum, ear canal and over the temporal artery. The rectal method is the most accurate method for measurement of temperature and fever is defined as rectal temperature of more than 38°C or 100.4°F. However, measurement of rectal temperature is not always possible in clinical practice. In children below the age of 4–5 years, axillary temperature may be used, if taken correctly. The axillary temperature is on an average 0.5–1°C or 1–2°F lower than the rectal temperature. Fever, if measured in the axilla, is defined as temperature more than 37.2°C or 99°F. In infants below the age of 3 months, if the axillary method shows fever, rectal temperatures should be measured to confirm fever. The oral temperature is on an average 0.5–1°F or 0.25–0.5°C lower than rectal temperature. Fever as measured in the oral cavity is defined as temperature more than 37.5°C or 99.5°F.

Mercury thermometers are no longer used in clinical practice. Electronic thermometers take only 30 seconds for recording temperature, are convenient to use, but are subject to calibration errors. The infrared thermometers used for measurement of ear/temporal artery temperatures are very quick and closely approximate rectal temperatures but are expensive. Forehead strip measurement of temperature is not accurate and not recommended.

Etiopathogenesis

Fever may be caused by multiple causes including infection, vaccines, biologic agents, tissue injury,

malignancy, drugs, autoimmune diseases, granulomatous diseases, metabolic disorders (gout) and genetic disorders such as familial Mediterranean fever. All these insults result in the production of endogenous pyrogens, such as interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)- α interferon- β , interferon- γ and lipid mediators such as prostaglandin E₂, which alter the temperature set point in the anterior hypothalamus leading to elevation in body temperature. In contrast to fever, the high body temperature in *heat illness* is due to increased heat production or reduced heat loss, with the hypothalamic set point being normal. Here, the core temperatures can rise to beyond 106°F. Common causes of heat illness are hyperthyroidism, anhidrotic ectodermal dysplasia, drugs such as anticholinergics and phenothiazines, heat stroke and malignant hyperthermia.

Evaluation of a Febrile Patient

Fever is a symptom and not a disease; hence, evaluation for cause is important. If temperatures are very high, heat illness should be suspected. The pattern of fever is generally not useful in arriving at a diagnosis since regular use of antipyretics has now become the norm. Presence of rigors is also not specific for malaria since they can be seen even in severe bacterial infections, abscesses, pyelonephritis and even viral infections such as influenza, periodic fevers (fever syndromes with regular periodicity) are seen in cyclic neutropenia, PFAPA syndrome (periodic fever, adenopathy, pharyngitis, aphthous ulcers) and other periodic fever syndromes such as familial Mediterranean fever and hyperimmunoglobulin (Ig) D syndromes. It is useful to classify fevers as short duration fevers and prolonged fevers as etiology and management strategies differ.

Management

Fever is a symptom and, therefore, treatment of the underlying cause is important. Treatment of fever *per se* may not always be needed. Fever has been shown to improve the immunologic response to certain infections in experimental models; whether this is clinically

significant is unknown. However, fever may be associated with adverse effects such as paradoxical suppression of immune response, increased insensible water losses, cardiopulmonary stress and triggering febrile seizures in predisposed patients.

Reduction of fever should be a priority in patients with past/family history of febrile seizures, those critically ill, those with cardiorespiratory failure, those with disturbed fluid and electrolyte balance, or with temperature exceeding 40°C (104°F). For the rest, treatment should be individualized; parental counseling is important.

The two commonly used drugs for antipyresis in children are paracetamol and ibuprofen. Other agents such as aspirin, nimesulide and mefenamic acid are associated with high incidence of adverse effects and are better avoided. Ibuprofen decreases fever at the same rate as paracetamol, the nadir with ibuprofen is slightly lower and duration of action is longer (6 hours) as compared to paracetamol (4 hours). However, the risk of side effects such as acute renal failure and gastrointestinal bleeding is theoretically higher with ibuprofen, though not substantiated by observational studies. Conversely, the consequences of paracetamol overdose (hepatic failure) are more sinister than those with ibuprofen. Considering all factors, it is reasonable to use paracetamol at a dose of 15 mg/kg every 4 hours (max. 5–6 doses/day) as the first-line drug for fever management. It is suggested to shift to ibuprofen in patients who do not adequately responded to paracetamol, at a dose of 10 mg/kg every 6 hours. There is some evidence to suggest a marginal benefit on amelioration of fever by combining paracetamol and ibuprofen as compared to using either drug alone. Tepid water sponging may be used as a complementary method to drug therapy in bringing down fever quickly in some children.

Heat illness is a medical emergency. The high temperatures can cause irreversible organ damage and should be brought down quickly. Since the hypothalamic set point is not altered, non-steroidal anti-inflammatory drugs, which act by reducing prostaglandin production, are ineffective. External cooling is needed with ice water sponging, cooling blankets, cold water enemas and gastric washes. At the same time, measures should be taken to correct the underlying condition.

Suggested Reading

- Lorin MI. Fever: pathogenesis and treatment. In: Feigin and Cherry's Textbook of Pediatric Infectious Diseases, 7th edn. Eds. Cherry J, Deonimier-Harrison GJ Kaplan SL, Steinbach WJ, Hotez PJ. Philadelphia, WB Saunders, 2013; 89–94.
- Crocetti M, Moghbeli N, Serwint J. Fever phobia revisited: Have parental misconceptions about fever changed in 20 years? *Pediatrics* 2001; 107:1241–6.

Short Duration Fevers

Short duration fevers lasting for less than 5–7 days are one of the most common reasons for pediatric outpatient

visits. The overwhelming majority are due to viral infections. Of greater concern are fevers without localizing signs/without focus in children below the age of 3 years (especially below 3 months) as they may indicate an underlying serious bacterial infection. Since *H. influenzae* and *S. pneumoniae* are important causes of serious bacterial infection, the algorithms suggested here may change with increasing immunization with *H. influenzae* and *S. pneumoniae* vaccines.

Fever without Focus In <1 Month

Fever in a neonate (<1 month of age) is generally a medical emergency. This is because of (i) 5–15% risk of serious bacterial infection such as sepsis, bacteremia, urinary tract infections, pneumonia, enteritis and bacterial meningitis, (ii) neonates may look well and still have serious bacterial infection and (iii) the implications of missing or delaying diagnosis of sepsis are serious.

Sometimes neonates get fever due to over clothing and warm weather ('dehydration fever') in which the baby looks well and active. This only warrants frequent feeding and nursing in less warm environment. The infant is kept under observation for other signs of sepsis and investigated if in doubt.

A detailed clinical assessment should be performed for a febrile neonate (Fig. 11.1). A toxic neonate is at high risk of serious bacterial infections and should be treated aggressively. The patient should be hospitalized to undergo a complete sepsis work up and administered antibiotics (3rd generation cephalosporin such as cefotaxime or ceftriaxone with or without an aminoglycoside) without awaiting the results of investigations. Other supportive therapy should be instituted, if required.

Management of a well appearing febrile neonate is controversial. If fever is thought to be due to over bundling then repeat temperature assessment should be done after 15–30 minutes. Most guidelines recommend hospitalization of well looking febrile infants less than 1 month of age as they may have serious infections. These infants

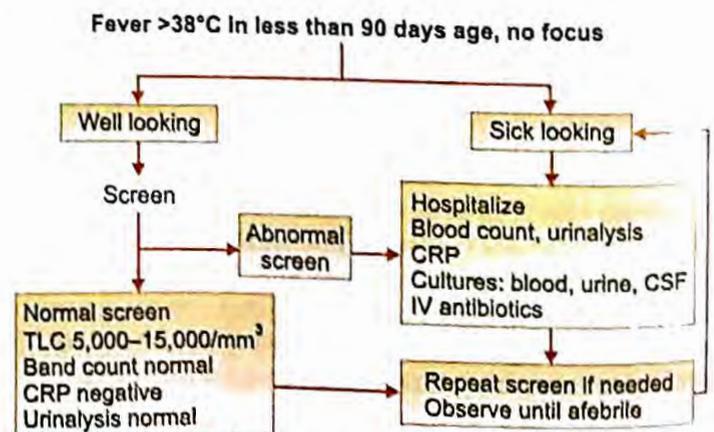


Fig. 11.1: Evaluation of fever in a patient less than 3 months old. CSF cerebrospinal fluid; TLC total leukocyte count; CRP C-reactive protein

should undergo basic evaluation including blood counts and C-reactive protein. Cultures should be sent if available. If the septic screen is positive, IV antibiotics should be started after doing a lumbar puncture and cerebrospinal fluid examination. If the screen is negative the baby should be observed, and a repeat screen sent 6–12 hours later. If repeat screen is also negative, observation of the neonate should continue till the baby is afebrile and culture reports are available. By this time, in most babies, the fever would have subsided or a focus would have developed.

Fever without Focus In Infants 1–3 Months Old

Infants in this age group like those aged less than 1 month are at high risk of serious bacterial disease (10%, with 2–3% risk of bacteremia). Also, they may look well and still have bacterial disease. The algorithm for management of these babies is fairly similar to those less than 1 month (Fig. 11.1). A detailed clinical assessment should be performed. A history of recent immunization should be obtained as fever may be related to the immunization.

All toxic/ill-appearing babies should be managed as an infant less than 1 month (discussed earlier). A well-looking infant 1–3 months of age should undergo a complete sepsis evaluation while in the outpatient department including leukocyte and platelet counts, band cell count, C-reactive protein, urinalysis, urine and blood cultures and if indicated smear for malarial parasite, and chest X-ray. CSF examination may be undertaken, if no other clue to focus of infection is found. If the screen is positive, the patient is hospitalized and treated with antibiotics. A well-looking infant with no clinical focus of infection and a negative screen (leukocyte count <15,000/cu mm, band count <20%, C-reactive protein negative, urine white cells <10/HPF) can be observed at home without antibiotics, provided the care takers are reliable and agree to bring the infant for reassessment 24 hours and 48 hours later.

Fever without Focus In Children Aged 3–36 Months

The risk of serious bacterial infections decreases with advancing age and in this age group it is 5%. A child presenting with fever without focus should be assessed completely. Detailed history is taken about vaccination, history of sick contacts in family and the condition of the child when fever is down. If the patient looks toxic, he should be hospitalized and undergo appropriate evaluation and treatment. In a non-toxic child with fever less than 39°C, one can merely observe. In children with fever more than 39°C, the risk of bacteremia is higher and it is recommended to do a leukocyte count and examine smear for malarial parasite. If the leukocyte count is >15,000/cu mm, blood culture should be sent and the patient administered IV ceftriaxone on either an inpatient or outpatient basis. A count less than 5000/cu mm should make one suspect viral infections, dengue and enteric

fever. If the count is less than 15,000/cu mm, observation is continued and if fever persists beyond 48 hours without development of a focus, a complete evaluation including complete blood counts, malarial parasite, C-reactive protein, urinalysis and blood culture is indicated.

Fever of Unknown Origin

Definition

The definition of fever of unknown origin (FUO) is fever >101°C lasting for 3 weeks or more for which no cause is apparent after 1 week of outpatient investigation. A practical definition of FUO is simply fever >101°F measured on several occasions over a 7-day period with normal preliminary investigations including at least complete blood counts, malarial smear, urinalysis and culture, blood culture, chest X-ray and ultrasound abdomen.

Causes

The principal causes of FUO are listed in Table 11.1; infections account for most causes (60–70%). Most common among infectious causes are enteric fever, malaria, pulmonary or extrapulmonary tuberculosis and urinary tract infections. Bacterial sinusitis may be a common cause of FUO even without the classical symptoms of upper respiratory infections. Malignancies including leukemia and lymphoma and autoimmune diseases chiefly systemic onset juvenile rheumatoid arthritis are important. Other causes include drug fever, temperature dysregulation, diabetes insipidus, sarcoidosis, ectodermal dysplasia and sensory autonomic neuropathies. Even with extensive investigations the cause of FUO remains undiagnosed in 10–20% of the cases.

Approach to FUO

The first step is to identify sick patients who need stabilization and urgent referral to a tertiary care centre. All attempts are made to reach an etiologic diagnosis. A detailed history is important, and includes:

- Whether and how fever was documented

Table 11.1: Causes of fever of unknown origin

Infectious causes

Enteric fever, malaria, urinary tract infections, tuberculosis, sinusitis, infectious mononucleosis, human immunodeficiency virus, rickettsial infections, hidden abscesses (liver, pelvic), mastoiditis, osteomyelitis, chronic meningitis, infective endocarditis, brucellosis, cytomegalovirus, toxoplasmosis, kala-azar

Autoimmune causes

Systemic onset juvenile rheumatoid arthritis, Kawasaki disease, systemic lupus erythematosus, inflammatory bowel disease, polyarteritis nodosa, Kikuchi disease

Malignant causes

Leukemia, lymphoma, hemophagocytic lymphohistiocytosis

- Duration and pattern of fever (distinguish from recurrent fever)
- Symptoms referable to all organ systems, weight loss
- History of recurrent infections, oral thrush; joint pain, rash, photosensitivity
- History of contact with tuberculosis and animals (brucellosis)
- Travel to endemic zones (kala-azar, rickettsia)
- Drug history particularly anticholinergics (drug fever)

History is followed by a complete physical examination.

Documentation of fever is necessary, followed by assessment of general activity, nutritional status and vitals. A head to toe examination, after removing all clothes, is vital. The physical examination should be repeated on daily basis as new findings may emerge that provide a clue to the etiology. One must keep Kawasaki disease in mind since diagnosis before the 10th day of fever is crucial to prevent coronary complications (Fig. 11.2).

Preliminary investigations, which should be done in all patients with FUO include complete blood counts, peripheral smear, malarial parasite, C-reactive protein, ESR, blood culture, Widal test, chest X-ray, tuberculin test, urinalysis and culture, liver function tests, serum creatinine and abdominal ultrasound. Specialized investigations are done, depending on clinical clues.

If a diagnosis is established on the basis of the above approach, appropriate treatment should be instituted. If no diagnosis is made, clinical reassessment and further investigations are merited. While second line investigations are being planned and executed, treatment with intravenous ceftriaxone may be considered as enteric fever is an important cause of FUO in our country, especially in those with negative clinical and preliminary investigations.

Second-line investigations include HIV ELISA, contrast enhanced CT of chest and abdomen, CT of the paranasal sinuses, 2D echocardiogram, complement level, antinuclear antibodies and rheumatoid factors, and if indicated bone marrow histology and cultures and tissue biopsies. Other serologic tests include brucella and Epstein-Barr virus serology and hepatitis B surface antigen. Tests that are of limited value include quantiferon gold and serology for *M. tuberculosis*.



Fig. 11.2: Kawasaki disease: (a) Red and cracked lips; (b) Palmar rash and swelling

It should be possible to make a diagnosis of the etiology of FUO in most cases. In a small number of cases, it may not be possible to arrive at the etiologic diagnosis. In such cases, periodic reassessments should be done as the disease may finally surface (e.g. lymphoma, systemic onset juvenile rheumatoid arthritis). Some cases of FUO may self-resolve over time. Empirical antitubercular therapy with four drugs for four weeks may be tried, if it is not possible to arrive at an etiologic diagnosis after exhaustive work up and if the patient is sick. *Empirical use of steroids should be avoided.*

Suggested Reading

- Antoon JW, Potisek NM, Lohr JA, Pediatric fever of unknown origin. *Pediatr Rev* 2015; 36:380–91.
- Chien YL. Clinical approach to fever of unknown origin in children. *J Microbiol Immunol Infect* 2017; 50:893–98.

Fever with Rash

Fever with rash is a common problem that might signify a serious disorder (dengue hemorrhagic fever, meningococemia) or conversely a minor drug allergy. There are a number of infectious and non-infectious causes of fever with rash (Table 11.2).

Evaluation

The most important factor that helps determine the etiology of an exanthematous febrile illness is the nature of rash. Rashes may be macular, maculopapular, vesicular,

Table 11.2: Common exanthematous illnesses seen in children*

Macular/ maculopapular rash

Measles, rubella, dengue, roseola infantum, erythema infectiosum, drug rash, infectious mononucleosis, chikungunya, HIV, adenoviral and enteroviral infections, *Mycoplasma pneumoniae*, secondary syphilis, brucellosis, scrub typhus, chronic hepatitis B, CMV, lupus, systemic JRA

Diffuse erythema with peeling or desquamation

Scarlet fever, **Stevens-Johnson syndrome, toxic epidermolysis, staphylococcal and streptococcal toxic shock syndrome, Kawasaki disease**

Vesicular rash

Varicella, herpes simplex, zoster, enteroviral infections (hand-foot-and-mouth disease), papulonecrotic TB

Petechial and/or purpuric rash

Meningococemia, dengue hemorrhagic fever, Indian spotted fever, gonococemia, hemorrhagic measles and chickenpox, cutaneous vasculitis, Henoch-Schönlein purpura

Urticarial rash

Scabies, cutaneous larva migrans, strongyloides, insect bites, pediculosis

Nodular rash

Molluscum contagiosum, disseminated histoplasmosis, cryptococcosis, erythema nodosum

*Common and serious conditions are in bold



Fig. 11.3: Diffuse erythematous rash in a patient with dengue

nodular, urticarial or purpuric (Table 11.2); overlap may occur with one etiology having varying presentations. Other factors that help in diagnosis are epidemiology, season, history of exposure, incubation period, age, vaccination status, prodromal symptoms and relation of rash with fever, distribution and progression of rash, involvement of mucous membranes and history of drug intake. Examination includes nature of the rash and distribution, involvement of palms and soles (dengue, Fig. 11.3; spotted fever; Kawasaki disease; Stevens-Johnson syndrome), involvement of mucous membranes, adenopathy, organomegaly and signs of meningeal irritation. Investigations that assist in diagnosis include complete blood counts, C-reactive protein, blood cultures and serology, and sometimes biopsy.

Management

All efforts are made to diagnose the serious entities first and institute treatment; a specific diagnosis is often not possible. In this situation, symptomatic therapy, close observation, explanation of danger signs to parents and staying away from school until the rash resolves is recommended. Often drugs and antibiotics are given to a child with fever and rash. Distinguishing this viral exanthem from drug-related rash is difficult; intense itching is common with the latter. Withholding the drug, symptomatic therapy and observation is recommended. Rechallenge with the medication may be permitted, if the rash was mild.

COMMON VIRAL INFECTIONS

Measles

Measles (rubeola) is a common and serious childhood exanthematous illness. Although immunization has led to remarkable reduction in mortality, measles is still estimated to cause 140,000 childhood deaths (2015), of which 50% occurred in India.

Etiopathogenesis

Measles is caused by an RNA virus belonging to the paramyxovirus family. The virus is transmitted by droplet spread from the secretions of the nose and throat usually 4 days before and 5 days after the rash. The disease is highly contagious with secondary attack rates in susceptible household contacts exceeding 90%. The portal of entry is the respiratory tract where the virus multiplies in the respiratory epithelium. Primary viremia occurs resulting in infection of the reticuloendothelial system followed by secondary viremia, which results in systemic symptoms. The incubation period is around 10 days.

Clinical Features

The disease is common in preschool children; infants are protected by transplacental antibodies, which decline by 9 months (hence the rationale for vaccination at this age). The prodromal phase is characterized by fever, rhinorrhea, conjunctival congestion and a dry hacking cough. Koplik spots, considered pathognomonic of measles, appear on the 2nd or 3rd day of the illness as gray/white grains of sand-like lesions with surrounding erythema opposite the lower second molars on the buccal mucosa. The rash usually appears on the fourth day with rise in fever as faint reddish macules behind the ears, along the hairline and on the posterior aspects of the cheeks (Fig. 11.4). The rash rapidly becomes maculopapular and spreads to the face, the neck, chest, arms, trunk, thighs and legs in that order over the next 2–3 days. It then starts fading in the same order that it appeared, and leaving behind branny desquamation and brownish discoloration that fades over the next 10 days.

Modified measles seen in partially immune individuals is a much milder and shorter illness. Hemorrhagic measles is characterized by a purpuric rash and bleeding from the nose, mouth or bowel.



Fig. 11.4: Conjunctival congestion and morbilliform rash of measles

Complications

Widespread mucosal damage and significant immunosuppression induced by measles account for the frequent complications seen with this viral infection. Complications are more frequent in the very young, the malnourished and the immunocompromised. The chief complications are otitis media and bacterial bronchopneumonia. The usual pathogens are pneumococcus, *Staphylococcus aureus* and sometimes gram-negative bacteria. Other respiratory complications include laryngitis, tracheitis, bronchitis, giant cell pneumonia, bronchiectasis and flaring of latent *M. tuberculosis* infection. Transient loss of tuberculin hypersensitivity is common following measles. Gastrointestinal complications include persistent diarrhea, appendicitis, hepatitis and ileocolitis. Measles can precipitate malnutrition and can cause noma or gangrene of the cheeks.

Acute encephalitis occurs in measles at a frequency of 1–2/1000 cases most commonly during the period of the rash, consequent to direct invasion of the brain. Post measles encephalitis occurs after recovery and is believed to be due to an immune mechanism, similar to other parainfectious/demyelinating encephalomyelitis. Measles is also responsible for the uniformly fatal subacute sclerosing panencephalitis (SSPE) seen several years after infection at a frequency of 1/100,000 cases.

Diagnosis

The diagnosis is clinical; it may be confirmed by estimating the levels of IgM antimeasles antibody that is present 3 days after the rash and persists for 1 month. Measles needs to be differentiated from other childhood exanthematous illnesses. The rash is milder and fever less prominent in rubella, enteroviral and adenoviral infections. In roseola infantum, the rash appears once fever disappears while in measles the fever increases with rash. In rickettsial infections, the face is spared which is always involved in measles. In meningococemia, the upper respiratory symptoms are absent and the rash rapidly becomes petechial. Drug rashes have history of antecedent drug intake. Kawasaki disease closely mimics measles; however, glossitis, cervical adenopathy, fissuring of lips, extreme irritability, edema of hands and desquamation are distinguishing clinical features.

Treatment

Treatment is supportive, comprising antipyretics, maintenance of hygiene, ensuring adequate fluid and caloric intake and humidification. Vitamin A reduces morbidity and mortality of measles and a single oral dose of 100,000 units below 1 year and 200,000 units over the age of 1 year is recommended. Complications should be managed appropriately.

Prevention

This is a preventable and potentially eradicable disease through immunization (Chapter 10).

Suggested Reading

- Measles position paper, 2017. www.who.int/immunization/policy World Health Organization.
- Measles vaccines: WHO position paper. *Wkly Epidemiol Rec* 2009;84 (35):349–60.
- Rota PA, Moss WJ, Takeda M, et al. Measles. *Nat Rev Dis Primers* 2016; doi:10.1038/nrdp.2016.49

Varicella (Chickenpox)

Chickenpox is a common childhood exanthematous illness. Though usually a mild self-limited illness, it can be a serious disease in neonates, immunocompromised patients, pregnant women and even healthy children and adults.

Etiopathogenesis

Chickenpox is caused by the varicella zoster virus, a DNA virus of the herpes virus family. The virus is present in respiratory secretions and the skin lesions of an affected child and is transmitted either by air-borne spread or through direct contact. The portal of entry is the respiratory tract. During the incubation period of 10–21 days, the virus replicates in the respiratory mucosa followed by viremic dissemination to skin and various organs. During the latter part of the incubation period, the virus is transported to the respiratory mucosa and leads to infectivity even prior to appearance of the rash. The period of infectivity lasts from 24–48 hours before the rash until all the vesicles are crusted (the scabs are not infective unlike smallpox). The disease is highly contagious with secondary attack rates of 80% among household contacts. Host immune response limits infection and promotes recovery. In immunocompromised children, unchecked replication and dissemination of virus leads to complications. VZV establishes lifelong latent infection in the sensory ganglia. Reactivation, especially during depressed immunity, leads to the dermatomal rash of herpes zoster.

Clinical Features

Chickenpox is rarely subclinical; though in some children, only a few lesions may be present. The peak age of disease is 5–10 years. The prodromal period is short with mild to moderate fever, malaise, headache and anorexia. The rash appears 24–48 hours after the prodromal symptoms as intensely pruritic erythematous macules first on the trunk. The rash rapidly spreads to the face and extremities while it evolves into papules, clear fluid-filled vesicles, clouded vesicles and then crusted vesicles (Fig. 11.5). Several crops of lesions appear and simultaneous presence of skin lesions in varying stages of evolution is a characteristic of varicella. The median number of lesions is around 300 but may vary from 10 to 1500. Systemic symptoms persist for 2–4 days after appearance of the rash. The rash lasts 3–7 days and leaves behind hypopigmented or hyperpigmented macules that persist for days to weeks. Scarring is unusual unless lesions are secondarily infected.



Fig. 11.5: The polymorphic rash of chickenpox

Complications

Secondary bacterial infections of the skin lesions may occasionally result in necrotizing fasciitis; usual organisms are *S. aureus* and *S. pyogenes*. Neurologic complications include meningoencephalitis, acute cerebellar ataxia, transverse myelitis, LGB syndrome and optic neuritis. Other complications include purpura fulminans due to antibodies against protein C, CNS vasculitis leading to stroke, autoimmune thrombocytopenic purpura, cold antibody-mediated immune hemolytic anemia and Reye syndrome.

The progressive varicella syndrome is a dreaded complication of chickenpox in the immunocompromised, neonates, pregnant women and sometimes even healthy children, adolescents and adults. This syndrome is characterized by continued development of lesions, hemorrhagic lesions, coagulopathy and visceral organ involvement including hepatitis, pneumonia and encephalitis; mortality rates are high despite therapy.

Chickenpox in pregnancy is associated with increased risk of severe disease in the mother. Congenital varicella syndrome may occur following infection in the first and second trimester at a frequency of 0.4–2% and is characterized by skin scarring, malformed extremities, cataracts and brain abnormalities (e.g. aplasia, calcifications). Finally, if the disease occurs in the mother 5 days before and 2 days after delivery, severe and often fatal neonatal disease may result.

Herpes zoster in children is characterized by a mild vesicular rash with dermatomal distribution; unlike adults pain is less and post-herpetic neuralgia unusual. The risk of herpes zoster is more in children who acquire chickenpox in infancy, those whose mothers developed varicella in the third trimester and in the immunocompromised.

Diagnosis

The diagnosis is clinical and usually not difficult. Chickenpox should be differentiated from other vesicular

exanthemata such as herpes simplex, enteroviral infections (hand-foot-and-mouth disease), insect bites and drug reactions. In atypical cases, the diagnosis is made on Tzanck smear of the lesions (showing multinucleated cells) and demonstration of anti-IgM antibodies to varicella.

Treatment

Management is symptomatic and includes antipyretics (aspirin is contraindicated due to risk of Reye syndrome and ibuprofen due to risk of necrotizing fasciitis), antipruritic agents and good hygiene. The child should not attend school until no new lesions appear and all lesions have crusted. Administration of oral acyclovir (20 mg/kg/dose four times a day for 5 days) within 24 hours of onset of rash in healthy children reduces the duration of rash by one day and lesions by 25%. There may be some benefit even if started within 24–48 hours of the rash but none beyond 48 hours. IV acyclovir (10 mg/kg every 8 hours for 14 days) is recommended for patients with complicated varicella and illness of any severity in high-risk patients such as neonates and immunocompromised children.

Prevention

Prevention against varicella with varicella vaccine and use of varicella zoster immune globulin (VZIG) for post-exposure prophylaxis are detailed in Chapter 10. VZIG is fairly expensive and not always available. Other options, which may be used are intravenous immunoglobulin and oral acyclovir.

Suggested Reading

- English R. Varicella. *Pediatr Rev* 2003;24:372–79.
- Gershon AA, Breuer J, Cohen JL, et al. Varicella zoster virus infections. *Nature Rev Dis Primers* 2015; 1: 15016; doi:10.1038/nrdp.2015.16.
- Wutzler P, Bonanni P, Burgess M, et al. Varicella vaccination—global experience. *Expert Rev Vaccines* 2017;16:833–843.

Infectious Mononucleosis

Infectious mononucleosis (IM), a syndrome characterized by fever, fatigue, sore throat and lymphadenopathy, is most often caused by a herpes virus, Epstein-Barr virus (EBV). Infectious mononucleosis-like illness can also be caused by toxoplasma, CMV, adenoviruses and primary HIV infection.

Epidemiology

The EBV virus, a DNA virus of the herpes virus family, is shed in oral secretions and transmitted by close intimate contact like kissing or exchange of saliva. The virus replicates in the oral epithelial cells then spreads to salivary glands travels in the B lymphocytes in the blood to the lymphoreticular system including lymph nodes, liver and spleen. The CD8 lymphocytes proliferate to check this replication of virus in the B lymphocytes and represent

the atypical lymphocytes seen in EBV infection. Like other herpes viruses, EBV establishes lifelong latent infection after the primary infection with frequent asymptomatic reactivations.

The epidemiology of IM is related to the age of primary acquisition of EBV infection. In developing countries, most EBV infection occurs in infancy and early childhood when it is either asymptomatic or similar to other childhood infections. For this reason, IM is uncommonly seen or reported in India. In developed countries, the age of acquisition of EBV infection shifts upwards and thus IM is seen more commonly.

Clinical Features

Symptomatic EBV infections in older children and adults are characterized by insidious onset with symptoms such as malaise, fatigue, fever, headache, nausea, sore throat, abdominal pain and myalgia. Examination shows pharyngeal inflammation with exudates and petechiae at the junction of soft and hard palate, generalized lymphadenopathy (cervical, less often axillary and inguinal), mild splenomegaly (50%) and hepatomegaly (10%). Maculopapular rashes are seen in 3–15% and in 30% of those who have received ampicillin or amoxicillin.

Complications are rare and include splenic rupture following minor trauma, airway obstruction due to enlargement of oropharyngeal lymphoid tissue, meningitis, seizures, ataxia, myocarditis, hemolytic anemia, thrombocytopenia, neutropenia, aplastic anemia, interstitial pneumonitis and pancreatitis.

Diagnosis

Most patients show leukocytosis and absolute lymphocytosis, with presence of atypical lymphocytes. The platelet counts are mildly low and hepatic transaminases elevated in 50% patients. The Paul-Bunnell test (heterophile antibody test) is used for screening. This test is based on agglutination of sheep/horse red cells by heterophile antibodies present in the serum of patients with EBV infection. This test may have false negative rates of 10% and remains positive for a few months to 2 years after infection. IgM antibody to viral capsid antigen (IgM VCA) is confirmatory for diagnosing acute infection.

IM should be differentiated from other causes of mononucleosis enumerated earlier, streptococcal pharyngitis and acute leukemia.

Treatment

Rest and symptomatic therapy are mainstays of management. Participation in strenuous activities and contact sports should be prohibited in the first 2–3 weeks of illness due to risk of splenic rupture. Treatment with prednisolone (1 mg/kg/day for 7 days) is advised for complications such as hemolytic anemia, airway obstruction, meningitis and thrombocytopenia with bleeding. Intranasal steroids may be used to relieve nasal obstruction caused by

enlarged adenoids. There is no clear role of acyclovir in treatment of EBV in the immunocompetent.

Other Manifestations of EBV Infections

EBV has oncogenic potential and has been causally associated with aggressive proliferative disorders such as virus associated hemophagocytic syndrome, oral hairy leukoplakia and lymphoid interstitial pneumonitis in patients with AIDS, nasopharyngeal carcinoma, Burkitt lymphoma, Hodgkin disease and tumors in immunocompromised patients (e.g. X-linked lymphoproliferative disease, leiomyosarcoma, CNS lymphoma).

Suggested Reading

- Dunmire SK, Verghese PS, Balfour HH JR. Epstein-Barr virus infection. *J Clin Virol* 2018;102:84–92.
- Stanfield BA, Luftig MA. Recent advances in understanding E-B virus. *F1000Res* 2017;6:386.

Roseola Infantum

Roseola infantum (exanthem subitum, sixth disease) is a common childhood exanthematous illness caused most commonly by a DNA human herpes virus-6 (HHV-6) and less commonly by HHV-7 and echovirus 16. HHV-6 and HHV-7 target the CD4 T cells and like other herpes viruses can remain latent in the body for several years after acute infection.

The peak age for roseola is between 6 months and 3 years. The prodromal period is characterized by upper respiratory signs such as rhinorrhea, pharyngeal inflammation, conjunctival redness, mild cervical and occipital adenopathy and sometimes palpebral edema. The classic clinical illness is heralded by high fever ranging from 38°C to 40°C associated with febrile seizures in 5–10% and lasting for 3–4 days. Fever declines abruptly and is followed by development of a rash within 12–24 hours. The rash is discrete erythematous and maculopapular which first appears on the trunk and then spreads to the face, neck and proximal extremities. It is nonpruritic, rarely becomes confluent and fades in 3–4 days. Infectiousness is low and outbreaks have not occurred. Roseola should be differentiated from childhood illnesses such as rubella, measles, enteroviruses and drug hypersensitivity. Treatment is symptomatic and prognosis excellent.

Suggested Reading

- Agut H, Bonnafous P, Gautheret-Dejean A. Update on infections with human herpes viruses 6A, 6B and 7. *Med Mal Infect* 2017;47:83–91.
- Stone RC, Micali GA, Schwartz RA. Roseola infantum and its causal human herpes viruses. *Int J Dermatol* 2014;53:397–403.

Erythema Infectiosum

Erythema infectiosum (fifth disease) is a common exanthematous illness of childhood caused by a small



Fig. 11.6: The "slapped cheek" rash of erythema infectiosum

DNA virus Parvovirus B19. This virus has tropism for cells of the erythroid lineage at the pronormoblast stage.

The peak age for erythema infectiosum is between 5–15 years. Transmission of infection is by the respiratory route and the incubation period is 4–28 days (mean 16–17 days). The prodromal phase is mild and consists of low-grade fever, headache and symptoms of mild upper respiratory tract infection. The characteristic rash first appears as erythematous flushing on the face in what is a slapped cheek appearance (Fig. 11.6). It spreads rapidly to trunk and proximal extremities as a diffuse erythematous macular rash that rapidly undergoes central clearing to give it a lacy or reticulated pattern. The rash gradually fades over a 1–3 weeks period. Complications include arthropathy, idiopathic thrombocytopenic purpura and aseptic meningitis. Fifth disease should be differentiated from measles, roseola, rubella and drug rash. Treatment is symptomatic.

Other serious manifestations of parvovirus B19 infection include arthralgia and arthropathy in adolescents and adults, transient aplastic crises in patients with chronic hemolytic anemia, chronic anemia, pancytopenia or marrow suppression, virus associated hemophagocytic syndrome in the immunocompromised, hydrops fetalis in pregnant women and rare episodes of myocarditis in healthy children and adults.

Suggested Reading

- Ramdass P, Mullick S, Farber HF. Viral skin diseases. *Prim Care* 2015; 42:517–67
- Servant-Delmas A, Morinet F. Update of the human parvovirus B 19 biology. *Transfus Clin Biol* 2016;23:5-12

Mumps

Mumps is an acute viral infection characterized by painful enlargement of salivary, most commonly the parotid glands. Mumps is caused by an RNA virus of genus Paramyxovirus; only one serotype is known.

Etiopathogenesis

Most cases occur between 5 and 15 years of age; infants are rarely affected due to the presence of transplacentally acquired maternal antibodies. Man is the only reservoir of infection; a carrier state does not exist. The incidence is high in winter and spring; infections occur by direct contact, airborne droplets and fomites contaminated by saliva and urine. The virus proliferates in the respiratory epithelium and enters the circulation; it then gets localized to the glandular and neural tissue. The virus has been isolated from saliva as long as 6 days before and 9 days after appearance of salivary gland swelling. Secondary infection rates vary from 40 to 80%. Mumps infection or immunization is believed to confer lifelong immunity.

Clinical Features

Following an incubation period of 2–4 weeks, the symptoms begin acutely with fever, malaise and headache. Mumps infection is characterized by unilateral or bilateral parotitis. This presents as earache, jaw tenderness while chewing, dryness of mouth and swelling at the angle of jaw. The ear lobe may appear to be pushed upwards and outwards. The defervescence and resolution takes about a week. Occasionally other salivary glands including the submaxillary and sublingual glands are affected.

The occurrence of epididymo-orchitis is common in adolescent boys or postpubertal men (unilateral in 85% cases) and occurs 1–2 weeks after parotitis. The testes are enlarged and tender. Some degree of atrophy develops in the affected testes; sterility is rare.

CNS involvement in the form of aseptic meningitis is seen in ~1–10% patients with parotitis. Recovery is generally uneventful. Mumps is one of the commonest causes of aseptic meningitis in children. The risk of encephalitis is between 0.02 and 0.3%, with satisfactory prognosis and of <2%. Other manifestations include auditory nerve damage with deafness, cerebellar ataxia, facial neuritis, transverse myelitis and Guillain-Barré syndrome. Uncommon presentations include pancreatitis (5% may trigger insulin-dependent diabetes mellitus), mastitis, oophoritis, nephritis and myocarditis.

Diagnosis

The diagnosis is based on clinical features. Serum amylase is elevated in almost 90% patients. The diagnosis may be confirmed by serum IgM ELISA. Mumps parotitis needs to be differentiated from suppurative parotitis, submandibular lymphadenitis, juvenile parotitis, calculus in Stensen duct and other infectious causes, e.g. coxsackie A and cytomegalovirus.

Treatment

Symptomatic treatment is given in the form of antipyretics and warm saline mouthwashes. Orchitis is treated by bed rest and local support. Aseptic meningitis responds well

to mannitol. Steroids may be used for symptomatic relief of orchitis and arthritis but do not alter the course of disease.

Prevention

The affected patient should be isolated until the parotid swelling has subsided. Mumps can be prevented by timely immunization (Chapter 10).

Suggested Reading

- Bockelmans C, Frawley TC, Long B, Koyfman A. Mumps: An emergency medicine focused update. *J Emerg Med* 2018;54:207–14.
- Center for Disease Control and Prevention, Mumps cases and outbreaks. www.cdc.gov, 2018.

Poliomyelitis

The polioviruses belong to the genus Enterovirus in the family Picornaviridae and comprise three serotypes: Types 1, 2 and 3, all of which can cause paralysis. Type 1 is most frequently responsible for the illness; type 2 is rarely involved.

Epidemiology

Poliomyelitis was a significant cause of childhood morbidity and mortality with a reported 350,000 cases in 1988. The Global Polio Eradication initiative was launched in 1988 using oral polio vaccine (OPV) as the eradication tool and employing a four pronged strategy comprising maintaining high routine immunization coverage, supplementary immunization activities, AFP surveillance and outbreak response immunization. The initiative was hugely successful with reduction of polio cases from 350,000 in 1988 to 37 reported cases in 2016. Paralysis due to polio virus type 2 has not been seen since 1999. The last wild polio case was reported from India on 13 January 2011 and India and the WHO South East Asia region has been certified polio free from 27 March 2014. Endemic transmission continues in Pakistan, Afghanistan and Nigeria. Patients with vaccine associated paralytic polio (VAPP) and paralysis associated with circulating vaccine derived polio virus (cVDPV) are reported. It is also realized that unlike smallpox vaccination, immunization against polio cannot stop. The WHO has thus launched the "Polio Eradication and End Game Strategic Plan 2013–2019" which entails a switch from trivalent to bivalent polio vaccine along with introduction of inactivated polio vaccine in the national immunization programs. The ultimate aim is to stop use of the oral polio vaccine altogether.

Etiopathogenesis

The virus is transmitted by both the feco-oral route (especially in developing countries where hygiene and sanitation is poor) and through the oral-pharyngeal route through droplet nuclei (in industrialized countries and during outbreaks). On average, the incubation period of the disease is 7–10 days (range 4–35 days).

Clinical Features

In 90–95% of infected individuals, poliovirus infection is inapparent. In the remaining 5–10% of individuals infected by poliovirus, one of the following syndromes may occur.

Abortive polio occurs in 4–8% of infections and is characterized by a minor illness with low grade fever, sore throat, vomiting, abdominal pain, loss of appetite and malaise. Recovery is rapid and complete; there is no paralysis.

Non-paralytic aseptic meningitis occurs in 1–2% infections, with headache, and neck, back and leg stiffness several days after illness similar to abortive polio. Recovery occurs by 2–10 days.

Paralytic poliomyelitis occurs in 0.5–1% infections. Symptoms occur in two phases, minor and major, separated by several days without symptoms. The minor phase consists of symptoms similar to those of abortive poliomyelitis. The major phase of illness begins with muscle pain, spasms and the return of fever. This is followed by rapid onset of flaccid paralysis that is usually complete within 72 hours.

Spinal paralytic poliomyelitis is severe with quadriplegia and paralysis of the trunk, abdominal and thoracic muscles. Affected muscles are floppy and reflexes are diminished. The sense of pain and touch are normal. Paralysis is asymmetrical, affecting legs more often than arms; weakness begins proximally and progresses to involve distal muscle groups (descending paralysis). *Bulbar polio* accounts for 2% cases and results from a cranial nerve lesion, resulting in respiratory insufficiency and difficulty in swallowing, eating or speaking. *Bulbospinal polio* is seen in ~20% and is a combination of spinal paralytic and bulbar polio.

Depending on the strain of poliovirus, the ratio between subclinical and clinical infections is estimated to range between 100:1 and 1000:1. Older children and adults run a greater risk of developing paralytic illness. The case fatality rate ranges between 2 and 20% among persons who develop the paralytic form of the disease. If there is bulbar or respiratory involvement, the case fatality rate approaches 40%.

Residual Paralysis

As the acute phase of illness (0–4 weeks) subsides, the recovery begins in paralyzed muscles. The extent of recovery is variable ranging from mild to severe residual paresis at 60 days, depending upon the extent of damage caused to the neurons by the virus. Maximum neurological recovery takes place in the first 6 months of the illness; slow recovery continues up to two years. After two years, no more recovery is expected and the child is said to have *postpolio residual paralysis*, which persists throughout life.

Diagnosis

The diagnosis is based on history and characteristic clinical features of asymmetric flaccid paralysis. *Stool examination* is recommended in every case of acute flaccid paralysis (AFP). Virus can be detected from onset to 8 or more weeks after paralysis; the highest probability of detection being in the first 2 weeks after onset of paralysis. Examination of *cerebrospinal fluid* (cell count, Gram stain, protein and glucose) is useful in eliminating other conditions that cause AFP. Current *serologic tests* cannot differentiate between wild and vaccine virus strains. Collection of blood specimens for culture or serology is not recommended.

Differential Diagnosis

It is not possible to clinically differentiate between wild and vaccine-associated paralytic polio (VAPP). The two diseases most commonly confused with polio are Guillain-Barré syndrome and transverse myelitis. Other conditions with a presentation similar to those of paralytic polio-myelitis include traumatic neuritis, rabies, meningitis/encephalitis, and illnesses due to toxins (diphtheria, botulism) (Chapter 19).

Treatment

Treatment should be early and appropriate to the stage and degree of paralysis. Children with bulbo-spinal polio and respiratory paralysis require hospitalization. Children with isolated limb paralysis can be managed at home. As the acute phase of illness subsides, recovery in muscle power is helped by physiotherapy, ambulation and prevention of deformities. Some children require orthosis at some stage for ambulation. Others with fixed deformities and contractures require orthopedic intervention.

Prevention

The available vaccines and the recommended schedule are discussed in Chapter 10.

Suggested Reading

- Polio Global Eradication Initiative. www.polioeradication.org
- World Health Organization. Poliomyelitis. www.who.int

Hand-Foot-and-Mouth Disease (HFMD)

HFMD is a common viral illness affecting primarily children below the age of 5 years. The illness is caused by viruses of the enterovirus genus, belonging to family Picornaviridae. This genus includes other infection causing viruses, including poliovirus, ECHO virus, Coxsackie virus and enteroviruses. Though many viruses can cause HFMD, Coxsackie virus A16 and enterovirus 71 are the most common. The disease commonly presents as outbreaks often in preschools and transmission is by direct contact with an affected patient or infected fomites.



Fig. 11.7: Vesicular rash of hand-foot-and-mouth disease

Clinical Features

The onset is with a prodrome characterized by low grade fever, feeling of being unwell, sore throat. This is followed by development of ulcers/ blisters in the oral cavity mostly on the posterior aspect, papulovesicular skin rash on the palms and soles and less commonly on buttocks, knees, elbows and genital area (Fig. 11.7). All manifestations may not be present in all patients. The illness resolves quickly over the 4–5 days in most patients.

Complications include loss of toe nails or finger nails 4 weeks after onset of disease which is temporary. Rare complications include aseptic meningitis, encephalitis, polio-like paralysis, myocarditis and respiratory distress syndrome. Mortality is reported in HFMD outbreaks particularly due to enterovirus 71 with neurologic complications, from China, Vietnam, Taiwan and Malaysia. Some experts believe that HFMD enteroviruses are occupying the ecologic niche created by eradication of polioviruses.

Diagnosis

Diagnosis is clinical and the disease should be differentiated from other illnesses causing oral ulcers such as herpangina, herpetic gingivostomatitis and aphthous ulcers and also from chicken pox and insect bite allergy.

Treatment and Prevention

Treatment is symptomatic with analgesics and soft diet. Isolation of affected children at home and promotion of hand hygiene is important. There is no vaccine available against HFMD.

Suggested Reading

- Hand-foot-and-mouth disease. www.mayoclinic.org
- Koh WM, Badaruddin H, La H, et al. Severity and burden of hand-foot-and-mouth disease in Asia. *BMJ Glob Health* 2018; 3(1): e000442

Viral Hepatitis

Hepatitis is a general term meaning inflammation of the liver and can be caused by a variety of different hepatotropic viruses such as hepatitis A, B, C, D and E. Hepatitis A and E are responsible for most of the waterborne (community acquired) hepatitis, while B, C and D are responsible for post-transfusion hepatitis. Since a considerable number of cases of both post-transfusion and community-acquired hepatitis are not identified as being caused by hepatitis A-E, investigators have sought to identify other potentially hepatotropic viral agents, including hepatitis G virus, TT virus and SEN virus.

Hepatitis A

Hepatitis A is caused by infection with the hepatitis A virus (HAV), a nonenveloped RNA virus. In humans, a single serotype of HAV exists. HAV infection induces lifelong protection against reinfection. HAV is extremely resistant to degradation by environmental conditions, a property that allows its maintenance and spread within populations. It is spread via the fecal oral route through contaminated food and water, and person-to-person spread under poor sanitary conditions. The severity of the disease increases with age at time of infection. In children below age 5, infection is asymptomatic or presents as an acute undifferentiated febrile illness. Classic hepatitis is seen in older children, adolescents and adults. Hence in developing countries with poor environmental hygienic conditions where most are infected in childhood, symptomatic disease is less common and outbreaks rare. India is a country with intermediate endemicity, a subset of population which is of good socioeconomic status escapes natural infection in childhood and gets symptomatic disease as adults.

Clinical Features

The incubation period ranges from 10 to 50 days (median 30 days), during which the patient remains asymptomatic despite active replication of the virus. Thereafter, there is a short prodromal phase lasting for up to a week characterized by symptoms like loss of appetite, fatigue, abdominal pain, nausea and vomiting, fever, diarrhea, dark urine and pale stools. In older patients, this prodromal phase is followed by an *icteric phase*, during which jaundice develops at total bilirubin levels exceeding 2–4 mg/dL and liver enzymes in hundreds/thousands. The icteric phase generally begins within 10 days of the initial symptoms. Fever improves after the first few days of jaundice. During the next few weeks in the *convalescent period*, patient shows complete recovery.

In around 0.1 to 1% of patients, extensive necrosis of the liver occurs during the first 6–8 weeks of illness. In this case, high fever, marked abdominal pain, vomiting, jaundice and the development of hepatic encephalopathy associated with coma and seizures occur. These are the

signs of fulminant hepatitis, which is more common as age advances and leads to death in 70–90% of the patients. In patients who survive, neither functional nor pathologic sequelae are common despite the widespread necrosis. Infection with HAV does not lead to chronic or persistent hepatitis. In some patients, there is a prolonged febrile cholestatic phase and some patients have a relapsing pattern.

Diagnosis

Laboratory evaluation of liver function includes estimation of total and direct bilirubin, transaminases, alkaline phosphatase, prothrombin time, total protein and albumin. The specific diagnosis of acute hepatitis A is made by finding anti-HAV IgM in the serum. Anti-HAV IgM is detectable about 3 weeks after exposure, always by the time symptoms occur, its titer increases over 4 to 6 weeks, then decline to non-detectable levels within 6 months of infection. As IgG anti-HAV persists lifelong after acute infection, detection of IgG anti-HAV alone indicates past infection.

Hepatitis A needs to be differentiated from other viral hepatitis chiefly E, and sometimes also from Wilson disease and autoimmune hepatitis.

Treatment

Therapy is supportive and is aimed at maintaining adequate nutrition. There is no evidence to suggest that restriction of fats has any beneficial effect on the course of the disease. Eggs, milk and butter actually help provide a correct caloric intake. Antiviral agents have no role because the hepatic injury appears to be immunopathologically mediated. Referral to a liver transplant centre is appropriate for patients with fulminant hepatitis. Steroids are sometimes indicated in patients with cholestatic/relapsing hepatitis.

Prevention

The ideal preventive strategy is improvement in sanitation, hygiene and water supply. Immunization is very effective (Chapter 10). Immunoglobulin G may be used for postexposure prophylaxis. If administered within 2 weeks of exposure, it either prevents development of disease or reduces its severity.

Suggested Reading

- Mathur P, Arora NK. Epidemiological transition of hepatitis A in India: issues for vaccination in developing countries. *Indian J Med Res* 2008; 128:699–704.
- Satsangi S, Chawla YK. Viral hepatitis: Indian scenario. *Med J Armed Forces India* 2016; 72:204–10.

Hepatitis B

Hepatitis B virus is a 3.2 Kb, circular, partially double stranded DNA virus containing 3200 nucleotides coding for core protein (HBcAg), precore protein (HBcAg), envelope glycoprotein (HBsAg), a DNA polymerase with

reverse transcriptase activity and the HBV-X protein that acts as a transcriptional activator for many host and viral genes and may have a role to play in hepatocellular carcinoma.

Epidemiology

It is estimated that 250 million people are living with hepatitis B infection worldwide; the illness resulted in approximately 887,000 deaths (2015) from cirrhosis and hepatocellular carcinoma. Global prevalence of HBV infection varies from 0.7% in the Americas region, 2% in South East Asia and 6% in Africa; carrier rates in India ~2–3%. HBV is transmitted through contact with blood and body fluids of an infected person. In highly endemic areas, HBV infections occur mainly due to perinatal transmission from carrier mothers to their infants or less commonly through horizontal transmission resulting from casual contact with infected children during first 5 years of life. It is estimated that in the absence of prophylaxis, 70–90% of HBsAg and HBeAg positive mothers will transmit infection as against only 10–40% of HBsAg positive but HBeAg negative mothers. HBV is not transmitted by breastfeeding. Other routes of transmission are unsafe injections, drug abuse, tattooing, medical procedures including dialysis and sexual transmission.

Pathogenesis and Clinical Features

It is estimated that 90% of perinatally infected children become chronic carriers, compared to 30–50% of those infected in childhood and 5% of those infected in adulthood. Perinatally infected children are usually asymptomatic. Most of them have high levels of viral replication in the liver with high levels of HBV DNA and HBeAg but normal liver enzymes and no clinical symptoms. This is called the *immunotolerant phase*. In the second and third decade of life, the phase of immune tolerance converts to a phase of *immune clearance* wherein there is immune-mediated destruction of the virus infected cells leading to abrupt increase in liver enzymes and less commonly symptoms of hepatitis and rarely hepatic decompensation. In some this immune clearance is associated with loss of HBeAg and development of anti-HBe antibody and later clearance of HBsAg (0.6% of infected children per year) (Fig. 11.8). In most cases, this phase is associated with only temporary loss of HBeAg and clearance of HBV DNA with return of antigenemia. Several such episodes may occur over the years with development of chronic hepatitis and later cirrhosis and hepatocellular carcinoma (HCC). In children infected in early childhood, the initial phase is of active replication, followed by non-replication and remission of disease or progression to chronic liver disease and HCC.

Treatment

The short-term goals of therapy are to enhance the activity of the immune system to fight the virus, prevent viral

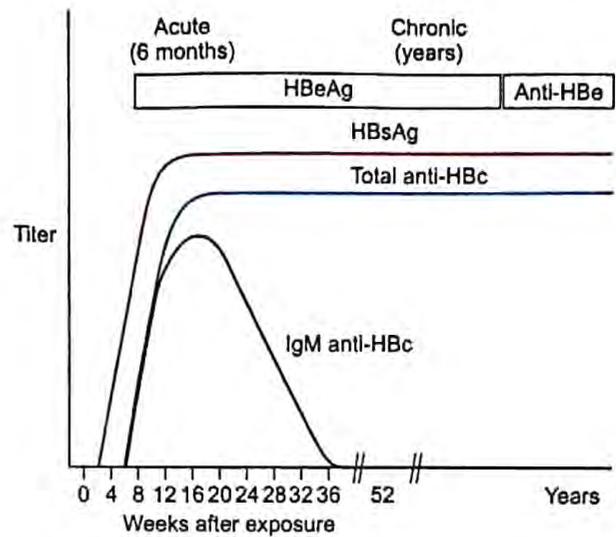


Fig. 11.8: Progression to chronic hepatitis B virus infection

replication leading to undetectable viral load, halt liver damage, achieve clearance of HBeAg and finally HBsAg, development of anti-HBeAb and anti-HBsAb so that long-term complications of cirrhosis and HCC are prevented. It is generally agreed that treatment should be initiated and is effective only when there is rise in the ALT levels to at least two times normal and evidence of liver disease on biopsy. Treatment rarely succeeds in the immunotolerant phase. There are two primary agents for therapy of chronic hepatitis B in children: Interferon (IFN) or lamivudine.

Interferons are a group of naturally occurring agents with antiviral, antineoplastic and immunomodulatory properties. Standard interferon is administered as thrice weekly injections for 6 months. Studies indicate that almost 30% lose HBeAg and halt liver damage with treatment and 90% of these continue to be HBsAg negative over 4–8 years follow-up. Antiviral resistance does not occur. The main limitations are treatment related side effects such as flu-like symptoms, headache, depression, loss of appetite, anemia, leukopenia and thrombocytopenia. Promising results are emerging using pegylated IFN in adults with chronic hepatitis B, but data in children are lacking.

Oral lamivudine is more convenient to take with fewer side effects and is usually prescribed for 1 year to begin with. There is reduction in liver damage with loss of HBeAg but limitations are relapse of viremia and antigenemia on stopping therapy and high incidence of development of YMDD mutants (10–30% after 1 year and 60–70% after 5 years).

Combinations of either INF- α 2a or INF- α 2b with lamivudine have comparable effects and slightly better results than monotherapy in children affected by chronic hepatitis. Other drugs recently approved for HBV infection in children include adefovir (above 12 years), entecavir

(above 16 years), telbivudine (above 16 years) and more recently tenofovir (above 12 years) (*see* Chapter 12).

Immunoprophylaxis

Hepatitis B immunoglobulin (HBIG) is used in the post-exposure prophylaxis of newborns of HBV-infected women. It is administered intramuscularly as soon as possible after birth and should be given concurrently with HBV vaccine, at a different site. The dose for infants is 0.5 mL. Combination of HBIG and HBV vaccination in infants born to HBsAg positive mothers prevents transmission in approximately 95% of those at risk (*see* Chapter 10).

Suggested Reading

- Nelson NP, Easterbrook PJ, McMahan BJ. Epidemiology of hepatitis B virus infections and impact of vaccination on disease. *Clin Liver Dis* 2016; 20:607–28.

Hepatitis D

Hepatitis delta virus (HDV) was first detected as a new nuclear antigen in the hepatocytes of patients infected with hepatitis B virus (HBV) and was frequently associated with severe acute or chronic hepatitis. Transmission of HDV requires either co-infection with HBV or superinfection in individuals who are HBV carriers. Although HDV infection is closely associated with HBV, HDV clearly belongs to a distinct virus group. Currently, HDV is assigned a floating genus, Deltavirus.

Hepatitis C

Hepatitis C virus (HCV) was recognized in 1989 as a major cause of non-A, non-B hepatitis. HCV is an enveloped, single-stranded, positive-sense ribonucleic acid (RNA) virus, classified as an independent genus (*Hepacivirus*) within the Flavivirus family.

Viral Variants

The HCV RNA-dependent RNA polymerase lacks proof-reading ability, which results in HCV being genetically heterogeneous. Based on analysis of HCV sequences, six major HCV genotypes are recognized. HCV genotypes 1 and 2 are the most prevalent worldwide. HCV genotype 3 is most common in Australia and the Indian subcontinent. The viral genotypic distribution in children generally parallel that reported regionally in adults. HCV genotype 1 correlates with higher serum viral levels and a less favorable response to antiviral treatment.

Epidemiology

The worldwide prevalence of HCV infection is approximately 3%, which represents an estimated 170 million infected persons. Infection occurs due to contact with blood and body fluids of infected people. The primary modes of infection in children are vertical transmission from infected mothers (rates ranging from 2 to 10% depending on the level of maternal viremia and

coinfection with HIV) and receipt of blood transfusions prior to the period when HCV testing became routine. HCV is not transmitted by breastfeeding. Transmission by unsafe injections, drug abuse, tattooing are other routes for disease transmission. Unlike HBV, HCV is not transmitted to household contacts and sexual transmission is infrequent.

Clinical Features

In adults, 85% of patients exposed to HCV will develop chronic infection, of which approximately 10–20% develops cirrhosis and some hepatocellular carcinoma. Chronic HCV is a common indication for liver transplant in the developed nations. However, the prognosis of childhood HCV infection is generally good. A significant percentage (~40%) of vertically infected children spontaneously clears HCV over a few years. The rate of spontaneous clearance reduces as age of acquisition of infection advances. Even chronically infected children remain asymptomatic; most have normal liver enzymes and a few changes on liver biopsy. Progression to chronic disease, hepatic failure and carcinoma are rare in children.

Diagnosis

The diagnosis of HCV infection is based on detection of antibodies against recombinant HCV antigens by enzyme immunoassay or rapid immunoblot assays or by detection of HCV RNA using nucleic acid tests. Enzyme immunoassays are fairly sensitive but less specific especially with false positive results in patients with elevated globulin levels such as those with autoimmune hepatitis. Recombinant immunoblot/immunochromatographic assays are less sensitive but more specific than enzyme immunoassay in detecting anti-HCV antibodies. Hence the EIAs are recommended as screening tests and the recombinant immunoblot assay as confirmatory tests. Patients with positive EIA and negative immunoblot assays are labeled as indeterminate and repeating tests after 4–6 weeks in such a setting is recommended. Antibodies against HCV are non protective and may last for life even if the patient has cleared HCV from the body. Diagnosis of perinatal infection, early infection (in the first 4–8 weeks) or active infection is by performing the HCV RNA PCR.

Therapy

Most childhood HCV infections do not need specific therapy. Treatment is indicated only in children with persistently elevated liver enzymes and abnormalities on liver biopsy. Standard treatment in these children includes interferon 2 α (preferably pegylated) with or without ribavirin for 24–48 weeks depending on the genotype. A number of new anti-viral medications (sofosbuvir, velpatasvir, ledipasvir, simprevir) have been approved for use in patients with hepatitis C, including those with compensated cirrhosis, HIV co-infection or severe kidney disease (*see* Chapter 12).

Suggested Reading

- NASPGHAN Practice Guidelines: Diagnosis and management of hepatitis C infection in infants, children, and adolescents. *JPGN* 2012; 54:838–55.

Hepatitis E

Hepatitis E virus was first described in 1978 after an epidemic affecting 52,000 individuals in Kashmir. Hepatitis E is caused by infection with the hepatitis E virus (HEV), a single-stranded RNA virus. Just like HAV, HEV is transmitted via the fecal oral route. It is usually transmitted through contaminated drinking water. Hepatitis E virus causes acute sporadic and epidemic viral hepatitis. Symptomatic HEV infection is most common in young adults aged 15–40 years and is uncommon in children where it is mostly asymptomatic and anicteric.

Clinical Features

The incubation period following exposure to HEV ranges from 3 to 8 weeks, with a mean of 40 days. The clinical presentation of hepatitis E is similar to hepatitis A. The severity of an HEV infection is generally greater than the severity of an HAV infection. In pregnant women, the disease is particularly severe where mortality approaches 20% with infections in the third trimester. Premature deliveries with high infant mortality up to 33% are observed. Chronic hepatitis E infection has been described in immunocompromised hosts.

Diagnosis

Laboratory evaluation of HEV is similar to that of HAV and is based on detection of HRV IgM. Antibodies to HEV (IgM and IgG) develop at the time symptoms occur, usually before the development of jaundice. IgM anti-HEV titer declines rapidly during early convalescence, while IgG anti-HEV persists for long duration and provides protection against subsequent infections.

Treatment

Treatment is generally supportive and symptomatic. There is some data about benefits of ribavirin therapy in patients with fulminant hepatitis, in pregnant women with severe hepatitis (despite teratogenicity of ribavirin) and in chronic infection in immunocompromised hosts.

Prevention

The principles of prevention include food, water and personal hygiene. Boiling water inactivates Hepatitis E but the effectiveness of chlorination is unknown. A recombinant genotype 1 vaccine has been commercially licensed in China which has shown good long-term protection and cross-protection against genotypes 2 and 4.

Suggested Reading

- Verghese VP, Robinson JL. A systematic review of hepatitis E virus infection in children. *Clin Infect Dis* 2014; 59:689–97.

Dengue

Dengue fever is an acute febrile illness characterized by fever, myalgia, arthralgia and rash. Severe dengue infection is characterized by abnormalities in hemostasis and by leakage of plasma from the capillaries; the latter may lead to shock (dengue shock syndrome).

Epidemiology

The global prevalence of dengue has increased, with the disease endemic in more than 100 countries in Africa, the Americas, the Eastern Mediterranean, south-east Asia and Western Pacific. South-east Asia and the Western Pacific are most seriously affected. WHO estimates 50 million annual cases of dengue infection across the world. During epidemics, attack rates among susceptible are ~40–50%. An estimated 500,000 cases with severe dengue infection require hospitalization every year; 2.5% patients die. Without proper treatment, case fatality rates in severe dengue infection (earlier called dengue hemorrhagic fever, DHF) exceed 20%. The spread of dengue is attributed to expanding geographic distribution of the four dengue viruses and their mosquito vectors, chiefly the predominantly urban species *Aedes aegypti*. A rapid rise in urban populations is bringing ever greater numbers of people into contact with this vector, especially in areas that favor mosquito breeding, e.g. where household water storage is common and where solid waste disposal services are inadequate.

Virus: Dengue fever is caused by any of the 4 dengue serotypes, arbo viruses of the family Flaviviridae. These RNA viruses are spherical, approximately 50 nm in diameter with approximately 11000 nucleotides. The envelop protein bears epitopes that are unique to the serotypes. Antibodies to these epitopes neutralize by interfering with entry of virus into the cells. There are other epitopes that are shared between dengue viruses (dengue subgroup antigens) and other flaviviruses (group antigens). Four well-defined dengue viruses are identified, DENV-1, DENV-2, DENV-3 and DENV-4. Genotyping is used to trace the movement of dengue viruses between different geographic regions.

Transmission: Dengue viruses are transmitted to humans through the bites of infected female *Aedes* mosquitoes. Mosquitoes acquire the virus while feeding on blood of an infected person. After incubation for 3–7 days, an infected mosquito is capable, during probing and blood feeding of transmitting the virus to susceptible individuals for the rest of its life. Infected female mosquitoes may also transmit the virus to their offspring by transovarial (via the eggs); this transmission is not well studied. Humans are the main amplifying host, although monkeys may become infected and serve as a source of virus for uninfected mosquitoes. The virus circulates in the blood of infected humans for 2–7 days, at approximately the

same time as fever. *Aedes* mosquitoes may acquire the virus when feeding on an individual.

Pathophysiology

The major pathophysiology that differentiates severe dengue from dengue fever is plasma leakage and abnormal hemostasis leading to rising hematocrit values, moderate to marked thrombocytopenia and varying degrees of bleeding. The cause of abnormal leakage of plasma is not entirely understood. However, rapid recovery without residual abnormality in vessels suggests it to be the result of release and interaction of biological mediators, capable of producing severe illness with minimal structural injury.

The pathogenesis of dengue and severe dengue infection is not clear. It is observed that sequential infection with any two of the four serotypes of dengue virus results in DHF/DSS in an endemic area. It is suggested that antibodies produced during the first infection are able to neutralize a second viral infection with the same serotype. However, when no neutralizing antibodies are present (i.e. infection due to another serotype), the second infection is under the influence of enhancing antibodies and the resulting infection and disease are severe. It is proposed that serotype cross-reactive antibodies generated from previous infection with a particular dengue virus serotype are not specific for other serotypes. Hence, they bind to the virions but do not neutralize them, and instead increase their uptake by antigen presenting cells (tissue dendritic cells, monocytes, macrophages). Enhanced antigen presentation by these cells results in activation and proliferation of memory T cells, and release of cytokines that contribute to the pathogenesis of DHF/DSS.

Endothelial cell dysfunction manifests as increased capillary permeability with microvascular leak, hemoconcentration and circulatory insufficiency. The transient nature of plasma leakage suggests that this might be mediated by a soluble mediator. Dengue viral infection is commonly associated with thrombocytopenia, due to molecular mimicry between dengue virus proteins (especially NS1) and endogenous self-proteins. There is activation of blood clotting and fibrinolytic pathways. Mild disseminated intravascular coagulation, liver injury and thrombocytopenia contribute to hemorrhage. Liver may show diffuse hepatitis with focal necrosis and steatosis; viral antigen may be detected on immunohistochemistry. Central nervous system involvement is attributed to direct neurotropic effect of the virus.

Clinical Manifestations

Dengue infection has varying clinical presentations and often with unpredictable clinical evolution and outcome. Incubation period varies between 3 and 7 days. Infants and young children may present with an undifferentiated febrile illness. The classic presentation of dengue fever is

usually seen in older children, adolescents and adults and can be described under three phases: Febrile, critical and recovery.

Febrile phase: Characterized by sudden onset of high-grade fever that may last for 2–7 days, there is facial flushing, skin erythema, bodyache, myalgia, arthralgia, headache, anorexia, nausea and vomiting. Occasionally the child may have sore throat, injected pharynx and conjunctival injection. A positive tourniquet test and minor hemorrhagic manifestations (petechiae, mucosal bleeding from nose and gums) may be seen in some patients. Liver may be enlarged and tender from 2 to 5 days and indicates risk for developing severe illness. There is progressive decrease in total white cell count and platelet count.

Critical phase: During defervescence, 3–7 days from onset of fever, the patient may show bleeding and shock with fall in platelet count and increase in packed cell volume (PCV). Some children show organ dysfunction with severe hepatitis, encephalitis or myocarditis and/or severe bleeding, even in the absence of plasma leakage or shock.

Recovery phase: After 24–48 hours in critical phase, a gradual reabsorption of extravascular compartment fluid takes place in next 48–72 hours. The general well-being improves, appetite returns, gastrointestinal symptoms abate, hemodynamic status stabilizes and diuresis ensues. Some patients may have a rash of 'isles of white in the sea of red.' Others exhibit pruritus, bradycardia and electrocardiographic changes; respiratory distress due to pulmonary edema is uncommon. PCV stabilizes or may be lower due to dilution. While leukocyte counts rise after defervescence, recovery of thrombocytopenia may take longer.

Unusual features: A few patients may present with persistent thrombocytopenia mimicking idiopathic thrombocytopenia, hemophagocytic lymphohistiocytosis and an extended course of illness in form of multi-organ dysfunction (extended dengue syndrome). Dengue in immunocompromised children shows higher incidence of organ dysfunction and longer time for platelet recovery.

Differential Diagnosis

Differential diagnosis includes other hemorrhagic fever, chikungunya infection, influenza, malaria, enteric fever, leptospirosis and less commonly meningococemia and rickettsiosis. Malaria, leptospirosis, flu, enteric fever and chikungunya infections may be coinfecting with dengue. The features of chikungunya infection are similar to dengue. However, fever is of shorter duration, and thrombocytopenia and bleeding are less frequent. Patients with chikungunya often have skin eruptions, mucosal lesions, polyarthralgia and encephalopathy.

Following clinical and laboratory features suggest presence of severe dengue infection:

Clinical criteria: Acute onset high-grade fever, hemorrhagic manifestations (positive tourniquet test), tender hepatomegaly, effusion in body cavities and/shock.

Laboratory criteria: Thrombocytopenia ($\leq 100\,000$ cells per mm^3 ; $<1-2$ platelets per oil immersion field), rising hematocrit

Tourniquet test: This test is part of the WHO case definition for dengue, and a marker of capillary fragility. The test is done by inflating the blood pressure cuff to a point midway between the systolic and diastolic blood pressure for 5 minutes. The cuff is deflated and removed. After waiting for 2 minutes, the number of petechiae is counted in the antecubital fossa. The presence of 10 or more petechiae per 1 square inch indicates a positive finding. This finding is present in more than 50% of cases.

Laboratory Investigations

Children with severe dengue infection show increasing PCV and low platelet and leukocyte counts with lymphocyte predominance. A low leukocyte count in a child with febrile illness during the endemic season suggests possible dengue infection. While malaria and enteric fever may have low white cell counts, leukopenia is more severe in dengue.

Blood levels of total protein and albumin are reduced, more marked in patients with shock. Levels of transaminases are raised; higher increase in SGOT than SGPT suggests dengue rather than other virus infection. Patients with severe dengue may show hyponatremia and acidosis, with increase in urea and creatinine. X-ray chest or ultrasound examination may show varying degrees of pleural effusion that is more common on the right, but occasionally bilateral. Ultrasound examination of abdomen may show ascites and enlarged gallbladder.

Confirmation of diagnosis of dengue is established by the following:

Direct methods: Virus isolation by culture; genome detection by PCR; NS1 antigen detection.

Indirect methods: IgM detection; IgG detection.

Virus isolation or PCR requires the sample to be obtained within the first 5 days of fever, is technically demanding, not universally available and hence of limited practical use. NS1 antigen is a highly conserved glycoprotein of dengue virus and secreted during the initial phase of illness. It disappears as antibodies appear and hence declines as illness advances and in secondary dengue infections. The specificity is $\sim 100\%$ and sensitivity in the first 4 days of illness is 90% in primary dengue and 70% in secondary dengue infection.

Antibody determination needs careful interpretation. Following primary dengue infection, 80% patients show detectable IgM antibodies by day 5, 99% by day 10 that peak by day 14 and are undetectable by 2–3 months. IgG antibodies rise later, peak to levels lower than IgM, decline slowly and remain detectable at low levels for life. Diagnosis of primary dengue infection is thus based on elevated IgM antibodies.

Management

Undifferentiated fever: Patients have non-specific symptoms. Treatment consists of paracetamol for fever and regular monitoring for development of any complications.

Dengue infection without warning signs: Patients with fever, bodyache, rashes or minor bleeding may be treated symptomatically. Fever and bodyache are best treated with paracetamol. Salicylates and other non-steroidal, anti-inflammatory drugs should be avoided as these may predispose to mucosal bleeds. Child should be encouraged to drink plenty of fluids. In epidemic situations, the primary care physician or health worker should monitor for warning signs (see below) along with hematocrit (PCV) and platelet count, if possible.

Dengue with warning signs: Children with suspected dengue infection who have any of the following need hospitalization: (i) abdominal pain or tenderness, (ii) persistent vomiting, (iii) clinical fluid accumulation, (iv) mucosal bleeding, (v) lethargy, restlessness, (vi) liver enlarged >2 cm, (vi) increase in PCV with concurrent or rapid decrease in platelet count.

These patients should be admitted in hospital and need intravenous fluids. Crystalloids are the preferred fluids. In the hospital, all children without hypotension should be given Ringer lactate or normal saline infusion at a rate of 7 mL/kg over one hour. After one hour, if PCV has decreased and vital parameters are improving; fluid infusion rate should be decreased to 5 mL/kg over next hour and to 3 mL/kg/hour for 24–48 hours with frequent monitoring of PCV and vital parameters. When the patient is stable as indicated by normal blood pressure, good oral intake and urine output, the child can be discharged (Fig. 11.9).

If at 1 hour, the PCV is rising and vital parameters do not show improvement, the infusion rate is increased to 10 mL/kg over next hour. In case of no improvement, fluid infusion rate may further be increased to 15 mL/kg in the 3rd hour. If no improvement is observed in vital parameters and PCV at end of 3 hours, colloids are given at 10 mL/kg. Once PCV and vital parameters are stable, the infusion rate is gradually reduced and stopped over 24–48 hours.

Severe dengue: Children having any of the following: (i) Severe plasma leakage leading to shock or fluid accumulation with respiratory distress; (ii) Severe bleeding; (iii) Severe organ involvement: high AST, ALT

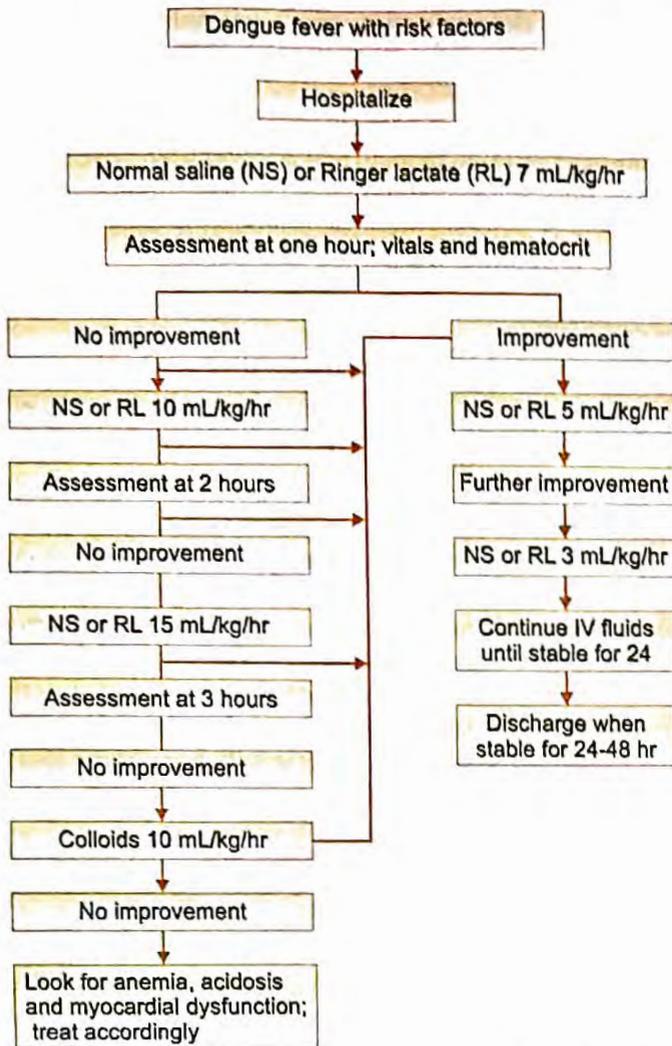


Fig. 11.9: Management of dengue fever with risk factors

>1000 U/L, impaired consciousness or involvement of heart and other organs.

Children classified as severe dengue should be hospitalized (preferably in intensive care) and treated with normal saline or Ringer lactate; 10–20 mL/kg is infused over 1 hour or as bolus, if blood pressure is unrecordable (earlier known as dengue shock syndrome, DSS IV). In critically sick children, it is preferable to establish two IV lines, one for administration of normal saline and other for infusing 5% dextrose and potassium. If there is no improvement in vital parameters and PCV is rising, colloids 10 mL/kg are given rapidly. If PCV is falling without improvement in vital parameters, blood transfusion is recommended (Fig. 11.10). Once improvement begins, fluid infusion rate is gradually decreased.

In addition to fluid management, oxygen should be administered to all patients with shock.

Management of Bleeding

Petechial spots or mild mucosal bleed, hemodynamically stable: Such patients need supportive care including bed rest, maintenance of hydration and monitoring. There is

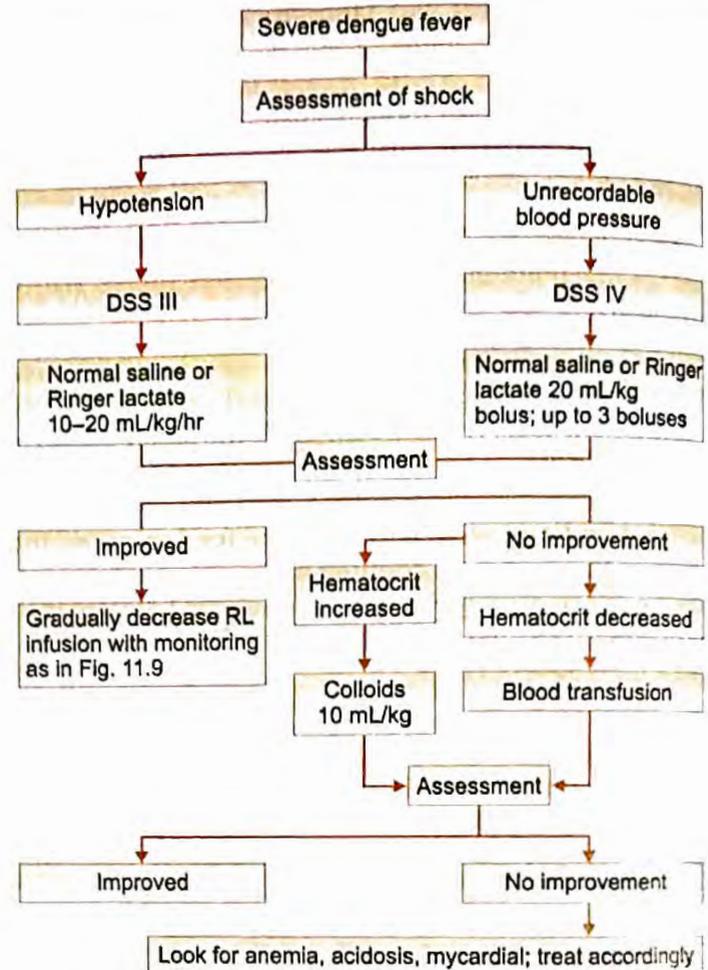


Fig. 11.10: Management of severe dengue fever

no role for use of prophylactic platelet rich plasma even with severe thrombocytopenia. Procedures predisposing to mucosal trauma and IM injections are avoided.

Severe bleeding and hemodynamic instability, excessive mucosal bleed: These patients are treated with blood transfusions and monitoring. There is little evidence to support use of platelet concentrates and/or fresh-frozen plasma for severe bleeding. When massive bleeding cannot be managed with fresh whole blood/fresh-packed cells and there is possibility of DIC, combination of fresh frozen plasma and platelet concentrates should be considered.

Management of Fluid Overload

Stable hemodynamic status and out of critical phase (>24–48 hours of defervescence): Intravenous fluids are discontinued, but close monitoring should continue. Oral frusemide 0.1–0.5 mg/kg/dose once or twice daily or continuous infusion of furosemide 0.1 mg/kg/hour may be administered judiciously.

Stable hemodynamic status but still within critical phase: The IV fluids are reduced. Diuretics are, however, avoided, to prevent intravascular volume depletion. Patients with

fluid overload, shock and low PCV may have occult hemorrhage should receive careful fresh whole blood transfusion. Patients in shock and high PCV should receive repeated small boluses of colloids.

Other supportive care: Organ dysfunction (liver, kidney) should be managed using standard guidelines. There is no role of therapy with corticosteroids, intravenous immunoglobulins or activated factor VII. Broad-spectrum antibiotics are indicated in case of superadded bacterial infection. Blood transfusion (20 mL/kg) is indicated when shock persists despite declining PCV (which indicates adequate fluid replacement). All children with hypotension should receive oxygen inhalation by nasal cannula/face mask or oxygen hood.

Monitoring

Monitoring of the patient is crucial in the first few hours of illness. Heart rate, respiratory rate, blood pressure and pulse pressure is monitored every 30 minutes till the patient is stable, then every 2–4 hours as long as the child is in the hospital. In critically ill children, central venous pressure and accurate urine output with an indwelling urinary catheter should be monitored. Absolute platelet counts should be checked once a day till there is a rising trend.

Prognosis

Dengue fever is a self-limited disease but mortality in severe dengue may be as high as 20–30%, if untreated. Early recognition of illness, careful monitoring and appropriate fluid therapy has resulted in considerable reduction of case fatality rate to <1%. Early recognition of shock is of paramount importance as the outcome of a patient with DSS depends on the duration of shock. If shock is identified when pulse pressure starts getting narrow and IV fluids are administered at this stage, the outcome is excellent.

Prevention

Preventive measures are directed towards elimination of adult mosquitoes and their larvae. During epidemics, aerial spraying/fogging with malathion is recommended for adult mosquitoes. Larval control measures by source reduction and use of larvicides are even more crucial. Mesocyclops, the shell fish are credited to eat and effectively eliminate larvae of *Aedes*. The strategy has been used with success by Australian scientists working in Vietnam by growing shell fish in ponds and water traps. *A. aegypti* breed in and around human dwellings and flourish in fresh water. Special drives must be launched during and soon after the rainy season to interrupt their breeding. There should be no stagnation of water in the bathroom, kitchen, terrace, lawn and other open places; stored water should be covered. Cooperation from every house owner, public establishment and the government

and its employees is crucial for the success of control program. A live-attenuated quadruple vaccine has been approved for use in some countries between 9 and 45 years of age.

Suggested Reading

- Dengue Guidelines for Diagnosis, Treatment, Prevention and Control. Joint publication of the World Health Organization (WHO) and the Special Program for Research and Training in Tropical Diseases, 2009.
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Chikungunya

Chikungunya, an acute disease with fever, arthritis and skin rash, is caused by an enveloped RNA virus. Because of severe arthritic symptoms, the disease was given the Swahili name of chikungunya (that which bends up). Outbreaks of the disease have been reported from Tanzania, South Africa, India and Philippines. Chikungunya re-emerged in India during 2005–06, causing 1.3 million cases in 13 states, chiefly Andhra Pradesh and Karnataka.

Epidemiology

The rural cycle of chikungunya transmission involves *Aedes africanus*, *A. fuscifer*, and wild primates, while the urban cycle involves *A. aegypti* and humans. In rural cycle (seen in Africa), the disease is endemic with a small number of cases occurring in most years. In urban areas, the outbreaks are sporadic and explosive with infection of a large population within weeks. In Asia, the virus may be maintained in urban cycle, with *A. aegypti* or require reinoculation before onset of epidemic. Outbreaks occur during the rainy season, associated with the population density of the mosquito vector, which breeds in household containers and puddles with peak activity in mid-morning and late afternoon. After an epidemic, the disease wanes for years because a large proportion of the population is immune.

Clinical Features

The disease has sudden onset, with incubation period of 2–12 days. Infection is characterized by fever, headache, fatigue, nausea, vomiting, rash and muscle and joint pain. Fever rises abruptly to 103–104°F and is accompanied by rigors that last for 2–3 days. Joint pain appears suddenly and is severe in intensity; the arthralgia and arthritis is polyarticular, migratory, and chiefly affects small joints of hands, wrist, ankle and feet with less involvement of larger joints. The joint pains may continue for months after the illness. Headache is present in 80% of cases in the acute stage. Photophobia and retro-orbital pain may also occur.

An itchy, transient maculopapular rash appears 4–8 days later affecting the trunk and limbs. Inguinal lymph nodes may be enlarged. Fatalities are rare and associated with young age, shock and thrombocytopenia. Rarely encephalopathy may occur in infants and young children.

Diagnosis

Chikungunya should be suspected in patients who presents with the characteristic triad of fever, rash and arthritis. Viremia is present in most patients during the initial 2–4 days of disease and may be isolated in cell cultures. Polymerase chain reaction can be used to confirm the infection. Virus specific IgM antibodies may be detected by capture ELISA and hemagglutination inhibition assays by 5–7 days of illness.

Treatment

Symptomatic treatment in the form of rest, fluids, and ibuprofen, naproxen, acetaminophen, or paracetamol may relieve symptoms. Aspirin should be avoided during acute phase of illness.

Prevention

Strategies for control include breaking the transmission cycle of *A. aegypti* and by holding the mosquito population at extremely low levels. A live-attenuated vaccine, developed recently, which induces long-term production of neutralizing antibodies, is being examined.

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HIV INFECTION, ACQUIRED IMMUNODEFICIENCY SYNDROME

HIV infection has become an important contributor to childhood morbidity and mortality, especially in developing countries and has undone many of the major gains in child health.

Epidemiology

It is estimated that more than 36 million persons worldwide were living with HIV infection at the end of 2016; 2.1 million of these were children under 15 years of age. More than 90% of HIV-infected individuals live in developing nations. Sub-Saharan Africa accounts for nearly 90% of the world population of HIV-infected children. India and Thailand dominate the epidemic in Southeast Asia, with expansion into Vietnam, China, and

Cambodia. There has been considerable progress in improving access to antiretroviral therapy. Without access to such therapy, 20% of vertically infected children will progress to AIDS or death in their first year of life and more than half of HIV-infected children will die before their fifth birthday.

HIV-1, HIV-2

HIV-1 and HIV-2 are members of the Retroviridae family and belong to the *Lentivirus* genus. The HIV-1 genome is single-stranded RNA that is 9.2 kb in size. The genome has three major sections: The gag region, which encodes the viral core proteins (p24, p17, p9, p6; these are derived from the precursor p55), the pol region, which encodes the viral enzymes (reverse transcriptase [p51], protease [p10], and integrase [p32]); and the env region, which encodes the viral envelope proteins (gp120 and gp41). The major external viral protein of HIV-1 is a heavily glycosylated gp120 protein which contains the binding site for the CD4 molecule, the most common T lymphocyte surface receptor for HIV.

Following viral attachment, gp120 and the CD4 molecules undergo conformational changes, allowing gp41 to interact with the fusion receptor on the cell surface. Viral fusion with the cell membrane allows entry of viral RNA into the cell cytoplasm. Viral DNA copies are then transcribed from the virion RNA through viral reverse transcriptase enzyme activity, and duplication of the DNA copies produces double-stranded circular DNA. Because the HIV-1 reverse transcriptase is error-prone, many mutations arise, creating wide genetic variation in HIV-1 isolates even within an individual patient. The circular DNA is transported into the cell nucleus where it is integrated into chromosomal DNA; this is called as the provirus. The provirus can remain dormant for extended periods. HIV-1 transcription is followed by translation. A capsid polyprotein is cleaved to produce, among other products, the virus-specific protease (p10). This enzyme is critical for HIV-1 assembly. The RNA genome is then incorporated into the newly formed viral capsid. As the new virus is formed, it buds through the cell membrane and is released.

HIV-2 is a rare cause of infection in children, more prevalent in western and southern Africa. If HIV-2 is suspected, a specific test that detects antibody to HIV-2 peptides should be used.

Transmission

Transmission of HIV-1 occurs via sexual contact, parenteral exposure to blood, or vertical transmission from mother to child. The primary route of infection in the pediatric population is vertical transmission. Most large studies in the United States and Europe have documented mother-to-child transmission rates in untreated women between 12 and 30%. In contrast, transmission rates in Africa and Asia are higher, up to 50%.

Vertical transmission of HIV can occur during the intrauterine or intrapartum periods, or through breastfeeding. Up to 30% of infected newborns are infected *in utero*. The highest percentages of HIV-infected children acquire the virus intrapartum. Breastfeeding is an important route of transmission, especially in the developing countries. The risk factors for vertical transmission include preterm delivery (<34 weeks gestation), a low maternal antenatal CD4 count, use of illicit drugs during pregnancy, >4 hours duration of ruptured membranes and birth weight <2500 g.

Transfusions of infected blood or blood products have accounted for a proportion of pediatric AIDS cases. Heat treatment of factor VIII concentrate and HIV antibody screening of donors have virtually eliminated HIV transmission to children with hemophilia. Blood donor screening has dramatically reduced, but not eliminated, the risk of transfusion-associated HIV infection. Sexual contact is a major route of transmission in adolescents.

Natural History

Before highly active antiretroviral therapy (HAART) was available, three distinct patterns of disease were described in children. Approximately 10–20% of HIV-infected newborns in developed countries presented with a rapid disease course, with onset of AIDS and symptoms during the first few months of life; if untreated, these patients died from complications by 4 years of age. In resource-poor countries, >85% of the HIV-infected newborns may have such a rapidly progressing disease.

It has been suggested that if intrauterine infection coincides with the period of rapid expansion of CD4 cells in the fetus, it could effectively infect the majority of the body's immunocompetent cells. Most children in this group have a positive HIV-1 culture and/or detectable virus in the plasma in the first 48 hours of life. This early evidence of viral presence suggests that the newborn was infected in utero. In contrast to the viral load in adults, the viral load in infants stays high for at least the first 2 years of life.

Majority of perinatally infected newborns (60–80%) present with the second pattern: Slower progression of disease with a median survival of 6 years. Many patients in this group have a negative viral culture or PCR in the first week of life and are, therefore, considered to be infected intrapartum. In a typical patient, the viral load rapidly increases by 2–3 months of age, and then slowly over 24 months. The third pattern (i.e. long-term survivors) occurs in a small percentage (<5%) of perinatally infected children who have minimal or no progression of disease with relatively normal CD4 counts and very low viral loads for longer than 8 years.

HIV-infected children have changes in the immune system that are similar to those in HIV-infected adults. CD4 cell depletion may be less dramatic because infants

normally have a relative lymphocytosis. Therefore, for example, a value of 1500 CD4 cells/mm³ in children <1 year of age is indicative of severe CD4 depletion and is comparable to <200 CD4 cells/mm³ in adults. Lymphopenia is relatively rare in perinatally infected children and is usually only seen in older children or those with end-stage disease.

B cell activation occurs in most children, as evidenced by hypergammaglobulinemia with high levels of anti-HIV-1 antibody. This response may reflect both dysregulation of T cell suppression of B-cell antibody synthesis and active CD4 enhancement of B lymphocyte humoral responses.

CD4 depletion and inadequate antibody responses lead to increased susceptibility to various infections and clinical features vary with the severity of immunodeficiency.

Clinical Features

The clinical manifestations of HIV infection vary widely among infants, children and adolescents. In most infants, physical examination at birth is normal. Initial signs and symptoms may be subtle and non-specific, such as lymphadenopathy, hepatosplenomegaly, failure to thrive, chronic or recurrent diarrhea, interstitial pneumonia or oral thrush and may be distinguishable from other causes only by their persistence. While systemic and pulmonary findings are common in the United States and Europe, chronic diarrhea, wasting, and severe malnutrition predominate in Africa. Symptoms more common in children than adults include recurrent bacterial infections, chronic parotid swelling, lymphocytic interstitial pneumonitis (LIP), and early onset of progressive neurologic deterioration.

Pediatric HIV disease is staged using two parameters: Clinical status (Table 11.3) and degree of immunologic impairment (Table 11.4).

Opportunistic Infections

Children with HIV infection and advanced or severe immunosuppression are susceptible to develop various opportunistic infections. The important pathogens include: *Pneumocystis jirovecii*, *Cryptosporidium*, *Cryptococcus*, *Isospora* and *CMV*.

Respiratory Diseases Complicating HIV Infection

P. jirovecii (previously *P. carinii*) pneumonia is the opportunistic infection that led to the initial description of AIDS. This is one of the commonest AIDS defining illnesses in children in the US and Europe; most cases occur between 3rd and 6th months of life. Even if a child develops the illness while on prophylaxis, therapy may be started with cotrimoxazole. With the use of appropriate therapy, the mortality decreases to less than 10%. Risk factors for mortality are severity of the episode and severity of the immunosuppression.

Table 11.3: WHO clinical staging of HIV/AIDS for children with confirmed HIV infection**Clinical stage 1**

Asymptomatic

Persistent generalized lymphadenopathy

Clinical stage 2Unexplained^a persistent hepatosplenomegaly

Papular pruritic eruptions

Fungal nail infection

Angular cheilitis

Lineal gingival erythema

Extensive wart virus infection

Extensive molluscum contagiosum

Recurrent oral ulceration

Unexplained^a persistent parotid enlargement

Herpes zoster

Recurrent or chronic upper respiratory tract infections (otitis media, otorrhea, sinusitis, tonsillitis)

Clinical stage 3Unexplained^a moderate malnutrition or wasting not adequately responding to standard therapyUnexplained^a persistent diarrhea (14 days or more)Unexplained^a persistent fever (above 37.5°C intermittent or constant, for longer than one month)

Persistent oral candidiasis (after the first 6–8 weeks of life)

Oral hairy leukoplakia

Acute necrotizing ulcerative gingivitis/periodontitis

Lymph node TB

Pulmonary TB

Severe recurrent bacterial pneumonia

Symptomatic lymphoid interstitial pneumonitis

Chronic HIV-associated lung disease including bronchiectasis

Unexplained anemia (<8 g/dL), neutropenia (<0.5 × 10⁹/L) or chronic thrombocytopenia (<50 × 10⁹/L)**Clinical stage 4^b**

Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy

Pneumocystis pneumonia

Recurrent severe bacterial infections (empyema, pyomyositis, bone, joint infection, meningitis; excluding pneumonia)

Chronic herpes simplex infection (orolabial or cutaneous for >1 month duration; visceral at any site)

Esophageal candidiasis (or candidiasis of trachea, bronchi or lungs)

Extrapulmonary/disseminated TB

Kaposi sarcoma

Cytomegalovirus infection (retinitis or CMV infection affecting another organ, with onset at age >1 month)

Central nervous system toxoplasmosis (after one month of life)

Extrapulmonary cryptococcosis (including meningitis)

HIV encephalopathy

Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidioidomycosis)

Disseminated non-tuberculous mycobacterial infection

Chronic cryptosporidiosis (with diarrhea)

Chronic isosporiasis

Cerebral or B cell non-Hodgkin lymphoma

Progressive multifocal leukoencephalopathy

Symptomatic HIV (associated nephropathy or cardiomyopathy)

^aUnexplained refers to where the condition is not explained by other causes^bAdditional specific conditions may be included in the regional classifications (e.g. reactivation of American trypanosomiasis, meningoencephalitis and/or myocarditis in Americas region, penicilliosis in Asia and HIV-associated rectovaginal fistula in Africa)

Table 11.4: Classification of immune suppression in children (CD4 levels in relation to severity of immune suppression)

HIV-associated immunodeficiency	Age-related CD4 cell values			
	<11 months	12–35 months	36–59 months	≥5 years
Not significant (normal CD4 cells)	>35%	>30%	>25%	>500 cells/mm ³
Mild	30–35%	25–30%	20–25%	350–499 cells/mm ³
Advanced	25–30%	20–25%	15–20%	200–349 cells/mm ³
Severe	<25%	<20%	<15%	<15%
	<1500 cells/mm ³	<750 cells/mm ³	<350 cells/mm ³	200 cells/mm ³

Recurrent bacterial pneumonia may be present in up to 90% HIV-infected children. Initial episodes often occur before the development of significant immunosuppression. As the immunosuppression increases the frequency increases. The common pathogens for community-acquired pneumonia are *S. pneumoniae*, *H. influenzae* and *S. aureus*. In children with severe immunosuppression and hospital-acquired infections, gram-negative organisms, such as, *Pseudomonas aeruginosa* gain importance. Clinical features in HIV-infected children are similar to those in other children. However, in severely immunocompromised children, the signs may be subtle. Often, the response to therapy is slow and the relapse rates are high. Bacteremia may be more common, seen in up to 50%.

Choice of antibiotics is based on local patterns of etiologies and susceptibilities. An appropriate choice is the combination of a broad-spectrum cephalosporin and an aminoglycoside. In areas with large proportion of MRSA, vancomycin, clindamycin, linezolid or other drugs may be used. Children with non-severe pneumonia can be managed as out-patients using a second or a third generation cephalosporin or coamoxiclav. Since *P. jirovecii* pneumonia cannot be excluded in most children with severe respiratory symptoms, cotrimoxazole is also used unless another diagnosis has been made.

Tuberculosis is a common medical concern. Co-existent TB and HIV infections accelerate the progression of both diseases. HIV-infected children are more likely to have extrapulmonary and disseminated tuberculosis; the course is also likely to be more rapid. The overall risk of active TB in children infected with HIV is at least 5- to 10-fold higher than in children not infected with HIV. The duration of antitubercular therapy in patients is same as that for not-HIV infected; a few children may need prolongation of treatment to 9–12 months. Close follow-up is essential to diagnose non-response or drug resistance. Rifampicin may show drug interactions with some antiretroviral agents (nevirapine, protease inhibitors).

Viral infections, chiefly respiratory syncytial virus, influenza and parainfluenza viruses, often result in symptomatic disease. Infections with adenovirus and measles virus might result in serious sequelae. Disseminated CMV is a known opportunistic infection, but pneumonia caused by the virus is rare.

Fungal infections present as a part of disseminated disease in immunocompromised children. Primary pulmonary fungal infections are uncommon.

Lymphoid interstitial pneumonitis (LIP) has been recognized as a distinctive marker for pediatric HIV infection and is considered in the criteria for AIDS in children. In absence of antiretroviral therapy, nearly 20% of HIV-infected children developed LIP. The etiology and pathogenesis of LIP are not well understood, but include: Exaggerated immune response to inhaled or circulating antigens, and/or primary infection of the lung with HIV, Epstein-Barr virus (EBV), or both. LIP is characterized by nodule formation and diffuse infiltration of the alveolar septa by lymphocytes, plasmacytoid lymphocytes, plasma cells and immunoblasts. There is no involvement of the blood vessels or destruction of the lung tissue. Children with LIP have a relatively good prognosis.

LIP is usually diagnosed in children with perinatally acquired HIV infection when they are older than 1 year of age. Most children with LIP are asymptomatic. Tachypnea, cough, wheezing and hypoxemia are in children with severe features; crepitations are uncommon. Clubbing is present in advanced disease. These patients can progress to chronic respiratory failure. Long-standing LIP may be associated with bronchiectasis. The presence of a reticulonodular pattern, with or without hilar lymphadenopathy, that persists on chest radiograph for 2 months or greater and that is unresponsive to antimicrobial therapy is considered presumptive evidence of LIP. A definitive diagnosis is made by histopathology.

Early disease is managed conservatively. The effect of antiretroviral agents is limited. Steroids are indicated, if children with LIP have symptoms and signs of chronic pulmonary disease, clubbing and/or hypoxemia. Treatment includes an initial 4- to 12-week course of prednisolone (2 mg/kg/d) followed by tapering to low dose medication, using oxygen saturation and clinical state as guide to improvement.

Gastrointestinal Diseases

Multiple microbes can cause gastrointestinal disease, including bacteria (*Salmonella*, *Campylobacter*, *Mycobacterium avium intracellulare* complex), protozoa (*Giardia*, *Isospora*, *Cryptosporidium*, microsporidia), viruses (CMV, HSV,

rotavirus) and fungi (*Candida*). Protozoal infections are severe and can be protracted in children. Children with *Cryptosporidium* infestation can have severe diarrhea leading to hypovolemic shock. AIDS enteropathy, a syndrome of malabsorption with partial villous atrophy not associated with specific pathogens, is the result of direct HIV infection of the gut.

Chronic liver inflammation is relatively common in HIV-infected children. In some children, hepatitis caused by CMV, hepatitis B or C viruses, or MAC may lead to liver failure and portal hypertension. It is important to recognize that several of the antiretroviral drugs such as didanosine, and protease inhibitors may also cause reversible elevation of transaminases.

Pancreatitis is uncommon in HIV-infected children. This may be the result of drug therapy, e.g. didanosine, lamivudine, nevirapine, or pentamidine. Rarely, opportunistic infections, such as MAC or CMV, may be responsible for acute pancreatitis.

Neurologic Diseases

The incidence of central nervous system (CNS) involvement in perinatally infected children may be more than 50% in developing countries but lower in developed countries, with a median onset at about one and a half years of age. The most common presentation is progressive encephalopathy with loss or plateau of developmental milestones, cognitive deterioration, impaired brain growth resulting in acquired microcephaly, and symmetric motor dysfunction. CNS infections: Meningitis due to bacterial pathogens, fungi such as *Cryptococcus* and a number of viruses may be responsible for the clinical features. CNS toxoplasmosis is exceedingly rare in young infants, but may occur in HIV-infected adolescents; the overwhelming majority has serum IgG antitoxoplasma antibodies.

Cardiovascular Involvement

Cardiac abnormalities in HIV-infected children are common, persistent, and often progressive; the majority is subclinical. Left ventricular structure and function progressively may deteriorate in the first 3 years of life, resulting in subsequent persistent cardiac dysfunction and increased left ventricular mass. Children with encephalopathy or other AIDS-defining conditions have the highest rate of adverse cardiac outcomes. Resting sinus tachycardia has been reported in up to nearly two-thirds and marked sinus arrhythmia in one-fifth of HIV-infected children. Gallop rhythm with tachypnea and hepatosplenomegaly appear to be the best clinical indicators of congestive heart failure; anticongestive therapy is generally very effective, especially when initiated early.

Renal Involvement

Nephropathy is an unusual presenting symptom of HIV infection, more commonly occurring in older symptomatic children. Nephrotic syndrome is the most common

manifestation; polyuria, oliguria, and hematuria have also been observed. Hypertension is unusual.

Diagnosis

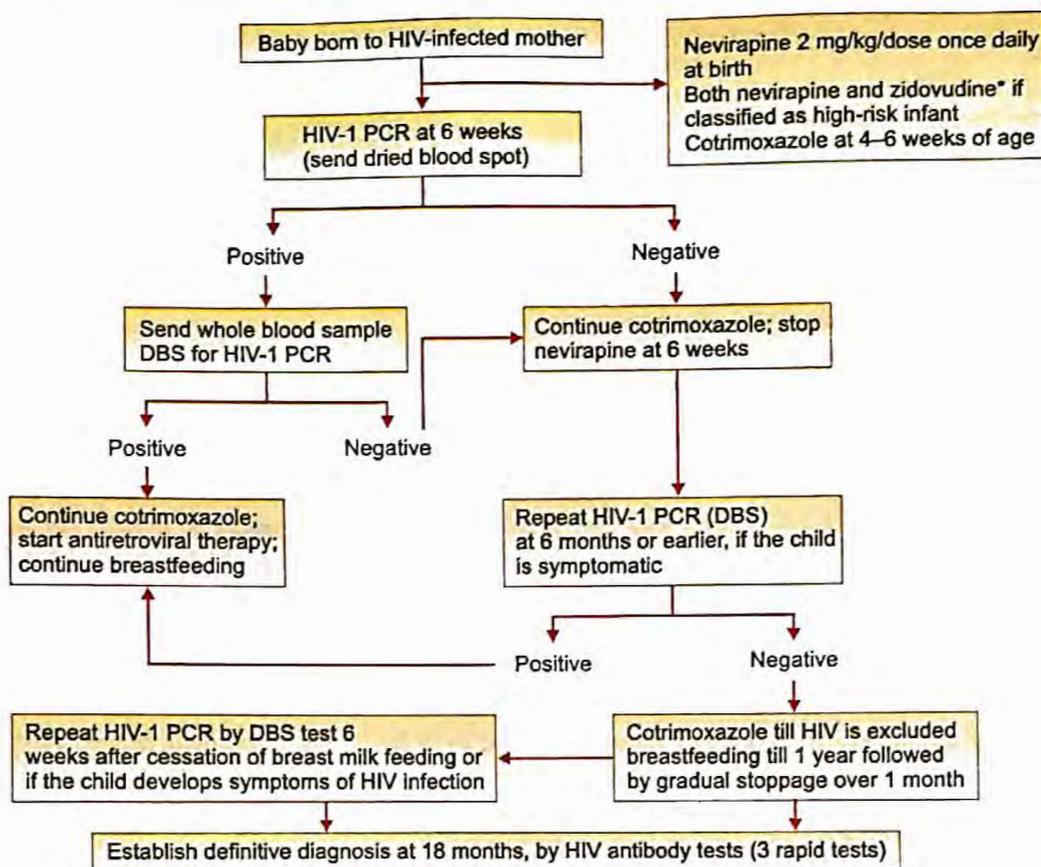
All infants born to HIV-infected mothers test antibody-positive at birth because of passive transfer of maternal HIV antibody across the placenta. Most uninfected infants lose maternal antibody between 6 and 12 months of age. As a small proportion of uninfected infants continue to have maternal HIV antibody in the blood up to 18 months of age, positive IgG antibody tests cannot be used to make a diagnosis of HIV infection in infants up to this age. In children >18 months old, demonstration of IgG antibody to HIV by a two or three reactive enzyme immunoassay (EIA) and confirmatory test (e.g. Western blot or immunofluorescence assay) can establish the diagnosis of HIV infection. While serologic tests were commonly used in the past, tests that allow for earlier definitive diagnosis have replaced antibody assays as the tests of choice for the diagnosis of HIV infection in infants.

Specific diagnostic assays, such as HIV proviral DNA or RNA PCR, HIV culture, or HIV p24 antigen are useful for diagnosis of young infants born to HIV-infected mothers (Fig. 11.11). By 6 months of age, the HIV culture and/or PCR identifies all infected infants, who are not having continued exposure due to breastfeeding. HIV RNA PCR is the preferred virological assay in developed countries. HIV culture has similar sensitivity to HIV RNA PCR; however, it is more technically complex and expensive, and results are often not available for 2-4 weeks. The p24 antigen assay is less sensitive than the other virological tests. Fig. 11.11 shows the algorithm for diagnosis of HIV infection in infants. The national program (Early Infant Diagnosis) now uses HIV total nucleic acid (RNA + proviral DNA) PCR test on dried blood spot samples; positive tests need confirmation with HIV PCR test on another sample.

Management

The management of HIV-infected child includes antiretroviral therapy, prophylaxis and treatment of opportunistic and common infections, adequate nutrition and immunization. Decisions about antiretroviral therapy (ART) for HIV-infected patients were earlier based on the magnitude of viral replication (i.e. viral load), CD4 lymphocyte count or percentage and clinical condition. The current World Health Organization guidelines recommend ART for all children irrespective of the immunologic or clinical stage.

Availability of antiretroviral therapy has transformed HIV infection from a uniformly fatal condition to a chronic infection, where children can lead a near normal life. Current therapy does not eradicate the virus and cure the child; it rather suppresses the virus replication for extended periods of time. The three main groups of drugs are nucleoside reverse transcriptase inhibitors (NRTI),



*Following infants are at higher risk of acquiring infection:

Mothers receiving <4 weeks of antiretroviral therapy at the time of delivery

Mothers having high viral load (RNA >1000 copies/mL) within 4 weeks before delivery

Mothers acquiring infection during pregnancy or breastfeeding

Mother first identified during postpartum period with or without a negative HIV test prenatally

Fig. 11.11: HIV diagnosis in children <18 months with DNA-PCR. DBS dried blood spot

non-nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PI). Highly active antiretroviral therapy (HAART) is a combination of 2 NRTI with a PI or an NNRTI. The National Program for management of HIV-infected children recommends combination of *zidovudine* or *abacavir* + *lamivudine* + *efavirenz* as first-line therapy; for children less than 3 years of age, a protease inhibitor is used instead of NNRTI (Table 11.5). Pediatric fixed dose combinations (FDC) have also been developed.

Cotrimoxazole Prophylaxis

In resource-limited settings, cotrimoxazole prophylaxis is recommended for all HIV-exposed infants starting at 4-6 weeks of age (or at first encounter with the health care system) and continued until HIV infection can be excluded. Cotrimoxazole is recommended for HIV-exposed breastfeeding children of all ages; prophylaxis should be continued until HIV infection is excluded by antibody testing (beyond 18 months of age) or virological testing (before 18 months of age), at least 6 weeks after cessation of breastfeeding.

All infants documented to be living with HIV should receive cotrimoxazole prophylaxis regardless of symptoms or CD4 percentage. After one year of age, cotrimoxazole prophylaxis is given to symptomatic children (WHO clinical stages 2, 3 or 4 for HIV disease) or children with CD4 <25%. All children who begin cotrimoxazole prophylaxis (irrespective of age) should continue until the age of 5 years, when they can be reassessed.

Isoniazid Prophylaxis

Current NACO guidelines recommend administration of isoniazid prophylaxis to all HIV-infected children who do not have evidence of active tuberculosis.

Nutrition

HIV-infected children often show failure to thrive and require nutritional rehabilitation.

Immunization

Vaccines recommended in the national schedule can be administered to HIV-infected children, except that

Table 11.5: Commonly used antiretroviral drugs

Drug	Dose	Side effects
Nucleoside reverse transcriptase inhibitors		
Abacavir	3 months–13 yr: 8 mg/kg/ dose q 12 hr >13 yr: 300 mg/dose q12 hr (max: 300 mg/dose)	Hypersensitivity
Didanosine	0–3 months: 50 mg/ m ² / dose q 12 hr 3 months–13 yr: 90–150 mg/m ² q 12 hr (max: 200 mg/dose) >13 yr; <60 kg: 125 mg q 12 hr >13 yr; >60 kg: 200 mg q 12 hr	Peripheral neuropathy, pancreatitis, pain abdomen, diarrhea
Lamivudine (3TC)	1 month–13 yr: 4 mg/kg q 12 hr >13 yr; <50 kg: 4 mg/kg/dose q 12 hr >13 yr; >50 kg: 150 mg/kg/dose q 12 hr	Pancreatitis, neuropathy, neutropenia
Zalcitabine	<13 yr: 0.01 mg/kg/dose q 8 hr >13 yr: 0.75 mg q 8 hr	Rash, peripheral neuropathy, pancreatitis
Zidovudine	Neonates: 2 mg/kg q 6 hr 3 months–13 yr: 90–180 mg/m ² q 6–8 hr	Anemia, myopathy
Non-nucleoside reverse transcriptase inhibitors		
Nevirapine (NVP)	2 months–13 yr: 120 mg/m ² (max: 200 mg) q 24 hr for 14 days; follow by 120–200 mg/m ² q 12 hr >13 yr: 200 mg q 24 hr for 14 days; increase to 200 mg q 12 hr, if no rash or other side effects	Skin rash, Steven Johnson syndrome
Efavirenz	>3 yr: 10–15 kg: 200 mg q 24 hr 15–20 kg: 250 mg q 24 hr; 20–25 kg: 300 mg q 24 hr 25–32.5 kg: 350 mg q 24 hr; 32.5–40 kg: 400 mg q 24 hr >40 kg: 600 mg q 24 hr	Skin rash, CNS symptoms, increased transaminase levels
Protease inhibitors		
Amprenavir	4–16 yr and <50 kg: 22.5 mg/kg q 12 hr (oral solution); 20 mg/ kg q 12 hr (capsules) >13 yr and >50 kg: 1200 mg q 12 hr (capsules)	
Indinavir	500 mg/m ² q8 hr; >13 yr: 800 mg q8 hr	Hyperbilirubinemia, stones
Lopinavir/ ritonavir	7–15 kg: 12 mg/kg lopinavir; 3 mg/kg ritonavir q 12 hr with 15–40 kg: 10 mg/kg lopinavir; 2.5 mg/kg ritonavir q 12 hr food >12 yr: 400 mg lopinavir; 100 mg ritonavir q 12 hr	Diarrhea, fatigue, headache, nausea; increased cholesterol and triglycerides
Nelfinavir	<13 yr: 50–55 mg/ kg q 12 hr >13 yr: 1250 mg q 12 hr (max: 2000 mg)	Diarrhea, abdominal pain
Ritonavir	<13 yr: 350–400 mg/m ² q 12 hr (start dose: 250 mg/m ²) >13 yr: 600 mg q 12 hr (start dose: 300 mg)	Bad taste, vomiting, nausea, diarrhea, rarely, hepatitis
Saquinavir	50 mg/kg q 8 hr >13 yr: 1200 mg q 8 hr soft gel capsules	Diarrhea, headache, skin rash

symptomatic HIV-infected children should not be given OPV and BCG.

Prevention of Mother-to-Child Transmission (MTCT)

The risk of MTCT can be reduced to under 2% by interventions that include antiretroviral therapy given to women during pregnancy and labor and antiretroviral prophylaxis to the infant in the first week of life, obstetrical interventions including elective cesarean delivery (prior

to the onset of labor and rupture of membranes), and complete avoidance of breastfeeding.

Antiretroviral Drug Regimens for Pregnant Women

For all HIV-infected pregnant women, antiretroviral therapy is indicated. The recommended regimen is a combination of zidovudine (AZT), lamivudine (3TC) and nevirapine (NVP) or efavirenz (EFV) during antepartum, intrapartum and postpartum period; EFV-based regimens

should not be newly-initiated during the first trimester of pregnancy. The ART regimen should be started as early as possible.

Antiretroviral Regimens for Infants Born to HIV-Infected Mothers

If mother received triple drug ART during pregnancy and entire breastfeeding, the infant should receive daily AZT or NVP from birth until 6 weeks of age (irrespective of feeding).

Intrapartum Interventions

Artificial rupture of membranes should be avoided, unless medically indicated. Delivery should be by elective cesarean section at 38 weeks before onset of labor and rupture of membranes. Procedures increasing exposure of child to maternal blood should be avoided.

Breastfeeding

The risk of HIV infection *via* breastfeeding is highest in the early months of breastfeeding. Factors that increase likelihood of transmission include detectable levels of HIV in breast milk, presence of mastitis and low maternal CD4+ T cell count. Exclusive breastfeeding has been reported to carry a lower risk of HIV transmission than mixed feeding and risk of mortality in non-breastfed infants in resource limited settings is increased. Currently, exclusive breastfeeding is recommended during the first months of life. WHO recommends that the transition between exclusive breastfeeding and early cessation of breastfeeding should be gradual and not an "early and abrupt cessation".

Suggested Reading

- WHO/UNAIDS. AIDS epidemic update Dec 2016.
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Influenza

The influenza virus is capable of causing disease in humans, birds and animals. Influenza has recently gained more prominence owing to the 2009 novel H1N1 pandemic.

Epidemiology

The influenza virus is an RNA virus of the Orthomyxoviridae family. Influenza A and B are the two types that cause human disease. Influenza A is further classified into subtypes based on the two surface proteins—hemagglutinin (H) and neuraminidase (N). Influenza B is classified into two distinct lineages—Yamagata and Victoria but not into subtypes. Influenza has a highly segmented genome that is prone to frequent mutations and reassortment. This

leads to frequent antigenic "drifts" (seen in both A and B) when there is minor change in antigenicity and "shifts" (seen only in A) where there is major change in antigenicity. The phenomena of antigenic change lead to evolution of new viruses, which result in annual outbreaks and occasionally pandemics. The novel H1N1 pandemic occurred due to emergence of a new swine origin influenza virus H1N1 which was pathogenic to humans and capable of rapid human-to-human transmission and to which there was no pre-existing immunity. It is estimated that the novel H1N1 pandemic between 2009 and 2010 caused 18,000 deaths globally (2000 in India) with case fatality rates ranging from 0.0004% to 1.5% (0.83% in India). The pandemic strain then became endemic and caused another epidemic in 2015 in India with 30000 cases and 2000 deaths. The currently circulating influenza virus strains are H3N2, pandemic H1N1 and influenza B.

Avian H5N1 commonly referred as bird flu is a highly pathogenic strain of influenza virus that infects and kills humans in close contact with diseased birds but has not acquired pandemic potential due to limited human-to-human transmissibility.

Influenza is transmitted from person to person through airborne droplet spread or through contact. The portal of entry is the respiratory tract and the virus attaches itself to the respiratory epithelium through hemagglutinin, the main virulence factor. The incubation period is 1–3 days and the period of infectivity is usually 7 days after illness onset and sometimes longer in those with severe disease. The attack rates are highest in children and young adults. In temperate climates, there is a clear defined influenza season in fall and winters, but in tropical countries like India, it occurs throughout the year with peak during the monsoons.

Clinical Features

In most individuals, influenza is a minor illness characterized by a combination of fever, runny nose, sore throat, cough, body ache, headache, abdominal pain, diarrhea and vomiting. The illness may have a biphasic course. Recovery usually occurs within a week. It is sometimes difficult to differentiate from common cold. Asymptomatic and subclinical infections are also very common.

A small proportion of individuals (less than 1%) can have complications and severe disease. The risk of complications is higher at extremes of age (children below 2 and the elderly), pregnant women and those who have just delivered, those with underlying comorbidities such as any chronic neurologic/metabolic/cardiac/pulmonary/renal disease, those who are immunocompromised and those with severe asthma. In the novel H1N1 epidemic, the elderly were spared due to pre-existent immunity and morbid obesity emerged as an important risk factor.

The most dreaded complication of influenza is pneumonia with acute respiratory distress syndrome,

respiratory failure and sometimes shock and renal failure. As many as 30% of these patients have bacterial coinfection with *S. pneumoniae* and *S. aureus*. Progression is very rapid and most patients require ventilator support over the next 24 hours. Occasionally, other complications such as encephalitis, seizures, quadriparesis and myocarditis have been reported. Complications usually set in by day 4 or 5 of illness. The red flag symptoms are persistent high fever of more than 3 days duration, reappearance of fever after initial defervescence, breathlessness, dyspnea, tachypnea, hemoptysis in older children and adolescents, extreme weakness, poor oral intake and altered sensorium.

Diagnosis

Influenza is primarily a clinical diagnosis. The complete blood count may show leukopenia and thrombocytopenia. Diagnosis is confirmed by antigen detection or PCR on throat or nasopharyngeal swabs. PCR-based tests are fairly sensitive and very specific but are of limited use in routine clinical practice. Specific therapy may thus begin before results become available. If the test is negative, therapy cannot be discontinued as sensitivity is only 60–70% and even lower, if the sample is not properly collected. Molecular diagnosis of influenza should be restricted to hospitalized patients with severe disease when a definitive diagnosis helps in tracking the severity of the outbreak.

Since the symptoms and lab findings of severe flu overlap those of other infections such as malaria, dengue, enteric fever, viral hepatitis and leptospirosis, it is important to conduct appropriate laboratory tests to exclude these illnesses.

Treatment

Definitive treatment of influenza is with M2 inhibitors (amantadine, rimantidine) or neuraminidase inhibitor drugs (oseltamivir, zanamivir). The duration of therapy is 5 days. These drugs reduce duration of symptoms, risk of complications and death. Though they are most effective, if given within first 48 hours, they are useful even if given later. The pandemic H1N1 strain and most current seasonal flu strains are resistant to the M2 inhibitors. Oseltamivir is the first-line drug and zanamivir is used in those with oseltamivir-resistant virus. Oseltamivir is well tolerated with occasional GI and neurological side effects.

For any patient presenting with influenza-like illness, the treatment strategy depends on two factors: The severity of illness and the likelihood of complications. In patients with mild disease who are not at risk for complications, only symptomatic treatment is indicated. Antibiotics and antivirals should not be prescribed. Patients should be counselled about the red flag signs and asked to seek medical care in the event these occur. These patients should be asked to stay at home till they are afebrile to prevent disease transmission to others. Patients who are at high risk for complications should be started on antiviral therapy irrespective of the severity of disease.

For patients who present with symptoms of severe illness or who have complications, antiviral treatment with oseltamivir should be started without delay. An effort should be made to rule out other illnesses with similar symptomatology. In patients with signs of lower respiratory involvement, antibiotics like coamoxyclov or cephalosporins (cefuroxime, ceftriaxone or cefpodoxime) should be used as bacterial coinfections are common.

Prevention

Vaccination is the most effective preventive strategy and is discussed further in Chapter 10. Chemoprophylaxis with oseltamivir is also effective in preventing influenza but is not routinely recommended due to risk of resistance. Household transmission can be reduced by good ventilation in the room, proper hand hygiene and adherence to cough etiquettes by the index case. School children show one of the highest infection rates and outbreaks are common in school. For reducing transmission in schools, the classrooms should be kept well ventilated, children should be trained in hand hygiene and cough etiquettes and sick children should be prohibited from attending school till they are afebrile. Temporary school closure may be considered during a massive pandemic. In order to prevent nosocomial transmission, standard infection control precautions including droplet isolation and routine immunization of health care workers are recommended.

Suggested Reading

- World Health Organization. Influenza update. www.who.int
- Kumar B, Asha K, Khanna M, et al. The emerging influenza virus threat: Arch Virol 2018; 163:831–44.

Zika Virus

Zika is an RNA flavivirus closely related to the dengue and chikungunya viruses which has recently assumed prominence due to its association with newborn microcephaly.

Epidemiology

The virus was first identified in a rhesus monkey in the Zika forest of Uganda in 1947 with only 13 human cases diagnosed till 2007. Since then, large outbreaks have happened in the Pacific islands of Micronesia, French Polynesia and New Caledonia. A very large outbreak was reported in Brazil in 2015 with almost a million cases. The virus has since spread worldwide including Asia. The WHO has declared it as a public health emergency of International Concern. No cases have been reported in India as yet; but India is at high risk for introduction of the virus due to presence of the *Aedes aegypti* mosquito.

The virus is transmitted primarily by the bite of *Aedes aegypti*. Other routes of transmission include vertical transmission from mother to child, sexual and possibly through blood transfusion.

Clinical Features and Complications

Many infections are asymptomatic. Clinical disease is characterized by low grade fever with arthralgia, myalgia, rash, conjunctivitis and lymphadenopathy. Symptomatology resembles dengue and chikungunya except that rash and conjunctivitis are more prominent than the other two illnesses.

There are two major complications of zika infection. The first is acute neurologic syndromes such as Guillain-Barre syndrome, myelitis and meningoencephalitis. However, more importantly are the teratogenic effects with an incidence of 30% in some cohort studies in Brazil. Infections in the first trimester and sometimes in the second trimester are associated with abortions, intrauterine deaths and stillbirths, microcephaly (13%) and ocular abnormalities.

Diagnosis

Diagnosis in the first seven days is by performing an RT PCR in blood and after seven days is by IgM MAC ELISA. ELISA can demonstrate cross-reactivity with other flaviviruses.

Treatment

There is no specific treatment and care is symptomatic and supportive. Prevention revolves around avoiding travel to zika-afflicted areas especially by pregnant women, and vector control. Candidate vaccines are in development.

Suggested Reading

- Bhardwaj S, Gokhale MD, Mourya DT. Zika virus: Current concerns in India. *Indian J Med Res* 2017; 146:572-75.

Ebola Virus

The Ebola virus is an RNA virus belonging to the family Filoviridae first described in 1976 near the Ebola river in Democratic Republic of Congo. Several outbreaks of hemorrhagic fever have been reported with high mortality.

Epidemiology

The Old World Fruit Bat is the natural reservoir of Ebola virus. Infection is transmitted to wild or farm animals (chimpanzees, pigs, monkeys) and humans through direct contact with bats or consumption of plants/products contaminated with bat feces or body fluids. Humans can also be infected by direct contact with infected animals or handling or consuming meat of infected animals. Human-to-human transmission to family members, caretakers and health care workers can occur through close contact or handling the fluids of infected patients.

Clinical Features

The incubation period varies from 2-21 days; initial symptoms are non-specific and consist of fever, headache,

weakness, nausea, vomiting, abdominal pain and joint and muscle aches. This is followed by bleeding from multiple sites and multiorgan failure, with fatality of 60%.

Diagnosis and Treatment

There is leukopenia and thrombocytopenia. Definitive diagnosis is by antigen detection, IgM ELISA, polymerase chain reaction and viral isolation. Treatment is supportive and symptomatic. Several novel therapies including serum of infected patients who have recovered from disease and nucleic acid-based therapies are under evaluation.

Prevention

Prevention centers around strict isolation of infected cases, safe burial practices and avoiding consumption of bush meat. Candidate vaccines are undergoing trials.

Suggested Reading

- Richards GA, Baker T, Amin P, et al. Ebola virus disease. *J Crit Care* 2018; 43:352-55.

Emerging Viruses in India

Crimean-Congo hemorrhagic fever (CCHF) virus is an RNA virus of the Bunyaviridae family normally infecting cattle and occasionally transmitted to humans by infected ticks. The virus is highly contagious and human-to-human transmission in household and hospital setting is not uncommon. Outbreaks of CCHF have been reported from various countries including Pakistan. It was first reported from India in 2011 from Gujarat. The presentation is that of a viral hemorrhagic fever with fever, body pain, headache, profuse bleeding, leukopenia, thrombocytopenia, altered liver functions, deranged coagulation parameters, rhabdomyolysis and renal failure. The disease mimics dengue with salient differences being early and more rapid platelet fall and rhabdomyolysis. Diagnosis is by specific PCR. Treatment is supportive; early administration of ribavirin is beneficial. Strict isolation of affected patients is crucial to prevent nosocomial transmission.

Hantaviruses, rodent-borne viruses, cause two important clinical syndromes: Hemorrhagic fever and renal syndrome (HFRS) in Europe and Asia including India and hantavirus cardiopulmonary syndrome in America. Rodents are natural hosts and humans acquire infection by inhalation of aerosols/contact with water contaminated by rodent excreta or saliva. In India, HFRS and asymptomatic hantavirus infection has been reported from Tamil Nadu. The disease presents as a febrile illness with body pain, headache, thrombocytopenia, elevated liver enzymes, bleeding and renal failure. Leukocytosis with shift to left differentiates it from dengue. Diagnosis is by specific IgM antibodies. Leptospirosis is a close differential. Coinfections of leptospirosis and hantavirus have also been reported. Treatment includes ribavirin and supportive care.

Nipah virus, an important cause of encephalitis, has been increasingly reported from West Bengal. Its natural asymptomatic hosts are fruit bats who can transmit infection and disease to pigs and humans. Human-to-human transmission has also been reported. Clinical features in humans are fever followed by features of encephalitis and sometimes pneumonia and respiratory distress. Mortality is as high as 70% and there are residual sequelae in survivors. Treatment is symptomatic and supportive. Prevention centers around limiting human exposure to raw date palm juice contaminated by fruit bat excreta and infected pigs.

Chandipura virus, a rhabdovirus, is implicated as a cause of epidemic viral encephalitis in children in several states in India. It is transmitted by bite of infected sandflies and is associated with high mortality and neurologic sequelae.

COMMON BACTERIAL INFECTIONS

Brucellosis

Brucellosis is a relatively uncommon chronic granulomatous infection that occurs worldwide including India and the Middle Eastern countries.

Etiopathogenesis

Brucella species are intracellular gram-negative coccobacilli. Their classification is based on their preferred hosts namely *B. melitensis* (sheep and goats), *B. abortus* (cattle), *B. suis* (pigs), *B. canis* (dogs). Brucellosis is a zoonosis and transmission to humans can occur through the consumption of infected unpasteurized milk and animal products, through direct contact with infected animal parts such as placenta by inoculation of skin and mucous membranes and by inhalation of infected aerosolized particles. The vast majority of cases worldwide are attributed to *B. melitensis*.

Clinical Features

The illness has protean manifestations; incubation period is usually between 7 days and 3 months. A history of exposure to animals especially drinking unpasteurized milk may be present. Fever is continuous or intermittent and often chronic and accompanied by profuse sweating, joint pains, hepatosplenomegaly and less common lymphadenopathy. In untreated cases, complications such as spondylitis, osteoarthritis, meningoenzephalitis, brain abscess, pneumonia and endocarditis can occur.

Diagnosis

Complete blood count reveals anemia, leukopenia and thrombocytopenia; liver enzymes are mildly elevated. The diagnosis is made on blood culture. Sensitivity of bone marrow cultures is even higher, as organisms are present in large amount in the reticuloendothelial system. Serum agglutination tests showing high antibody titers (above

1:160 or 1:320) are considered diagnostic. Common differential diagnoses include tuberculosis, enteric fever, chronic malaria, HIV, sarcoidosis and lymphoproliferative disorders.

Treatment

Treatment consists of the combination of doxycycline and rifampicin for 6 weeks supplemented with intramuscular streptomycin or gentamicin for the first 1-2 weeks. For children less than 8 years of age, combinations containing rifampicin and cotrimoxazole for 6 weeks with or without aminoglycosides are recommended. Treatment may need to be prolonged for endocarditis and neurobrucellosis.

Suggested Reading

- Dean AS, Crump L, Greter H, et al. Clinical manifestations of human brucellosis. *PLoS Negl Trop Dis* 2012; 6: e1929.

Staphylococcal Infections

Staphylococcus, a gram-positive coccus, is a common cause of both community acquired and nosocomial diseases in humans.

Etiopathogenesis

Staphylococci are functionally classified on basis of production of an enzyme and virulence factor coagulase. Coagulase-positive *Staphylococcus* is termed as *S. aureus* while *S. saprophyticus* and *S. epidermidis* are important coagulase-negative staphylococci (CONS). CONS usually colonize the skin of all people and *S. aureus* the nares, axilla and perineum of around 20-25% of the population. Staphylococcal infection is acquired usually by direct contact with an infected patient or carrier and sometimes contaminated objects. Airborne spread is less common. Predisposing factors for staphylococcal infections include breach in the mucocutaneous barrier, previous viral infections such as measles, depressed immunity and prosthetic material such as shunts and central venous catheters.

Clinical Features

Common infections include those of skin and soft tissues like furuncles, impetigo, carbuncles, abscesses and cellulitis. In some situations, the bacteria invade the fascia and muscle causing necrotizing fasciitis, an infection that is associated with very high morbidity and mortality. Staphylococcal scalded skin syndrome is another bullous infection commonly seen in infants produced by exfoliative toxin producing *S. aureus*.

S. aureus is an important cause of respiratory infections such as sinusitis, otitis media, pneumonia, lung abscess and empyema. Staphylococcal pneumonia commonly occurs after antecedent viral infections, is rapidly progressive and associated with a high rate of complications such as pneumatoceles, abscess and empyema (Fig. 11.12). *S. aureus* is the chief cause of acute infective endocarditis



Fig. 11.12: Staphylococcal pneumonia with pneumatocele

in patients with native and prosthetic valves and sometimes with no risk factors. It is rapidly progressive, locally destructive and is associated with significant complications. It is also the commonest cause of pyopericardium an illness with high rates of constrictive pericarditis.

S. aureus is the commonest cause of musculoskeletal infections such as osteomyelitis, septic arthritis and pyomyositis. CNS infections, such as meningitis, usually occur following trauma or neurosurgery. *S. aureus* is also a common etiologic agent of subdural empyema, brain abscess and shunt infections. Enterotoxin producing *S. aureus* is a common cause of food poisoning that is characterized by fever and profuse vomiting.

Toxic shock syndrome (TSS) results from a locally non-invasive toxigenic strain, characterized by fever, shock, erythematous skin rash, hepatic derangement, sensorial changes and high mortality. Disseminated staphylococcal disease is seen in previously healthy children and characterized by suppurative staphylococcal infections at multiple sites either together or serially.

CONS are usually pathogens of lower virulence than *S. aureus*. Since they colonize the skin, they are often cultured as contaminants, if blood cultures are not collected by aseptic techniques. They are commonly implicated in bacteremia in low birth weight babies or in those with central venous catheters, subacute infective endocarditis, CNS shunt infections, infections associated with peritoneal dialysis catheters and prosthetic joints, urinary tract infections and postoperative surgical site infections.

Treatment

The most important treatment strategies are surgical drainage and antibiotics. Antibiotic therapy of staphylococcal infections has become complicated due to evolving resistance in staphylococci. More than 90% of the current day organisms are resistant to penicillin due to production of a beta lactamase or penicillinase that destroys the beta

lactam ring of penicillin. Most of them, however, are sensitive to penicillinase-resistant penicillins such as cloxacillin, methicillin and cephalosporins and are termed MSSA. Some staphylococci, however, have acquired resistance to methicillin by production of an altered penicillin-binding protein and are termed MRSA. MRSA were till some time back only reported as causative agents of nosocomial infections but are now reported even in community-acquired infections.

The drug of choice for treating MSSA infections is cloxacillin. Other alternatives are first generation cephalosporins (cephalexin, cefadroxil for outpatient therapy or ceftazidime for serious infections), second generation cephalosporins (cefuroxime), third generation cephalosporins (ceftriaxone) and clindamycin. Since cloxacillin is not easily available, ceftazidime and ceftriaxone are increasingly used for serious infections. If MRSA infections are proven or suspected, medications like vancomycin, linezolid and teicoplanin are used. Daptomycin acts well against both MSSA and MRSA.

Most *S. aureus* infections need removal of any prosthetic material to ensure cure and prolonged therapy ranging from 2 weeks for bacteremia and up to 4–6 weeks for osteomyelitis, septic arthritis and endocarditis.

Suggested Reading

- Jung N, Rieg S. Essentials in the management of *S. aureus* blood stream infection. Infection 2018 doi: 10.1007/s15010-018-1130-8.
- Tong SY, Daris JS, Eichemberger E, et al. Staphylococcus aureus infections; epidemiology, pathophysiology, manifestations and management. Clin Microbiol Rev 2015; 28:603–61.

Pneumococcal Infections

Pneumococcus is one of the most common bacterial causes of pediatric infections particularly pneumonia. It is estimated that 50% of deaths due to severe pneumonia are caused by pneumococcus.

Etiopathogenesis

Pneumococcus is a gram-positive diplococcus with a thick polysaccharide capsule. This capsule is the most important virulence factor and determines the various serotypes of the pneumococcus. Almost 90 serotypes of pneumococcus exist but only a handful cause disease. Serotypes 1, 3, 4, 5, 6A and 6B, 9V, 14, 18C, 19A, 19F and 23 commonly cause human disease and are incorporated in the vaccines. Pneumococci colonize the nasopharynx; these rates are highest in young children. Risk factors for disease include extremes of age, splenic dysfunction, immunodeficiency especially HIV, any chronic disease and CSF leaks.

Clinical Features

Pneumococcal infections are distributed like a pyramid, the base being non-invasive disease such as otitis media, sinusitis and pneumonia and the apex comprising of invasive disease like severe pneumonia, bacteremia and

meningitis. It is estimated that for every 1000 cases of otitis media, there is 1 case of meningitis. Other less common invasive diseases due to pneumococci are osteomyelitis, septic arthritis, cellulitis and peritonitis.

Pneumococcus is responsible for 30% of all acute bacterial meningitis and is associated with high rate of complications like subdural empyema, morbidity and mortality. Pneumococcal bacteremia presents usually as fever without focus in infants and children below 3 years, and needs aggressive therapy. Pneumococcal pneumonia has a lobar distribution with necrosis and empyema being common complications.

Diagnosis

The gold standard for diagnosis is culture. Low culture yields are responsible for under recognition of pneumococcus as a common pathogen. Pneumococcus unlike *Salmonella* is difficult to culture, especially if antibiotics have been administered. Special media containing sheep blood are required and delays in transportation and improper storage further reduce recovery. In pneumonia, isolation rates from blood are low, and the ideal sample of lung aspirate cannot be obtained in routine clinical practice. Other tests useful in diagnosis are Gram stain (Fig. 11.13), latex agglutination tests in CSF and pleural fluids and recently PCR.

Treatment

Penicillin and its derivatives such as ampicillin and amoxicillin are the drugs of choice for treatment of pneumococcal infections; ceftriaxone is a satisfactory alternative. Like many other bacteria, resistance in pneumococcus is being increasingly reported (more from the West and relatively less from India). Resistance to beta-lactams is due to altered penicillin-binding protein that may be intermediate or high level. Intermediate resistance can be overcome by using higher doses of penicillin or amoxicillin, but high level resistance requires use of alternative drugs like fluoroquinolones, vancomycin, or teicoplanin.

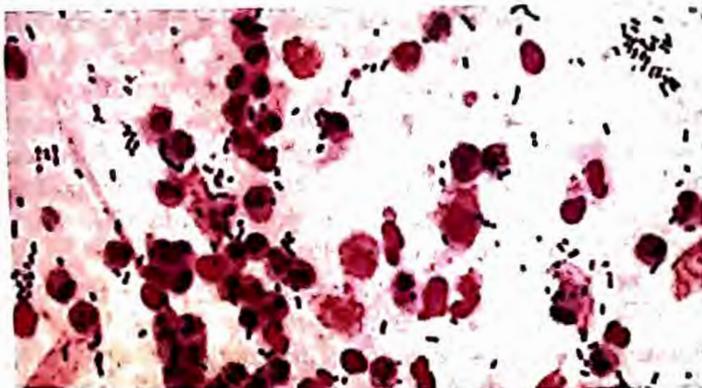


Fig. 11.13: Gram stain of pus showing abundant gram-positive diplococci, pneumococci

Suggested Reading

- Global pneumococcal disease and vaccine, www.cdc.gov/pneumococcal/global.html
- Maraga NF. Pneumococcal infections. *Pediatr Rev* 2014; 35:299-310.

Diphtheria

Diphtheria is an acute bacterial infection caused by gram-positive bacillus *Corynebacterium diphtheriae*. Though the incidence of diphtheria has decreased remarkably following increasing immunization, cases do occur in unvaccinated children and adults who have lost their immunity.

Etiopathogenesis

The secretions and discharges from infected person or carrier are the main source of infection. The infection is transmitted by contact or via droplets of secretion. The portal of entry is commonly the respiratory tract. The incubation period of the disease is 2-5 days. *C. diphtheriae* proliferates and liberates powerful exotoxin which is the principal cause of systemic and local lesions. The exotoxin causes necrosis of the epithelial cells and liberates serous and fibrinous material which forms a grayish white pseudomembrane which bleeds on being dislodged. The surrounding tissue is inflamed and edematous. The organs principally affected by the exotoxin include the heart, kidney and myocardium.

Clinical Features

The onset is generally acute with fever, malaise and headache. The child has a toxic look. The clinical features depend on the site of involvement. The commonest form is faucial or tonsillopharyngeal diphtheria in which there is redness and swelling over the fauces. The exudates coalesce to form a grayish white pseudomembrane, which extends to surrounding areas. The cervical lymph nodes are enlarged leading to a bull neck appearance. Sore throat, dysphagia and muffled voice are frequently present. In nasal diphtheria, there is unilateral or bilateral serosanguineous discharge from the nose and excoriation of upper lip. In laryngotracheal diphtheria, the membrane over the larynx leads to brassy cough, stridor and respiratory distress. Diphtheritic lesions may occasionally also be found in skin and conjunctiva.

The commonest complication is respiratory failure due to occlusion of the airways by the membrane. Myocarditis generally occurs by second week of illness and can lead to symptoms of congestive cardiac failure, arrhythmias and sudden death. Neurological complications include: (i) Palatal palsy, which occurs in second week and is clinically manifested by nasal twang and nasal regurgitation; (ii) ocular palsy in third week; (iii) loss of accommodation, manifested by visual blurring and inability to read; (iv) generalized polyneuritis occurs by third to sixth weeks of illness. Renal complications include oliguria and proteinuria.

Diagnosis

There should be a high index of suspicion. Rapid diagnosis is enabled by Albert stain of a swab from the oropharynx or larynx. Culture, however, takes 8 hours to become available. Faucial diphtheria should be differentiated from acute streptococcal membranous tonsillitis (patients have high fever but are less toxic and the membrane is confined to the tonsils), viral (adenovirus) membranous tonsillitis (high fever, sore throat, membranous tonsillitis with normal leukocyte count, self-limited course of 4–8 days), herpetic tonsillitis/aphthous stomatitis, thrush, infectious mononucleosis (generalized rash, lymphadenopathy, abnormal lymphocytosis, positive Paul-Bunnell test), agranulocytosis and leukemia.

Management

The most important component of therapy is neutralization of bacterial toxin by administration of antitoxin. Diphtheria antitoxin (IV/IM) should be administered soon as infection with diphtheria bacilli is suspected even earlier than bacteriological confirmation before the bacteria have fixed to the tissues. The degree of protection offered by the diphtheria antitoxin is inversely proportional to the duration of clinical illness. Repeat doses of antitoxin may be given, if clinical improvement is suboptimal.

Antibiotics such as penicillin or erythromycin should be used to terminate toxin production, limit proliferation of bacteria, prevent spread of organism to contacts and prevent the development of carriers. This should be followed by active immunization as clinical disease does not confer active immunity.

Bed rest is advocated for two to three weeks. Children should be monitored for airway obstruction and managed; tracheostomy may be required in some cases. Sudden exertion should be avoided and changes in rate and rhythm of heart should be looked for. Children with palatal palsy should be fed by nasogastric feeding. Generalized weakness due to polyneuritis is treated as for poliomyelitis or Guillain-Barre syndrome.

Prevention and Control

The patient should be isolated until two successive cultures of throat and nose are negative for diphtheria bacillus. All contaminated articles from discharges should be disinfected. All household/other contacts should be observed carefully for development of active lesions, cultured for *C. diphtheriae* and given chemoprophylaxis with oral erythromycin for 7 days or single dose benzathine penicillin. Previously immunized asymptomatic patients should receive a booster dose of diphtheria toxoid. Those not fully immunized should receive immunization for their age (Chapter 10).

Suggested Reading

- Clarke KEN. Review of the epidemiology of diphtheria: 2000-16. www.who.int

- Zibners L. Diphtheria, pertussis and tetanus: evidence based management of pediatric patients in the emergency department. *Pediatr Emerg Med Pract* 2017; 14:1-24.

Pertussis (Whooping Cough)

Pertussis is an acute highly contagious respiratory tract infection, caused by *Bordetella pertussis*. It may affect any susceptible host but is more common and serious in infancy and early childhood. The disease is characterized by intense spasmodic cough. Similar illness is also caused by *B. parapertussis*, *B. bronchoseptica* and adenoviral infections 1, 2, 3 and 5. The disease is under recognized and under reported due to low awareness, non-classical cases and limited availability of diagnostic tests. The worldwide prevalence of the illness has declined following widespread vaccination. The disease continues to be endemic in India with 25000 reported cases in 2015.

Epidemiology

Pertussis is extremely contagious with attack rates as high as 100% in susceptible individuals exposed to aerosol droplets. *B. pertussis* does not survive for prolonged periods in the environment. Chronic carriage in humans is not known. After intense exposure as in households, the rate of subclinical infection is as high as 80% in fully immunized and naturally immune individuals. Protection against typical disease wanes 3–5 years after vaccination and is unmeasurable after 12 years. Coughing adolescents and adults are the major reservoir of *B. pertussis* and are the usual sources for index cases in infants and children.

Features

The incubation period of the disease is 7–14 days. The clinical presentation can be divided into three stages.

The *catarrhal phase* lasts for 1–2 weeks and is the most infectious. The initial manifestations are indistinguishable from upper respiratory tract infections. The child has cough, coryza with little nasopharyngeal secretions. Unlike the upper respiratory infections, the cough does not improve in a few days but becomes more severe and frequent with the passage of time. Though the cough may not be typically paroxysmal in early stages, it tends to be annoying and frequent at night. The paroxysmal nature of the cough is suspected towards the latter part of this phase.

The *paroxysmal stage* lasts for 2–6 weeks in which cough progresses to episodic paroxysms of increasing intensity ending with high-pitched inspiratory whoop. The whoop is produced by the air rushing in during inspiration through the half-open glottis. The whoop may not always be present in infants who present with apneic or cyanotic spells. The child coughs up thick tenacious mucus. The paroxysms of cough may occur frequently and terminate by vomiting. Repeated thrusting of tongue over the teeth causes ulceration of the frenulum of the tongue. Paroxysms of cough are precipitated by food, cold air and

cold liquids. In infants <3 months, this stage may be considerably prolonged.

In the *convalescent phase*, the intensity and paroxysms of cough decrease gradually over 1–4 weeks. The vomiting becomes less frequent. Appetite, general condition and health gradually improve.

Complications

- Young infants show apnea, leukocytosis and pulmonary hypertension and high mortality
- *Respiratory complications*: Otitis media, pneumonia, atelectasis, emphysema, bronchiectasis, pneumothorax and pneumomediastinum
- *Neurological complications*: Seizures and encephalopathy (2–7%)
- *Bleeding episodes*: Epistaxis, retinal or subconjunctival bleeds, intracranial hemorrhage.
- Inguinal hernia, rectal prolapse
- Malnutrition due to persistent vomiting and disinclination to eat
- Flare up of tuberculosis

Diagnosis

The diagnosis of whooping cough is based on clinical features. There may be a lymphocytic leukocytosis and low ESR. Specific diagnosis depends on isolation of the organism from nasopharyngeal swab or cough plate cultured on Bordet-Gengou medium. Culture positivity declines with advancing illness and administration of antibiotics. Other diagnostic tests including serology and PCR in throat swab are not routinely available. Differentials for pertussis include adenoviral infections, endobronchial tuberculosis, extrinsic compression of airways by lymph nodes, inhaled foreign body and reactive airway disease.

Management

General measures include providing adequate nutrition and hydration and avoiding factors aggravating cough. Macrolides including erythromycin, azithromycin or clarithromycin are the drugs of choice. Antibiotics terminate the respiratory tract carriage of *B. pertussis* thus reducing the period of communicability but do not shorten the course of illness. Nebulization with salbutamol is sometimes effective in reducing bronchospasm and controlling bouts of cough. Cough suppressants and antihistaminic agents should be avoided.

Prevention

Chemoprophylaxis with erythromycin is recommended for close family contacts especially children <2 years of age. Non-immunized and partially immunized contacts should be vaccinated (Chapter 10).

Suggested Reading

- Yeung KHT, Duclos P, Nelson EAS, Hutubessy RCW. An update of the global burden of pertussis in children younger than 5 years. *Lancet Infect Dis* 2017; 17:974–80.

Enteric Fever

The term enteric fever includes typhoid fever caused by *Salmonella enterica* var *typhi* and paratyphoid fever caused by *S. enterica* var *paratyphi* A, B or C. Paratyphoid infections constitute about 20% of all cases of enteric fever worldwide. As enteric fever is a disease transmitted by the feco-oral route, its greatest burden is in resource-limited countries where water supply and sanitary conditions are poor. In a community based study in urban slums of Delhi, the incidence was estimated to be 980/100,000 population with 44% of the cases occurring in children below 5 years.

Enteric fever is one of the commonest causes of fever lasting for more than 7 days in clinical practice in India.

Etiopathogenesis

S. enterica serotype *typhi/paratyphi* is a gram-negative, non-lactose fermenting, flagellate bacterium. The somatic or O antigen is shared among various salmonellae; the flagellar or H antigen is specific to the serovar. *S. enterica* var *typhi* also possesses a Vi polysaccharide capsule.

The infective dose of typhoid/paratyphoid bacillus varies from 10^3 to 10^6 organisms. The organism must survive the gastric barrier to reach the small intestine; conditions which reduce gastric acidity, such as antacids, H_2 receptor blockers and proton pump inhibitors reduce the infective dose. On reaching the small intestine, the organism penetrates the mucosa and infects lymphoid follicles and subsequently the draining mesenteric nodes and the liver and spleen. It multiplies in the reticulo-endothelial system and after incubation period varying from 7–14 days spills into the bloodstream and is widely disseminated, especially to liver, spleen, bone marrow, gallbladder and Peyer patches of the terminal ileum. This marks the onset of clinical manifestations of enteric fever. Infection leads to local and systemic immune responses, which are, however, inadequate to prevent relapse or reinfection.

Clinical Features

There is no appreciable difference between the manifestations of typhoid and paratyphoid fever. The hallmark of enteric fever is fever which starts as a low grade fever and then shows stepwise increase peaking to as high as $103\text{--}104^\circ\text{C}$ by the end of the first week. This pattern differentiates it from viral fever where the peak is usually at the onset of fever. With fever, there is associated malaise, dull headache, anorexia, nausea, poorly localized abdominal discomfort, mild cough and malaise. There may be diarrhea; constipation in children is rare. Physical findings are unremarkable with the exception of a coated

tongue, tumid abdomen and sometimes hepatosplenomegaly. The rash described in Western textbooks is seldom or never seen in Indian subjects. Infants and young children with enteric fever may have diarrhea as a predominant manifestation or a short-lasting undifferentiated febrile illness. In the absence of treatment, fever may continue for 3–4 weeks followed by natural remission or by development of complications.

Complications

The commonest intestinal complications are bleeding or perforation seen in the 2nd or 3rd week of illness in 10–15% adult patients, but less frequently in children. Bleeding is due to erosion of a necrotic Peyer's patch through the wall of a vessel and is usually mild but can, sometimes, be life-threatening. Perforation is a dreaded complication manifesting as acute abdomen, with high mortality unless appropriately treated.

The term severe or complicated enteric fever is used for patients presenting with neurological complications such as delirium, coma, obtundation, stupor or shock and is associated with mortality rates as high as 50%. Other complications include hepatic and splenic abscesses, hepatitis, cholecystitis, pneumonia, disseminated intravascular coagulation, psychosis, ataxia or meningitis. The case fatality rate is less than 1% in appropriately treated cases but may be 10–20% in inadequately treated or complicated cases.

Relapse: Relapse may occur in 5–15% of treated cases, usually due to the organism with the same susceptibility as the original attack and is relatively a milder illness. Rate of relapse is dependent on choice of drug therapy. It is higher with beta lactams such as cefixime or ceftriaxone as compared to quinolones and azithromycin.

Carrier state: Although 5–10% adult patients may shed *Salmonella* in stool following an acute attack for up to 3 months, only 1–4% excrete bacilli for more than 1 year. These individuals are potential sources of infection for family members and contacts and for the community, if they are in occupations that involve food processing. There is no data on carrier prevalence in children; routine examination of stool following recovery from enteric fever is not recommended.

Diagnosis

Leukocyte counts may be normal to low with absolute eosinopenia and neutrophilic predominance. Anemia and thrombocytopenia may occur in advanced illness. There may be mild elevation of transaminases to 2–3 times normal (SGOT being higher than SGPT). A very high C-reactive protein sometimes helps to differentiate enteric from viral fevers, especially dengue. Ultrasound abdomen shows mesenteric adenitis with splenomegaly.

The gold standard for diagnosis is blood culture. The sensitivity is greatest in the first week at around 90% but

drops to 40% in the 4th week. Its overall sensitivity is 60%, which reduces to 20–40% after antibiotics. *Salmonella* is an easy organism to culture and use of bile broth media and automated culture systems such as BACTEC improve recovery. Sufficient blood should be collected (10 mL in adults and 5 mL in children) and a blood: media ratio of 1:5 should be maintained. The use of clot culture methods does not significantly improve recovery rates. Bone marrow cultures have higher yield as compared to peripheral blood cultures as *Salmonella* is a pathogen of the reticuloendothelial system and should be sent, if a bone marrow examination is done as part of work-up for pyrexia of unknown origin. Owing to very low recovery rates, stool cultures and urine cultures are not recommended. Antimicrobial susceptibility testing of the isolate is important in the era of multidrug resistance.

The Widal test detects presence of IgG and IgM antibodies to H (flagellar antigen) of *S. enterica* var *typhi* and *paratyphi* A and B, and O (somatic antigen) common to *typhi* and *paratyphi* A and B. Anti-O titers are both IgG and IgM that rise and decline early, while anti-H is primarily IgG that rise and decline late in course of the disease. The conventional method of interpretation of the Widal test has been to demonstrate fourfold rise in antibody titers in two samples. Since this is often not practical, a single titer of at least 1:160 for both O and H is considered positive. Even with this compromise, the Widal test has several limitations. Sensitivity is low in the first week of illness and in patients treated with prior antibiotics. Specificity is low owing to anamnestic reactions, prior vaccination, cross-reactivity with other *Enterobacteriaceae* and subclinical infections in endemic areas.

Treatment

Indications for inpatient treatment: Most cases of enteric fever can be managed at home with oral antibiotics and advice to seek medical follow-up in case of failure to respond to therapy or development of complications. Children with persistent vomiting, poor oral intake, severe diarrhea or abdominal distension usually require intravenous (IV) antibiotics and IV fluids, necessitating admission to hospital.

Antimicrobial susceptibility: The antimicrobial sensitivity of *S. typhi/paratyphi* has shown changes over the decades. Though resistance to chloramphenicol was first noted soon after its first use in 1940s, it was not until 1972 that chloramphenicol-resistant typhoid fever became a major problem. Multidrug-resistant typhoid fever (MDRTF) became a common occurrence by the end of 1990s, with emergence of *S. typhi* simultaneously resistant to all the drugs that were used as first-line treatment (chloramphenicol, trimethoprim, sulfamethoxazole and ampicillin). Fluoroquinolones were introduced in the late 1980s and early 1990s and produced very good results initially, but

the past decade has seen a progressive increase in the minimum inhibitory concentrations (MIC) of ciprofloxacin in *S. typhi* and *paratyphi* and resistance rates to fluoroquinolones/nalidixic acid now approach 90%. Alongside the rise in resistance to quinolones, there has been return in sensitivity to first-line antibiotics such as chloramphenicol, cotrimoxazole and ampicillin. However, concerns of toxicity and inconsistent reports of sensitivity preclude their widespread use. There are recent sporadic reports of resistance to ceftriaxone due to production of novel type of beta lactamases. *Salmonella* may show *in vitro* susceptibility to aminoglycosides and second-generation cephalosporins, but these are not effective *in vivo*, and should not for treatment.

Choice for empirical therapy: Where enteric fever is clinically suspected but cultures have not been sent for, reports are awaited or are sterile, empirical therapy may be started. Choice for empirical therapy is guided by various factors including the severity of the illness, inpatient/outpatient therapy, presence of complications and local sensitivity patterns.

For uncomplicated enteric fever, oral cefixime at a dose of 20 mg/kg/day (ceiling dose of 1200 mg) is the drug of choice. Azithromycin (10–20 mg/kg/day) is a good second choice agent; chloramphenicol (50 mg/kg/day), amoxicillin and cotrimoxazole are other second-line agents. Clinical efficacy is more or less the same with all these drugs with each drug having its own advantages and limitations. The choice of medication depends on individual preference, experience, and level of comfort and cost considerations. Once culture results are available, therapy can be modified. There is no data at present to support use of combination therapy in enteric fever.

For severe illness and where complications are present, intravenous ceftriaxone and cefotaxime are used a dose of 100 mg/kg/day and 200 mg/kg/day, respectively. In patients with history of penicillin or cephalosporin allergy, aztreonam, chloramphenicol (in higher than usual doses) and cotrimoxazole (in higher than usual doses) are used as second-line agents. Parenteral treatment is continued until defervescence has occurred, oral intake has improved and complications resolved. Thereafter, therapy can be switched to oral cefixime to complete a total duration of 14 days. Other oral drugs that may be used for switch over therapy include azithromycin, cotrimoxazole and amoxicillin.

In culture proven enteric fever, if defervescence does not occur by day 7, causes such as drug fever, thrombophlebitis, hepatic or splenic abscesses, hemophagocytic syndrome and coinfections need to be excluded. If cultures are negative and defervescence has not occurred by day 7, a thorough search for alternative etiology for fever should be made and ceftriaxone continued.

Therapy of relapses: Relapse rates vary with the type of drug and are most common with beta lactams (ceftriaxone,

cefixime) especially if shorter duration of therapy is used. Although relapses may be satisfactorily treated with the same drug as used for primary therapy, azithromycin is the preferred drug since it is associated with very low relapse rates.

Prevention

The most effective and desirable method for preventing enteric fever is by improving hygiene and sanitation. This will yield additional dividends of reduction in the burden of other water-borne illnesses as well. Vaccination as the other major preventive strategy, is discussed in Chapter 10.

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Leptospirosis

Leptospirosis is a zoonotic disease with worldwide distribution, caused by spirochetes of the genus *Leptospira*. Most cases occur in tropical and subtropical countries. While rats are the principal source of human infection, dogs, cats, livestock and wild animals are other important animal reservoirs. Infected animals may excrete the spirochete in urine for several weeks. The survival of excreted organisms depends on the moisture content and temperature of the soil. Humans acquire infection after being exposed to water or soil contaminated with rat urine. Agricultural workers, sewage workers, veterinarians, meat handlers, rodent control workers and laboratory personnel are at risk of getting infected because of occupational exposure. Infection is also common in the monsoons and during flooding.

Pathogenesis

Leptospira enter the body through abrasions and cuts in skin or through mucous membranes, and spread to all organs hematogenously. The organisms damage the endothelial lining of small blood vessels, with leakage and extravasation of blood cells, hemorrhage, and ischemic damage to various organs including liver, kidneys, meninges and muscles.

Clinical Features

Human infection with *Leptospira* may range from asymptomatic infection to severe and often fatal multiorgan involvement. Symptomatic infection presents as a relatively mild anicteric febrile illness in over 70% of patients, aseptic meningitis in about 20%; severe leptospirosis with hepatorenal dysfunction (Weil's disease) develops in 5–10% individuals. The incubation period is usually 1–2 weeks.

The illness is often biphasic. In the initial or septicemic phase lasting 2–7 days, the onset is abrupt with high grade fever with rigors and chills, lethargy, severe myalgia, headache, nausea, vomiting. Patient may have conjunctival suffusion with photophobia and orbital pain, generalized lymphadenopathy and hepatosplenomegaly. Transient maculopapular erythematous rash may be seen in <10% cases. Hypotension with bradycardia and circulatory collapse is rarely seen. Some patients develop acute respiratory distress syndrome with respiratory failure. Most patients become asymptomatic within one week.

In some patients, after a brief asymptomatic phase, the second phase, called the immune or leptospiruric phase, becomes manifest wherein *Leptospira* localize to various tissues to cause tissue specific signs and symptoms. In this phase, circulating autoantibodies to *Leptospira* are present; organisms can no more be isolated from blood or CSF but persist in tissues like kidneys and aqueous humor. During the immune phase, some children may develop aseptic meningitis or uveitis with recurrence of fever. Encephalitis, cranial nerve palsies, paralysis and papilledema are rare manifestations. Central nervous system abnormalities usually normalize within one week; mortality is rare.

In icteric leptospirosis (Weil's syndrome) after the initial phase of fever, patients develop severe hepatic and renal dysfunction. Jaundice, hepatomegaly and tenderness in right upper quadrant are usually detected. Splenomegaly found in 20% of cases. Non-oliguric renal failure with azotemia may develop, often during the second week of illness. All patients have abnormal urinary finding on urinalysis in the form of hematuria, proteinuria and casts. Hemorrhagic manifestations are rare but when present, may include epistaxis, hemoptysis and gastrointestinal and adrenal hemorrhage. Transient thrombocytopenia may occur. Mortality is 5–15%.

Diagnosis

Complete blood count shows anemia, leukocytosis with polymorph predominance and thrombocytopenia. The CRP is elevated and liver enzymes are mildly elevated with SGOT more than SGPT; CPK levels are high. In patients with Weil's disease, there is elevated serum creatinine, deranged coagulation parameters and direct hyperbilirubinemia with elevated transaminases.

Specific diagnosis is established by serologic testing, microscopic demonstration of the organism, culture or PCR. Serologic diagnosis is possible after 5 days of illness. The gold standard for serologic diagnosis is the microscopic agglutination test (MAT), which is only available in reference centers. Commercial kits for serologic diagnosis include rapid tests and IgM ELISA but these tests are often associated with cross-reactivity and false positivity with other infections such as enteric fever and malaria. Demonstration of organism in tissues or urine

by dark field microscopy or immunofluorescence and cultures are not routinely available. However, it is now possible to diagnose the illness in the first few days by PCR in blood.

Leptospirosis should be differentiated from other febrile illnesses commonly seen in the monsoon season such as malaria, dengue, enteric fever, acute viral hepatitis and hanta virus infections.

Treatment

Treatment should be initiated as early as possible. For severe leptospirosis, parenteral penicillin G (6–8 million U/m²/24 hr q 4 hr IV for 7 days) is the drug of choice. Ceftriaxone and IV tetracycline are also acceptable alternatives. For oral treatment, amoxicillin and in children above 8 years, doxycycline are preferred.

Prevention

Prevention entails avoidance of exposure to contaminated water. Single dose doxycycline or amoxicillin following exposure can also prevent illness.

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Tetanus

Tetanus is caused by the bacterium *Clostridium tetani*, a spore-forming, anaerobic, gram-positive, motile bacillus, found in human and animal feces. These spores are widespread in the environment. From an estimated 80,000 deaths from neonatal tetanus in India in 1990, less than 500 cases were reported in 2015 thus certifying India as free of maternal/neonatal tetanus. Elimination of neonatal tetanus has been defined as less than 1 case of neonatal tetanus per 1000 live births in every district of the country.

Pathogenesis

C. tetani is a non-invasive organism. The spores of the organism remain nonpathogenic in soil or contaminated tissues until conditions are favorable for transformation into vegetative form. Transformation occurs in the presence of locally decreased oxygen reduction potential, typically in devitalized tissue, in the presence of a foreign body, trauma and crush injury and suppurative infections. Two types of toxins are produced by the organism, *tetanolysin* and *tetanospasmin*. *Tetanospasmin* is the main toxin responsible for the manifestations of the disease. It binds to the neuromuscular junction at the site of injury, and undergoes retrograde axonal transport to reach the presynaptic nerve terminal where it prevents the release of inhibitory neurotransmitters glycine and GABA leading to uncontrolled contraction of muscles.

Clinical Features

Tetanus mainly affects the unimmunized and partly immunized individuals. The disease may occur in various forms: Neonatal, generalized, localized, and cephalic. The most common forms are generalized and neonatal tetanus.

Generalized tetanus has an incubation period of approximately 8 days (range 2–14 days). However, the disease may occur months after the initial injury. The incubation period depends on the distance of the site of injury from the central nervous system. The faster is the onset of symptoms, the poorer is the prognosis. Characteristically, there is descending paralysis, with initial involvement of the jaw muscles. There is spasm of the masseters leading to trismus or lockjaw. Subsequent involvement of the neck, back and abdominal muscles occurs, soon involving the whole body. As the disease progresses, minimal stimuli may lead to generalized spasms, the hallmark of the disease and contribute to serious complications and eventually death. Typically, the sensorium of the patient is preserved. There is difficulty in swallowing. Autonomic instability may occur, with blood pressure fluctuations in the form of hypertension or hypotension, diaphoresis and arrhythmias. Recovery usually begins after 3 weeks and approximately takes four weeks. Recovery from tetanus occurs by sprouting new nerve terminals in the spinal cord leading to relaxation of the contracted muscles.

Neonatal tetanus is a major cause of mortality in developing countries. Pregnant women who are not immunized against tetanus do not pass on protective antibodies to their babies. Infection results from unhygienic birth practices, most commonly when the umbilical cord is contaminated at the time of cutting. Symptoms usually appear by the third day after birth, never in the first two days of life and rarely after the age of two weeks. Excessive unexplained crying followed by refusal of feeds and apathy are the common initial symptoms. The baby develops progressive feeding difficulty, becomes rigid, develops paralysis, and may develop opisthotonic posturing and experience painful spasms. The mouth is kept slightly open due to pull and spasm of the neck (Fig. 11.14). There is generalized rigidity and opisthotonus in extension. Spasms of larynx and respiratory muscles are characteristically induced by stimuli such as touch, noise and bright light, resulting in episodes of apnea and cyanosis. The case fatality is high (70–100%).

Localized tetanus is less severe in comparison, and is characterized by rigidity and pain confined to the muscles adjacent to the wound. It may lead to generalized tetanus later. In patients with isolated localized tetanus, the mortality is less than 1%. *Cephalic tetanus* is a form of local tetanus, which occurs due to injury of the bulbar muscles, has a poor prognosis.



Fig. 11.14: Neonatal tetanus (Courtesy: Dr Amarjeet Mehta, Jaipur)

Treatment

Most patients require intensive care management and good supportive care. The aims of treatment are airway maintenance, prevention of further toxin absorption, relieving clinical features, e.g. spasms, controlling autonomic instability and antibiotics. Airway management may require intubation and mechanical ventilation, especially in severe cases and if the infant gets frequent episodes of laryngeal spasms, apneic attacks or central respiratory failure. Neutralization of free toxin is done by administering human tetanus immunoglobulin; however, antitoxin cannot dislodge the toxin already fixed to the nerve roots. The route of administration is intramuscular or intrathecal. The usual dose is 500 to 1000 IU. Antibiotic therapy is needed to abolish the bacteria from the wound site; commonly used agents are crystalline penicillin or metronidazole.

Spasms are precipitated by minimal stimuli, therefore, efforts should be made to avoid noxious stimuli including bright lights, pain and loud noises. Relief of spasms is done using benzodiazepines. The most commonly used agent is diazepam, either as an intermittent IV bolus or as continuous infusion. Diazepam prevents further spasms by causing GABA-mediated central inhibition. It also helps by reducing anxiety and promoting muscle relaxation. Other agents used for severe spasms include pancuronium bromide. Autonomic instability is controlled with the use of alpha and beta adrenergic blockers, and IV magnesium.

All patients should receive a complete course of immunization with tetanus toxoid once recovered, as the disease does not induce protective antibodies.

Prognosis

The disease has high mortality rate in spite of adequate supportive care, which may reach up to 50% in severe generalized tetanus and 90% in neonatal form. The outcome depends on the incubation period, the site of

injury, the rate of progression of illness, and presence of autonomic instability. Survivors do not manifest any neurological sequelae, except when apneic episodes are unduly prolonged and unattended. The prognosis in neonatal tetanus is worse, if (i) onset of symptoms occurs within the first weeks of life, (ii) interval between lockjaw and onset of spasms is less than 48 hours, (iii) high fever and tachycardia are present, (iv) spasms, especially of larynx resulting in apnea are severe and frequent.

Prevention

Immunization with tetanus toxoid leads to induction of protective antibodies, and is discussed in Chapter 10. Maternal and neonatal tetanus can be effectively prevented by immunizing the mother during pregnancy, and ensuring clean delivery and cord care.

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TUBERCULOSIS

Tuberculosis, caused by *Mycobacterium tuberculosis*, kills nearly 2 million people every year. More than 90% cases occur in the developing countries, where resources for optimal treatment are limited.

Magnitude

Since most children acquire the organism from adults, the epidemiology of childhood tuberculosis follows that in adults. While the global burden of the illness is unclear, it is estimated that ~10% cases occur in childhood. Tuberculosis infection and disease among children are much more prevalent in developing countries, where resources for control are scarce. It is estimated that in developing countries, the annual risk of tuberculosis infection in children is 2–5%. The estimated lifetime risk of developing tuberculosis for a young child infected with *M. tuberculosis*, as indicated by positive tuberculin test, is about 10%. About 5% of those infected are likely to develop disease in the first year after infection and the remaining 5% later. These rates increase about sixfold in HIV-infected individuals.

Reasons for an increase in childhood tuberculosis include inadequate facilities for diagnosis, prevention and therapy, the HIV pandemic, and emergence of drug resistance with nearly 170000 children dying every year. Due to improved standard of living, the incidence of tuberculosis has declined in affluent and highly developed countries. However, it continues to be a public health problem in underprivileged countries of Asia, Africa and South America.

Epidemiology

Agent: All patients of pulmonary tuberculosis and most cases of extrapulmonary disease are caused by human type strain of *M. tuberculosis*. A few cases of extrapulmonary illness particularly the tubercular lymphadenitis may be due to the bovine strain.

Reservoir of infection: Infection is spread by patients suffering from pulmonary tuberculosis, who discharge tubercle bacilli in sputum or nasopharyngeal secretions during bouts of coughing or sneezing. Such patients are called open or infective cases. In children, a few infections may occur transplacentally (congenital tuberculosis).

Mode of infection: The usual mode of infection is through inhalation of droplets of infected secretions. Infected sputum from open cases of tuberculosis dries up, and tubercle bacilli are resuspended in dust and air that might be inhaled. Infection through ingestion of infected material is rare. Rarely infection is transmitted through skin, mucous membrane or transplacentally.

Host Factors

No age is exempt from tuberculosis. Tubercle bacilli are not transferred across the healthy placenta but the fetus may be infected from an infected placenta. The frequency of infection increases with age. An infant is more likely to develop disease after an infection compared to an older child.

Adolescents, especially girls, are prone to develop active tuberculosis disease during puberty. Undernourished children are more susceptible to develop tuberculosis, probably due to depressed immune defense. Tuberculosis may precipitate severe malnutrition in infants with undernutrition. A malnourished patient who does not respond to dietary therapy should be investigated for tuberculosis.

Children with primary or secondary immune deficiencies develop disseminated disease. Illnesses that affect cell-mediated immunity (including measles) increase the susceptibility of disease. The risk of infection is associated with the extent of contact and burden of organisms in the sputum. Patients with smear positive pulmonary tuberculosis are more likely to transmit infection. An increased risk of infection is seen in institutional settings (nursing homes, correctional centers and homeless shelters).

Pathology

The inhaled tubercle bacilli lodge in pulmonary alveoli and cause inflammation with hyperemia and congestion. Initially, polymorphonuclear leukocytes infiltrate the site, but their phagocytic ability is low and they are soon eliminated. The further course depends on the immune response of the host. If host resistance is good, the inflammatory exudate around the primary focus is

absorbed and the caseous area inspissated. Healing occurs by fibrosis and calcification. When the cell-mediated immune response is weak, the bacilli continue to multiply and the inflammatory process extends to the contiguous areas.

Progressive primary disease is a serious complication of the pulmonary primary complex (PPC) in which the PPC, instead of resolving/calcifying, enlarges steadily and develops a large caseous center. The center liquefies and may empty into an adjacent bronchus leading to formation of a cavity, which characteristically is associated with large numbers of tubercle bacilli. Next, the bacilli may spread to other parts of the lobe or the entire lung, resulting in lobar consolidation or bronchopneumonia. Cavitory disease is uncommon in young children. The enlarged lymph nodes may compress the neighboring airway. Ball-valve effect due to incomplete obstruction may lead to trapping of air distal to obstruction (emphysema). Enlarged paratracheal nodes may cause stridor and respiratory distress, and subcarinal nodes impinge on the esophagus and cause dysphagia. If obstruction of the bronchus is complete, atelectasis may occur.

Outcome of Bronchial Obstruction

- i. Complete expansion and resolution of chest X-ray findings
- ii. Disappearance of the segmental lesions
- iii. Scarring and progressive compression of the lobe or segment leading to bronchiectasis

A caseated lymph node may erode through the wall of the bronchus, leading to tuberculous bronchitis or endobronchial tuberculosis. Fibrosis and bronchiectatic changes may supervene. Discharge of bacteria into the lumen may lead to their bronchial dissemination.

Hematogenous dissemination from infected lymph nodes occurs early in course, resulting in foci of infection in various organs (e.g. Simon focus in apex of the lungs). If the host immunity is good, these foci are contained and disease does not occur. Lowered host immunity, as in infants, severely malnourished children and immunodeficiency, may lead to activation of these metastatic foci and occurrence of disease. Massive hematogenous seeding with *M. tuberculosis*, usually within 3–6 months after initial infection, leads to miliary tuberculosis where all lesions are of similar size.

Pulmonary tuberculosis resulting from endogenous reactivation of foci of infection is uncommon in children; but may be seen in adolescents. The commonest site for this type of disease is the apex of the lung (Puhl lesion), because blood flow is sluggish at apex. Regional lymph nodes are usually not involved. Miliary and meningeal tuberculosis usually occur within 1 year of the primary lesion.

Clinical Features

The incubation period varies between 4 and 8 weeks. The onset of symptoms is insidious, but may be acute in miliary tuberculosis. Primary infection usually passes off

unrecognized. Asymptomatic infection is defined as infection associated with tuberculin hypersensitivity and a positive tuberculin test, without significant clinical or radiological findings.

Symptoms in children with PPC include mild fever, anorexia and weight loss; occasionally PPC are detected during evaluation of intercurrent infection. Cough is inconsistent and may be absent even in advanced disease. Irritating dry cough can be a symptom of bronchial and tracheal compression due to enlarged lymph nodes. Lymph nodes may continue to enlarge even after resolution of parenchymal infiltrates, and lead to compression of neighboring bronchi.

Progressive primary disease (PPD) is the result of the progression of primary disease. Children with PPD present with high-grade fever and cough. Expectoration of sputum and hemoptysis are associated with advanced disease and development of cavity or ulceration of bronchi. Cavitating pulmonary tuberculosis is uncommon in childhood. Children with endobronchial tuberculosis usually present with fever, troublesome cough (with or without expectoration). Dyspnea, wheezing and cyanosis may be present. Partial compression of the airway can lead to emphysema; features of collapse are seen with large airway compression.

Miliary tuberculosis, characterized by hematogenous spread and multiple systemic foci, is common in infants and young children. The onset of illness is sudden and clinical features depend on the number of disseminated organisms and involved organs. Unlike other forms of tuberculosis, the child shows high-grade fever; dyspnea, cyanosis and altered sensorium are associated. There are hardly any pulmonary findings, but fine crepitations and rhonchi may be present. Patients often show lymphadenopathy and hepatosplenomegaly. Choroid tubercles may be seen in ~50% and meningitis in 20–30%.

Pleural effusion follows the rupture of a subpleural focus into pleural cavity, but may also occur following hematogenous spread from the primary focus. The effusion occurs because of hypersensitivity to tubercular proteins. Minor effusions are usually asymptomatic. Tuberculous effusion is uncommon in children younger than 5 years of age, and is rarely associated with segmental lesion and miliary tuberculosis. The onset may be insidious or acute with fever, cough, dyspnea, pain and a pleural rub. Increase in effusion may make breathing shallow and difficult. Early signs include decreased chest wall movement, impaired percussion note and reduced air entry on affected side. As fluid collection increases, signs of pleural effusion are more definite.

Extrathoracic Tuberculosis

The most common forms of extrathoracic disease in children include tuberculosis of the superficial lymph nodes (scrofula) and the central nervous system. Other rare forms of extrathoracic disease include osteoarticular,

abdominal, gastrointestinal, genitourinary, cutaneous and congenital disease.

Tuberculosis of superficial lymph nodes may be associated with drinking unpasteurized cow milk or extension of primary lesions of upper lung or abdomen leading to involvement of the supraclavicular, anterior cervical, tonsillar and submandibular nodes. Although lymph nodes may become fixed to surrounding tissues, low grade fever may be the only systemic symptom. A primary focus is visible radiologically in 30 to 70% patients; tuberculin test is usually reactive. Although spontaneous resolution may occur, untreated lymphadenitis frequently progresses to caseating necrosis, capsular rupture, and spread to adjacent nodes and overlying skin, resulting in a draining sinus tract.

Central nervous system disease is the most serious complication of tuberculosis and arises from formation of a caseous lesion in the cerebral cortex or meninges, due to occult lymphohematogenous spread. Infants and young children are likely to experience rapid progression to hydrocephalus, seizures and raised intracranial pressure. In older children, signs and symptoms progress over several weeks, beginning with fever, headache, irritability and drowsiness. The disease advances with lethargy, vomiting, nuchal rigidity, seizures, hypertonia and focal signs. The final stage of disease is marked by coma, hypertension, decerebrate and decorticate posturing and death. Rapid confirmation of the diagnosis can be difficult because of variable cerebrospinal characteristics, nonreactive tuberculin tests (40%) and normal chest radiographs (50%). Since better outcomes are associated with early institution of therapy, the diagnosis should be considered in any child with basilar meningitis, hydrocephalus or cranial nerve involvement.

Tuberculosis of abdomen is due to hematogenous spread from the lungs. It may, however, be secondary to swallowing of the infected sputum by a patient with pulmonary lesions. Patients with abdominal tuberculosis may remain asymptomatic initially. Symptomatic patients show toxemia and have colicky abdominal pain, vomiting and constipation. The abdomen feels characteristically doughy; abdominal wall is not rigid but tense. The rolled up omentum and enlarged lymph nodes appear as irregular nodular masses with ascites; liver and spleen are often enlarged.

Children may rarely present with hemophagocytic lymphohistiocytosis (HLH), immune hemolytic anemia, superior mediastinal syndrome, pneumothorax and immune reconstitution inflammatory syndrome (IRIS) in form of paradoxical worsening of symptoms after starting antituberculous drugs, especially in children with immune deficiency.

Diagnosis

The diagnosis of tuberculosis in children is based on clinical features, chest roentgenogram, tuberculin testing

and history of contact with adult patients. Clinical features may be nonspecific and chest radiograph and tuberculin test are difficult to interpret. In addition, these do not give conclusive evidence for the disease. While demonstration of mycobacterium in various clinical specimens is the gold standard, this is often not possible in children due to the paucibacillary nature of the illness.

History of contact: A contact is defined as a child who lives in a household with an adult taking antitubercular therapy or having taken such therapy in the past 2 years. A history of contact is available in less than one-third of the patients. Contacts can often be traced to a maid servant, cook, domestic aid or gardener in case of patients from well-to-do families with healthy parents. Tracing of contact is useful for confirming the diagnosis, as well as protection of other susceptible children from the disease.

Laboratory Tests

Diagnostic tests for pulmonary tuberculosis can be divided into 2 categories based on demonstration of: (i) *M. tuberculosis* or one of its components; (ii) host response to *M. tuberculosis*.

Tubercle bacteria can be demonstrated by (i) Ziehl-Neelsen (acid-fast) staining, (ii) special stains, (iii) cultures, and (iv) cartridge-based nucleic acid amplification test. The above methods can be used on sputum, induced sputum, gastric or bronchoscopic lavage fluid, or pleural fluid. The best specimen for demonstration of *M. tuberculosis* in children is the early morning gastric aspirate obtained by using a nasogastric tube. For better results, at least two specimens of gastric aspirates are recommended. Fluorescence microscopy (using auramine-rhodamine stains) may improve yield further. In young children who are not able to provide sputum, that can be induced by nebulized hypertonic saline (3–5%). Older children may provide expectoration at end of the procedure. In young children, a nasopharyngeal aspirate is collected and processed like sputum for smear and culture.

Culture: Lowenstein-Jensen (LJ) medium is the most widely used medium for determination of characteristic features of colonial morphology, growth rate and pigment production. Though the culture technique is simple, 7–10 weeks of incubation is necessary for detection of organisms. Microscopic examination of thin layer culture plate may lead to detection of microcolonies of *M. tuberculosis* as early as after 7 days. The yield of culture of gastric aspirate varies from 30–50% in children with tuberculosis. In view of the excessively long period for isolation of *M. tuberculosis* by conventional culture, LJ media has been replaced by mycobacterial growth indicator tube (MGIT) system. In this system, culture is positive in majority by end of 2 weeks, though final result is available by the end of 6 weeks.

Cartridge-based nucleic acid amplification test (CBNAAT): The test, based on real-time polymerase chain reaction, is

preferred for diagnosis of pulmonary tuberculosis; results are available in less than 2 hours. CBNAAT identifies presence of *M. tuberculosis* and provides information on rifampicin resistance. The sensitivity and specificity of two gastric aspirates for diagnosing pulmonary tuberculosis in children ranges between 60–70% and 90–100%, respectively. Its utility in extrapulmonary tuberculosis is lower.

Serodiagnosis: ELISA has been used to detect antibodies to various antigens of the bacillus. Despite a number of studies, current techniques have no role for the diagnosis of tuberculosis in children.

Methods to diagnose latent infection: Till date, tuberculin skin test was the only method to diagnose latent tuberculosis infection. Recently, a new test based on interferon gamma release assay (IGRA) has been developed. This *in vitro* test estimates a component of cell-mediated immunity to *M. tuberculosis*, based on quantitation of interferon-gamma (IFN- γ) released from sensitized lymphocytes in whole blood incubated overnight with antigens specific for the bacterial species. Two tests are available: QuantiFERON[®] gold TB test (QFT) and ELISPOT. In countries with high prevalence of tuberculosis, it is recommended to continue using tuberculin skin test that is considerably less expensive than IGRA.

Tuberculin skin test: The tuberculin or Mantoux test is commonly used to make the diagnosis of tuberculosis in children. Although currently available test antigens are not 100% sensitive or specific, no better diagnostic test is widely available. Infection with *M. tuberculosis* produces a delayed hypersensitivity reaction to its specific antigenic components. All purified protein derivative (PPD) lots are bioassayed to demonstrate equal potency. The standard test dose of a preparation is defined as dose of that product that is biologically equivalent to 5 TU of PPD-S or 2 TU of tuberculin PPD RT23. The reaction to tuberculin typically begins 5–6 hours after the intradermal injection and reaches maximal induration at 48–72 hours; vesiculation and necrosis are rare.

Variability of the tuberculin test may be reduced by attention to administration and reading. A 26-gauge needle and tuberculin syringe are used to inject 0.1 mL of PPD intradermally into the volar aspect of the forearm. Forty-eight to 72 hours later, the diameter of induration is measured transversely to the long axis of forearm and recorded in millimeters. A non-reactive tuberculin test does not exclude latent or active tuberculosis. Numerous factors can diminish tuberculin reactivity, resulting in a false negative reaction (Table 11.6). Because some antigens in PPD are shared with other mycobacteria and Bacillus Calmette–Guerin (BCG), false-positive reactions can occur in those infected with other mycobacteria or following vaccination. Although BCG vaccination of older children or adults results in greater initial and more persistent cross-reactivity, most individuals lose cross-reactivity within 10 years of vaccination. Interpretation of the skin

Table 11.6: Causes of false positive and false negative tuberculin skin test (Mantoux test)

False negative results	False positive results
Infections	Infections due to atypical mycobacteria
Viral (measles, mumps, chickenpox, HIV)	BCG vaccination
Bacterial (enteric fever, typhus, leprosy, pertussis, severe TB)	Infection at the site of test
Live vaccines (measles, mumps, polio, varicella)	
Chronic renal failure, liver failure	
Hodgkin disease, lymphoma, chronic leukemia, sarcoidosis	
Corticosteroids, immunosuppressive agents	
Newborn, elderly patients	
Factors related to tuberculin	
Exposure to light, heat, chemicals; contamination	
Improper dilution; adsorption	
Factors related to technique	
Injection of too little antigen	
Subcutaneous injection	
Delayed administration after drawing into syringe	
Injection close to other skin tests	
Inexperienced reader; errors in recording	

test is based on risk of infection and progression to disease (Table 11.7).

BCG test: An accelerated response after injection of the vaccine is observed in individuals suffering from tuberculosis. Induration of more than 5–6 mm after 3 days of BCG vaccine is considered a positive reaction. However, due to high antigen load, there are higher chances of false positive results and this test is not recommended.

Radiology: Chest radiograph has an important role in diagnosis of pulmonary tuberculosis. In extrapulmonary tuberculosis, presence of lesions on chest radiograph supports diagnosis. The typical chest X-ray appearance of a pulmonary primary complex (PPC) is that of a consolidation of variable size, usually unifocal and homogenous (Fig. 11.15). Enlarged lymph nodes are seen in the hila and right paratracheal region. Adenopathy

Table 11.7: Interpretation of Mantoux test

Size of induration	Interpretation
<10 mm	Negative; no active disease
5–10 mm	Borderline; consider positive in immunocompromised host; contact with adult patient with sputum AFB positive tuberculosis
>10 mm	Positive; suggests disease in presence of clinical features

alone may be the sole feature of primary tuberculosis.

Consolidation in progressive primary disease (PPD) is usually heterogeneous, with poorly marginated predilection for apical or posterior segments of upper lobe or superior segment of lower lobe (Fig. 11.16). There may be features of collapse (Fig. 11.17). Bronchiectasis may occur because of (i) destruction and fibrosis of lung parenchyma resulting in retraction and irreversible bronchial dilatation, and (ii) cicatricial bronchostenosis secondary to localized endobronchial infection resulting in obstructive pneumonitis and distal bronchiectasis. In children, cavitary disease is uncommon.

Pleural effusion may occur with or without lung lesions (Fig. 11.18). In miliary tuberculosis, there are multiple lesions of size 2–5 mm (Fig. 11.19). Occasionally, the chest radiograph may be normal and lymphadenopathy is

detected on computed tomography. CT features such as low attenuation lymph nodes with peripheral enhancement, lymph node calcification, branching centrilobular nodules and miliary nodules are helpful in suggesting the diagnosis where the radiograph is normal or equivocal. Contrast MRI is useful for CNS tuberculosis, since it demonstrates localized lesions, meningeal enhancement, brainstem lesions and ventricular dilatation.

Histopathology: Lymph nodes, liver and other tissues may be examined for histological evidence of tuberculosis by fine needle aspiration cytology.

Diagnostic Algorithm for Tuberculosis

The diagnosis of tuberculosis disease in children is challenging. Even in advanced nations, the diagnosis is

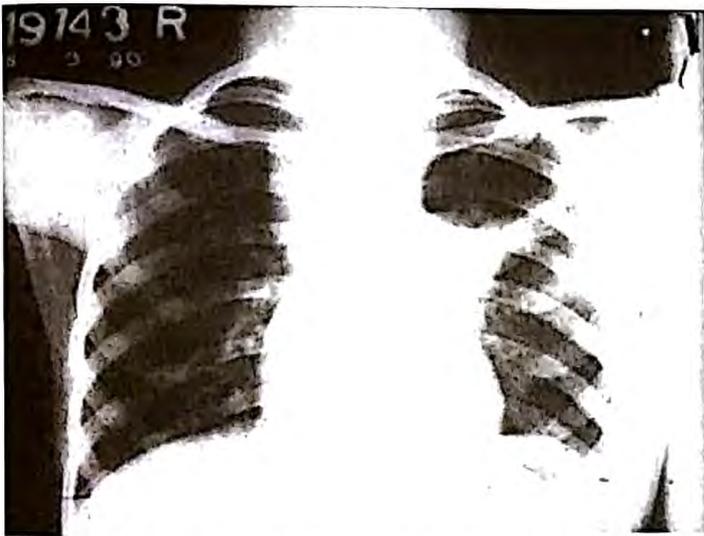


Fig. 11.15: Pulmonary primary complex (PPC) showing left hilar adenopathy with ill-defined parenchymal lesion



Fig. 11.16: Progressive pulmonary disease showing consolidation

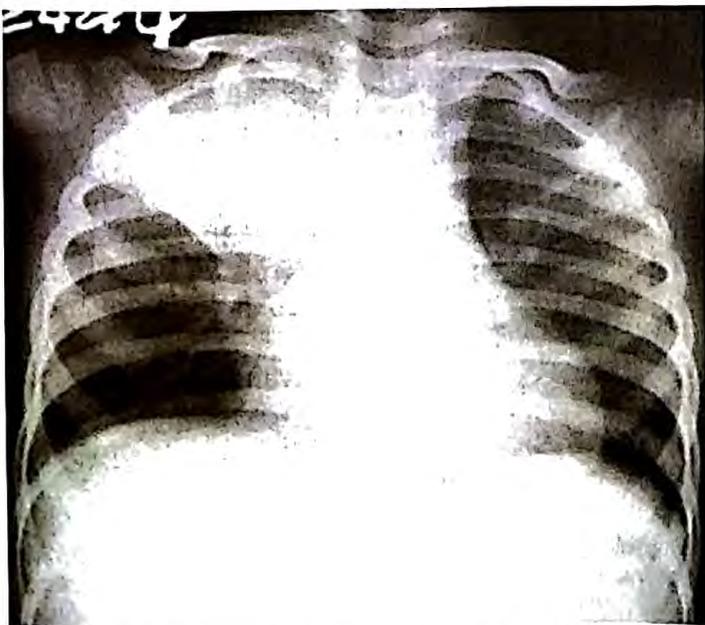


Fig. 11.17: Collapse with consolidation of right upper lobe



Fig. 11.18: Massive pleural effusion on left side, with mediastinal shift



Fig. 11.19: Miliary shadows with right paratracheal adenopathy

made by combination of a positive tuberculin test, chest radiograph, physical examination and history of contact with a patient (Fig. 11.20). Newer diagnostic methods, such as CBNAAT, have improved the yield of microbiologically confirmed tuberculosis.

Treatment

The principles of therapy in children with tuberculosis are similar to that of adults. Medications used for treatment of tuberculosis in children are given in Table 11.8.

Drug Regimens

Changes have occurred in the therapeutic approach to childhood tuberculosis. Short course therapy, with treatment duration of 6 months, is now standard practice.

The major problem in inclusion of children in Directly Observed Treatment Short course (DOTS) program has been a difficulty in demonstration of AFB and classification of different manifestations according to categories described for adults. A joint statement of the Indian Academy of Pediatrics and Revised National Tuberculosis Control Program (RNTCP) has proposed to classify children into two categories. Table 11.9 gives the categories of tuberculosis, as defined by WHO, along with suggested clinical condition in children. In view of increasing INH resistance, use of three drugs (INH, rifampicin and ethambutol) instead of two (INH and rifampicin) is suggested during the continuation phase.

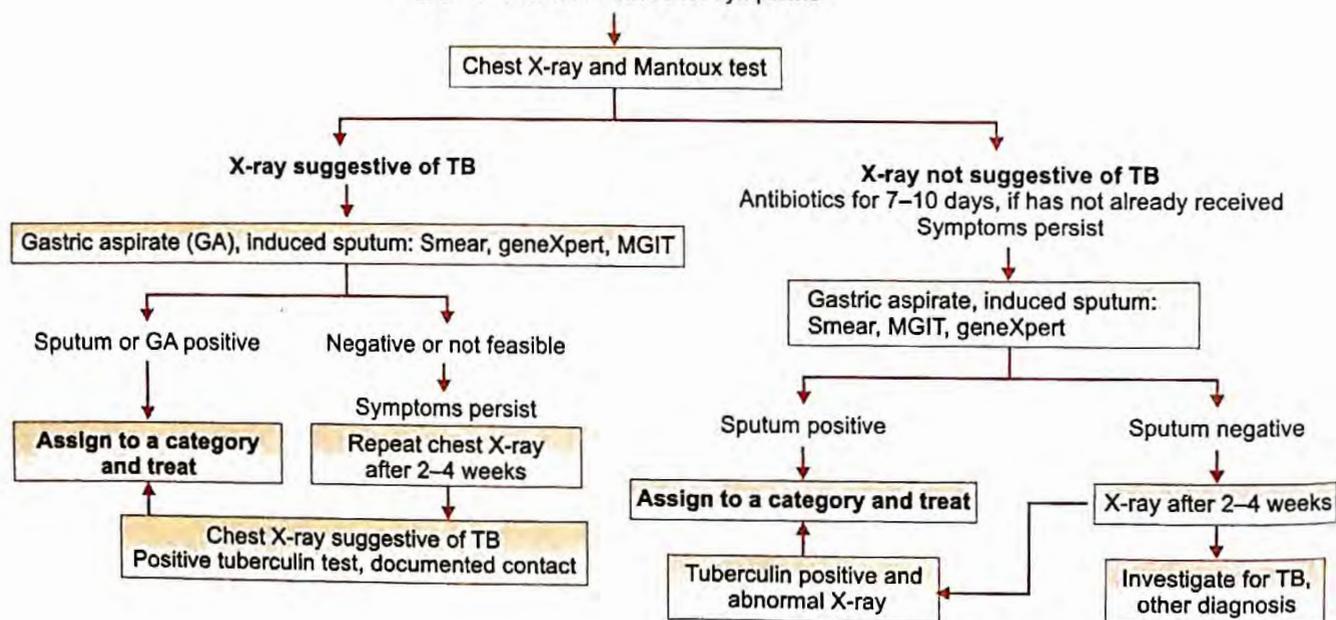
Corticosteroids

Additional therapy with these agents is useful in treating patients with CNS and rarely pulmonary tuberculosis, especially when host inflammatory reaction contributes to tissue damage. Short courses of corticosteroids are indicated in children with endobronchial tuberculosis (with localized emphysema, segmental pulmonary lesions or respiratory distress) and severe miliary tuberculosis (if alveolocapillary block is suspected). Significant improvement in symptoms is seen in children

Suspected pulmonary TB

- Fever and/or cough >2 weeks
- \pm Loss of weight or no weight gain
- History of contact with suspected or diagnosed active TB

Look for alternative cause for symptoms



Investigation for alternative diagnosis or screening for *M. tuberculosis*:
 Mediastinal nodes: Chest CT; CT/ultrasound-guided aspiration, biopsy.
 Parenchymal lesions: Bronchoscopy; bronchoalveolar lavage

Fig. 11.20: Diagnostic algorithm for pediatric tuberculosis

Table 11.8: Doses and side effects of antitubercular drugs

Medication	Dose (mg/kg/day; frequency)	Side effects
Isoniazid	10–15; q 24 h	Hepatotoxicity, hypersensitivity rash, fever, peripheral or optic neuritis, psychosis, seizures
Rifampicin	10–20; q 24 h	Nausea, vomiting, hepatotoxicity, flu-like syndrome, blood dyscrasia, arthralgia, wheezing
Streptomycin	20–25; q 24 h	Ototoxicity: Vestibular or hearing loss; rash, fever, arthralgia; neuromuscular blockade, peripheral neuritis
Ethambutol	15–25; q 12 h	Hypersensitivity reaction: Rash, fever, joint pain; optic neuritis, GI upset, confusion, dizziness
Pyrazinamide	25–35; q 24 h	GI upset, hepatotoxicity, hyperuricemia, photosensitivity, dysuria, malaise, arthralgia, fever, thrombocytopenia
Ethionamide	15–20; q 12 h	GI upset, hepatotoxicity, peripheral neuropathy, gynecomastia, rash, alopecia, headache, diplopia, tremors, hypothyroidism
Cycloserine	15–20; q 12 h	Seizures, psychosis, peripheral neuritis

Table 11.9: Standardized clinical categories for tuberculosis (TB) and clinical conditions

Categories	Suggested by WHO	Suggested conditions (for adults)	Suggested regimens* in children
Category I	New sputum positive Pulmonary TB Serious extrapulmonary TB Osteoarticular TB Genitourinary TB Central nervous system TB Pericardial TB	PPC, PPD, TBL Pleural effusion Abdominal TB	2HRZE + 4HRE
Category II	Relapse Treatment failure Return after default	Relapse Treatment failure Interrupted treatment	2SHRZE + 1HRZE + 5HRE

PPC: Pulmonary primary complex; PPD: Progressive primary disease; TB: Tuberculosis; TBL: Tubercular lymphadenitis

H isoniazid, R rifampicin, Z pyrazinamide, E ethambutol, S streptomycin

*Numerical denotes months for which the drug is to be given; e.g. 4HR is 4 months of INH and rifampicin

All children in household of an adult patient with sputum positive tuberculosis should be screened for evidence of infection. Children exposed to adults with sputum positive illness should receive 6 months of isoniazid prophylaxis.

with tuberculous pericardial effusion, but not pleural effusion. The medication used is prednisolone, at doses of 1–2 mg/kg/day for 4–6 weeks.

Infant born to Mother with Tuberculosis

Congenital tuberculosis is rare, the fetus infected either hematogenously (through umbilical vessels) or by ingestion of infected amniotic fluid. In the former, the primary focus is in the liver and in latter, the lungs. It is often difficult to differentiate between congenital and postnatally acquired tuberculosis. Infants born to mothers with active tuberculosis should be screened for disease by examination, tuberculin test and X-ray chest. If examination and investigations are negative for the disease, the infant should receive INH prophylaxis (10 mg/kg/day for 6 months). The infant is examined regularly for features suggestive of tuberculosis. Infants with congenital tuberculosis are treated with 4 medications (INH, rifampicin, pyrazinamide, ethambutol) in intensive phase for 2 months, followed by 3 drugs (isoniazid, rifampicin, ethambutol) during maintenance for 4 months.

Management of a Child in Contact with an Adult with Tuberculosis

One-third of children with adult contacts with active tuberculosis show features of infection. Infection is more common in younger children, and those with severe malnutrition, absence of BCG vaccination, sputum positive contacts and exposure to tobacco smoke. Children <5-year-old who are in contact with adult patients with pulmonary tuberculosis should receive INH prophylaxis (10 mg/kg/day for 6 months) after excluding presence of disease.

Monitoring of Therapy

Response to treatment is judged by clinical, radiological, bacteriological and laboratory assessment.

Clinical Criteria

Clinical improvement judges the response of therapy. The child should be seen every 2–4 weeks initially, then every 4–8 weeks. Most children show improvement in symptoms (fever, cough, appetite, well being) within a few weeks. The child is examined for weight gain and improvement in chest findings. Compliance to therapy should be ensured.

In presence of unsatisfactory response or worsening of features, the initial basis of diagnosis is reviewed, especially if there are no issues with compliance. The possibility of drug resistant tuberculosis should be considered. Following completion of therapy, patients are reviewed every 3–6 months for 2 years.

Radiological Criteria

Clinical improvement precedes radiological clearance. The first chest X-ray is done after 8 weeks' therapy, i.e. at the end of intensive phase. In patients who show increase or little change in radiological features coupled with delayed clinical response, prolongation of intensive phase by one-month is suggested. Further films are taken after 4 weeks and child, if better, should be shifted to continuation phase; else the patient is investigated for failure of treatment and drug resistance. The degree of radiological clearance is graded as: (i) complete, (ii) moderate ($\frac{1}{2}$ – $\frac{2}{3}$ rd clearance), (iii) mild ($\frac{1}{3}$ rd decrease in size), or (iv) no clearance or appearance of new lesion(s). One need not treat till complete radiological clearance, since improvement may continue even after stoppage of therapy.

Microbiological Criteria

Childhood tuberculosis is paucibacillary. In children, where isolation of *M. tuberculosis* was possible at the time of diagnosis, efforts are made to document disappearance of bacilli during therapy. If smear was positive initially, repeat sampling is done at 2 and 6 months.

Suspecting Drug-Resistant Tuberculosis

Children in the following categories are at risk of developing drug resistant tuberculosis: Contact with adult patients with proven drug resistance; irregular treatment or recent death due to tuberculosis; children not responding to standard antitubercular therapy; children who respond initially but later show deterioration. Appearance of new lymph nodes on treatment, and persistence or isolated non-clearance of radiologic shadows are not considered indicators of drug resistant tuberculosis.

Drug-Resistant Tuberculosis

Clinicians should neither miss nor overdiagnose the disease. Problems with overdiagnosis of drug-resistant tuberculosis are multiple: Second-line drugs are less effective; they have more side effects; and are expensive. A physician may suspect drug resistance based on the above criteria, but before making a diagnosis, all attempts are made to demonstrate AFB from appropriate samples and obtain culture and sensitivity. If the diagnosis is confirmed or not established, these patients must be referred to centers treating patients with drug resistance.

Suggested Reading

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Mycobacteria Other than Tuberculosis (MOTT)

Atypical mycobacteria or non-tuberculous mycobacteria (NTM) or mycobacteria other than tuberculosis (MOTT) are environmental pathogens that are being increasingly recognized as cause of human disease. These bacteria are classified depending on the rapidity of growth in media as rapid growers which grow within 7 days and slow growers, as those which take longer to grow. Acquisition is through contact with the environment; human-to-human or animal-to-human transmission almost never occurs. Though asymptomatic infection can occur, there is no recognized latent infection or reactivation disease. NTM infections may occur in previously healthy or those with underlying immunodeficiency, like HIV.

Lymphatic disease is the most common manifestation of NTM disease in children. It usually presents as painless cervical adenitis in children aged 1–5 years with no systemic symptoms. The main differential is tuberculous lymphadenitis. The definitive diagnosis is by culture; the usual causative organisms are MAC (*Mycobacterium avium intracellulare*), *M. scrofulaceum* and *M. hemophilium*. Treatment is complete excision of the lymph nodes.

Pulmonary disease due to NTM occurs in adults with underlying pulmonary problems and is usually due to MAC, *M. kansasii* and *M. abscessus*. Disseminated NTM disease, mainly in adults and less commonly children with advanced HIV infection, is usually due to MAC and presents as fever, weight loss, night sweats, abdominal pain, diarrhea and anemia. Blood cultures are positive. Skin and soft tissue infections are usually a consequence of trauma or health care procedures. These are usually due to *M. abscessus*, *M. chelonae*, *M. fortuitum*, *M. ulcerans* and *M. marinum*. They have been implicated in infections following injections, central lines, peritoneal dialysis catheters, laparoscopy, liposuction, cosmetic procedures, implants and prosthesis, LASIK and surgery. These mycobacteria species are usually hardy, resist the commonly used disinfectants and hence occur when surgical (chiefly laparoscopic) equipment is rinsed with tap water and inadequately disinfected. Usually these infections present as indolent abscesses that do not respond to the usual antibiotics.

Microbiologic diagnosis of NTM infections is possible in specialized laboratories where identification and speciation is done by advanced biochemical or molecular methods. Treatment depends on the causative organism and its sensitivity. MAC is usually treated with combination therapy consisting of a macrolide (clarithromycin/azithromycin), rifampicin, ethambutol and during initial stages with an aminoglycoside for 12–18 months. Treatment of the rapidly growing mycobacteria (*M. abscessus*, *M. chelonae*, *M. fortuitum*) includes a combination of clarithromycin, quinolones, aminoglycosides, tobramycin, amikacin, imipenem, minocycline, linezolid and clofazimine.

Suggested Reading

- ATS/IDSA Statement: Diagnosis, treatment and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med* 2007; 175:367–416.
- BTS Guidelines for the management of non-tuberculous mycobacterial pulmonary disease. *Thorax* 2017; 72:969–10.

RICKETTSIAL AND MYCOPLASMA INFECTIONS

Rickettsial Infections

Rickettsial diseases are a group of febrile illnesses caused by obligate intracellular gram-negative bacilli and transmitted to man by arthropod vectors. Rickettsial diseases are often under diagnosed due to poor awareness.

Epidemiology

Rickettsia are a group of motile, gram-negative, nonspore-forming, highly pleomorphic bacteria that present as cocci, rods or thread-like obligate, intracellular parasites. Rickettsia are classified on basis of clinical features and epidemiology into the typhus group (epidemic typhus, endemic typhus and scrub typhus), the spotted fever group (Rocky mountain spotted fever, Indian spotted fever), Q fever, trench fever and ehrlichiosis. Scrub typhus caused by *R. tsutsugamushi*, Indian spotted fever caused by *R. conorii* and Q fever caused by *C. burnetii* are prevalent

in India. Cases have been reported from all states chiefly from rural and forested areas and occasionally also urban areas.

Scrub typhus is transmitted by bite of the trombiculid mite and Indian spotted fever by ticks. Rickettsial disease is due to invasion of the endothelial region of the vasculature and subsequent microvasculitis. This process especially affects the brain, cardiac and skeletal muscle, skin, liver, lungs and kidneys.

Clinical Manifestations

Incubation period varies from 2 to 14 days. A history of exposure to ticks, history of origin from an endemic area or a similar illness in family members may be forthcoming. Severity of manifestations varies from a mild, self-limiting illness to a life-threatening disease.

Initially, the illness appears to be nonspecific and patients present with unrelenting headache, very high fever, anorexia, myalgias, restlessness, calf muscle pain and tenderness. Gastrointestinal symptoms include abdominal pain, nausea, vomiting, and diarrhea. Skin rash is usually not present until after 2–4 days of illness. The typical triad of fever, headache and rash is observed in only half of the patients. In spotted fever, rash is initially discrete pale rose red blanching macules or maculopapules on the extremities. Later, the rash spreads to involve the entire body including palms and soles and may be petechial or present as palpable purpura (Fig. 11.21). In severe form of the disease, petechiae may enlarge into ecchymosis, which can become necrotic. Severe vaso-occlusive disease secondary to rickettsial vasculitis and thrombosis is infrequent but can result in gangrene of the digits, toes, earlobes, scrotum, nose or entire limbs (Fig. 11.21). In scrub typhus, rash is seen initially on trunk or may not be present at all. Painless eschar, the tache noire, at the initial site of tick attachment is seen in scrub typhus.

Complications may involve any organ system and include encephalopathy, pulmonary edema, myocarditis, hepatic failure, acute renal failure and vascular collapse.



Fig. 11.21: Spotted fever showing: (a) Maculopapular rash on the soles; (b) Necrotic rash chiefly in gluteal region and legs; and (c) Gangrene of digits of hand, earlobe (Courtesy: Dr Atul Kulkarni, Sholapur)

Laboratory Diagnosis

Total leukocyte count is initially normal or low but leukopenia develops as the disease progresses. Anemia, thrombocytopenia, hyponatremia and elevated serum aminotransferases are seen. Specific diagnosis of a rickettsial illness is confirmed by serological testing. Serological evidence of infection occurs not earlier than the second week of illness; hence a specific diagnosis may not be available until after the patient has fully recovered or worsened. The gold standard for serodiagnosis is the immunofluorescence assay for detection of IgG and IgM. ELISA is specific and sensitive allowing detection of IgG and IgM antibodies. The Weil-Felix test is an agglutination test that detects antibodies to various *Proteus* species containing antigen with cross-reacting epitopes to members of the genus *Rickettsia*. The test, however, has low sensitivity and specificity.

If clinical suspicion for rickettsia is high, then empiric therapy should be started without waiting for a confirmatory test.

Differential Diagnosis

Spotted fever can mimic a number of febrile illnesses. Most important of these are meningococemia, typhoid fever, dengue fever, malaria, measles, secondary syphilis, leptospirosis, toxic shock syndrome, scarlet fever, rubella, Kawasaki disease, parvoviral infection, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, Henoch-Schönlein purpura, hepatitis, dengue fever and infectious mononucleosis.

Treatment

Doxycycline is the drug of choice for all age groups even in children below 8 years. Therapy should continue for a minimum of 5–7 days and for at least 3 days until the patient is afebrile in order to avoid relapse. Patients usually become afebrile within 48 hours and thus the entire therapy lasts for less than 10 days. In patients with severe disease, admission to an intensive care unit and appropriate supportive therapy may be required.

Prevention

No vaccines are available. Known tick infested areas should be avoided. Daily inspection of body for ticks is particularly important. Health education of people about mode of transmission by ticks and means of personal protection is important. Prophylactic antimicrobial therapy is not recommended.

Suggested Reading

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Mycoplasma Infections

Etiology

Mycoplasma are the smallest free-living life forms in nature. The most important species causing human disease is *M. pneumoniae*. The genital mycoplasmas (*M. hominis* and *Ureaplasma urealyticum*) are associated with genital tract disease in adults and sometimes neonatal disease.

Epidemiology

Newborns can get infected by genital mycoplasma during delivery. *M. pneumoniae* can infect children of any age but disease is uncommon below 3–5 years. In school-aged children and adolescents, it causes up to 30–40% of all community-acquired pneumonia and almost 20% of pneumonia requiring hospitalization.

Clinical Manifestations

The commonest manifestations of mycoplasma disease are low grade fever, cough, headache, malaise, pharyngitis, rhinorrhea and sometimes otitis media. Pneumonia is associated with a few clinical signs and is of varying severity. Patients rarely appear ill and hence the term “walking pneumonia”. There is marked disparity between the clinical symptoms and signs and the radiographic picture. The radiographic picture is variable; the most common finding is thickened bronchial shadow, streaks of interstitial infiltration, and areas of atelectasis primarily in lower lobes. One-third children have hilar adenopathy. Pleural effusions occur in 5–20% of the cases. In some children, fulminant pneumonia and respiratory failure may occur.

Extrapulmonary manifestations can coexist, follow or occur independently of respiratory disease and include dermatologic features (morbilliform rash, papulovesicular exanthem, erythema nodosum, erythema multiforme, Stevens-Johnson syndrome), neurologic manifestations (encephalitis, aseptic meningitis, transverse myelitis, peripheral neuropathies and radiculopathies) and cold antibody-mediated immune hemolytic anemia. Rarely, the GIT, heart, kidneys and joints may be involved.

Neonates with genital *Mycoplasma* infection may present with cough/wheezing or sepsis, meningitis and brain abscess.

Diagnosis

Complete blood count shows anemia, leukocytosis with neutrophilia and elevated ESR. Liver transaminases can be mildly elevated. Cold agglutinins may be present. Specific diagnosis is most commonly done by demonstration of antimycoplasma IgM by ELISA. IgM antibodies appear usually 7 days after infection and may be negative in early disease. They remain elevated for a long time. Mycoplasma-specific PCR from respiratory secretions is very sensitive and specific but expensive and not easily

available. Most multiplex PCR kits for diagnosis of respiratory infections include *Mycoplasma*.

Treatment

Since *Mycoplasma* lack cell walls, all cell wall active antibiotics including beta lactams are inactive. Macrolides are the drugs of choice; recommended regimens include azithromycin 10 mg/kg in one dose on the first day and 5 mg/kg in one dose for four days, clarithromycin 15 mg/kg/day in two divided doses for 10 days, or erythromycin 30 to 40 mg/kg/day in four divided doses for 10 days. In children older than 8 years, tetracycline 20 to 50 mg/kg/day in four divided doses (maximum daily dose 1 to 2 g) and doxycycline 2 to 4 mg/kg/day in one or two divided doses (maximum daily dose 100 to 200 mg) for 10 days are also effective.

The role of anti-*Mycoplasma* therapy in improving the outcome of mycoplasma pneumonia is controversial. Nonetheless, empiric treatment for *Mycoplasma* should be considered in children older than 5 years presenting with suspected mycoplasma pneumonia, those who are not responding to standard beta lactam therapy and possibly those with severe/very severe pneumonia.

Extrapulmonary *Mycoplasma* infection is often immune-mediated and may need additional therapeutic modalities including steroids and plasmapheresis.

Suggested Reading

- Colin AA, Yousef S, Forno E, Korppi M. Treatment of *Mycoplasma pneumoniae* in pediatric lower respiratory infection. *Pediatrics* 2014; 133:1124–5.

FUNGAL INFECTIONS

Fungi have become an increasingly common cause of disease in humans. Superficial fungal infections are detailed in Chapter 26. We discuss some of the serious invasive fungal infections, including invasive candidiasis, aspergillosis, mucormycosis and cryptococcosis.

Invasive Candidiasis

The major infection causing species of *Candida* are *C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. krusei* and *C. glabrata*. It commonly causes superficial infections such as thrush, vaginitis, paronychia, etc. Colonization with *Candida* at mucosal sites in patients on antibiotic therapy is also common. Invasive infections with *Candida* usually happen as nosocomial infections in individuals with impaired defenses such as preterm neonates in the neonatal intensive care unit, critically sick children in the pediatric intensive care unit and children with cancer on chemotherapy or following stem cell transplant. The usual risk factors for invasive candidiasis include prolonged intensive stay, broad-spectrum antibiotic therapy, renal failure, corticosteroid and other immunosuppressive therapy, renal failure, use of total

parenteral nutrition especially intralipids, neutropenia, central venous catheters, etc. Commonest form of invasive candidiasis is bloodstream infection and less commonly meningitis, endocarditis, osteomyelitis and septic arthritis. Clinical features are similar as bacterial sepsis and outcomes are poor, if therapy is not initiated early.

Diagnosis is primarily by fungal blood cultures which are only 50% sensitive. It is, therefore, important to have a high index of suspicion so that empirical therapy may be started early in patients with high likelihood of infection.

Fluconazole is the drug of choice especially because of low cost, ease of administration and availability of oral switchover. However, there has been a recent increase in incidence of infection by fluconazole-resistant *Candida* for which treatment with drugs like amphotericin B, echinocandins may be required. At the same time, isolation of *Candida* from non-sterile sites like tracheal secretions, urine and stool is common in critically sick children and should not be treated unless other features favoring invasive infection are present.

Aspergillosis

Aspergillus is a ubiquitously distributed filamented fungus; the two common species causing human infection are *A. fumigatus* and *A. niger*. *Aspergillus* causes certain non-invasive infections like otomycosis, sinusitis, aspergilloma and allergic bronchopulmonary aspergillosis. More sinister is invasive aspergillosis which can have mortality as high as 50%. Invasive aspergillosis always occurs in the immunocompromised; common predisposing factors include patients with cancer undergoing chemotherapy and resultant neutropenia, stem cell transplant recipients and patients on other immunosuppressive drugs. Common sites of involvement are the lungs (Fig. 11.22) and sinuses. Clinical symptoms and signs depend on the site of involvement. Diagnosis is primarily by radiology and histopathologic demonstration of the invasive hyphae in biopsy samples and finally by culture. Estimation of galactomannan in serum/bronchoalveolar lavage samples has emerged as a non-invasive diagnostic test. Treatment should be aggressive. The drug of choice is voriconazole. Other options are amphotericin B and caspofungin. Fluconazole has no activity against *Aspergillus*. Surgical resection may be required in non-responding cases.

Mucormycosis

Mucormycosis refers to infection with the filamented fungi of the genus *Mucor* and *Rhizopus*. The hyphae are broad and aseptate unlike those of *Aspergillus* that are narrow and septate. Mucormycosis is an invasive infection that primarily occurs in patients with risk factors such as diabetic ketoacidosis, cancer chemotherapy, transplant recipients, iron overload and receipt of immunosuppressive drugs. Sites of involvement are mainly the

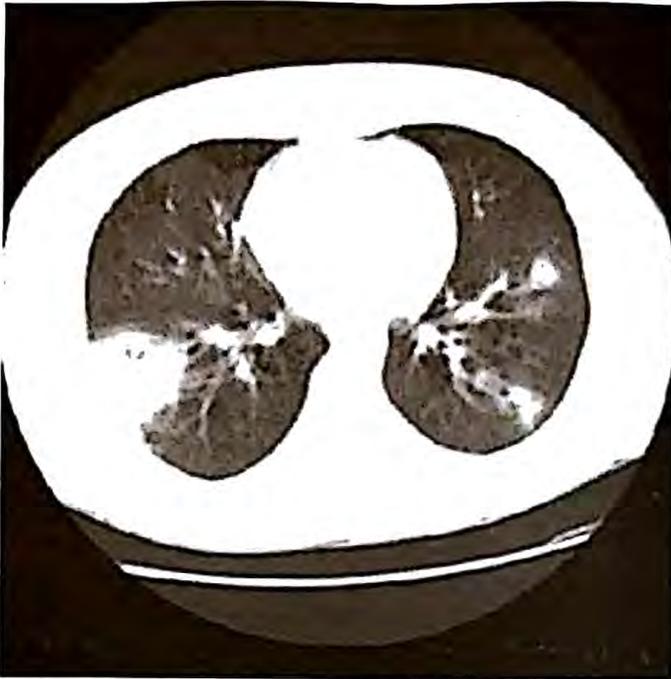


Fig. 11.22: Multiple air space opacities with irregular borders and internal cavitation suggestive of invasive aspergillosis

nasal sinuses and less commonly pulmonary, gastrointestinal and skin/soft tissue. Infection can sometimes occur due to direct inoculation in traumatic/surgical wounds and injection sites. Clinical features depend on the site involved; in the nasal form pain, swelling, bloody discharge and presence of blackish eschars on nasal examination are common. Confirmation of diagnosis is by demonstration of the characteristic hyphae on histopathology and fungal cultures. Treatment includes radical surgical debridement, antifungal therapy with amphotericin B and correction of underlying predisposing factors.

Cryptococcosis

Infection with *Cryptococcus neoformans* is commonly seen in HIV-infected individuals with advanced immunosuppression and less commonly in other immunocompromised patients such as those on long-term steroids, or those with CD4 lymphocytopenia. Rarely, it may occur in the immunocompetent (usually due to *C. gattii*). The disease most often affects the central nervous system; pulmonary and disseminated forms are less common. Clinical symptoms include headache, vomiting, altered sensorium, signs of meningism and less commonly neurologic deficits. CSF is usually under increased pressure and has high protein with pleocytosis. The diagnosis is confirmed by demonstrating cryptococci in the CSF by India ink, cryptococcal antigen testing and finally culture. Treatment includes antifungal therapy with amphotericin B and flucytosine for 2 weeks followed by fluconazole for prolonged periods. Reduction of elevated pressure by serial lumbar punctures is also crucial.

Suggested Reading

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PROTOZOAL INFECTIONS

Malaria

Malaria the most important protozoal disease of man is caused by the genus *Plasmodium*. There are four species pathogenic to man, *P. vivax*, *P. falciparum*, *P. malariae* and *P. ovale* of which the first two occur in India. Most of the malaria deaths are attributable to *P. falciparum*.

Epidemiology

Malaria is an important tropical disease, afflicting 350–500 million patients annually with over one million deaths. Of regions endemic for malaria, >70% cases are in Sub-Saharan Africa. Malaria is also an important cause of morbidity and mortality in South Asia including India. The National Vector-Borne Disease Control Program reported around 0.8 million cases of malaria in India in 2014 with some 300 deaths; 60% of the cases were due to *P. falciparum*. Large number of cases are reported from Orissa, Chhattisgarh, West Bengal, Karnataka, Jharkhand, Madhya Pradesh, Uttar Pradesh, Assam, Gujarat and Rajasthan. About 10% cases are reported from the urban areas, due to construction activities, population migration, and inappropriate water storage and disposal.

Transmission

The infectious stage of the parasite, the sporozoite, is transmitted to the host by the bite of the female *Anopheles* mosquito. Six species of anopheline mosquitoes are important in the transmission of the disease, namely *Anopheles culicifacies* (rural), *A. fluviatilis*, *A. stephensi* (urban), *A. minimus*, *A. philippinensis* and *A. sundaicus*. To enable development of parasites in the vector's body and make it capable of transmitting the disease, the vector must be susceptible, feed on human blood and live at least for 10–12 days after an infective blood meal. The vector should be present in large number or sufficient density to be of importance. Resting habits of the mosquito are important for planning control measures. Mosquitoes usually breed in edges of streams, water tanks, pits, cisterns and overhead tanks. *A. stephensi* breed in wells, cisterns, fountains and overhead tanks, *A. fluviatilis* in moving water and *A. sundaicus* in brackish water. Breeding sites such as burrowed pits, pools, ponds, marshy areas and unregulated irrigation channels are conducive to mosquito breeding and spread of malaria. Mosquitoes thrive best in temperature between 20 and 30°C, relative humidity 60% and in areas with good rainfall. The peak transmission season of malaria is between July and November. Malaria is uncommon at altitudes over 2000 m above sea level.

Efficient vectors are those that bite humans in preference to cattle, have high biting rates and where the duration of sporogony is shorter and who are long lived (hence they outlive sporogony). More efficient the vector, greater the burden of malaria; *A. gambiae* the vector in Sub-Saharan Africa is a very efficient vector and is largely responsible for the huge burden of malaria in that area.

Life Cycle of Parasite

Humans

Hepatic or tissue phase: When an infectious mosquito bites a human, it injects sporozoites, which circulate and invade hepatocytes and reticuloendothelial tissues within 30 minutes of the bite. During hepatic infection, *P. vivax* produces 2000–15000 merozoites and *P. falciparum* produces 40000 merozoites by repeated divisions. These merozoites are released and invade erythrocytes at end of the hepatic phase. The first hepatic phase is asymptomatic and constitutes the incubation period. This cycle lasts at least 10 days (1–2 weeks for falciparum infection).

Erythrocytic phase: After replication in the liver (exoerythrocytic schizogony), the parasites undergo asexual multiplication in the erythrocytes (erythrocytic schizogony). In erythrocytes, parasites develop into ring forms, mature trophozoites and then multinucleated schizonts, which rupture and release more merozoites. Repeated cycles of erythrocyte invasion and rupture lead to chills, fever, headache, fatigue, and signs of organ dysfunction.

A key feature of the life cycle of *P. falciparum* is cytoadherence, whereby erythrocytes infected with mature parasites adhere to endothelial cells in the microvasculature. This process is presumably advantageous to the parasite, since it prevents the passage of abnormal erythrocytes through the spleen. High concentrations of *P. falciparum* infected erythrocytes in the microvasculature and a complex interplay of host and parasite factors lead to the manifestations of severe malaria, including cerebral malaria, noncardiogenic pulmonary edema and renal failure. Because of the ability of mature *P. falciparum* organisms in the erythrocytic stage to adhere to endothelial cells, only ring forms circulate (except in very severe infections), and levels of peripheral parasitemia may be low despite substantial infection.

Gametocytic phase: After several stages of schizogony, some merozoites are converted to gametocytes (Fig. 11.23) which are taken up by the mosquitoes. They do not cause symptoms but are responsible for transmission of malaria.

Exoerythrocytic phase: Termination of the erythrocytic schizogony does not necessarily terminate the infection with malaria because merozoites of *P. vivax*, but not those of *P. falciparum*, may go into a dormant stage (hypnozoite)



Fig. 11.23: Gametocyte of *P. falciparum*

in the liver and cause relapses by invading the bloodstream weeks or even years later. This intermittent release of schizonts in case of *P. vivax* and *P. ovale* may last for 2–3 years and for *P. malariae* for 10–20 years.

Mosquito: The gametocytes are ingested by an *Anopheles* mosquito during a blood meal. The gametocyte forms survive in the stomach of the mosquito; all other stages are destroyed. The parasites' multiplication in the mosquito is known as the sporogonic cycle. While in the mosquito stomach, fertilization of female gametes generates motile and elongated zygotes (ookinetes) that invade the midgut wall and develop into oocysts (resting stage). These oocysts grow, rupture and release sporozoites that reach the mosquito salivary glands. Inoculation of the sporozoites into a human host perpetuates the life cycle.

Immunity Against Malaria

Innate and acquired resistance: Innate resistance in malaria may be due to differences in the surface receptor, intraerythrocytic factors or yet unknown causes. Epidemiologic observations suggest that patients with sickle cell trait, thalassemia and glucose-6-phosphate dehydrogenase deficiency are relatively immune to malaria. Homozygotes of sickle cell disease are not protected from malaria but heterozygotes are immune. Variations in HLA frequency may also determine the prevalence of malaria.

Acquired immunity against malaria is both cell-mediated and humoral. The first response to malarial infection is *phagocytosis* in the spleen or the hyperplastic reticuloendothelial cells of the parasitized erythrocytes. IgM antibodies against the merozoites help in opsono-

phagocytosis of the RBC in spleen. Malarial immunity in endemic areas increases with age and disappears when the individual leaves the endemic area; a phenomenon known as premunition.

Clinical Features

The clinical manifestations and severity of malaria depend largely on the species of the parasite and endemicity of disease. Most cases of severe or complicated malaria are due to *P. falciparum*; there are increasing number of reports due to severe disease by *P. vivax*. In highly endemic areas with "stable malaria" such as Sub-Saharan Africa, children below 5 years and pregnant women are most affected with severe anemia and cerebral malaria being prominent manifestations. In areas of lower endemicity including most areas of India, all ages including children and young adults are affected.

The incubation period of malaria varies between 9 and 30 days, being the least for *P. falciparum* and longest for *P. malariae* infections. The onset of the disease is sudden with fever, headache, loss of appetite, lassitude and pain in the limbs. The fever may be continuous or remittent for several days before it becomes classically intermittent. The illness, then, is characterized by a *cold stage* (chills and rigors with headache, nausea, malaise and anorexia); *hot stage* (dry flushed skin, rapid respiration and marked thirst); and *sweating stage* (temperature falls by crisis). In most children, the classic intermittent fever is not seen.

On basis of severity, malaria is classified as "complicated or severe" and uncomplicated malaria. Severe malaria can affect virtually every organ system and has a mortality rate of approximately 20%. The criteria for severe malaria are listed in Table 11.10. Presence of any of the criteria with asexual parasitemia with *P. falciparum* or *P. vivax* classifies malaria as severe and should be treated as such. Presence of thrombocytopenia alone is not a criteria for defining severe malaria.

Diagnosis

Specific diagnosis: The gold standard for diagnosis of malaria is careful examination of a properly prepared thick film. Thick smears have sensitivity of detecting 5–10 parasites/ μL . Thin smears have a lower sensitivity of 200 parasites/ μL but enable species identification. Microscopy also provides information about the parasite load (number of infected red cells/total red cells), prognosis (mature schizonts and pigmented neutrophils indicating a poor prognosis) and tracks response to therapy. Additionally peripheral smears are cheap and readily available. The main drawback is need for expertise and that they are time consuming (careful examination of 100 fields needs 20 minutes). Sometimes peripheral smears may be negative due to partial antimalarial treatment or sequestration of parasitized cells in deep vascular beds. Repeating smears every 6–8 hourly at least three times is

Table 11.10: Criteria for severe malaria

Clinical findings

Impaired consciousness or unarousable coma
Prostration; generalized weakness; patient unable walk or sit up without assistance
Failure to feed
Multiple convulsions—more than two episodes in 24 hours
Deep breathing, respiratory distress; acidotic breathing
Circulatory collapse or shock; systolic pressure <70 mm Hg (adults) and <50 mm Hg (children)
Clinical jaundice and evidence of other vital organ dysfunction
Hemoglobinuria
Abnormal spontaneous bleeding
Pulmonary edema
Laboratory findings
Hypoglycemia (blood glucose <40 mg/dL)
Metabolic acidosis (plasma bicarbonate <15 mEq/L)
Severe normocytic anemia (Hb <5 g/dL, packed cell volume <15%)

Hemoglobinuria

Hyperparasitemia (>2% or 100 000/ μL in low intensity transmission areas; >5% or 250 000/ μL with high stable malaria transmission intensity)
Hyperlactatemia (lactate >5 mmol/L)
Renal impairment (serum creatinine >3 mg/dL)

recommended, if the clinical suspicion for malaria is high and the initial smear is negative.

Rapid diagnostic tests (RDTs) have revolutionized the diagnosis of malaria and obviated other methods such as quantitative buffy coat (QBC) and acridine orange stains. These tests detect malaria antigens (PfHRP2/PfPR2/aldolase) from asexual and/or sexual forms of the parasite as color changes on antibody coated lines on the strips (Fig. 11.24). In general, these are quick and simple to use, distinguish between the major forms of human malaria, and are useful when reliable microscopy is not available. Disadvantages include cost, lower sensitivity than microscopy (detect 100–200 parasites/ μL), variation in quality from batch-to-batch and need for rigorous storage conditions. In addition, they do not give information on the parasite load and cannot be used to monitor response. The OptiMAL test based on detection of parasite LDH and tests based on plasmodium aldolase are superior



Fig. 11.24: OptiMAL test for rapid diagnosis of malaria. Expected reaction patterns on the OptiMAL test strip for a negative patient, and patients with vivax and falciparum malaria

to the Parasight F test, which is based on detection of HRP2 antigen of *P. falciparum* as the latter is positive even in past infection and cannot be used to diagnose *P. vivax* malaria.

Polymerase chain reaction (PCR) has been found to be highly sensitive and specific for detecting all species of malaria, particularly in cases of low level parasitemia but is not available commercially and hence of limited practical utility.

Test useful for disease management and assessing severity: These include complete blood counts, prothrombin time; blood levels of glucose, electrolytes, pH, bicarbonate, anion gap, lactate, bilirubin transaminases and creatinine. A chest X-ray is done in patients with respiratory distress; urinalysis is also required. Blood cultures should be sent in patients presenting with shock. Repeated assessments of blood glucose are important.

Differential Diagnosis

Common differentials include other tropical and monsoon infections like typhoid fever, leptospirosis, dengue, viral hepatitis, influenza, chikungunya and rickettsial infections. Cerebral malaria should be differentiated from other causes of acute febrile encephalopathy such as meningitis and encephalitis. Patients with algid malaria (those in shock) mimic meningococemia and gram-negative shock.

Treatment of Uncomplicated Malaria

In a setting of suspected uncomplicated malaria, establishing a lab diagnosis is a must before giving empirical therapy. This is to prevent irrational therapy and consequent drug resistance and also to avoid missing other causes of febrile illness.

Vivax malaria: The drug of choice for managing vivax malaria is chloroquine. Resistance to chloroquine has been rarely reported in India. The total dose is 25 mg/kg; first dose is 10 mg/kg, followed by 10 mg/kg after 24 hours and 5 mg/kg at 48 hours (Table 11.11). Fever should be

brought down before giving chloroquine to reduce the risk of vomiting. Radical therapy with primaquine is indicated for vivax malaria to eliminate the exoerythrocytic stages in liver and reduce risk of relapses. Primaquine (0.25–0.3 mg/kg/day for 14 days) also has schizonticidal effect and is given as combination therapy for vivax malaria with chloroquine. G6PD level should be checked prior to administering primaquine. For patients who relapse despite standard primaquine, higher doses (0.5–0.75 mg/kg) can be used. Primaquine is contraindicated in those with severe G6PD deficiency, infants, pregnant and breastfeeding women. In patients with mild G6PD deficiency, 0.75 mg/kg can be given weekly for 8 weeks. For patients who cannot be given primaquine, relapses may be prevented by administering chloroquine as suppressive therapy at a dose of 10 mg/kg weekly for 3–6 months.

Quinine and pyrimethamine sulfadoxine do not have adequate activity against vivax malaria and should not be used for treatment. The combination of artemether with lumefantrine is associated with higher risk of relapse in vivax malaria as compared to chloroquine; new combinations of dihydroartemisinin piperazine or artemolane piperazine are better.

Uncomplicated falciparum malaria: Falciparum malaria should always be treated with combination therapy, in view of its efficacy and lower risk of emergence of resistance. Both agents should have an independent mode of action and should be effective in the area where they are used. Pyrimethamine sulfadoxine is not combination therapy as both partner drugs have similar mechanism of action. Similarly, if an area has resistance to pyrimethamine sulfadoxine and mefloquine, then these should not be used as part of combination therapy.

Artemisinin-based combination therapy (ACT) is the treatment of choice for falciparum malaria (Table 11.9). Artemisinin (qinghaosu) is the antimalarial extract isolated from *Artemisia annua*. Artemisinin and its derivatives (artemether, artesunate, arteether) are the most rapidly

Table 11.11: Drug doses for oral antimalarial drugs

Chloroquine (tablets 250 mg salt with 150 mg base; syrup 50 mg base/5 mL)	Loading dose; 10 mg/kg of base; 10 mg/kg after 24 hours and then 5 mg/kg at 48 hours
Primaquine (7.5/15 mg tablets)	0.25–0.75 mg/kg
Artemether and lumefantrine (tablets having 20 mg artemether and 120 mg lumefantrine; syrup artemether 40 mg and 240 mg lumefantrine per 5 mL)	Weighing 5–14 kg, 15–24 kg, 25–34 kg and >34 kg is 1, 2, 3 and 4 tablets, respectively. Administer 0, 8, 24, 36, 48 and 60 hours 1.7 mg/kg of artemether twice daily for 3 days
Artemether (syrup 40 mg/5 mL)	4 mg/kg/day single dose
Mefloquine (250 mg tablets)	25 mg/kg; two doses of 15 mg/kg and 10 mg/kg 8 hours apart
Pyrimethamine sulfadoxine	1.25 mg/kg of pyrimethamine single dose
Doxycycline	3.5 mg/kg/day
Clindamycin	10 mg/kg/day twice daily
Quinine (tablets contain 300 mg)	10 mg/kg thrice daily

acting of all antimalarials; they also have wide spectrum antimalarial effect from ring forms to mature trophozoites (like chloroquine and unlike quinine that acts only on mature forms). Artemether lumefantrine is the most commonly used oral ACT. Other drugs such as mefloquine, amodiaquine and pyrimethamine-sulfadoxine may be used in combination with artesunate in areas where resistance to these drugs is uncommon. Arterolane maleate plus piperazine phosphate is also an effective ACT. Oral quinine with clindamycin or doxycycline (in children >8-year-old) for 7 days is an alternate treatment, but is associated with poor tolerability of oral quinine and need for prolonged therapy.

Chloroquine should not be used for treatment for falciparum malaria unless there is demonstrable sensitivity to the medication; similarly mefloquine and pyrimethamine sulfadoxine monotherapy is not recommended. At the end of antimalarial therapy, a single gametocidal dose of primaquine (0.75 mg/kg) is recommended to reduce community transmission of malaria.

Uncomplicated mixed malaria: Uncomplicated mixed malaria should be treated as *P. falciparum* malaria with ACT. The preferred ACT, if available, for mixed malaria is either dihydroartemisinin with piperazine or arterolane with piperazine. Primaquine should be used as mentioned above.

Treatment of Complicated Malaria

The treatment of severe malaria is an emergency as it is associated with high mortality approaching 20%. If the suspicion of malaria is strong then treatment should be initiated without waiting for confirmation of diagnosis. Severe malaria whether due to falciparum or vivax should be treated similarly. Supportive care and treatment of complications are as important as antimalarial therapy. Broad spectrum antibiotics are administered if patient is in shock or secondary infection is suspected.

Treatment should be parenteral as most patients are not able to take orally and the bioavailability of oral drugs is unpredictable. Artemisinin-based therapy is considered superior to quinine in reducing mortality.

Artemisinin-based therapy: Parenteral formulations of artesunate, artemether and arteether are commercially available; artesunate is preferred. Artesunate is available as a dry powder which is reconstituted with sodium bicarbonate and given as a bolus injection. Artemether and arteether are given by the intramuscular route. The dose of artesunate is 3 mg/kg in children with weight less than 20 kg, and 2.4 mg/kg in patients weighing >20 kg. For artemether the dose is 3.2 mg/kg stat and then repeated after 12 and 24 hours and then daily. Parasite counts start declining 5–6 hours after institution of therapy; asexual parasitemia disappears after mean of 72 hours. Once the patient is better, a full course of oral ACT

is administered (see above). A single dose of primaquine 0.75 mg/kg should be used to reduce risk of transmission. Artemisinin derivatives have a good safety profile. Local reactions after intramuscular administration are rare and much less frequent as compared to IM quinine. Cardiotoxic effects in the form of prolongation of the QT interval in patients receiving high dose artemether have been reported. Artemisinins should not be combined with other cardiotoxic drugs such as quinine and halofantrine. Physicians should be aware about reports of neurotoxicity, especially with repeated use, and unregulated therapy.

Quinine-based therapy: Quinine acts principally on the mature trophozoite stage of parasite development; it does not prevent sequestration or further development of formed meronts and does not kill the pre-erythrocytic or sexual stage of *Plasmodium falciparum*. Parenteral quinine is available as dihydrochloride salt in concentrations of 300 mg/mL. Quinine must always be given by rate controlled intravenous infusion and never by bolus or push injection. It is recommended to administer a loading dose of quinine, i.e. 20 mg salt/kg diluted in 10 mL/kg of normal saline/dextrose over a period of 4 hours. The objective of loading dose is to provide therapeutic levels as early as possible in the course of treatment, without overshoot to toxic levels. The loading dose should be avoided if there is reliable evidence that the patient has received quinine/halofantrine/mefloquine in the past 24 hours (halofantrine and mefloquine produce additive cardiac toxicity). After the loading dose, quinine is continued at a dose of 10 mg salt/kg as infusion over 2 hours every 8 hours. Intramuscular quinine is another alternative for initial therapy if facilities for controlled IV quinine administration are not available; subcutaneous administration may cause skin necrosis.

The parasite counts start declining only after 24 hours, slower than artemisinin derivatives. The patient is switched to therapy with oral quinine as soon as possible. If parenteral quinine is continued beyond 48 hours or if renal failure supervenes, the maintenance dose should be reduced to 5–7 mg/kg to avoid quinine toxicity. Total duration of therapy is 7 days. A second drug such as pyrimethamine sulphadoxine, doxycycline or clindamycin should be added. A single dose of primaquine 0.75 mg/kg is given on completion of quinine therapy to eradicate gametocytes and prevent transmission.

The only contraindication to use of quinine is evidence of severe quinine allergy and G6PD deficiency. Thrombocytopenia, jaundice, renal failure, hypotension are not contraindications for quinine administration. Minor side effects including tinnitus, deafness, headache, nausea and visual disturbances (cinchonism) are common in conscious patients but do not warrant dose reduction. Serious side effects with parenteral quinine are rare, if it is administered properly. Quinine produces prolongation of the QTc interval on the ECG but significant conduction or

repolarization abnormalities are rare. Routine ECG monitoring during quinine infusion is not required, if there is no evidence of preexisting heart disease. Frequent blood glucose monitoring is necessary during therapy. Quinine can cause marked intravascular hemolysis (blackwater fever); change of therapy to artemisinin derivatives may be required. Quinine can cause immune-mediated thrombocytopenia, which is suspected, if platelet counts fail to recover despite clinical improvement.

Treatment Failures, Recrudescence and Relapse

An optimal response to therapy is defined as counts which on day 1 are less than day 0, counts on day 3 are <25% of count on day 0, no parasites are seen in peripheral blood 72 hours after starting therapy and up to 28 days and there is no fever after 72 hours.

Patients with parasitologically confirmed malaria who continue to have fever 72 hours after starting therapy are occasionally seen in clinical practice. If peripheral smear for malaria is negative, the causes include IV thrombophlebitis, secondary bacterial infections, coinfections such as typhoid or rarely immune phenomena. If drug resistance is suspected than treatment should be changed to either ACT combination or quinine.

Reappearance of asexual parasites within 28 days of treatment is defined as recrudescence or late treatment failure. Causes for recrudescence include choice of wrong drug, wrong dose, poor compliance or drug resistance. Recrudescence is fairly common in falciparum malaria, if artemisinin monotherapy is used; and in vivax malaria, if ACT is used. Treatment of recrudescence includes optimizing drug therapy or change to an alternative regime.

Control and Prevention of Malaria

Control and prevention of malaria is based on elimination of the vector by strategies like insecticide spraying, use of insecticide treated bed nets and elimination of breeding places. The latest malaria vaccine RTS, S/AS01 acts against *P. falciparum*. Phase 3 trials on African children, aged 6 weeks to 17 months, show efficacy ranging from 18–39%. In holoendemic areas like Africa, chemoprophylaxis with pyrimethamine sulfadoxine administered twice during pregnancy to reduce prevalence of maternal anemia and low birth weight is practised.

Chemoprophylaxis against malaria is recommended for travelers from non-endemic areas to endemic areas. Drugs used include weekly chloroquine (for areas that are chloroquine sensitive), weekly mefloquine, weekly chloroquine and daily proguanil, daily doxycycline and daily atovaquone-proguanil (expensive but safest). Prophylaxis should be started at least 1–2 weeks before departure and continued for 4 weeks after return (except atovaquone-proguanil where it can be started on the day of departure). For travelers to India, prophylaxis with either weekly mefloquine 5 mg/kg or daily atovaquone-proguanil is advised.

National Vector Borne Disease Control Programme (NVBDCP)

The NVBDCP strategies are two folds: Early case detection and prompt treatment and vector control. It has laid out guidelines for detection and management of malaria. NVBDCP recommends treatment of uncomplicated vivax malaria with chloroquine and falciparum malaria with ACT. Artemisinin monotherapy is banned in India and is marketed only as combinations. Strategies for vector control include source control, elimination of breeding places, biologic control with use of larvivorous fish in water bodies, and finally chemical vector control by indoor residual spray, space fogging and use of chemical larvicides like abate in water bodies.

Suggested Reading

- National Vector Borne Disease Control Program, Ministry of Health and Family Welfare, Government of India. Malaria. <http://www.nvbdc.gov.in/iec.html>
- WHO. Guidelines for the treatment of malaria. 3rd edn, 2015; 1–317. www.who.int/malaria/docs/TreatmentGuidelines2015.pdf
- WHO. Malaria. <http://www.who.int/malaria/areas/treatment/overview/en/>

Leishmaniasis

Leishmaniasis is a disease caused by parasites of the genus *Leishmania*, which are transmitted by bites of female sandflies. There are three major clinical forms: Visceral leishmaniasis (VL), cutaneous leishmaniasis, and mucocutaneous leishmaniasis (espundia). VL and cutaneous forms of the disease seen in India are caused by *Leishmania donovani*. Kala azar, the Indian term for VL, denotes hyperpigmentation seen in these patients; ~200000 cases are reported annually, most often from Bihar and eastern UP.

Transmission and Etio-pathogenesis

The parasite exists in the human or animal reservoir as amastigotes (non-flagellated, oval Leishman-Donovan bodies) and in the sandfly and culture medium as flagellated promastigotes. In India and Sudan, humans are the chief reservoir (anthroponotic cycle). The female sandfly (genus *Phlebotomus*) ingests the amastigotes, which develop into promastigotes in its digestive tract, migrates to the proboscis (salivary glands) and is injected into the susceptible host when the sandfly takes its next feed. Within the host, promastigotes infect macrophages and develop into amastigotes. Amastigotes multiply in cells of the mononuclear phagocyte system (monocytes, macrophages, histiocytes, Kupffer cells and reticuloendothelial cells in spleen and lymphoid tissue).

Children aged 1–4 years are considered more susceptible to the disease. The protective response is primarily cell mediated immunity that results in subclinical infection and spontaneous cure in most cases. Failure of immunity results in illness, such that for every case of VL, there are about 30 subclinical infections.

Malnutrition and HIV infection also predispose to clinical disease.

Clinical Features

Visceral leishmaniasis: The incubation period is generally 3 to 8 months. Features include high grade fever, weight loss, hepatosplenomegaly and abdominal discomfort. There are no rigors and the patient does not appear toxic. Splenohepatomegaly, with spleen larger than the liver, is usual. Spleen is huge, firm, smooth and nontender and palpable by end of first month of illness; moderate hepatomegaly is seen in ~80%. Unlike African VL, lymphadenopathy is infrequent in Indian VL (<5%). Hyperpigmentation of skin is a feature of Indian VL, seen in about two-thirds of patients and affecting the face, hands and upper trunk. Progressive emaciation occurs in all cases, though appetite is preserved. Cough and diarrhea are common. Bleeding manifestations in the form of petechial hemorrhages, epistaxis and gum bleeding may be seen. Pedal edema may occur due to hypoalbuminemia, however, jaundice is uncommon. Diminished cell-mediated immunity may account for a high incidence of secondary infections. Pancytopenia and hypergammaglobulinemia are characteristic.

The disease may begin insidiously and be asymptomatic initially, but usually runs a chronic course that may be fatal without or despite treatment. Death usually occurs within 2 years in 75–95% cases, because of severe secondary bacterial infections or gastrointestinal bleeding in advanced disease.

Post-kala-azar dermal leishmaniasis (PKDL): A small proportion of patients in Africa and India may show PKDL that develops 1–10 years after resolution of VL. Hypopigmented macular, maculopapular or nodular skin lesions are seen first in the perioral area, chin and lips, and later appear over the neck, extensor surfaces of the arms, trunk, and legs. Lesions spare the scalp, palms, soles, axillae and perineum. Lepromatous leprosy is a close differential, but peripheral nerves are spared. Skin lesions may persist for up to 20 years. These patients may act as chronic reservoir of infection.

Diagnosis

There is pancytopenia, mild elevation of liver enzymes and hypergammaglobulinemia with reversal of albumin globulin ratio. The aldehyde test has poor sensitivity and specificity and is no longer used.

Definitive diagnosis of VL is usually based on microscopic detection of amastigotes in smears of tissue aspirates or biopsy samples. Bone marrow aspirate or biopsy is frequently the tissue of choice with sensitivity between 55 and 97%. Lymph node aspirate or biopsy (sensitivity 60%), liver biopsy (sensitivity 85%) and splenic aspirates (sensitivity 97%) may also be used. PCR methods on tissue samples and peripheral blood with very high sensitivities have been developed.

Immunochromatographic strip and ELISA for leishmanial anti-K39 antibody has been used successfully for serodiagnosis with high sensitivity (>90%) and specificity (~90%). Antibody titers to K39 decrease following successful therapy, and increase during relapse making it a useful test to recognize treatment failure. Newer methods with high sensitivity and specificity include the detection of Leishmania antigen and antibody in the urine.

Treatment

Drugs available for treatment of VL in India include sodium stibogluconate, amphotericin B, lipid formulation amphotericin B and miltefosine. Sodium stibogluconate was considered first line therapy for VL in India. However, need for prolonged therapy, adverse effects and increasing resistance are its major limitations. In certain areas of Bihar, the resistance rates exceed 50%.

The National Vector Borne Disease Control Programme recommends that in areas where stibogluconate resistance rates are more than 10%, amphotericin B deoxycholate be used. Side effects of amphotericin include fever, chills, hypokalemia and nephrotoxicity. Liposomal amphotericin B dosed as 1 mg/kg/day over 3–5 days or a single dose of 5 mg/kg is highly efficacious with fewer adverse effects. Indigenous lipid formulations of amphotericin B (2 mg/kg) mixed with 100 mL of 20% fat emulsion and dosed for 5 doses approaches success rates more than 90% and at considerably lower cost, compared to liposomal amphotericin B and even stibogluconate.

Miltefosine is an orally active agent. Treatment with this drug for 3–4 weeks results in cure rates of 95–100%, comparable to that with amphotericin. Mild gastrointestinal side effects may be seen. Other effective drugs used for treating leishmaniasis include pentamidine and paromomycin. Recommended treatment regimens are summarized in Table 11.12.

Severe anemia and thrombocytopenia may necessitate packed cell and platelet transfusions. The child should receive a nutritious diet, and coexisting nutritional deficiencies should be corrected. Concurrent infections should be treated using appropriate antimicrobial agents.

Response to treatment: Fever, spleen size, hemoglobin, blood cell counts, serum albumin, and body weight are monitored for response to therapy. In most patients, the fever subsides within 7 days, blood counts and hemoglobin levels rise, the patient feels better, and spleen becomes smaller within 2 weeks. Parasitological cure should be documented at the end of therapy by splenic or bone marrow aspiration. As relapses are common in this disease, patient should be followed for at least 6 months before considering a definite cure. The spleen may take 6–12 months to regress completely. Relapse is suggested by an increase of spleen size, a fall in hemoglobin levels and should be confirmed by the demonstration of parasites.

Table 11.12: Treatment of visceral leishmaniasis

Drug	Dose	Duration
Sodium stibogluconate	20 mg/kg/day IM or IV	28 days
Amphotericin B	1 mg/kg alternate day	28 days
Liposomal amphotericin B	1 mg/kg/day IV	5 days
Miltefosine	2.5 mg/kg/day oral	28 days
Pentamidine	4 mg/kg IV/IM thrice weekly	8 weeks
Paramomycin (aminosidine)	16–20 mg/kg/day IV/IM	21 days

PKDL: Treatment is indicated only for those who have severe and prolonged disease. Pentavalent antimonials (2-month course) and liposomal amphotericin B are both effective.

Prevention and Control

Control of leishmaniasis involves controlling the source of infection and eradicating the vector. Where sand flies are mostly endophilic (rest mostly indoors after feeding), spraying houses with insecticide is effective; use of treated and untreated bed nets is effective where sand flies are endophagic (feed mainly indoors). Insecticide treatment of dogs and dog collars is useful where canines are important reservoirs. In India, where anthroponotic transmission is important, effective treatment of patients, especially those with PKDL (who act as long-term reservoirs), has been found to be effective in controlling transmission when combined with vector control. There is no effective vaccine for prevention of leishmaniasis.

Suggested Reading

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Amebiasis

Amebiasis is defined as infection with *Entamoeba histolytica*. Clinical features of amebiasis due to *E. histolytica* range from asymptomatic colonization to amebic dysentery and invasive extraintestinal amebiasis.

Epidemiology

E. histolytica is thought to infect 10% of the world population, and 2–55% Indians. However, these are overestimates, because two morphologically identical, genetically distinct but apparently nonpathogenic species, namely *E. dispar* and *E. moshkovskii*, are now recognized as causing most asymptomatic cases.

Amebic dysentery and extraintestinal amebiasis is associated with high morbidity and mortality and is a major public health problem globally, especially in adults in developing countries. It is less common in children and some estimates suggest that it is responsible for less than 3% diarrhea in children <5 years.

Etiopathogenesis

The organism exists in nature as a cyst or trophozoite. Each ingested cyst excysts in the small intestine to produce eight trophozoites that colonize the mucosa of the large intestine. Trophozoites may cause tissue invasion and destruction through several virulence factors, with little or no local inflammation, resulting in characteristic flask-shaped ulcers, seen commonly in cecum, transverse colon and sigmoid colon. Extraintestinal complications occur when trophozoites invade the bloodstream and migrate through the portal circulation, to lodge, usually in the liver.

Clinical Features

Asymptomatic cyst passage is the most common manifestation of *E. histolytica*, in most cases, the infection resolves spontaneously, but uncommonly, these individuals may later present with amebic dysentery and other invasive manifestations.

After a variable incubation period of weeks to months, about 10% individuals colonized with *E. histolytica* develop symptomatic disease, in form of colitis or extraintestinal disease. Amebic colitis presents as abdominal pain or tenderness (~80%), with watery, bloody or mucous diarrhea. Some may have only intermittent diarrhea alternating with constipation. Fever is unusual. Occasionally fulminant amebic colitis may occur, with profuse bloody diarrhea, fever, widespread abdominal pain, diffuse tenderness and pronounced leukocytosis. Toxic megacolon, ameboma, cutaneous amebiasis and rectovaginal fistulae can occur as complications of intestinal amebiasis.

Amebic liver abscess is seen in about 1% of infected individuals and may occur months to years after infection. While some individuals may have concurrent amebic colitis, more commonly there are no bowel symptoms. The child usually presents with fever with chills and rigors and right upper quadrant pain of acute onset (<10 days). Examination reveals toxic appearance, right upper quadrant tenderness and hepatomegaly; jaundice is unusual (10–15%). Cough, along with dullness or crepitations in the right lung base may be present. Complications include rupture into the pleura, which has a relatively good prognosis, and rupture into the pericardium and superinfection with bacteria, which are more serious.

Diagnosis

Diagnosis of amoebic colitis is established by demonstration of motile trophozoites by direct microscopic examina-

tion of fresh fecal sample. At least 3 stool specimens taken on consecutive days should be examined because the test has poor sensitivity (<60%; ~90% with 3 fresh samples). Stool contains plenty of erythrocytes but few leukocytes unlike bacillary dysentery where leukocytes are plentiful. Presence of ingested erythrocytes within trophozoites is pathognomonic for *E. histolytica*. Presence of cysts of *E. histolytica* in stool samples is of no clinical significance and should not be treated.

Serological tests are routinely employed for diagnosis of extra intestinal disease with *E. histolytica* especially for differentiating amebic from pyogenic liver abscess. Commonly used serologic tests in clinical practice are ELISA, IHA and IFA. They are positive in 70–80% patients with invasive disease at presentation, and in >90% cases beyond first week of symptoms. However, they can persist for years and thus are of limited utility in endemic areas. Thus a negative test is more useful than a positive test in ruling out infection.

In case of liver abscess, chest radiograph shows elevated diaphragm and pleural reaction on the right side. Ultrasound, CT, MRI, or isotope scan can localize the abscess in most cases. Leukocytosis without eosinophilia, mild anemia, raised alkaline phosphatase and high erythrocyte sedimentation rate are common findings in these patients.

Treatment

The practice of giving antiamebic drugs for all children presenting with diarrhea should be strongly discouraged since amebiasis is relatively uncommon in young children.

Metronidazole is the drug of choice for treating amebic colitis (dosed at 30 mg/kg/day in 3 divided doses for 7–10 days). Alternatives include tinidazole (50 mg/kg/day for 3 days), ornidazole and secnidazole. Since metronidazole does not destroy the cysts, a luminal agent such as diloxanide furoate (20 mg/kg/day in 3 divided doses for 10 days) should be used to eradicate colonization. When possible, fulminant amebic colitis, even with perforation, is managed conservatively, with the addition of antibiotics to deal with bowel flora. Radiographic monitoring of the abdomen by CT scan, coupled with the judicious use of percutaneous catheter drainage to obtain suspect fluid, might aid in management.

Most amebic liver-abscesses, even large ones, can be cured without drainage with IV metronidazole (50 mg/kg/day in three divided doses for 7–10 days). Most patients show response to treatment (reduced fever and abdominal pain) within 72–96 hours. Individuals with amebic liver abscess should also receive a luminal agent to eliminate intestinal colonization. Abscess cavity resolves slowly over a period of several months.

Aspiration is reserved for individuals in whom diagnosis is uncertain (where pyogenic abscess or bacterial superinfection is a concern), those who have not responded to metronidazole therapy (persistent fever or

abdominal pain after 4 days of treatment), individuals with large left lobe abscesses (risk of rupture into the pericardium), size more than 8–10 cm (suggesting impending rupture) and severely ill patients with accelerated clinical course and large abscesses (suggesting imminent rupture). Aspiration, percutaneous catheter drainage, or both, improve outcomes in the treatment of amebic empyema after liver abscess rupture, and percutaneous catheter (or, if necessary, surgical) drainage could be lifesaving in the treatment of amebic pericarditis.

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Giardiasis

Giardiasis, caused by *Giardia lamblia* (also known as *G. intestinalis* or *G. duodenalis*), is a prominent cause of diarrhea in children and in travelers.

Epidemiology

The infection is endemic in developing countries with poor sanitation. Breast milk protects against giardiasis by virtue of the glycoconjugates and secretory IgA. Individuals with malnutrition, humoral immunodeficiencies and cystic fibrosis are particularly susceptible. Children appear to be more severely affected than adults.

Etiopathogenesis

Giardia exists in two stages, cysts and trophozoites. Outside human body it exists as cysts, which are hardy, capable of surviving in cool moist environments for up to 2 months and in chlorinated water, but are destroyed by boiling for 10 minutes. Transmission of infection is through cysts, which may be ingested in contaminated water or food or spread by person to person contact. Ingestion of 10–100 cysts is sufficient for causing infection. Low pH of the duodenum facilitates excystation and release of trophozoites. Trophozoites colonize the duodenum and proximal jejunum of the host, where they attach to the intestinal brush border. Unlike amebiasis, there are no invasive or locally destructive lesions. It is believed that the infection causes diarrhea, via a combination of intestinal malabsorption and hypersecretion. These effects cause malabsorption and maldigestion and, in addition, facilitate the development of chronic enteric disorders, including inflammatory bowel disease, irritable bowel syndrome and allergies. Steatorrhea is attributed to pancreatic involvement, or bacterial overgrowth in the duodenum and upper jejunum, and deconjugation of bile salts with release of free bile acids.

Clinical Features

The incubation period after ingestion of cysts is 1–2 weeks. Most infections in children and adults are *asymptomatic*. *Symptomatic* infections are more common in children than in adults, and usually take the form of acute diarrhea with sudden onset of explosive, watery, foul smelling stools, along with nausea and anorexia; others may also have abdominal distension, flatulence, epigastric cramps and mild fever. There is no blood or mucus in stools. The illness may last 3–4 days and is usually self-limiting in normal immunocompetent children. Variable degree of malabsorption may occur. Some patients may have a protracted course, with persistent or recurrent mild to moderate symptoms such as brief episodes of loose foul smelling stools alternating with constipation. Persistent diarrhea may be seen in 30–50% cases. A few children may develop chronic diarrhea, lactose and fat malabsorption and failure to thrive.

Diagnosis

The diagnosis is made by microscopic examination of stools. At least 3 fresh specimens of stools collected on alternate days are examined to achieve sensitivity of 90%, because multiplication, and passage of giardial cysts is often intermittent. There is no blood or leukocytes in stools. Enzyme immunoassay (EIA) and direct fluorescent antibody test for *Giardia* antigens and PCR in stools are reported to have better sensitivity and require less expertise than traditional microscopy. When diagnosis is suspected but stool testing is negative, duodenal aspirate may yield high concentration of *Giardia* when fresh wet mount is examined for trophozoites. Where duodenal aspirate is negative, intestinal biopsy may be considered in presence of suggestive features like lactose malabsorption, radiographic findings (edema or segmentation in small intestine), absent secretory IgA or hypogammaglobulinemia.

Treatment

All symptomatic cases (acute and persistent diarrhea, failure to thrive, malabsorption syndrome) and asymptomatic cyst carriers require drug treatment. Treatment options include nitroimidazoles derivatives, especially metronidazole and tinidazole, and nitazoxanide. Metronidazole is given at a dose of 15 mg/kg/day for 5–7 days; it has 80–90% efficacy and is inexpensive, but has frequent adverse effects and has to be given three times a day. Tinidazole has the advantage of high efficacy (>90%) and single dose treatment (50 mg/kg once), while nitazoxanide has high efficacy (80–90%) and low incidence of adverse effects. Nitazoxanide is given for 3 days, in two doses (100 mg bid for 1–4 years; 200 mg bid for 4–12 years; 500 mg bid for >12 years). Second-line alternatives include albendazole, furazolidone, paromomycin and quinacrine.

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Amebic Meningoencephalitis

Amebic meningoencephalitis refers to infection of the central nervous system by free-living amoebae. The disease occurs in two clinical forms: Primary amebic meningoencephalitis caused by *Naegleria fowleri* and granulomatous amebic encephalitis induced by amoebae of spp. of *Acanthamoeba* and *Balamuthia*.

Primary Amebic Meningoencephalitis (PAM)

N. fowleri causes fulminating meningoencephalitis, mostly in children and healthy young adults who have a recent history of swimming in fresh water lakes, pools and ponds, usually during hot summers. The amoebae enter the nose through contaminated water (or air), penetrate the nasal mucosa and the cribriform plate and travel along the olfactory nerves to the brain leading to a diffuse hemorrhagic necrotizing meningoencephalitis.

Signs and symptoms are suggestive of acute pyogenic meningitis. Microscopic demonstration of motile amoebae in fresh cerebrospinal fluid is required for diagnosis. CSF evaluation is otherwise similar to that seen with acute pyogenic meningitis with high leukocyte count (usually in thousands) with polymorphonuclear predominance, and elevated proteins.

Disease progression is rapid; this along with the limited awareness about the disease and consequent non-institution of specific therapy, leads to death within 5–10 days; however, survivors are reported occasionally. Infection with *Naegleria* must be considered in differential diagnosis of a patient with pyogenic meningitis presenting with history of swimming in fresh water, non-specific cerebral edema on CT, and no evidence of bacteria on Gram stain, antigen detection assays and culture. A combination of high dose amphotericin B (IV and intrathecal), rifampicin and chloramphenicol has been employed for therapy with limited efficacy.

Granulomatous Amebic Encephalitis (GAE)

This is an infection with *Acanthamoeba* species (rarely, *Balamuthia* species) that is acquired through lung or skin and spreads hematogenously. *Acanthamoeba* infection is usually seen in immunocompromised patients, such as those with AIDS, SLE or post-renal transplant. *Balamuthia* can affect normal hosts. Clinically, GAE runs a subacute or chronic course similar to tubercular meningitis, and if untreated, is fatal. CSF examination reveals elevated proteins and lymphocytic leukocytosis, trophozoites are

rarely present. CT scan of brain may reveal granulomatous lesions and ventricular dilatation, mimicking tuberculosis and other fungal infections. The diagnosis is established by brain biopsy and demonstration of the cysts in brain tissue. Treatment has been attempted with combination of fluconazole, ketoconazole, sulfonamides and cotrimoxazole, but prognosis is poor.

Suggested Reading

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CONGENITAL AND PERINATAL INFECTIONS

Congenital and perinatal infections are often referred to by the acronym "TORCH". This refers to toxoplasmosis (T), rubella (R), cytomegalovirus (C) and herpes simplex (H). The others group (O) is ever expanding and includes several other infections like varicella zoster, syphilis, malaria, tuberculosis, HIV, HCV, HBV, enterovirus, parvovirus. Zika is the latest addition to this group.

General Principles

Fetal and neonatal infection and affection due to TRCH occurs predominantly with primary infection in the mother. Latent infection or reactivation affects the baby infrequently (exception syphilis). Not all infection in mothers is transmitted to the baby due to the placental barrier and not all infected babies are affected. The transmissibility and severity of fetal affection depends on the timing of gestation. Infections during the first trimester have most devastating consequences. Congenital and perinatal infections can manifest during pregnancy as USG findings, soon after birth or later in life. Common manifestations of intrauterine infections are abortions (recurrent only with syphilis, not with others), intrauterine growth retardation, intrauterine death, prematurity, deafness, chorioretinitis, aseptic meningitis, microcephaly and mental retardation, lymphadenopathy, hepatosplenomegaly, neonatal hepatitis, anemia, thrombocytopenia and skeletal abnormalities. Specific features are discussed below.

Tests that are useful in diagnosis include complete blood count, liver and renal functions, skeletal survey, fundus examination, hearing evaluation and imaging of the central nervous system. Specific diagnosis is by serology (TORCH screen). However, serologic diagnosis by IgM and IgG estimation should be done in both baby and mother and interpreted with caution.

Treatment is possible and rewarding for toxoplasmosis, syphilis, herpes simplex, only partly successful for CMV and not available for rubella and many others. Prenatal screening for syphilis, HIV and HBV and preconceptional immunization with rubella and varicella vaccines is important to reduce the burden of the TORCH infections.

Congenital Toxoplasmosis

Maternal primary infection, which is generally subclinical may lead to fetal infection and disease. The transmissibility increases but the risk of fetal disease decreases with advancing pregnancy. Clinical features are similar to those mentioned earlier. Intracranial calcification, hydrocephalus and chorioretinitis form the classical triad of the disease. Infants asymptomatic at birth may later present with mental retardation and deafness. Diagnosis is confirmed by demonstrating positive toxoplasma IgM in serum of the affected child. Treatment is recommended for all affected babies, even if they are asymptomatic. Therapy with pyrimethamine, sulfadiazine and folic acid for a duration of 1 year is recommended. Since maternal infection results from ingestion of food or water contaminated with oocysts or tachyzoites in infected meat, prevention includes advising pregnant women to wash fruits and vegetables carefully, limit contact with soil and refrain from eating undercooked meat.

Congenital Rubella

Transmissibility is highest in the first trimester and so is the rate of fetal disease (90% at <11 weeks). The fetus is completely spared if infection occurs beyond 16 weeks. The classical triad of congenital rubella syndrome consists of deafness, cataract and congenital heart disease. Delayed manifestations such as diabetes mellitus and renal disease have also been described. Diagnosis is by demonstration of positive rubella IgM in cord or neonatal blood. No treatment exists. A unequivocal diagnosis of rubella in the first trimester of pregnancy is an indication for maternal termination of pregnancy. Vaccinating all children and particularly all adolescent girls against rubella is recommended to reduce the burden of congenital rubella.

Congenital CMV

Congenital CMV is reported to be the commonest congenital infection. Transmission and fetal disease occurs throughout pregnancy. The overall transmission rate with primary infection is 30% and 10% of all babies infected are symptomatic. CMV remains latent in the body and can reactivate any time; similarly reinfections can also occur. The transmission risk with reactivation or reinfection is around 1% and only 5–10% of infected babies are symptomatic. But since reactivations and reinfections are commoner than primary infections, they contribute to half the burden of congenital CMV.

Congenital infection can affect all organ systems; periventricular calcification is characteristic (Fig. 11.25). CMV transmission can also occur during delivery and breastfeeding and is of consequence only in the preterm and very low birth weight babies. In this setting, it presents as a sepsis like illness with pneumonia and respiratory distress. CMV transmission due to blood and blood products can also cause anemia, thrombocytopenia and hepatosplenomegaly in preterm infants.



Fig. 11.25: Classical periventricular calcification of CMV

The diagnosis of congenital CMV is confirmed by a positive IgM in the first two weeks of life. The sensitivity is low and a negative IgM does not rule out CMV. The detection of CMV by PCR on urine or blood is more sensitive. A positive CMV IgM or PCR after the first 2 weeks of life can also occur due to postnatal transmission and is not specific for diagnosis of congenital CMV. Antiviral treatment with ganciclovir is available, but indicated only in patients with progressive neurologic disease and deafness.

Perinatal HSV

The transmission of HSV to babies usually occurs during delivery in mothers who develop primary genital herpes at that time. Reactivation of genital herpes is associated with very low rates of transmission and disease. Infected babies may be asymptomatic or have fulminant disease. Three forms of disease have been described; that limited to skin, eyes and mouth with vesicular eruption, CNS disease that presents as meningitis with seizures and altered sensorium and disseminated disease that presents as sepsis like illness with high mortality. The latter two may not have associated skin eruption which further complicates diagnosis.

Diagnosis is by Tzanck smear of the skin lesions, culture or PCR of lesions or cerebrospinal fluid. HSV serology has no role in diagnosis. Neonates with suspected or confirmed infection should be promptly treated with acyclovir. The dose is 20 mg/kg 8 hourly for 14–21 days followed by oral acyclovir for 6 months. Babies born to mothers with active primary herpetic lesions during labor should be considered for elective cesarean section if membranes are unruptured.

Congenital Syphilis

Syphilis is the only maternal infection that is associated with recurrent abortions. Maternal syphilis can be trans-

mitted throughout pregnancy, more commonly during later pregnancy. Apart from the features mentioned earlier, infected babies show pathognomic features like skeletal lesions, snuffles, pneumonia alba and bullous skin lesions. Some babies manifest delayed features like depressed nasal bridge, notched central incisors, keratitis, saber shins and frontal bossing.

Diagnosis is by quantitative VDRL estimation in the baby and its comparison with maternal VDRL; CSF evaluation is a must. Treatment is with procaine penicillin; ceftriaxone may be used if procaine penicillin is not available. Babies should be followed up with serial VDRL estimation till the age of 1 year to document a response.

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HELMINTHIC INFESTATIONS

Helminthic infestations contribute to significant disease burden in children in developing countries. Helminthiasis is caused by three groups of worms, nematodes (roundworms), cestodes (tapeworms) and trematodes (flukes). Nematodes may be further classified as intestinal nematodes and tissue nematodes. All these groups differ significantly in life cycle, mode of infection, pathogenesis and clinical manifestations.

Intestinal Nematodes

This group includes *Ascaris lumbricoides* (roundworm), *Enterobius vermicularis* (pinworm, threadworm), *Ankylostoma duodenale* (old world hookworm), *Necator americanus* (new world hookworm), *Trichuris trichura* (whipworm) and *Strongyloides stercoralis*. These infections are common where hygiene and sanitation are poor and where there is improper disposal of sewage.

Life Cycle

Ascaris, *Strongyloides*, *Necator* and *Ankylostoma* inhabit the small intestine, *Enterobius* is lodged in the cecum and *Trichuris* inhabits the large intestine. Eggs are released in the feces with the exception of *Enterobius* where they are released on the perianal skin. The eggs embryonate in the environment and become infective. In *Ascaris*, *Enterobius* and *Trichura*, infection occurs by ingestion of embryonated eggs. The larvae are released in the intestines and mature into adult worms locally in case of trichuriasis and enterobiasis, while in case of ascariasis they migrate through the intestinal wall, into the portal circulation, the liver, heart, lungs, trachea, swallowed into the pharynx and finally mature into adult worms in the small intestine. In case of *Necator*, *Ankylostoma* and *Strongyloides* infection occurs by penetration of the skin by filariform larvae, which then through the systemic circulation reach the

heart, then the lungs, trachea, pharynx and finally mature into adult worms in the intestines. *Strongyloides* is unique among the intestinal nematodes in several respects: Larvae divide parthenogenetically in the small intestine, development of the eggs into infective larvae occurs within the intestine leading to autoinfections and retroinfections.

Clinical Features

Clinical features depend on the worm burden and vary from asymptomatic infection to severe morbidity. Penetration of the skin by the larvae of *Ancylostoma*, *Necator* and *Strongyloides* may cause a maculopapular itchy rash. Migration of the larvae through the lungs in case of ascaris and hookworm may cause Loeffler syndrome characterized by fever, cough, dyspnea, wheeze, urticaria, eosinophilia and lung infiltrates. Other causes of Loeffler syndrome include filarial infection, visceral larva migrans, schistosomiasis and allergic bronchopulmonary aspergillosis. Visceral larva migrans refers to infection by dog/ cat ascaris where the larva have an aberrant life cycle and cause prominent visceral manifestations such as fever, eosinophilia, bronchospasm and hepatosplenomegaly. Cutaneous larva migrans characterized by an erythematous, serpiginous, pruritic eruption refers to infection by non-human hookworms where the larva migrate through the epidermis and are unable to mature.

Ascaris being the largest worm has the most prominent intestinal manifestations. Heavy infestation can lead to vague abdominal discomfort, abdominal distension, vomiting, irritability, poor growth and nutritional deficiencies. A large mass of worms may cause bowel obstruction and migration of the worms can result in cholecystitis, cholangitis, pancreatitis and rarely intrahepatic abscess.

Hookworms (*Ankylostoma*, *Necator*) suck blood from the intestine and lead to iron deficiency anemia, hypoalbuminemia and edema. The severity of anemia varies and with heavy infestations, transfusion may be needed. Heavy infestation with *Trichuris* may cause dysentery, anemia, rectal prolapse, abdominal pain, distension, hypoproteinemia and growth retardation. Manifestations of enterobiasis include perianal or vulval itching caused by migration of the gravid females to the perianal skin to lay eggs. *Strongyloides* is associated with abdominal pain, vomiting, diarrhea, bleeding, steatorrhea and weight loss. Ulceration and strictures of the duodenum may occur. Hyperinfection syndrome due to *Strongyloides* occurs in the immunocompromised (high dose steroids, chemotherapy, transplant, HIV) and is characterized by dissemination of massive numbers of larvae into various body organs (pulmonary infiltrates, meningitis) gram-negative sepsis and high mortality.

Diagnosis

The diagnosis of most intestinal nematodes is by examination of feces for the characteristic eggs. In

enterobiasis, the eggs are present on the perianal skin from which they can be lifted using the scotch tape method. In strongyloidiasis, fresh stool should be examined for larvae as eggs are rarely present; wet mount examination of centrifuged CSF and bronchoalveolar lavage may also help. Peripheral blood examination may reveal eosinophilia (striking in *Strongyloides*, visceral larva migrans). In ascariasis, the worms may be incidentally observed in the biliary or pancreatic ducts by ultrasound or in the intestines during contrast studies of the gastrointestinal tract. Serology may also be used to diagnose *Strongyloides*.

Treatment

All family members should be treated. Antiparasitic drugs available for nematode infections including albendazole (200 mg for children aged 1–2 years and 400 mg for those aged 2 years and above, taken with a fatty meal), mebendazole (100 mg twice daily for 3 days or 500 mg single dose), pyrantel pamoate (11 mg/kg, max dose 1 gm), ivermectin in a daily dose of 150–200 µg/kg. Nitazoxanide is a new drug (100 mg for children aged 1–3 years, 200 µg for children aged 4–11 years and 500 mg for older children adolescents) dosed twice daily for 3 days (Table 11.13). For pinworm, it is essential to stress on personal hygiene, keep nails clipped short, clean bed linen thoroughly and ensure hand washing before meals.

Prevention

Eradication of nematodes is possible only with improved hygiene and sanitation and appropriate sewage disposal. There is limited rationale for periodic deworming in healthy children.

Tissue Nematodes

Tissue nematodes of significance in India include *Wuchereria bancrofti*, *Brugia malayi* (causes of lymphatic filariasis) and *Dracunculus medinensis* (guinea worm). Lymphatic filariasis is endemic in several Indian states, chiefly Bihar and Kerala.

Life Cycle

Humans are infected by bite of the vector which in most instances in India is the *Culex* mosquito. The bite releases the infective larvae which migrate to the lymphatics and grow into adult males and females in about one year. They mate and release thousands of larvae termed as microfilaria which stay in the lung arterioles during the day and emerge in the systemic circulation at night. They are then taken up the insect vector where they develop further and become infective to humans. The life span of the adult worms is usually 5–10 years but can be up to 40 years.

Clinical Features

The acute symptoms of filarial disease are fever, lymphangitis, epididymo-orchitis and adenolymphangitis

Table 11.13: Treatment of intestinal nematode infections

Helminth	Primary	Alternative	Comment
Ascaris	Single dose albendazole	Mebendazole, pyrantel pamoate, ivermectin, nitazoxanide	Heavy infestation described
Hookworm	Albendazole	Mebendazole, pyrantel pamoate	Ivermectin ineffective 3 day regime of mebendazole better than a single dose Adjunctive iron required in most
Enterobius	Single dose albendazole	Single dose pyrantel or mebendazole (100 mg)	Repeat in 2 weeks Hand hygiene; nails clipped short, bed linen hygiene
Trichuris	Albendazole for 3 days	Mebendazole, ivermectin for 3 days	Treatment not very effective
Strongyloides	Ivermectin for 2 days	Albendazole twice daily for 7 days (not very effective)	Hyperinfection: prolonged or repeated treatment
Cutaneous larva migrans	Ivermectin for 1–2 days	Albendazole twice daily for 3 days	
Visceral larva migrans	Antihistaminics and steroids Albendazole/ mebendazole twice daily for 5 days		Anthelmintics controversial

(Fig. 11.26). In around 0.5% of infected patients a distinct immunologic reaction to the microfilaria results in an entity called tropical pulmonary eosinophilia. Features of this condition include cough that worsens at night, wheezing, low grade fever, enlarged neck nodes, interstitial infiltrates on chest X-ray marked peripheral blood eosinophilia (more than 3000/cu mm) and very high serum IgE levels. This syndrome can also result from the pulmonary phase of ascariasis and hookworms, visceral larvae migrans due to zoonotic ascaris and strongyloides infections. Chronic manifestations of lymphatic filariasis seen usually in adults include hydrocele, lymphedema and elephantiasis.

Diagnosis

This is largely clinical and confirmed by demonstrating the microfilaria in Geimsa stained thin and thick blood smears obtained from finger pricks. The time of collection

depends on the feeding habits of vector. In case of *W. bancrofti*, night time collection is preferred. Diethyl-carbamazine (DEC) can be used as a provocative agent to facilitate day time collections. The filarial antigen can also be detected by immunochromatography-based card tests.

Treatment

Most of the symptoms are due to the adult worms but paradoxically treatment suppresses or reduces microfilaria but does not affect the adult worms. Treatment is usually with a single dose of DEC (6 mg/kg) or ivermectin 200 µg/kg and albendazole 400 mg. Corticosteroids may need to be used to manage allergic reactions of dying microfilaria. Treatment may need to be repeated every 6–12 months for reappearing microfilaria till the adult worms spontaneously die. For tropical pulmonary eosinophilia, treatment with DEC at a dose of 6 mg/kg/

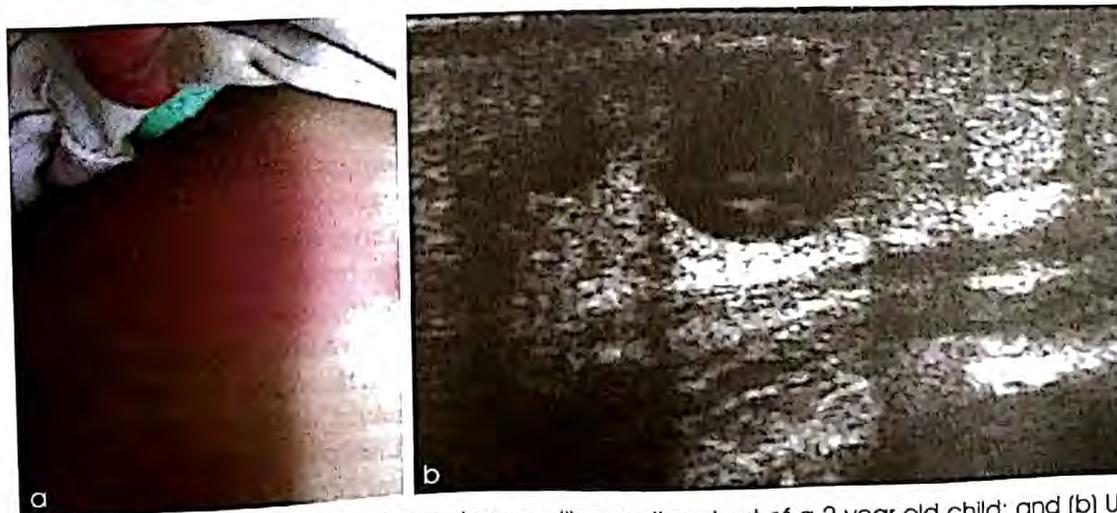


Fig. 11.26: (a) Filariasis manifesting as an erythematous swelling on the chest of a 2-year-old child; and (b) Ultrasound showing the convoluted worm in the soft tissue

day for 12–21 days is recommended. Chronic complications need surgical treatment.

Prevention

Since lymphatic filariasis causes considerable morbidity, the National Vector Borne Disease Control Programme (NVBDCP) has envisaged elimination of lymphatic filariasis by 2015. The strategy employed is mass drug administration of single dose of DEC with/without albendazole annually to all residents of an endemic district for 5 years. Vector control is also important.

Suggested Reading

- Raju K, Jambulingam P, Sabesan S, Vanamail P. Lymphatic filariasis in India: epidemiology and control measures. *J Postgrad Med.* 2010; 56(3):232–8.
- Guideline. Alternative mass drug administration regimens to eliminate lymphatic filariasis. Geneva: World Health Organization; 2017.

Cestodes

The cestodes that infect humans include giant tapeworms like *Taenia saginata*, *T. solium* and *Diphyllobothrium latum*, dwarf tapeworms like *Hymenolepis nana* and zoonotic cestodes like *Echinococcus granulosus* and *E. multilocularis*. Infection with *T. saginata* and *T. solium* is acquired through ingestion of cysticercus in contaminated food, while *Echinococcus* infection is through ingestion of eggs, and *D. latum* infection is carried to man by ingestion of cysts in freshwater fish.

Teniasis and Cysticercosis

Two species of tapeworms infest humans, *Taenia solium* or the pork tapeworm and *T. saginata* or beef tapeworm, the names reflecting the principal intermediate hosts for each of them. Man is the only definitive host for both the parasites. While the pork tapeworm has a scolex with suckers and hooks that aid its attachment to the intestinal wall, hooks are absent in *T. saginata*. Taeniasis refers to intestinal infection by the adult tapeworm, and cysticercosis results from larval lodging in various sites.

Epidemiology

Cysticercosis is the most common parasitic disease worldwide, with an estimated prevalence of more than 50 million persons. Neurocysticercosis, the neurologic manifestation of cysticercosis, is the most prevalent infection of the brain worldwide.

Pathogenesis

The life cycle of *T. solium* and *T. saginata* begins as a larva in pigs/cattle, and human infection is acquired by ingestion of these larvae in undercooked pork or beef. The larvae attach to the human gut and grow into adult tapeworms. The adult tapeworm sheds proglottids containing hundreds of tapeworm eggs into human feces.

When ingested by pigs or cattle, these eggs develop into larvae that invade the intestinal wall, enter the bloodstream and lodge in various tissues to develop into cysts.

The eggs of beef tapeworm are not infectious to humans. Humans may ingest *T. solium* eggs, usually by feco-oral transmission (contamination of food by food handlers with poor hand hygiene, or ingestion of raw fruits or vegetables fertilized with contaminated human waste), or sometimes through autoinfection (reflux of eggs from intestine into the stomach by reverse peristalsis). Thus humans become dead-end hosts of the larval stage of the parasite, and develop cysticercosis in various body tissues. Ingestion of encysted pork does not directly cause cysticercosis; rather, it causes an intestinal infection with the adult tapeworm and a human reservoir for *T. solium* eggs. Cysticercosis can therefore occur in persons who do not eat pork.

Initially the larvae become encysted, which helps viable cysts avoid initial host reaction and destruction by the host. This phase that may last for 5–10 years is often clinically silent except when cyst location or size causes signs or symptoms. Degenerating cysts release larval antigens that produce a vigorous host response with release of inflammatory mediators and surrounding edema. After this phase, the encysted larvae degenerate entirely, die and often calcify.

Clinical Features

Infection with adult worm is mostly symptomatic, but some children may have non-specific symptoms like nausea, abdominal pain and diarrhea. These patients may also develop cysticercosis through auto-infection.

The clinical features of cysticercosis depend on the location of the cysts and overall cyst burden. In about 2 months, the larvae mature into cysticerci of about 2 mm to 2 cm size. Cysts can lodge in the brain, skeletal muscle, subcutaneous tissues, spinal column and eyes. The two sites associated with high morbidity are the brain, the most common (60–90%) location for cysts, and the eye, the least common site (1–3%). Cysts in the brain parenchyma (parenchymal neurocysticercosis) cause focal or generalized seizures and, less commonly, headache, focal neurologic deficits, or behavioral abnormality. Heavy cyst burden can cause encephalopathy with fever, headache, nausea, vomiting, altered mental status and seizures. Cysts in the subarachnoid or ventricular spaces may cause meningeal signs and symptoms, obstructive hydrocephalus or cranial nerve palsies (by nerve entrapment); those located in the spinal column can cause radicular pain or paresthesias. Ocular cysts in the subretinal space or vitreous humor can impair vision by inflammation or through retinal detachment, while those in the extraocular muscles may limit the range of eye movements and those in the subconjunctival tissue present as a nodular

swelling. Skeletal muscle or subcutaneous cysticercosis may be either asymptomatic or cause localized pain and nodules.

Diagnosis

The diagnosis of teniasis is established by the demonstration of eggs or proglottids in the stools. Patients may pass motile segments of worms through anus.

Diagnosis of neurocysticercosis is based on contrast CT or contrast MRI of brain; MRI is superior to CT (Fig. 11.27). Demonstration of a solitary contrast-enhancing lesion less than 20 mm in diameter and producing no midline shift is highly sensitive for neurocysticercosis; if the scolex is visible, it is pathognomonic. Cystic, nonenhancing lesions suggest viable, non-degenerating cysts; cystic, enhancing lesions indicate degenerating cysts with some surrounding inflammation; and calcified cysts suggest old cysts that have already died. Ocular or extraocular muscle cysticercosis can be picked up on CT or ultrasound, or by detailed eye examination. Detection of antibodies by enzyme-linked immunoblot assay or enzyme-linked immunosorbent assay of the serum or cerebrospinal fluid has a sensitivity of 65–98% and a specificity of 67–100%, varying with the cyst burden, location, and phase of the infection; the immunoblot assay is the preferred test. Biopsy of the skin or muscle provides a definitive diagnosis in ambiguous situations, and may be the diagnostic method of choice for ocular, extraocular muscle, or painful muscular or subcutaneous cysts.

Treatment

Infestation with the adult tapeworm (teniasis) is treated with praziquantel (5–10 mg/kg once) or niclosamide (50 mg/kg once). Therapeutic options in neurocysticercosis include medications, surgery, or watchful waiting. The decision depends upon multiple factors, including symptoms and the location, number, stage, and size of cysts. Single active parenchymal lesions usually resolve spontaneously and may not require anticysticercal drugs. Watchful waiting is also indicated for calcified cysts because they are already dead, hence children with seizures and calcified inactive lesions on CT do not require specific therapy apart from anticonvulsants. The commonly used antiepileptics are phenytoin and carbamazepine, which should be continued for at least one year and then tapered or continued based on radiologic resolution.

A meta-analysis demonstrated that cysticidal drug therapy in patients with multiple and live cysticerci is associated with reduced seizures and increased resolution of lesions in the brain parenchyma. Two effective anticysticercal drugs are available: Albendazole (15 mg/kg/day bid, max dose of 800 mg/day for 7–30 days) or praziquantel (50 mg/kg/day tid for 15–29 days). Albendazole is more effective than praziquantel. A 7-day course of albendazole is perhaps as effective as a 28-day



Fig. 11.27: Multiple lesions of neurocysticercosis on brain imaging

course for single lesions, though longer courses of 30 days are preferred for giant or subarachnoid cysts. Use of antihelminthic medications is associated with the risk of an overwhelming inflammatory response from degenerating cysts. This can be prevented by giving oral corticosteroids (prednisolone or dexamethasone) for 2–3 days before and during treatment. Intraocular cysticercosis should be ruled out before using antihelminthic medications as therapy may cause inflammation and threaten vision.

Treatment of subarachnoid and intraventricular neurocysticercosis is complicated and risky. Cysts in these locations are usually managed surgically because medical treatment is associated with the risk of inflammation; however, recent reports suggest that high-dose albendazole (30 mg/kg/day) is associated with clearance of these cysts. A ventriculoperitoneal shunt should be placed in all patients with evidence of significant obstructive hydrocephalus.

Surgical removal of the cyst is considered the treatment of choice for intraocular cysts; antihelminthic medication should be avoided as discussed earlier. Cysts in the extraocular muscle may be treated with albendazole and steroids, or surgically excised. Isolated skeletal muscle or subcutaneous cysticercosis requires no specific treatment unless, it is painful, and then simple excision may suffice.

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- Kraft R. Cysticercosis: an emerging parasitic disease *Am Fam Physician* 2007; 76:91–6.
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- Zammarchi L, Bonati M, Strohmeier M, et al. Screening, diagnosis and management of human cysticercosis and taeniasis: Technical recommendations COHEMI project study group. *Trop Med Int Health* 2017; 22:881–94.

Hymenolepiasis

Infection with *Hymenolepis nana*, also known as the dwarf tapeworm, is very common in developing countries. Man acts as both definitive and intermediate host because the entire life cycle may be completed in human host; however, rodents, ticks and fleas may serve as the intermediate host. The infestation usually results from poor hygiene. The adult worm lives in the jejunum. Transmission is mainly feco-oral, but autoinfection may also occur, such that one host may harbor upto thousands of adult worms. Symptoms are usually non-specific, including mild abdominal discomfort, poor appetite and cosmophilia, some show growth retardation. The infection is a major cause of eosinophilia. The diagnosis is based on the demonstration of characteristic eggs in stools. Treatment is with praziquantel (25 mg/kg once) or niclosamide (50 mg/kg once, maximum 2 g).

Echinococcosis (Hydatid Disease)

Human echinococcosis is an infestation caused by larval stages of members of the genus *Echinococcus*, and is characterized by production of unilocular or multilocular cysts in the lung and liver. Echinococcosis is endemic in most continents of the world, with hyperendemic areas in Western China, North Africa, West Asia and areas of South America.

Pathogenesis

Hydatidosis is a zoonosis caused by two *Echinococcus* species, *E. granulosus* and *E. multilocularis*. The parasite eggs are transmitted from members of the canine family like dogs and wolves, to various wild and domestic animals like sheep, cattle and goats, which act as intermediate hosts. Humans are accidental hosts. Eggs from the adult worm are passed in the stools that may contaminate the water and soil, and also the fur coats of dogs. Ingestion of food or water contaminated with eggs or direct contact with infected dogs may result in humans being infected accidentally. Eggs hatch in the intestines to release larvae that penetrate the intestinal mucosa, and traverse the venous or lymphatic system to reach the liver, lungs and, less commonly, other target organs.

In the target organs, larvae develop into characteristic multiloculated fluid-filled cysts, called *hydatid cysts*. In children, lung cysts are common, whereas in adults, cysts are more commonly seen in the right lobe of the liver. Other tissues that may be involved include bone, brain, genitourinary tract, intestines and subcutaneous tissue. The cyst may keep on expanding over several years.

Life cycle of *E. multilocularis* is the same except that rodents and mice serve as intermediate hosts, and the cysts

are multilocular that proliferate exogenously and also metastasize.

Clinical Features

Symptoms depend on the target organ involved. Very often, liver cysts may regress spontaneously without becoming symptomatic. Otherwise, cysts may become symptomatic after several years when significant mass effect results in abdominal pain vomiting, increase in abdominal girth and a palpable mass; jaundice is rare. Alveolar cysts have a more malignant course. Direct spread of infected tissue may result in cysts in the peritoneal cavity, kidneys, adrenal gland or bones. Lung cyst may present with chest pain, cough, hemoptysis and breathlessness. Involvement of the genitourinary tract may manifest as passage of cysts in the urine (hydatiduria) and hematuria. Rupture or leakage from a hydatid cyst may cause anaphylaxis, manifest as fever, itching and rash, and results in dissemination of infectious scolices. Rare but potentially serious complications include compression of important structures in the central nervous system, bone, heart, eyes or genitourinary tract.

Diagnosis

Physical examination may reveal a palpable mass, hepatomegaly or subcutaneous nodules. Ultrasonography is the most valuable tool in diagnosing echinococcal cysts. Lung hydatids may be visible on plain X ray. MRI and CT may be used for further delineation (Fig. 11.28). Diagnostic aspiration is generally contraindicated because of risk of infection and anaphylaxis. Antibody detection by ELISA is more sensitive but less specific. The test uses partially purified antigens that cross-reacts with other parasites such as cysticercosis and schistosomiasis.

Management

Treatment depends on the stage and location of the lesion, and importantly the experience of the treating center and includes albendazole, surgical excision orPAIR (percutaneous aspiration, instillation of hypertonic saline or another scolicidal agent; and reaspiration after 15 minutes).

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- Czernak BV, Akhan O, Hiemetzberger R, et al. Echinococcosis of the liver *Abdom Imaging* 2008; 33:133–43.
- Nabarro LE, Amin Z, Chiodini PL. Current management of cystic echinococcosis. *Clin Infect Dis* 2015; 60:721–8.

RATIONAL ANTIMICROBIAL THERAPY AND ANTIMICROBIAL RESISTANCE

Rational antimicrobial therapy refers to using antimicrobials only when indicated; the right drug for the right duration through the right route and in the right dose. Irrational use of antibiotics compromises treatment



Fig. 11.28: Large hydatid cyst of the liver

outcomes, increases adverse effects and cost of therapy. Irrational use of antimicrobials is the biggest driver for antimicrobial resistance. Rising antimicrobial resistance is responsible for increasing morbidity, mortality and treatment cost of infections.

The most important antimicrobial resistance challenges are:

- Resistance in gram-negative bacilli due to production of extended spectrum beta-lactamases and carbapenemases (New Delhi metallo-beta-lactamase)
- Multidrug-resistant tuberculosis
- Chloroquine-resistant falciparum malaria
- Resistance in HIV.

Examples of Irrational Therapy

- Prescribing antimicrobials when not indicated, e.g. using antibiotics to treat viral upper respiratory tract infections and viral gastroenteritis
- Prescribing multiple antimicrobials at the same time, irrational combinations and changing them frequently
- Using high end antimicrobials such as carbapenems to treat community acquired infections and using drugs for MRSA such as vancomycin when not indicated.
- Using fewer drugs than indicated for diseases such as tuberculosis, HIV, malaria.

Causes

- Practitioner errors due to inadequate knowledge about microbial etiology and resistance patterns. Other reasons are fear of missing a diagnosis, in order to circumvent investigations and sometimes due to pressure from parents. The wrong belief that use of newer and multiple antimicrobials is beneficial also drives practitioners to over use antibiotics.
- Self medication by parents and as per pharmacist recommendations
- Aggressive marketing of antimicrobials by pharmaceutical companies

- Ready availability of antimicrobials over the counter and licensing of irrational fixed drug combinations such as cefixime-ofloxacin.

Solutions

- Education of medical practitioners about rational antimicrobial practices from the undergraduate level through postgraduation and for practicing doctors.
- Development of evidence-based guidelines to treat common infections and ensuring that they are implemented.
- Educating the public and parents about the hazards of overuse of antibiotics
- Legislation to prevent over the counter availability of antimicrobials and licensing of irrational fixed drug combinations
- Preventing overuse of antimicrobials in the veterinary industry
- Establishing antimicrobial stewardship programs in hospitals targeting use of antimicrobials in inpatients especially intensive care units.

Suggested Reading

- Marston HD, Dixon DM, Knisely JM. Antimicrobial resistance. JAMA 2016; 316:1193–1204.

HEALTHCARE-ASSOCIATED INFECTIONS AND INFECTION CONTROL

Healthcare-associated infections (HAIs) are termed as those infections that occur in hospitalized patients and were neither present nor incubating at the time of admission. They include those infections that occur as a result of hospital visit (varicella following exposure in the emergency room or outpatient visit), or in hospitalized patients (diarrhea) or health care personnel (see Chapter 28).

Types of HAIs

These may range from minor infections such as viral upper respiratory tract infections, diarrhea to serious infections. Immunocompromised children, those in the intensive care unit and those who undergo surgery are at the greatest risk for serious infections. These infections include central line-associated bloodstream infections (CLABSI), health care-associated pneumonia (HAP), catheter associated urinary tract infections (CAUTIs), surgical site infections (SSIs) and *C. difficile* associated diarrhea.

Etiology of HAIs

The etiology of health care associated infections in India is predominantly resistant gram-negative bacilli including ESBL (extended spectrum beta-lactamase), AmpC beta-lactamases and now even carbapenamase producing *E. coli*, *Klebsiella*, *Pseudomonas* and *Acinetobacter* spp. Gram-positive pathogens including *S. aureus* and enterococcus are less common. *Candida* is emerging as an important pathogen.

Clinical Manifestations

The clinical manifestations include new onset fever, hemodynamic compromise, respiratory deterioration and diarrhea depending on the site of HAIs. Some of the HAIs can be rapidly progressive and lead to septic shock and multiorgan dysfunction in a few hours. HAIs need to be differentiated from non-infectious causes of fever such as drug fever, thrombophlebitis, pulmonary embolism and atelectasis. Mere isolation of bacteria from non sterile site cultures such as trachea, urine, stool and drains is not indicative of HAIs and should not be treated.

Consequences of HAIs

HAIs can lead to significant morbidity, mortality and lengthen duration and cost of hospital stay. More importantly they lead to increase use of high end antimicrobials that further amplify the problem of antimicrobial resistance.

Treatment

Management entails early recognition and sending appropriate cultures including blood, endotracheal aspirates, urine and pus, and starting broad-spectrum antibiotics pending reports. The choice of antibiotics varies with the severity and site of infection, prior antibiotic exposure, local antimicrobial resistance patterns and host comorbidities such as renal/ hepatic dysfunction. Usually this regime comprises beta-lactam-beta-lactamase inhibitor

combinations such as piperacillin tazobactam or cefoperazone sulbactam or carbapenems with or without amikacin and antifungals. In certain ICUs with high prevalence of carbapenem resistance, colistin may be needed. Source control such as removal of infected lines and drainage of pus is crucial. In the interests of antimicrobial stewardship, the role of de-escalation and optimization of therapy at 48-72 hours once culture results are available cannot be overemphasized.

Prevention

Infection prevention and control is the cardinal strategy to prevent HAIs. The most important is hand hygiene with antimicrobial soap and water or alcohol-based hand rub before and after each patient contact, before sterile procedures and after contact with patient surroundings. Implementing prevention bundles for CLABSI/ HAP/ CAUTI and SSI are integral to any infection control program. Maintaining a clean hospital environment with attention to air and water quality and following standard and transmission based precautions are other components of preventive strategy.

Suggested Reading

- Foster CB, Sabella C. Health care-associated infections in children. JAMA 2011; 305:1480-81.
- Patrick SW, Kwai AT, Kleinman K, et al. Health care-associated infections among critically ill children in the US. Pediatrics 2014; 134:1-10.

Diseases of Gastrointestinal System and Liver

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GASTROINTESTINAL SYSTEM

Most diseases of the gastrointestinal (GI) tract present with a few symptoms, such as vomiting, dysphagia, abdominal pain, distension, diarrhea, constipation, gastrointestinal bleeding and failure to thrive. Appropriate evaluation requires an assessment of symptoms and signs, listing differential diagnosis and planning investigations.

Vomiting

Vomiting refers to acute expulsion of gastric contents through the mouth. Vomiting should be differentiated from regurgitation, especially in infants. Regurgitation is the involuntary and effortless expulsion of small amounts of gastric contents that is not accompanied by nausea. Recurrent or persistent vomiting requires thorough evaluation and treatment. Persistent vomiting may be complicated by dehydration, hypokalemic hypochloremic metabolic alkalosis, malnutrition and constipation. Vigorous vomiting can uncommonly result in esophageal mucosal tear (Mallory-Weiss syndrome) or rupture (Boerhaave syndrome).

Vomiting is a common, but often nonspecific, symptom that may be acute, chronic or recurrent (Table 12.1). Short-lasting vomiting with acute onset is the most common form and is often caused by viral infections. Chronic vomiting may be (i) cyclic, characterized by ≥ 5 stereotype episodes occurring at high intensity (≥ 4 emesis/hr) and infrequently (≤ 2 episodes/week), with normalcy in between; or (ii) chronic, characterized by frequent episodes (> 2 /week) at low intensity (1–2 emesis/hr) (Fig. 12.1). While chronic vomiting is usually caused by a gastrointestinal etiology, cyclic vomiting is predominantly due to neurologic, metabolic and endocrine causes.

Evaluation

A detailed history and examination often gives clue to the diagnosis. The etiology of vomiting varies according to age; while infectious causes occur across all ages, most congenital anomalies, e.g. atresia or stenosis and metabolic disorders, present in the neonatal period or infancy. The

Table 12.1: Causes of vomiting

<i>Gastrointestinal</i>	<i>Nongastrointestinal</i>
Acute	
Gastroenteritis	Infections, e.g. urinary tract infection, meningitis, encephalitis, pertussis
Hepatitis	
Appendicitis	
Small intestinal obstruction, (malrotation, volvulus, intussusception)	Raised intracranial tension
Cholecystitis	Diabetic ketoacidosis
Pancreatitis	Defects in fatty acid oxidation or respiratory chain
	Drug or toxin induced
Chronic	
Gastroesophageal reflux	Raised intracranial tension
Gastritis	Chronic sinusitis
Gastric outlet obstruction (hypertrophic pyloric stenosis, peptic ulcer)	Uremia
Small bowel obstruction (duodenal stenosis, annular pancreas, superior mesenteric artery syndrome)	Overfeeding
Food allergy	
Achalasia cardia	
Gastroparesis	
Eosinophilic esophagitis	
Recurrent	
Cyclic vomiting	Urea cycle defects
Abdominal migraine	Diabetic ketoacidosis
Malrotation with volvulus	Addison disease

first step is to find out whether the vomitus is bilious or non-bilious. This determines the site of disease. Lesions beyond the ampulla of Vater cause bilious vomiting and those proximal to it lead to non-bilious vomiting. Associated features may indicate etiology, e.g. vomitus containing stale food of previous day (suggests gastric outlet obstruction), visible peristalsis (obstruction), vomiting in early morning (intracranial neoplasm or cyclic vomiting syndrome), vertigo (middle ear disorder) and

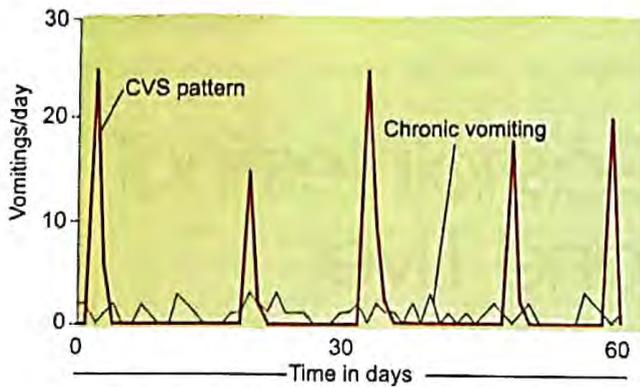


Fig. 12.1: Chronic and cyclic pattern of vomiting

hypotonia (mitochondrial disorders). The 'red flag' symptoms and signs in a child with vomiting are the presence of blood or bile in the vomitus, severe abdominal pain with abdominal distension or tenderness, projectile vomiting, persistent tachycardia or hypotension, neck stiffness and/or photophobia. These patients need immediate investigation in a hospital.

Workup for chronic vomiting should include evaluation for cause with blood chemistry (blood sugar, electrolytes, serum amylase and liver enzymes); ultrasound abdomen, upper gastrointestinal endoscopy and, as indicated by available clues, barium studies (meal and small bowel follow-through), gastric emptying scan, CT or MRI brain, metabolic testing or urine analysis. It is important to remember that children with cyclic vomiting should be evaluated during symptomatic attack before starting intravenous fluids since test results are typically non-contributory during asymptomatic periods.

Evaluation of a child with acute vomiting should include assessment of hydration, electrolytes, creatinine and plain X-ray abdomen (in suspected surgical causes). Promethazine and ondansetron are useful in postoperative vomiting and to abort episodes of cyclical vomiting. Ondansetron, given alone or with dexamethasone, is preferred for chemotherapy-related vomiting. Domperidone and metoclopramide are useful in patients with gastroparesis. Antihistaminics like diphenhydramine help in motion sickness. Management of the underlying condition is essential.

Some common disorders presenting with vomiting are described below.

Idiopathic Hypertrophic Pyloric Stenosis

Hypertrophic pyloric stenosis is the most common surgical disorder of the gastrointestinal tract in infants. The pylorus is thickened and elongated with narrowing of its lumen due to hypertrophy of the circular muscle fibers of pylorus.

Clinical presentation: Patients present with non-bilious vomiting that gradually increases in frequency and severity to become projectile in nature. The disorder is 4–6 times more common in boys than girls. Most patients present with vomiting starting beyond 3 weeks of age;

however, about 20% are symptomatic since birth and presentation is delayed until 5 months of age in others. Constipation is common. Recurrent and persistent vomiting causes dehydration, malnutrition and hypochloremic alkalosis. As the stomach muscles contract forcibly to overcome the obstruction, a vigorous peristaltic wave can be seen to move from left hypochondrium to umbilicus, particularly on examination after feeding. A firm olive-shaped mass is palpable in the mid-epigastrium in 75–80% infants, especially after feeds.

Evaluation: Ultrasound abdomen is the diagnostic investigation and shows muscle thickness of ≥ 4 mm and pylorus length of ≥ 16 mm. The ultrasound is 100% sensitive and nearly 90% specific in diagnosis of hypertrophic pyloric stenosis. However, in case of doubt, an upper GI barium study (Fig. 12.2) or an upper GI endoscopy should be performed.

Management: The treatment includes rapid correction of dehydration and electrolyte abnormalities. The treatment of choice is surgical; a Ramstedt pyloromyotomy is performed.

Cyclic Vomiting

This is defined as occurrence of stereotypic episodes of intense nausea and vomiting as defined previously, with complete normalcy between episodes and the absence of a metabolic, neurologic or gastrointestinal disorder. An episode may last for an hour to 10 days and occurs at least 1 week apart. Episodes are often triggered by physical or emotional stress. The patient should have had at least



Fig. 12.2: Upper gastrointestinal barium study showing narrowing and elongation of pyloric channel in idiopathic hypertrophic pyloric stenosis

5 episodes in all or 3 episodes during a 6-month period. Typically, the attacks begin in early morning with symptoms of autonomic surge, e.g. lethargy, pallor, mild fever, headache, tachycardia, hypertension, diarrhea and abdominal pain. Most subjects have onset in preschool or school age. Family history of migraine and/or motion sickness is noted in 30–40% cases. Symptoms may overlap with abdominal migraine.

Management: Known precipitants of the episodes should be avoided. Management of an attack includes providing a quiet environment, administration of intravenous fluids, use of serotonin 5-HT₃ antagonists such as ondansetron (0.3–0.4 mg/kg/dose IV q 4–6 hr up to 20 mg) and sedation with lorazepam (0.05–0.1 mg/kg/dose IV every 6 hr). Agents recommended for prophylaxis against future attacks are cyproheptadine (0.25–0.5 mg/kg/day in two or three divided doses) in children below 5 years and, in older children, amitriptyline (initiate at 0.25–0.5 mg/kg/day at bedtime; may increase up to maximum of 1.0–1.5 mg/kg/day) or propranolol (0.25–1 mg/kg/day; up to 10 mg q 8–12 hr).

Gastroesophageal Reflux Disease (GERD)

Gastroesophageal reflux (GER) is passage of gastric contents into the esophagus with or without regurgitation and vomiting. GER is a normal physiologic process that occurs several times a day in healthy infants, children and adults. When this reflux of gastric contents causes troublesome symptoms and/or complications, it is known as GERD. About 50% of healthy 3–4-month-old infants regurgitate at least once per day and most of them outgrow this by 1 year of age. Follow-up studies suggest that infants with persistent spitting beyond 3 months of age are at an increased risk of developing GERD in childhood. Children with obesity, repaired esophageal atresia, cystic fibrosis, hiatal hernia, preterm babies and a family history of GERD are at risk of developing severe chronic GERD. Neurologically impaired children like those with cerebral palsy have increased risk of severe GERD due to multiple factors like low pressure of the lower esophageal sphincter and predominant supine position.

Clinical features: The common symptoms associated with GERD in children are: (i) recurrent regurgitation; (ii) weight loss or poor weight gain; (iii) irritability (in infants); (iv) heartburn or chest pain (older children); (v) hematemesis, dysphagia and odynophagia (if complicated by esophagitis or stricture esophagus); (vi) wheezing, stridor, cough and hoarseness; and (vii) Sandifer syndrome, an uncommon manifestation, characterized by spasmodic torsional dystonia with arching of the back and opisthotonic posturing.

Evaluation: A detailed history and physical examination are generally sufficient to establish the diagnosis of GERD. Useful investigations are as follows:

24 hours ambulatory esophageal pH monitoring is a validated method for quantitative measurement of esophageal acid exposure (Fig. 12.3). It is also used to evaluate the efficacy of anti-secretory therapy and to correlate symptoms (e.g. cough, chest pain) with acid reflux episodes.

Combined 24 hours multiple intraluminal impedance and pH monitoring detects acid, weakly acid and nonacid reflux episodes. It is thus superior to pH monitoring alone which detects only acid reflux episodes. Its main utility is to evaluate the temporal relationship between symptoms and GER episodes.

Upper GI endoscopy may show erosions or mucosal breaks in the distal esophageal mucosa, the most reliable evidence of reflux esophagitis. Mucosal erythema and pallor are highly subjective and nonspecific findings. Complications like stricture esophagus (Fig. 12.4) and Barrett's esophagus can be picked up at endoscopy. Histological features like elongated rete pegs, basal cell layer hyperplasia and dilated intercellular spaces, alone or in combination, are suggestive of reflux esophagitis.

Endoscopic biopsy is important to evaluate other causes of esophagitis and to diagnose Barrett's esophagus. While not useful for the diagnosis of GERD, **barium contrast radiography** helps rule out anatomic abnormalities of the upper gastrointestinal tract that may cause symptoms similar to those of GERD. This investigation should be done in all infants with vomiting.

Nuclear scintigraphy has a role in the diagnosis of pulmonary aspiration in patients with chronic and refractory respiratory symptoms due to GERD.

Empiric trial of acid suppression: Using proton pump inhibitors for up to 4 weeks is justified in older children or adolescents with typical symptoms suggesting GERD.

Management: Treatment of GERD depends on patient's age and nature and severity of symptoms and includes lifestyle changes, pharmacologic therapy and surgery.

Lifestyle changes: Infants should be placed in left lateral position with the head end elevated by 30° in the postprandial period to reduce the frequency of reflux. Cow milk protein allergy is sometimes a cause of unexplained crying and vomiting in infants. Therefore, formula-fed infants with recurrent vomiting may benefit from a 2–4 weeks trial of an extensively hydrolyzed protein formula. Infants with inadequate weight gain because of losses by regurgitation may benefit from increasing the energy density of formula. Careful follow-up with charting of caloric intake and weight gain is essential.

For children and adolescents with GERD, measures that are useful include: Dietary modification (to avoid caffeine, chocolate and spicy foods), weight loss if obese, sleeping in the left lateral position with elevation of the head-end of the bed, avoidance of alcohol and cessation of smoking.

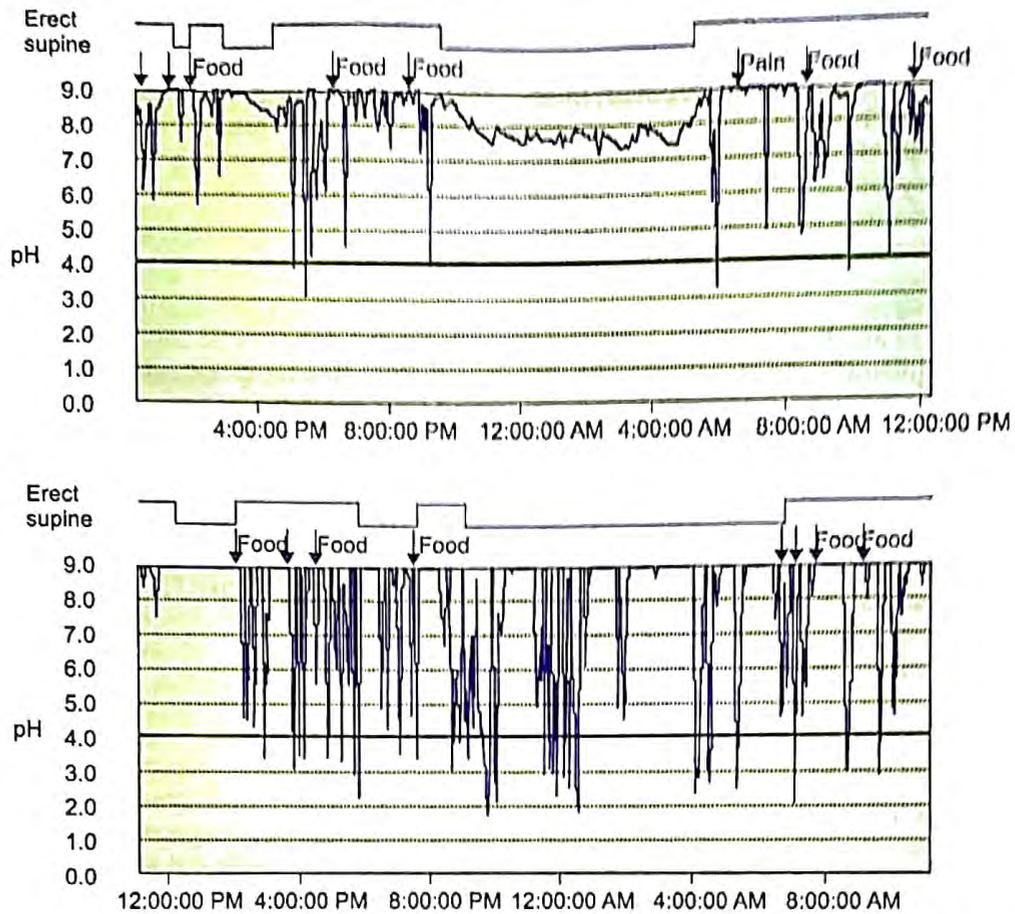


Fig. 12.3: 24 hours esophageal pH study. Upper panel shows a normal study and lower panel shows frequent episodes of acidic reflux with drop in pH to <4 suggestive of GERD



Fig. 12.4: Upper gastrointestinal endoscopy showing ulceration with stricture formation in reflux esophagitis

Histamine-2 receptor antagonists like ranitidine (5–10 mg/kg/day in 2–3 divided doses) decrease acid secretion by inhibiting receptors on gastric parietal cells. Development of tachyphylaxis is a problem with these agents. They are

chiefly used in infants with GERD in whom PPI are still not approved for use.

Proton pump inhibitors (PPIs) inhibit acid secretion by blocking $\text{Na}^+\text{-K}^+\text{-ATPase}$, the final common pathway of parietal cell acid secretion. PPIs are the agent of choice for GERD. PPIs maintain intragastric $\text{pH} \geq 4$ for long periods and inhibit meal-induced acid secretion. PPIs currently approved for use in children are omeprazole (0.7–3.3 mg/kg/day, max 80 mg), lansoprazole (1–3 mg/kg/day, max 60 mg) and esomeprazole (10 mg/day below 20 kg, 10–20 mg above 20 kg in children between 1 and 11 years of age, 20–40 mg above 12 years of age). Children with typical symptoms of chronic heartburn should be treated with lifestyle changes and 2–4 weeks trial of PPI. In patients with endoscopically diagnosed reflux esophagitis or established non-erosive reflux disease, PPIs for 3 months constitute initial therapy.

Antacid therapy is not recommended for most patients with GERD. There is insufficient evidence to justify the routine use of prokinetic or other agents such as cisapride, metoclopramide, domperidone, bethanechol, erythromycin or baclofen for GERD.

Surgical therapy: Fundoplication decreases reflux by increasing the baseline lower esophageal sphincter

pressure, decreasing the number of episodes of transient lower esophageal sphincter relaxation and increasing the nadir pressure during swallow-induced relaxation, increasing the length of intra-abdominal esophagus, accentuating the angle of His and reducing a hiatal hernia, if present. Antireflux surgery may be of benefit in selected children with chronic-relapsing GERD with intractable symptoms or risk of life-threatening complications.

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Dysphagia

Dysphagia refers to a sensation of food being hindered in its passage from the mouth to the stomach, i.e. difficulty in swallowing. *Odynophagia* is painful swallowing and *globus* is the sensation of a lump in the throat. Dysphagia can be divided into two distinct groups:

Oropharyngeal or transfer dysphagia: Presence of drooling, choking, coughing and nasal regurgitation suggests oropharyngeal dysphagia. Disorders involving chewing, oral transfer or pharyngeal phase of swallowing cause this.

The main causes are cerebral palsy, bulbar poliomyelitis, muscular dystrophy, brainstem tumors and neuropathy.

Esophageal dysphagia: This occurs due to conditions involving esophageal phase of swallowing, i.e. coordinated peristalsis of esophageal body with simultaneous relaxation of LES. Etiology of esophageal dysphagia can be broadly divided into two groups: Motor causes (e.g. achalasia cardia and diffuse esophageal spasm) and structural causes (e.g. strictures, foreign body, Schatzki's ring, esophageal web, eosinophilic esophagitis and extrinsic compression by aberrant vessel or mediastinal mass).

Differential Diagnosis and Evaluation

The important causes of dysphagia and their evaluation are shown in Table 12.2 as well as discussed below.

Congenital esophageal stenosis: This may be of three types: Web or diaphragm, fibromuscular stenosis and stenosis due to cartilaginous tracheobronchial remnants. Symptoms of vomiting or chest infection due to aspiration typically develop around 6 months of age when weaning is started.

Foreign bodies in esophagus: Sharp foreign bodies and batteries can cause damage by perforation secondary to pressure or chemical necrosis and can present with

Table 12.2: Evaluation and management of esophageal lesions that cause dysphagia

Etiology	Investigation	Finding	Treatment
Corrosive (acid or alkali) stricture	Barium swallow and meal; upper GI endoscopy	Narrowing in one or multiple, short or long, segments of esophagus; may show contracted stomach or pyloric stenosis	Endoscopic dilatation (Balloon or Savary-Gilliard dilators)
Stricture after repair of tracheoesophageal fistula	Barium swallow (Fig. 12.5)	Narrowing of a short segment of esophagus	Endoscopic dilatation
Congenital stricture	Barium swallow; CT chest	Stricture in middle or lower esophagus; cartilaginous tissue in stricture	Endoscopic dilatation or surgery
Postsclerotherapy stricture	Barium swallow; upper GI endoscopy	Narrowing in lower end of esophagus	Endoscopic dilatation
Peptic stricture	Barium swallow; endoscopy; 24 hours pH study	Narrowing in lower esophagus; may show hiatus hernia or erosions	Endoscopic dilatation; proton pump inhibitor after dilatations
Foreign body	Plain X-ray; upper GI endoscopy (Fig. 12.6)	Type of foreign body and site of impaction	Endoscopic retrieval
Achalasia cardia	Barium swallow; endoscopy esophageal manometry	Beak-like narrowing in lower esophagus	Pneumatic dilatation; Heller's cardiomyotomy
Infectious esophagitis (in immunocompromised children)	Upper GI endoscopy; endoscopic biopsy	White curd-like deposits (<i>Candida</i>); ulcers (cytomegalovirus, herpes)	Fluconazole (<i>Candida</i>); ganciclovir (cytomegalovirus) or acyclovir (herpes)

GI: Gastrointestinal



Fig. 12.5: Post-TEF stricture. Black arrow shows the short stricture and white arrow shows the dilated proximal esophagus



Fig. 12.6: Upper GI endoscopy showing foreign body (coin) in esophagus

dysphagia, mediastinitis and/or upper gastrointestinal bleeding. The vast majority of foreign bodies pass unimpeded through the GI tract. The most frequent sites of impaction are at the cricopharynx, mid esophagus at tracheal bifurcation and just above the LES.

Guidelines recommend that no foreign body should be left in esophagus for more than 24 hours. Endoscopic removal under sedation or anesthesia is the standard of therapy.

Achalasia cardia: Children present with dysphagia, vomiting, weight loss, respiratory symptoms and slow eating whereas toddlers present with coughing and



Fig. 12.7: Barium swallow showing achalasia cardia

feeding aversion with failure to thrive. The onset is gradual and the average age at diagnosis in children is around 8–9 years. The barium swallow shows esophageal dilatation with beak-like narrowing at the LES (Fig. 12.7). Manometry is the most sensitive and specific tool and shows absent peristalsis in esophagus; incomplete/absent LES relaxation and raised intraesophageal pressure. Endoscopy is useful to exclude other etiologies of dysphagia.

Endoscopic pneumatic balloon dilatation and Heller's cardiomyotomy with antireflux procedure are two main therapeutic modalities. The experience with per oral endoscopic myotomy (POEM) is limited.

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Constipation

Constipation is defined as a delay or difficulty in defecation, present for 2 or more weeks and sufficient to cause significant distress to the patient. It is increasingly being recognized as a very common problem in children and is associated with both physical and psychological morbidity and a poor quality of life. The normal stool frequency decreases from 4 or more per day during infancy to once per day at 4 years of age. A stool frequency of ≤ 2 /week is considered abnormal for all ages. The majority of patients have functional constipation; organic cause is found in ~15% (Table 12.3).

Approach

Details about pattern of stooling, time of first passage of meconium, presence of blood in stools, diet, stressful life

Table 12.3: Causes of constipation

Intestinal nerve/muscle disorders: Hirschsprung disease, intestinal neuronal dysplasia, pseudo-obstruction, spinal cord abnormalities (tethered cord, myelomeningocele)

Anorectal: Anteriorly placed anus, anal stenosis, rectal stricture, pelvic mass (sacral teratoma)

Systemic disease: Hypothyroidism, celiac disease, diabetes insipidus, diabetes mellitus, hypercalcemia, cystic fibrosis, myotonic dystrophy

Developmental: Mental retardation, autism

Drugs: Opiates, anticholinergic agents, phenobarbitone, vincristine, lead

events, drug intake and previous surgeries should be known. A predominantly liquid and low fiber diet (milk based) is common and contributes to constipation. A complete physical and neurological examination is essential. Examination for features of spina bifida (pigmentation or tuft of hair on lower back), power in lower limbs, perianal sensation, voluntary contraction and tone of anal sphincter and amount and consistency of stool in rectum on per rectal examination are extremely useful for diagnosis.

'Red flags' like failure to thrive, blood in stools, recurrent fever with loose stools (enterocolitis), recurrent vomiting, lump in abdomen, recurrent chest infections and features of hypothyroidism should alert the physician to suspect organic etiology.

Functional Constipation

The increase in intake of low residue diet and sedentary lifestyle is responsible for the increase in functional constipation in children. Functional constipation is defined by the presence of at least 2 or more of the following criteria: (i) two or fewer defecations in the toilet per week; (ii) at least 1 episode of fecal incontinence per week; (iii) history of retentive posturing or excessive volitional stool retention; (iv) history of painful or hard bowel movements; (v) presence of a large fecal mass in the rectum; and (vi) history of passage of large diameter stools that may obstruct the toilet.

Children with functional constipation pass large or hard stools and display stool withholding behavior, characterized by stiffening of whole body and screaming in infants, to walking on tiptoes or tightening of buttocks in older children. This is often misunderstood by parents as if the child is trying to defecate. Often an acute illness, change in diet, coercive toilet training or non-availability of clean toilet leads to non-passage of stools. The stools become hard and cause pain on passage which leads to association of defecation with pain and withholding. This further increases stool size and hardness with more pain on defecation. Children with functional constipation have abdominal pain (10–70%), anorexia (10–25%), enuresis or urinary tract infections (30%) and psychological problems (20%).

Management: No investigations are required for diagnosis in the majority of children with functional constipation. However, an X-ray abdomen may be done to document impaction in select situations, e.g. an obese child who is not willing for a per rectal examination. Two main steps in the management are disimpaction and maintenance therapy.

Disimpaction is required in patients who have a rectal impaction, i.e. presence of a large hard mass of feces on per rectal examination or abdominal fecoliths or retentive encopresis. Rectal impaction is responsible for progressive dilatation of the rectum over time and increased threshold volume for rectal sensation and defecation. This 'clean out' is essential, if maintenance therapy is to be effective. The oral route is preferred over rectal as it is less invasive. Total bowel wash is done to clean the entire colon using polyethylene glycol (PEG) in a dose of 1.5 g/kg/day for 3–4 days at home. Alternatively, PEG electrolyte solution can be given in the dose of 15–40 mL/kg/hr till the rectal output is clear and devoid of solid fecal material. In young children, this should be done using a nasogastric tube and in hospital under supervision. Intravenous fluids may be required in small children to maintain adequate hydration. An alternative to oral administration of PEG is the use of phosphate enema (contraindicated in <1-year-old) or sodium dioctyl sulfosuccinate enema, 30–60 mL/10 kg body weight to a maximum of 120 mL, once or twice daily for 1–2 days. Repeated rectal enemas should be avoided.

The aim of *maintenance therapy* is to promote regular stooling and prevent reimpaction. Success of this therapy is defined as passage of 1–2 soft stools per day and no soiling. It includes the following components:

- i. **Behavioral training** involves establishing a positive routine of sitting on toilet for passing stools after meals regularly (2–3 times per day for 5–10 min) and documenting all stool passage. Embarrassment or punishment should be avoided.
- ii. **Dietary changes:** A nutritious diet with fruit/vegetables and adequate fluids is given. A short trial of milk and milk product free diet may be done in refractory cases suspected to have bovine milk allergy.
- iii. **Medication:** Regular and tailor-made (as per response) laxative use is the key to success and this should be explained to the family. Osmotic laxatives, like lactulose (1–3 mL/kg/day), and PEG (0.8–1.0 g/kg/day), are the first-line agents. Stimulant laxatives like senna or bisacodyl are to be used only intermittently as a rescue therapy to avoid impaction. Prokinetics like cisapride are not recommended. In infants, mineral oil and stimulant laxatives should not be used. Glycerin suppository is preferred over enema for impaction in infants. Premature withdrawal of medications is a very common cause of relapse.

Prognosis: Most of the children need maintenance therapy for 6–24 months. About 50–60% patients achieve success at 1 year and 70–80% in the long-term. Nearly 50% patients will have a relapse after successful therapy. In nearly one-third patients, constipation persists even after puberty.

Other Etiologies of Constipation

A subgroup of children with constipation who fail to respond to medical management despite compliance or have red flags will need evaluation for organic disorders. The main modalities of investigation are as follows:

Rectal biopsy: A full thickness rectal biopsy or suction biopsy with mucosa and submucosa is required to rule out Hirschsprung disease, neuronal intestinal dysplasia and hypoganglionosis.

Anorectal manometry: In normal persons, the internal anal sphincter shows relaxation on distension of rectum with a balloon (or stools). This is known as rectoanal inhibitory reflex and its presence excludes the diagnosis of Hirschsprung disease.

MRI of lumbosacral spine: It is useful for diagnosis of spina bifida occulta or tethered cord.

Colonic transit study: Assessment of total and segmental colonic transit time is done either by radiopaque markers or by scintigraphy. Based on transit studies, various patterns of colonic motility have been defined: Normal colonic transit, slow transit constipation (prolonged transit throughout the colon) and outlet obstruction (delayed transit through anorectum) (Fig. 12.8).

Metabolic, endocrine and others: It is useful to screen for hypothyroidism, cystic fibrosis, hypercalcemia, celiac disease and lead poisoning.

Hirschsprung Disease

Hirschsprung disease is the commonest congenital gut motility disorder with an incidence of 1 in 5000 and is characterized by lack of ganglionic cells in the submucosal and myenteric plexuses of the distal intestine. The distal rectum is aganglionic and the aganglionosis extends proximally in a variable length of colon. The absence of enteric neurons leads to tonic contraction of the aganglionic segment and functional obstruction. This multigenic disorder can be familial or sporadic. Down syndrome is one of the most common associated malformations. Hirschsprung disease is classified by the length of involved intestine, with ~75% cases involving only the colon distal to splenic flexure (classic form or short segment disease), ~20% involving colon proximal to splenic flexure and ~5% cases involving entire colon and small bowel as well.

Affected infants present shortly after birth with constipation and signs of distal obstruction. About 60–90% children with Hirschsprung disease fail to pass meconium in first 48 hours of life. Occasionally, the disease is missed and the child presents later with chronic constipation, failure to thrive and episodes of enterocolitis (loose stools with blood and mucus). Presence of empty rectum on per rectal examination with a gush of liquid stools on withdrawal of finger suggests the diagnosis.

In neonatal period, plain X-ray abdomen reveals bowel distension with multiple air-fluid levels and paucity of air in pelvis. A carefully performed barium enema without prior colonic preparation and slow injection of contrast clearly delineates the narrow aganglionic bowel, transition zone and proximal dilated colon in Hirschsprung disease (Fig. 12.9). In contrast, in functional constipation, the rectum is grossly dilated, with a rectum to sigmoid ratio



Fig. 12.8: Colonic transit study showing retained radiopaque markers in the left colon suggestive of outlet obstruction in a child with constipation

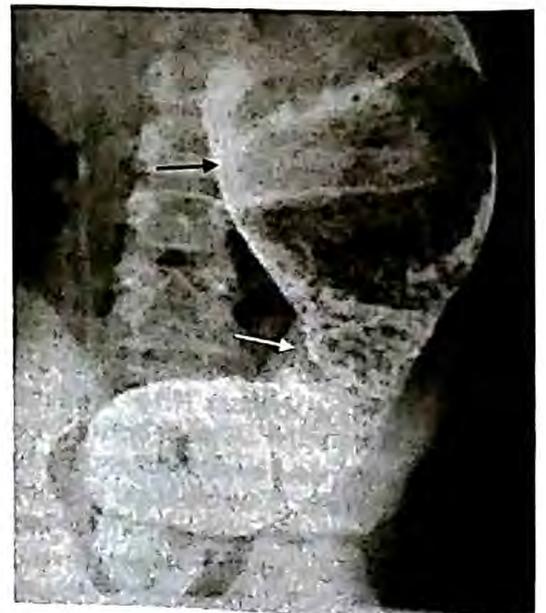


Fig. 12.9: Barium enema showing Hirschsprung disease. Black arrow shows the dilated proximal segment and white arrow shows the transition zone

Table 12.4: Differences between functional constipation and Hirschsprung disease

Feature	Functional constipation	Hirschsprung disease
Passage of meconium	Normal	Delayed
Onset of symptoms	Beyond 1 year of age	Within infancy
Encopresis	Yes	No
Stool withholding behavior	Yes	No
Episodes of enterocolitis	No	Yes
Growth failure	No	Yes
Abdomen	Not distended; may have palpable fecoliths	Distended
Per rectal examination	Soft to hard stools present	Empty rectum with gush of stools on removing the finger
Barium enema	Rectum larger than sigmoid; ratio >1	Rectosigmoid ratio <1; transition zone seen
Anorectal manometry	Rectoanal inhibitory reflex present	Rectoanal inhibitory reflex absent
Rectal biopsy	Ganglions present	Ganglions absent

of >1 and absence of transition zone. However, a normal study does not exclude Hirschsprung disease. Absence of rectoanal inhibitory reflex on anorectal manometry suggests Hirschsprung disease. Rectal biopsy is the gold standard in diagnosing Hirschsprung disease, with full thickness biopsy being ideal. Documentation of the absence of ganglionic cells in the myenteric and submucosal plexus is essential for the diagnosis. Hypertrophied nerves with increase in acetylcholinesterase activity in the parasympathetic nerve fibers are seen in the aganglionic segment. The main differences between functional constipation and Hirschsprung disease are shown in Table 12.4.

Management depends on timing of diagnosis and is essentially surgical; the role of medical management is restricted to stabilizing the general condition and treating episodes of enterocolitis. Definitive surgical treatment involves resection of the aganglionic bowel, pull through and anastomosis of normally innervated ganglionic bowel close to the anal margin. Effort is made to preserve the anal canal and sphincter mechanism, thus preserving continence. In patients with delayed presentation, a colostomy in the ganglionic bowel is performed initially to relieve the obstruction and allow the dilated hypertrophied proximal bowel to return to normal. Subsequently, definitive surgery is performed. Now less invasive, laparoscopic and single staged surgeries are performed, in comparison to previous 2–3 staged procedure. In the long-term, majority show improvement but nearly two-thirds of patients have some form of constipation or continence problem.

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Abdominal Pain

Abdominal pain is a common manifestation of multiple pathologies which vary from benign to life-threatening conditions. The pain may be acute or chronic in nature. To be able to arrive at a diagnosis, careful history and examination and appropriate investigations are necessary.

An understanding of pain perception in the abdomen and location of pain provides valuable information (Fig. 12.10).

The gut is innervated by the enteric nervous system which is involved in regulating secretion, motility and in sensory perception of visceral pain. The enteric nervous system is also influenced by the central nervous system. Stretching of the overlying visceral peritoneum or inflammation results in pain sensation. The pain from the stomach and proximal intestine is sensed in the epigastrium; from the midgut to the periumbilical area; and from the transverse colon to the suprapubic area. The inflammation in the parietal peritoneum causes pain in the overlying abdominal wall. Thus, the pain of appendicitis is referred to the periumbilical area when the inflammation is restricted to the visceral peritoneum, but is perceived in the right iliac fossa when the inflammatory fluid comes in contact with the parietal peritoneum. Pain arising from retroperitoneal structures is referred to the back as it is sensed by the somatic nerves in the posterior abdominal wall. Referred pain is common in abdominal pathologies; a subdiaphragmatic collection on the right side may manifest as right shoulder pain and ureteric pain is referred to the corresponding side as testicular pain. Radiation of pancreatic pain to the back and ureteric pain from loin to groin are also known.

Physicians must distinguish abdominal pain due to emergent diagnoses like appendicitis or intussusception from benign conditions like gastroenteritis or constipation. Examination should be meticulous including examination of genitalia as torsion of testes or incarcerated hernia can be easily overlooked. Differential diagnosis should be considered in terms of age as many diagnoses are seen more commonly in children of certain age groups as shown in Table 12.5.

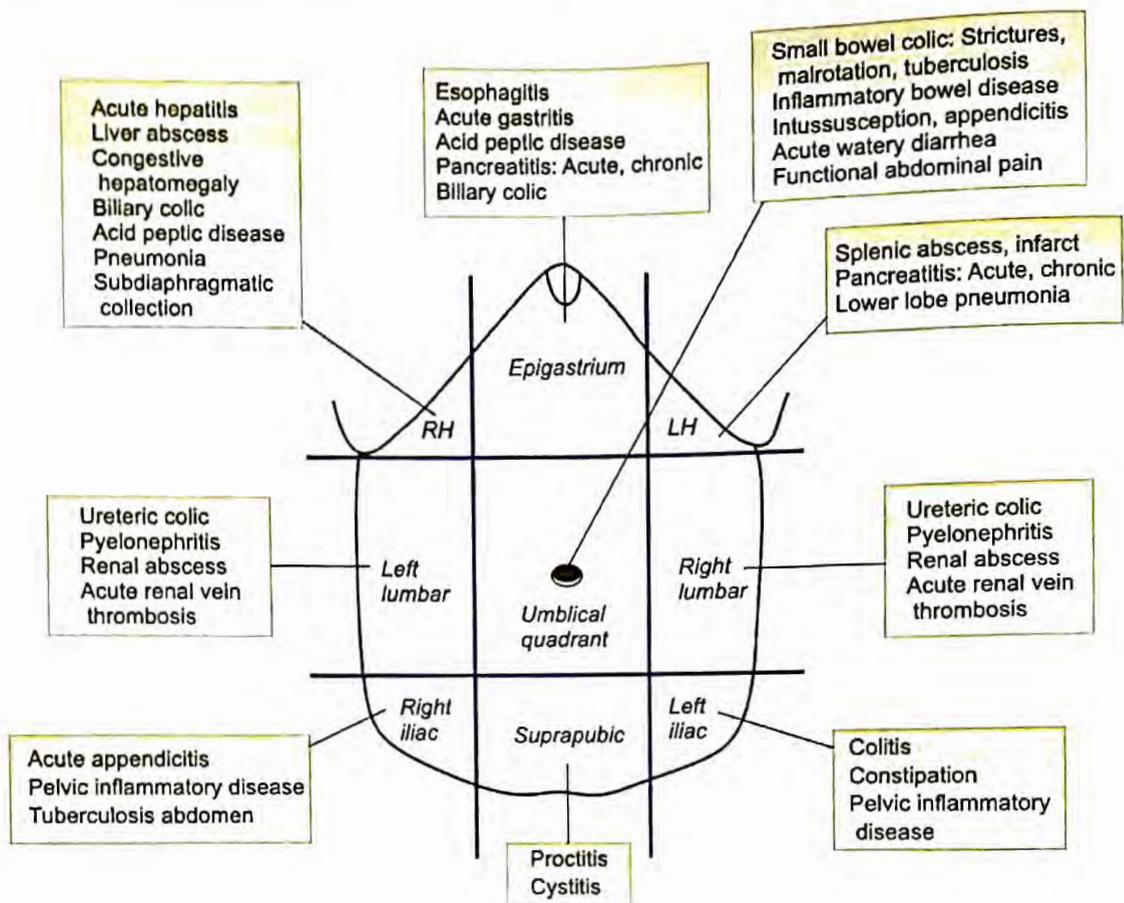


Fig. 12.10: Causes of abdominal pain as per site of pain. RH right hypochondrium; LH left hypochondrium

Table 12.5: Common causes of abdominal pain

Infants and young children (<2 years of age): Colic, acute gastroenteritis, intussusception, malrotation of gut with volvulus, incarcerated hernia, trauma, necrotizing enterocolitis

Preschool children (2–5 years of age): Acute gastroenteritis, urinary tract infections, constipation, intussusception, acute appendicitis, malrotation of gut with volvulus, intestinal perforation with peritonitis, choledochal cyst, lower lobe pneumonia, incarcerated hernia, torsion testis, acute pancreatitis, diabetic ketoacidosis, Henoch-Schönlein purpura, Meckel diverticulum, trauma

Older children and adolescents: Acute gastroenteritis, gastritis, acute appendicitis, Crohn disease, constipation, urinary tract infections, dysmenorrhea, pelvic inflammatory disease, ectopic pregnancy, Mittelschmerz, renal calculi, acute pancreatitis, cholecystitis, pneumonia, trauma, early phase of acute viral hepatitis, testicular or ovarian torsion, intestinal obstruction, perforation or peritonitis

Acute Appendicitis

Acute appendicitis is the commonest pediatric surgical emergency and is more common in older children. The condition is considered as occurring due to obstruction of the appendiceal lumen by either fecolith or lymphoid tissue, e.g. following viral infection. The obstruction,

distention and infection in the appendix causes progressive inflammation and, subsequently, perforation. The patient presents with fever and anorexia followed by pain in the periumbilical area. Vomiting follows the periumbilical pain, unlike in gastroenteritis. As the inflammatory fluid spreads, the pain is then felt in the right iliac fossa (McBurney point) towards which the child characteristically points with a finger. A retrocecal inflamed appendix may be difficult to diagnose and may manifest as spasm at the hip. The diagnosis is most often based on clinical suspicion after history and examination. Palpation reveals localized tenderness and is best elicited, if there is rebound tenderness.

Hemogram shows polymorphonuclear leukocytosis. Urine microscopy should be done to rule out urinary tract infection. Abdominal ultrasound detects a dilated (>6 mm) tubular, aperistaltic structure which is not compressible and is surrounded by fluid. Ultrasound has a sensitivity of 85–90% and specificity of 95–100% for diagnosing appendicitis. Computed tomography may be done occasionally, if the diagnosis is in doubt. In up to one-third of patients, the appendix ruptures before surgery. Intravenous fluids and antibiotics for gram-negative and anaerobic coverage should be given in all cases. Early surgery is necessary to prevent complications like perforation, appendiceal abscess and sepsis.

Intussusception

This is a common cause of intestinal obstruction in children between 3 months and 6 years. Intussusception refers to the telescoping of a proximal segment of intestine (intussusceptum) into a distal segment (intussusciens). This may be ileocolic, colocolic or ileoileal. Most cases occur in infants during the weaning period following introduction of a new food, vaccination or upper respiratory tract infection. An area of enlarged submucosal Peyer's patch probably acts as a lead point. Beyond two years of age, the possibility of a submucosal lead point like lipoma and polyp that needs surgical resection should be considered as failure to resect them will lead to recurrence. Inflammatory conditions, like Henoch-Schönlein purpura, also result in intussusception. As a result, there is venous congestion, bowel edema leading to arterial obstruction, bowel ischemia, necrosis, perforation and shock. The classic triad of abdominal pain, red currant jelly stools (blood and mucus) and palpable mass is seen only in a small percentage of children. X-ray abdomen shows paucity of air in right lower quadrant. Ultrasound is the investigation of choice that confirms the diagnosis ('doughnut' sign) and provides information about presence of a mass as lead point. Vascularity of bowel is best assessed on color Doppler. Barium enema shows a characteristic 'claw' sign, if the intussusception involves colon. Early reduction either with saline (under ultrasound guidance), barium contrast (both diagnostic and therapeutic) or with air insufflation is advisable. Reduction with air is safer with lower recurrence rates. Failure of radiological reduction or suspected intestinal gangrene may necessitate surgery and resection.

Gallstones (Cholelithiasis)

Gallstones are of three main types: Cholesterol stones with >50% cholesterol, pigment (black or brown) stones and mixed types. Pigment stones are common in children with hemolytic anemia. High-risk groups for gallstones include children with hemolytic anemia, obesity, ileal resection or disease, intake of drugs like ceftriaxone, progressive familial intrahepatic cholestasis type III and total parenteral nutrition. Overall, hemolytic anemia and other predisposing conditions account for 20–30% and 30–40% of gallstones, respectively, while 30–40% cases remain idiopathic.

Clinical presentation: Typical presentation is with acute or recurrent episodes of right upper quadrant or epigastric pain which may radiate to the right shoulder. Icterus and pain radiating to the back is suggestive of a stone in common bile duct or ampulla causing pancreatitis. Fever is uncommon; however, if present, it suggests presence of cholecystitis or cholangitis.

Diagnosis: Serum bilirubin and alkaline phosphatase are elevated, if the stone is in the common bile duct. Raised amylase suggests pancreatitis. Ultrasonography is the

investigation of choice for diagnosis of gallstones. MRCP and ERCP have a better accuracy than ultrasonography in diagnosing common bile duct stones. These children should be investigated with hemoglobin, reticulocyte count, peripheral blood picture and other investigations to look for hemolytic disease.

Management: Symptomatic cholelithiasis is treated by open or laparoscopic cholecystectomy. Common bile duct calculi can be removed by ERCP or at surgery by common bile duct exploration. Children with asymptomatic gallstones without underlying predisposing factors can be safely followed up. Patients with sickle cell disease should be subjected to prophylactic cholecystectomy, even if gallstones are asymptomatic. Children with other hemolytic anemias should be screened by ultrasonography, if they are being considered for splenectomy and cholecystectomy should be done along with splenectomy in those having gallstones.

Choledochal Cyst

Choledochal cyst refers to abnormal cystic dilatation of biliary tree either as a single or multiple dilatations. This may or may not have associated intrahepatic cystic dilatations. It can present in the neonatal period as cholestasis, mimicking biliary atresia (5% of all neonatal cholestasis), or in the older child with recurrent episodes of pain, obstructive jaundice or mass in right upper quadrant. Acute or recurrent pancreatitis may be the presentation of choledochal cyst, either due to stone impaction at lower end of common bile duct, or due to anomalous pancreatobiliary junction known to be associated with choledochal cyst. Biliary peritonitis secondary to bile duct perforation can complicate a choledochal cyst. Untreated cases may go on to develop secondary biliary cirrhosis.

Ultrasonography is the investigation of choice to diagnose choledochal cyst. MRCP is done to define the anatomy of the pancreaticobiliary ductal system before surgical excision (Fig. 12.11). Definitive treatment is with cyst resection and hepaticojejunostomy in the majority as there is a risk of malignancy (cholangiocarcinoma) in the epithelium of the cyst, if left *in situ*. Antibiotics and supportive therapy are required before surgery for a child presenting with obstructive jaundice and cholangitis.

Malrotation

Rotational abnormalities developing during the maturation of the gut cause recurrent obstruction, occurring as either the Ladd's band or volvulus of the gut over the narrow mesenteric pedicle. About 80–90% cases of volvulus occur within the first year of life. Abdominal pain with bilious vomiting suggests small bowel obstruction; abdominal distension may not be a prominent finding. Findings of malrotation are confirmed on barium meal follow through (BMFT), which shows duodenojejunal



Fig. 12.11: Magnetic resonance cholangiopancreatography (MRCP) showing choledochal cyst

junction on the right of the spine (rather than to the left of midline at the level of pylorus), an abnormally positioned caecum and small bowel loops on the right side of abdomen (Fig. 12.12). If volvulus is also present, the contrast abruptly tapers into a corkscrew appearance at the level of the second portion of duodenum.

After resuscitation, emergency laparotomy is required for correction of the defect, usually by the Ladd's procedure, which includes derotation of the volvulus, division of the Ladd's band, widening of the base of the mesentery, placement of bowel in a state of nonrotation and appendectomy.

Peptic Ulcer

Both gastric and duodenal ulcers occur infrequently in children. Ulcers may be primary, i.e. related to *Helicobacter pylori* or secondary, e.g. due to drugs (NSAIDs, steroids), stress (shock, sepsis and ischemia), corrosives, Ménétrier's disease, Crohn's disease and Zollinger-Ellison syndrome.

Clinical presentation depends on the age. Neonates typically present with bleeding and perforation from a gastric ulcer, usually occurring in the setting of another underlying problem, such as sepsis or respiratory distress. Older infants and toddlers frequently vomit, eat poorly and have upper GI bleeding. Older children may have the classical epigastric pain which is relieved by eating. However, this is noted only in a minority; most patients have pain that is ill-localized and similar to that seen in functional dyspepsia. Overt or occult bleeding is seen in approximately half of school-age children with ulcer disease. Gastrointestinal bleeding, vomiting with obstruction and severe pain due to perforation suggest complicated ulcers. Ulcers associated with *Helicobacter pylori* infection affect older children, family history of ulcer disease is usually noted and upper GI endoscopy shows



Fig. 12.12: Barium meal follow through showing malrotation of intestine

antral nodularity as compared to ulcers without such infection. Mechanical ventilation and coagulopathy increase risk of bleeding in stress ulcers.

Diagnosis is established by upper GI endoscopy by direct visualization of location (gastric or duodenal), number and size of ulcer (Fig. 12.13). Endoscopic management can be done at the same time in ulcers with active bleeding or ooze or those with a visible vessel. One can also obtain gastric biopsies for *Helicobacter pylori* testing.

Proton pump inhibitors are the mainstay of therapy. Actively bleeding ulcers require endoscopic therapy, with sclerosant or adrenaline injection, application of heater probe or bipolar electrocoagulation, or placement of hemoclip over bleeding vessel. Evaluation for *Helicobacter*



Fig. 12.13: Upper gastrointestinal endoscopy showing duodenal ulcer in the first part of duodenum

pylori is essential in all cases with peptic ulcer and merits specific therapy with two of three antibiotics (amoxicillin, metronidazole, clarithromycin) and proton pump inhibitor. Predisposing factors, including NSAIDs, should be avoided. Surgery is indicated in children presenting with gastric outlet obstruction or uncontrolled bleeding despite drug and endoscopic treatment.

Acute Pancreatitis

Acute pancreatitis is less common in children than adults and occurs chiefly due to trauma, drugs (valproate, L-asparaginase), viral infections (mumps), hemolytic uremic syndrome, congenital biliary anomalies, Henoch-Schönlein purpura and occasionally, gallstones, hypercalcemia or hypertriglyceridemia. Diagnosis is based on presence of upper abdominal pain (with or without radiation to the back), elevated serum amylase or lipase and radiological imaging (ultrasonography, CT scan) showing bulky, edematous pancreas. Acute severe pancreatitis may result in acute respiratory distress syndrome, acute renal failure, shock, GI bleed, disseminated intravascular coagulation, hypoglycemia, hypocalcemia or infected pancreatic necrosis. Late complications include pancreatic abscess and pseudocyst formation (Fig. 12.14). Early supportive care in intensive care is critical in severe acute pancreatitis. Radiological, endoscopic or surgical interventions may be required for patients with pseudocyst, pancreatic abscess or infected necrosis.

Chronic Abdominal Pain

Chronic abdominal pain refers to the pain that is either episodic or continuous and lasts for a period of at least 2 months. The prevalence of chronic abdominal pain in children varies from 0.5 to 19% and depends on the age group evaluated. The principles of diagnosis with regard to clinical evaluation are similar to that in acute abdominal pain but the etiologies differ. In addition to organic causes,

an important cause is nonorganic abdominal pain which is responsible for nearly 75% of all cases. As per the Rome III criteria, such pain is termed 'abdominal pain related to functional gastrointestinal disorders.'

Chronic Pancreatitis

This condition is characterized by recurrent episodes of abdominal pain and exocrine and/or endocrine pancreatic insufficiency. On imaging, diagnosis is based on demonstration of pancreatic calcification and/or dilated pancreatic duct. Chronic pancreatitis in children may be idiopathic or hereditary, autoimmune, tropical, metabolic (hypercalcemia) or secondary to recurrent acute pancreatitis.

Children present initially with repeated episodes of pancreatic pain. Chronic diarrhea with fat malabsorption (exocrine insufficiency) and symptoms of diabetes mellitus develop later along with failure to thrive. Local complications include pseudocyst, pancreatic ascites, pancreatic duct stricture, biliary strictures and portal hypertension due to splenic vein thrombosis. These patients are also at an increased risk of pancreatic carcinoma, particularly those with hereditary pancreatitis.

X-ray abdomen may show pancreatic calcification. Ultrasound and CT scan demonstrates ductal dilatation (Fig. 12.15), strictures, calcification and altered size or echotexture of pancreas. ERCP and MRCP help define the pancreatic ductal anatomy (e.g. prominent stricture, intraductal calculi) and planning of endoscopic or surgical therapy. Exocrine pancreatic insufficiency is confirmed by demonstrating excess fat and reduced pancreatic elastase or chymotrypsin in stool. Fasting and postprandial blood sugar help evaluate for endocrine insufficiency. Evaluation for etiology should include looking for hypercalcemia or hyperlipidemia and testing for mutations in cationic trypsinogen gene to confirm hereditary pancreatitis.

Treatment includes supportive therapy during acute attacks, administration of antioxidants and oral pancreatic enzyme supplements for exocrine pancreatic insufficiency

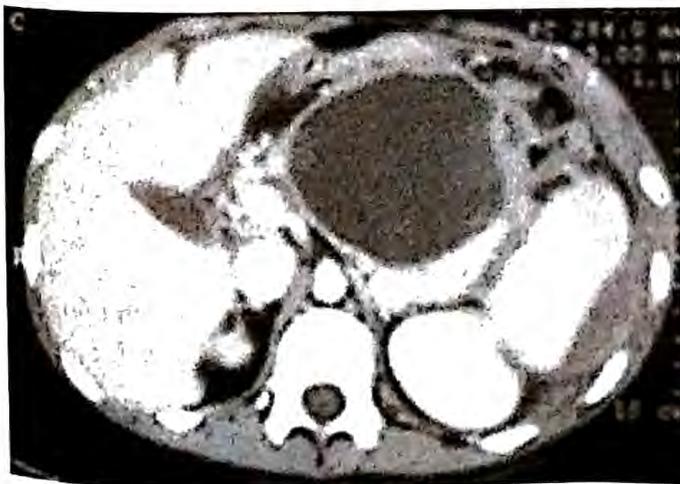


Fig. 12.14: Contrast-enhanced CT scan showing pseudocyst in a patient with acute pancreatitis

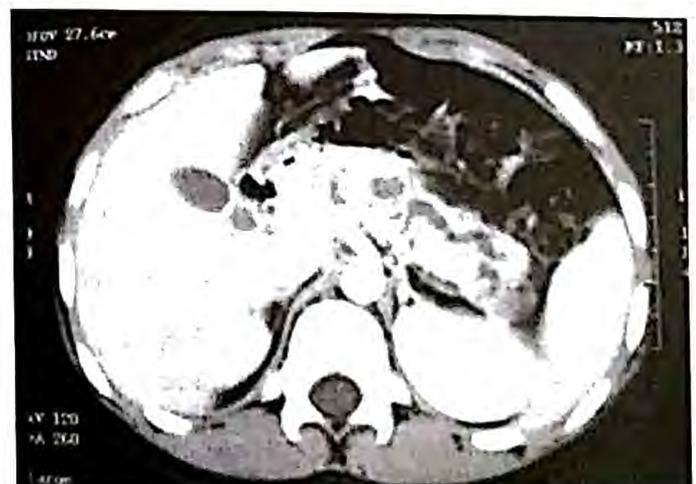


Fig. 12.15: CT scan showing dilated main pancreatic duct in chronic pancreatitis

and endoscopic, radiological or surgical treatment for pseudocyst, ductal stricture and other complications. Surgical procedures like partial pancreatectomy or lateral pancreatojejunostomy are required in patients not responding to medical therapy. Celiac ganglion block is another alternative for pain control. Management of diabetes mellitus, if present, is essential.

Abdominal Pain Related to Functional Gastrointestinal Disorders

Abdominal pain related to functional GI disorders is diagnosed in the presence of pain that is present at least once a week in the preceding 2 months and the absence of an organic cause such as an inflammatory, anatomic, metabolic and neoplastic process. The pain is typically periumbilical and is clearly localized by the child.

After extensive studies, the most accepted understanding of childhood functional abdominal pain is of 'visceral hyperalgesia', referring to an altered excessive perception of normal gut motility that is interpreted by the child as pain. This perception is influenced by the psychosocial stressors in school and home. The focus on the pain is further heightened by the growing concern in the family and the frequent visits to the doctors. Children of parents with increased anxiety and functional GI problems have an increased risk of developing functional pain in abdomen. The different types of functional gastrointestinal disorders associated with abdominal pain are as follows:

Functional dyspepsia: Persistent or recurrent pain or discomfort is centered in the upper abdomen, located above the umbilicus and not relieved by defecation nor associated with a change in stool frequency or form (i.e. no irritable bowel syndrome).

Irritable bowel syndrome: Abdominal discomfort or pain is associated with two or more of the following: improvement with defecation, onset associated with a change in frequency of stool and onset associated with a change in consistency of stool.

Abdominal migraine: Paroxysmal episodes of intense, acute periumbilical pain are noted, lasting for an hour or more with intervening periods of normal health lasting weeks to months. The episodes of pain interfere with normal activities and are associated with two or more of the following: Anorexia, nausea, vomiting, headache, photophobia and pallor.

Childhood functional abdominal pain: This refers to episodic or continuous periumbilical abdominal pain that meets insufficient criteria for other types of FGIDs (functional gastrointestinal disorders). The criteria for childhood functional abdominal pain syndrome are satisfied, if the child has functional abdominal pain for at least 25% of the time plus one or more of the following: Some loss of daily functioning and additional somatic symptoms such as headache, limb pain, or difficulty in sleeping.

Table 12.6: 'Red flag' signs or features that indicate serious illness in a child with abdominal pain

Pain localized away from umbilicus in right/left upper or lower quadrant
Nocturnal pain
Failure to thrive; weight loss
Significant vomiting; bilious vomiting
Gastrointestinal blood loss
Chronic diarrhea
Persistent fever
Jaundice
Arthritis; rash
Family history of inflammatory bowel disease
Localized tenderness or mass in abdomen; organomegaly
Perianal fistulae

Among the various types mentioned above, functional abdominal pain is the most common. The diagnosis of childhood functional abdominal pain hinges on confidently ruling out organic etiology using a careful history and examination; extensive investigations are unnecessary. The history should include not only details of pain but also family details, child's emotional environment in home and school, personality, coping skills, school performance and stress factors. The presence of alarming symptoms (Table 12.6) increases the probability of organic disorder and justifies further diagnostic testing. In the absence of red flags, the diagnostic yield of investigations is poor. Hemogram, ESR, stool routine and occult blood, and urine microscopy should be carried out in all cases to rule out organic disease. Abdominal ultrasonography is not helpful; the presence of lymph nodes of <10 mm is not a significant finding. Further investigation is required only in those with alarm symptoms and based on the likely diagnosis.

The aim of management of children with functional abdominal pain is to make a positive diagnosis, normalize the lifestyle to not allow pain to curtail daily activities or school performance, and to rectify psychological factors. The crux of management is counseling the parents and the child, both jointly and separately. Parents need to be reassured about the benign nature of the ailment and emphasis is laid upon avoiding too much attention to the child. The concept of visceral hyperalgesia should be explained to parents. Provision of a nutritious diet with adequate fiber and avoiding intake of carbonated beverages and refined food helps in reducing bloating. The role of amitriptyline and hypnotherapy is restricted to a few refractory cases.

Suggested Reading

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ACUTE DIARRHEA

Diarrhea is defined as a change in consistency and frequency of stools, i.e. liquid or watery stools, that occur >3 times a day. If there is associated blood in stools, it is termed *dysentery*. In the vast majority of cases, these acute episodes subside within 7 days. Acute diarrhea may persist for >2 weeks in 5–15% cases, which is labeled as *persistent diarrhea*.

The global annual burden of diarrhea is huge, affecting 3–5 billion cases and causing approximately 2 million deaths a year. Diarrhea accounts for over 20% of all deaths in under-five children. The two most important consequences of diarrhea in children are malnutrition and dehydration. Malnutrition and diarrhea form a vicious cycle, since malnutrition increases the risk and severity of diarrhea. Impaired absorption, loss of nutrients, increased catabolism and improper feeding in diarrhea aggravate the severity of malnutrition. A child may lose as much water and electrolytes from the body during an episode of diarrhea as an adult, which translates into a higher proportion of total body water loss in the child. Significant dehydration with abnormal electrolyte and acid-base status occurs in 2–5% of all cases of diarrhea, which may be fatal.

Etiology

Intestinal infections are the most common cause of acute diarrhea. However, certain drugs, food allergy, systemic infections (e.g. urinary tract infection and otitis media) and surgical conditions (e.g. appendicitis or Hirschsprung disease) can also present as acute onset diarrhea. Causative agents of acute diarrhea (Table 12.7) can be identified in nearly 70–80% episodes of acute diarrhea. Rotavirus remains the leading cause of severe, dehydrating gastroenteritis worldwide. In India, rotavirus and enterotoxigenic *E. coli* account for nearly half of the total diarrheal episodes among children. In rotavirus diarrhea, vomiting is an early feature and diarrhea is more severe. Cholera accounts for 5–10% cases; it is endemic in some parts and may occur in outbreaks. In cholera, stools are like rice water, vomiting is common and rapid onset of severe dehydration occurs within hours. Apart from enterotoxin producing *E. coli* (ETEC), which accounts for nearly 20% of childhood diarrhea, enteroinvasive *E. coli* (EIEC) and enterohemorrhagic *E. coli* (EHEC) can cause dysentery. EHEC may also cause hemolytic uremic syndrome. *Shigella* and *Salmonella* species are isolated in 3–7% of childhood diarrheas. *Shigella* accounts for majority of cases of dysentery whereas *Entamoeba histolytica* accounts for only 5% of dysentery. *Giardia lamblia* rarely causes acute diarrhea. Infection with *Candida albicans* can cause acute diarrhea in patients with malnutrition, immunocompromised state or following prolonged antibiotic treatment. *Clostridium difficile* should be suspected in patients who have received broad-spectrum antibiotics.

Table 12.7: Causes of acute diarrhea

Bacterial

Escherichia coli: Enterotoxigenic, enteropathogenic, enteroinvasive*, enterohemorrhagic* and enteroaggregative types
*Shigella**: *S. sonnei*, *S. flexneri*, *S. boydii* and *S. dysenteriae*
Vibrio cholerae serogroups O1 and O139
*Salmonella**: Chiefly *S. typhi* and *S. paratyphi* A, B or C
Campylobacter species*

Viral

Rotavirus
 Human caliciviruses: *Norovirus* spp.; *Sapovirus* spp.
 Enteric adenoviruses serotypes 40 and 41
 Others: Astroviruses, coronaviruses, cytomegalovirus, picornavirus

Parasitic

Giardia lamblia
Cryptosporidium parvum
*Entamoeba histolytica**
Cyclospora cayetanensis
Isospora belli

*Cause diarrhea with or without dysentery

Risk Factors

Factors determining susceptibility to diarrhea include poor sanitation and personal hygiene, nonavailability of safe drinking water, unsafe food preparation practices and low rates of breastfeeding and immunization. Young children (<2 years) and those with malnutrition are more susceptible to acute diarrhea and have more severe and prolonged episodes. Risk factors for prolonged and recurrent episodes of diarrhea include presence of hypochlorhydria (due to *Helicobacter pylori* infection or therapy with proton pump inhibitors), selective IgA deficiency, infection with human immunodeficiency virus (HIV) and other chronic conditions. Alteration of normal intestinal microflora by antibiotics can predispose to *C. difficile* infection.

Pathogenesis and Clinical Findings

Approximately 60% of a child's body weight is water, present in two fluid compartments: The extracellular fluid (ECF) and intracellular fluid (ICF). The ECF includes circulating blood, intestinal fluid and secretions. Diarrheal losses come from ECF, which is relatively rich in sodium and has low potassium. Loss of water from the body causes a reduction or shrinkage of ECF volume. In half of these cases, the concentration of sodium in the plasma remains nearly normal (about 140 mEq/L); in another 40–45% cases, excessive sodium is lost in the stools leading to a relative decline in serum sodium (hyponatremia) and a fall in ECF osmolality. This causes movement of water from the ECF to ICF compartment, causing further shrinkage of the already reduced extracellular compartment volume in hyponatremic dehydration. In about 5%

cases of diarrhea, especially if the child has been given fluids with extra salt, serum sodium levels may be elevated to >150 mEq/L and ECF osmolality is increased.

Normally, skin turgor or elasticity is maintained by tissue water and fat. Shrinkage of extracellular water in both hypo- and isonatremic dehydration impairs skin elasticity. On pinching, it takes a few seconds for the skin fold to return to normal. In patients with hypernatremic dehydration, water moves from inside the cells to the ECF compartment due to the increased osmolality of ECF, and therefore, partially masks the loss of skin turgor. The skin appears soggy, doughy or leathery. In this situation, a severe case of hypernatremic dehydration is likely to be erroneously underestimated as mild dehydration, unless severe sequelae of dehydration such as circulatory or renal impairment are noted.

As the ECF compartment is depleted, the blood volume is reduced. This results in a weak, thready pulse, low blood pressure and cold extremities. Because of low hydrostatic pressure in the renal glomeruli, the filtration of urine is reduced. This is ominous because poorly functioning kidneys cannot regulate metabolic derangements. Urine flow is a good indicator of the severity of illness. Severe cases are associated with renal failure.

Diarrheal stools contain large amounts of potassium. Therefore, serum level of potassium invariably falls, if diarrhea persists for more than a few days. This is more pronounced in children with severe malnutrition with already depleted potassium stores. Affected children present with abdominal distension, paralytic ileus and muscle hypotonia. Electrocardiogram may show ST depression and flat T waves. Since intestinal secretions are alkaline, considerable bicarbonate is lost in diarrheal stools and acidosis usually accompanies dehydration. Patients remain asymptomatic till the base excess falls to 12 mmol/L. Below this level, breathing becomes deep and rapid (Kussmaul breathing).

Clinical features can be summed up as follows. The child is thirsty and slightly irritable in early and mild cases of diarrhea. As the diarrhea continues and dehydration worsens, the child becomes more irritable and develops a pinched look. The fontanelle, if open, is depressed, the eyes appear sunken and the tongue and the inner side of cheeks appear dry. Abdomen may become distended in hypokalemia. The child passes urine at longer intervals. As acidosis worsens, the breathing becomes deep and rapid. In extreme cases, the child appears moribund, with weak and thready pulses, low blood pressure and reduced urine output. Children with severe dehydration may succumb rapidly, if not treated promptly.

Assessment of Child with Acute Diarrhea

Goals of assessment: These are to: (i) determine the type of diarrhea, i.e. acute watery diarrhea, dysentery or persistent diarrhea; (ii) look for dehydration and other

complications; (iii) assess for malnutrition; (iv) rule out nondiarrheal illness especially systemic infection; and (v) assess feeding, both preillness and during illness.

History: This should include information on: (i) onset of diarrhea; duration and number of stools per day; (ii) blood in stools; (iii) number of episodes of vomiting; (iv) presence of fever, cough, or other significant symptoms (e.g. convulsions, recent measles); (v) type and amount of fluids (including breast milk) and food taken during the illness and pre-illness feeding practices; (vi) drugs or other local remedies taken (including opioids or antispasmodic drugs like loperamide that may cause abdominal distension); and (vii) immunization history.

Examination: The most important assessment is for dehydration. The degree of dehydration is assessed as per Table 12.8. One should look at the child's general condition, whether he/she is alert, restless or irritable or lethargic or unconscious. Other important assessments are for the appearance of eyes (normal or sunken) and the ability to drink water or ORS solution, whether taken normally or refused, taken eagerly, or an inability to drink due to lethargy or coma. Dehydration is also assessed by feeling for skin turgor; following pinching, the abdominal skin may flatten immediately, go back slowly or return very slowly (more than 2 seconds). Based on the degree of dehydration after history and examination, the estimated fluid loss is calculated as follows:

Degree of dehydration	Assessment of fluid loss
No dehydration	<50 mL/kg
Some dehydration	50–100 mL/kg
Severe dehydration	>100 mL/kg

In addition, one should examine for features of malnutrition (anthropometry for weight and height; examination for wasting, edema and signs of vitamin deficiency), systemic infection (presence of cough, high grade fever, fast breathing and/or chest indrawing suggests pneumonia; high grade fever with splenomegaly suggests malaria) and fungal infections (oral thrush or perianal satellite lesions).

Laboratory investigations: The large majority of acute diarrheal episodes can be managed effectively even in absence of laboratory investigations. *Stool microscopy* is not helpful in management except in selected situations, such as cholera (darting motion suggests *Vibrio cholerae*) and giardiasis (trophozoites). *Stool culture* is of little value in routine management of acute diarrhea. It is useful to decide on antibiotic therapy in patients with *Shigella* dysentery who do not respond to the initial empiric antibiotics. Tests for stool pH and reducing substances are not indicated in acute diarrhea. Hemogram, blood gas estimation, serum electrolytes, renal function tests are not indicated routinely and are performed, only if the child has associated findings like pallor, labored breathing,

Table 12.8: Assessment of dehydration in patients with diarrhea

Look at			
Condition ¹	Well alert	Restless, irritable	Lethargic or unconscious; floppy
Eyes ²	Normal	Sunken	Very sunken and dry
Tears	Present	Absent	Absent
Mouth and tongue ³	Moist	Dry	Very dry
Thirst	Drinks normally; not thirsty	Thirsty, drinks eagerly	'Drinks poorly' or is not able to drink
Feel			
Skin pinch ⁴	Goes back quickly	Goes back slowly	Goes back very slowly
Decide			
	The patient has no signs of dehydration	If the patient has two or more signs, there is some dehydration	If the patient has two or more signs, there is severe dehydration
Treat			
	Use treatment Plan A	Weigh the patient, if possible, and use treatment Plan B	Weigh the patient and use treatment Plan C urgently

¹A lethargic child is not simply asleep; the child cannot be fully awakened; has a dull mental state and the child may appear to be drifting into unconsciousness.

²In some infants and children, the eyes normally appear somewhat sunken. It is helpful to ask the mother, if the child's eyes are normal or more sunken than usual.

³Dryness of the mouth and tongue can also be palpated with a clean finger. The mouth may be dry in a child who habitually breathes through the mouth. The mouth may be wet in a dehydrated child owing to recent vomiting or drinking.

⁴The skin pinch is less useful in infants or children with marasmus (severe wasting), kwashiorkor (severe malnutrition with edema) and in obese children.

altered sensorium, seizures, paralytic ileus or oliguria which suggests acid-base imbalance, dyselectrolytemia or renal failure.

Principles of Management

Management of acute diarrhea has four major components: (i) rehydration and maintaining hydration; (ii) ensuring adequate feeding; (iii) oral supplementation of zinc; and (iv) early recognition of danger signs and treatment of complications.

The cornerstone of acute diarrhea management is rehydration by using oral rehydration solutions. After the history and examination, the child's dehydration status is classified as no dehydration, some dehydration or severe dehydration and appropriate treatment is started.

Physiological basis for oral rehydration therapy: In most cases of acute diarrhea, sodium and chloride are actively secreted from the gut mucosa due to pathogen-induced dysfunction of several actively functioning absorption pumps. However, glucose dependent sodium pump remains intact and functional transporting one molecule of glucose and dragging along a molecule of sodium and one of water across intestinal mucosa resulting in repletion of sodium and water losses. The glucose dependent sodium and water absorption is the principle behind replacing glucose and sodium in 1:1 molar ratio in the WHO oral rehydration solution (ORS). An important consideration in making ORT is that the osmolarity of the replacement fluid should not exceed that of blood (290 mmol/L). Keeping the intestinal lumen at lower osmolarity as compared to blood allows for greater absorption of fluids into the bloodstream across

concentration gradient, which also results in electrolyte absorption (by solvent drag). Since the concentration of glucose increases osmolarity, it is suggested that glucose concentration should not exceed 111 mmol/L. Meta-analyses have shown that use of low osmolarity ORS causes reduction of stool output, decrease in vomiting and decrease in the use of unscheduled intravenous fluids without increasing the risk of hyponatremia. For this reason, the recommendation for use of standard WHO ORS (having osmolarity of 311 mmol/L) was changed to low osmolarity WHO ORS (having osmolarity of 245 mmol/L). Since 2004, based on the WHO/UNICEF and IAP recommendations, the Government of India has adopted the low osmolarity ORS as the single universal ORS to be used for all ages and all types of diarrhea. The composition of the low osmolarity ORS is given in Table 12.9.

In the absence of WHO ORS, one may administer culturally acceptable appropriate homemade fluids as shown in Table 12.10. Oral solutions should be given by a spoon or katori and in sips or small volumes rather than a large volume at one time as this increases the retention of oral fluids.

Table 12.9: Composition of WHO recommended ORS

Constituent	g/L	Osmole or ion	mmol/L
Sodium chloride	2.6	Sodium	75
Glucose, anhydrous	13.5	Chloride	65
Potassium chloride	1.5	Glucose, anhydrous	75
Trisodium citrate, dihydrate	2.9	Potassium Citrate	20 10
Total osmolarity			245

Table 12.10: Home available fluids for acute diarrhea**Acceptable home available fluids**

Fluids that contain salt (preferable)	Oral rehydration solution, salted drinks (e.g. salted rice water or salted yoghurt drink), vegetable or chicken soup with salt
Fluids that do not contain salt (acceptable)	Plain water, water in which a cereal has been cooked (e.g. unsalted rice water), unsalted soup, yoghurt drinks without salt, green coconut water, weak unsweetened tea, unsweetened fresh fruit juice
Unsuitable home available fluids	Commercial carbonated beverages, commercial fruit juices, sweetened tea

Treatment Plan A: Treatment of "No Dehydration"

Such children may be treated at home after explanation of feeding and the danger signs to the mother/caregiver. The mother may be given WHO ORS for use at home as per Table 12.11. Danger signs requiring medical attention are those of continuing diarrhea beyond 3 days, increased volume/frequency of stools, repeated vomiting, increasing thirst, refusal to feed, fever or blood in stools.

Treatment Plan B: Treatment of "Some Dehydration"

All cases with obvious signs of dehydration need to be treated in a health center or hospital. However, oral fluid therapy must be commenced promptly and continued during transport. Fluid requirement is calculated under the following three headings: (i) provision of normal daily fluid requirements; (ii) rehydration to correct the existing water or electrolyte deficits; and (iii) maintenance to replace ongoing losses to prevent recurrence of dehydration.

i. *The daily fluid requirements* in children are calculated as follows:

Up to 10 kg	= 100 mL/kg
10–20 kg	= 50 mL/kg
>20 kg	= 20 mL/kg

As an example, the daily fluid requirement in a child weighing 15 kg will be 1250 mL (first 10 kg, $10 \times 100 = 1000$ mL; another 5 kg, $5 \times 50 = 250$ mL, total $1000 + 250 = 1250$ mL).

Table 12.11: Oral rehydration therapy to prevent dehydration (Plan A)

Age	ORS or other culturally appropriate ORT fluids after each loose stool	ORS to provide for use at home
<24 mo	50–100 mL	500 mL/day
2–10 yr	100–200 mL	1000 mL/day
>10 yr	Ad lib	2000 mL/day

Explain use of ORS, i.e. the amount to be given, how to mix. Give a teaspoonful every 1–2 min for a child under 2 years. Give frequent sips from a cup for an older child. If the child vomits, wait for 10 min. Then give the solution more slowly (for example, a spoonful every 2–3 min). If diarrhea continues after the ORS packets are used up, tell the mother to give other fluids as described above or return for more ORS.

ii. *Deficit replacement or rehydration therapy* is calculated as 75 mL/kg of ORS, to be given over 4 hours. If ORS cannot be taken orally, then nasogastric tube can be used. If child's weight cannot be taken, then only age may be used to calculate fluid requirement as shown in Table 12.12.

If, after 4 hours, the child still has some dehydration, then another treatment with ORS (as in rehydration therapy) is to be given. This therapy is effective in 95% cases. Oral rehydration therapy may be ineffective in children with a high stool purge rate of >5 mL/kg body weight/hr, persistent vomiting >3 /hr, paralytic ileus and incorrect preparation of ORS (very dilute solution).

iii. *Maintenance fluid therapy to replace losses.* This phase should begin when signs of dehydration disappear, usually within 4 hours. ORS should be administered in volumes equal to diarrheal losses, usually to a maximum of 10 mL/kg per stool. Breastfeeding and semisolid food are continued after replacement of deficit. Plain water can be offered in between.

Treatment Plan C: Children with "Severe Dehydration"

Intravenous fluids should be started immediately using Ringer lactate with 5% dextrose. Normal saline or plain Ringer solution may be used as an alternative, but 5% dextrose alone is not effective. A total of 100 mL/kg of fluid is given, over 6 hours in children <12 months and over 3 hours in children >12 months as shown below.

Table 12.12: Guidelines for treating patients with some dehydration (Plan B)

Age	<4 mo	4–11 mo	12–23 mo	2–4 yr	5–14 yr	≥ 15 yr
Weight	<5 kg	5–8 kg	8–11 kg	11–16 kg	16–20 kg	>30 kg
ORS, mL	200–400	400–600	600–800	800–1200	1200–2200	>2200
Number of glasses	1–2	2–3	3–4	4–6	6–11	12–20

The approximate amount of ORS required (in mL) can also be calculated by multiplying the patient's weight (in kg) times 75. When body weight is not known, the approximate amount of ORS solution to give in the first 4 hours is given according to age.

For infants under-6 months who are not breastfed, also give 100–200 mL clean water during this period.

Encourage breastfeeding

Age	30 mL/kg	70 mL/kg
<12 mo	1 hr*	5 hr
>12 mo	30 min*	2 ½ hr

*The above can be repeated, if child continues to have feeble/non-palpable radial pulse

ORS solution should be started simultaneously, if the child can take orally. If IV fluids cannot be given (for reasons of access, logistic availability or during transport), nasogastric feeding is given at 20 mL/kg/hr for 6 hours (total 120 mL/kg). The child should be reassessed every 1–2 hours; if there is repeated vomiting or abdominal distension, the oral or nasogastric fluids are given more slowly. If there is no improvement in hydration after 3 hours, IV fluids should be started as early as possible.

The child should be reassessed every 15–30 min for pulses and hydration status after the first bolus of 100 mL/kg of IV fluid. Management following the first bolus of intravenous hydration is to be done as follows:

- Persistence of severe dehydration.* Intravenous infusion is repeated.
- Hydration is improved but some dehydration is present.* IV fluids are discontinued; ORS is administered over 4 hours according to Plan B
- There is no dehydration.* IV fluids are discontinued; treatment Plan A is followed.

The child should be observed for at least 6 hours before discharge, to confirm that the mother is able to maintain the child's hydration by giving ORS solution.

Unique problems in infants below 2 months of age: Breastfeeding must continue during the rehydration process, whenever the infant is able to suck. Complications like septicemia, paralytic ileus and severe electrolyte disturbance are more likely in young infants with diarrhea than at later ages. Diarrhea in these infants should be ideally treated as inpatient by experienced physicians at treatment centers with appropriate facilities. This allows for careful assessment of need of systemic antibiotics and monitoring.

Nutritional Management of Diarrhea

Children with severe malnutrition (marasmus or kwashiorkor) are at an increased risk of developing both acute diarrhea and its complications, such as severe systemic infection, dehydration, heart failure, vitamin and mineral deficiencies. Feeding should not be restricted in such patients as this aggravates complications and increases morbidity and mortality. Early feeding during diarrhea not only decreases the stool volume by facilitating sodium and water absorption along with the nutrients, but also facilitates early gut epithelial recovery and prevents malnutrition. Once the child's status starts improving, a higher than recommended intake is given to facilitate complete catch-up growth.

Following are the recommendations on dietary management of acute diarrhea:

- In exclusively breastfed infants, breastfeeding should continue as it helps in better weight gain and decreases the risk of persistent diarrhea.
- Optimally energy dense foods with the least bulk, recommended for routine feeding in the household, should be offered in small quantities but frequently (every 2–3 hours).
- Staple foods do not provide optimal calories per unit weight and these should be enriched with fat or oil and sugar, e.g. *khichri* with oil, rice with milk or curd and sugar, mashed banana with milk or curd, mashed potatoes with oil and lentil.
- Foods with high fiber content, e.g. coarse fruits and vegetables should be avoided.
- In nonbreastfed infants, cow or buffalo milk can be given undiluted after correction of dehydration together with semisolid foods. Milk should not be diluted with water during any phase of acute diarrhea. Alternatively, milk cereal mixtures, e.g. *dalia*, sago or milk-rice mixture, are preferable.
- Routine lactose-free feeding, e.g. soy formula is not required during acute diarrhea even when reducing substances are detected in the stools.
- During recovery, an intake of at least 125% of recommended dietary allowances should be attempted with nutrient dense foods; this should continue until the child reaches pre-illness weight and ideally until the child achieves a normal nutritional status.

Zinc Supplementation

Zinc deficiency has been found to be widespread among children in developing countries. Intestinal zinc losses during diarrhea aggravate pre-existing zinc deficiency. Zinc supplementation is now part of the standard care along with ORS in children with acute diarrhea. It is helpful in decreasing severity and duration of diarrhea and also risk of persistent diarrhea. Zinc is recommended to be supplemented as sulfate, acetate or gluconate formulation, at a dose of 20 mg of elemental zinc per day for children >6 months for a period of 14 days.

Symptomatic Treatment

An occasional vomit in a child with acute diarrhea does not need antiemetics. If vomiting is severe or recurrent and interferes with ORS intake, then a single dose of ondansetron (0.1–0.2 mg/kg/dose) should be given. Children with refractory vomiting despite administration of ondansetron may require intravenous fluids.

Abdominal distension does not require specific treatment, if bowel sounds are present and the distension is mild. Paralytic ileus should be suspected, if bowel sounds are absent and abdomen is distended. Paralytic ileus can occur due to hypokalemia, intake of antimotility

agents, necrotizing enterocolitis or septicemia. In these cases, oral intake should be withheld. Hypokalemia along with paralytic ileus necessitates intravenous fluids and nasogastric aspiration. Potassium chloride (30–40 mEq/L) should be administered intravenously with parenteral fluids provided the child is passing urine.

Convulsions associated with diarrhea may be due to (i) hypo- or hypernatremia; (ii) hypoglycemia; (iii) hypokalemia following bicarbonate therapy for acidosis; (iv) encephalitis; (v) meningitis; (vi) febrile seizures; or (vii) cerebral venous or sagittal sinus thrombosis. The management depends on the etiology.

Drug Therapy

Most episodes of diarrhea are self-limiting and do not require any drug therapy except in a few situations. Antibiotics are not recommended for routine treatment of acute diarrhea in children. In acute diarrhea, antimicrobials are indicated in bacillary dysentery, cholera, amebiasis and giardiasis. *Escherichia coli* are normal gut flora and their growth on stool culture is not an indication for antibiotics. Acute diarrhea may be the manifestation of systemic infection and malnourished, prematurely born and young infants are at a high risk. Thus such babies should be screened and given adequate days of age appropriate systemic antibiotics for sepsis. Presence of (i) poor sucking; (ii) abdominal distension; (iii) fever or hypothermia; (iv) fast breathing; and (v) significant lethargy or inactivity in well-nourished, well-hydrated infants points towards sepsis.

There is little scientific evidence that *binding agents* based on pectin, kaolin or bismuth salts are useful. Their use is not recommended in acute diarrhea. *Antimotility agents* such as synthetic analogues of opiates (diphenoxylate hydrochloride or lomotil and loperamide or imodium) reduce peristalsis or gut motility and should not be used in children with acute diarrhea. Reduction of gut motility allows more time for the harmful bacteria to multiply. These drugs may cause distension of abdomen, paralytic ileus, bacterial overgrowth and sepsis and can be dangerous, even fatal, in infants.

Antisecretory agents have been used in acute diarrhea. Racecadotril is an antisecretory drug that exerts its antidiarrheal effects by inhibiting intestinal enkephalinase. Recent studies reported some evidence in favour of racecadotril over placebo or no intervention in reducing the stool output and duration of diarrhea in children with acute diarrhea. However, more data on efficacy is needed before it can be recommended for routine use in all children with acute diarrhea.

Probiotics, defined as microorganisms that exert beneficial effects on human health when they colonize the bowel, have been proposed as adjunctive therapy in the treatment of acute diarrhea. Several microorganisms like *Lactobacillus rhamnosus* (formerly *Lactobacillus casei* strain GG or

Lactobacillus GG), *L. plantarum*, several strains of bifidobacteria, *Enterococcus faecium* SF68 and the yeast *Saccharomyces boulardii* have been shown to have some efficacy in reducing the duration of acute diarrhea, if started in very early phase of illness. The efficacy of probiotic preparations is strain and concentration (dose) specific. However, the routine use of probiotics in patients with acute diarrhea is not recommended.

Prevention of Diarrhea and Malnutrition

Prevention of diarrhea and its nutritional consequences should receive major emphasis in health education. The three main measures to achieve this are:

- i. *Proper nutrition*: Since breast milk offers distinct advantages in promoting growth and development of the infant and protection from diarrheal illness, its continuation should be encouraged. Exclusive breastfeeding may not be adequate to sustain growth beyond the first 6 months of life. Therefore, supplementary feeding with energy-rich food mixtures containing adequate amounts of nutrients should be introduced by 6 months of age without stopping breastfeeding.
- ii. *Adequate sanitation*: Improvement of environment sanitation, clean water supply, adequate sewage disposal system and protection of food from exposure to bacterial contamination are effective long-term strategies for control of all infectious illnesses including diarrhea. Three 'Cs'; clean hands, clean container and clean environment are the key messages. Mother should be properly educated about this. Complementary foods should be protected from contamination during preparation, storage, and at the time of administration.
- iii. *Vaccination*: Evidence suggests that with improvement in sanitation and hygiene in developing countries, the burden of bacterial and parasitic infection has decreased and viral agents have assumed an increasingly important etiologic role. Effective vaccines are now available against the commonest agent, i.e. rotavirus and their use might be an effective strategy for preventing acute diarrhea.

Suggested Reading

- Bhatnagar S, Lodha R, Choudhury P, Sachdev HPS, Shah N, Narayan S, et al. IAP Guidelines 2006 on management of acute diarrhea. *Indian Pediatr* 2007; 44:380.
- Piecick-Lech M, Shamir R, Guarino A, Szajewska H. Review article: the management of acute gastroenteritis in children. *Aliment Pharmacol Ther.* 2013; 37(3):289–303.

Dysentery

Dysentery refers to the presence of grossly visible blood in the stools and is a consequence of infection of the colon by either bacteria or ameba. Bacillary dysentery is much more common in children than amebic dysentery. The bacteria causing bloody diarrhea are *Shigella* species

(*S. dysenteriae*, *S. flexneri*, *S. boydii* and *S. sonnei*), enteroinvasive and enterohemorrhagic *E. coli*, *Salmonella* and *Campylobacter jejuni*. *S. flexneri* is the commonest organism reported in developing countries and *S. dysenteriae* is associated with epidemics of dysentery.

A child with bacillary dysentery presents with fever and diarrhea. Diarrhea may be watery to start with, but then shows mucus and blood mixed with stools. There is tenesmus, which refers to ineffectual defecation along with straining and suprapubic discomfort. The illness may be complicated by dehydration, dyselectrolytemia, hemolytic uremic syndrome, convulsions, toxic megacolon, intestinal perforation, rectal prolapse and, very rarely, Shigella encephalopathy.

Administration of ORS, continuation of oral diet, zinc supplementation and antibiotics are the components of treatment. Stool culture and sensitivity should be sent before starting empirical antibiotics. Antimicrobial agents are the mainstay of therapy of all cases of shigellosis. Based on safety, low cost and efficacy, ciprofloxacin (15 mg/kg/day in two divided doses for 3 days) has been recommended by World Health Organization (WHO) as the first line antibiotic for shigellosis. However, antimicrobial resistance to fluoroquinolones had increased significantly from 2002 to 2011 and only ceftriaxone has been shown to be uniformly effective. Keeping this in mind, intravenous ceftriaxone (50–100 mg/kg/day for 3–5 days) should be the first line of treatment in a sick child. In a stable child, either ciprofloxacin or oral cefixime may be given, but the patient should be monitored for clinical improvement within 48 hours (decrease in fever, stool frequency and blood in stools). If no improvement is seen at 48 hours, antibiotics should be changed appropriately. Oral azithromycin (10 mg/kg/day for 3 days) can be used for shigellosis but the experience is limited.

Amebic dysentery is less common among children. The onset is insidious. Tinidazole or metronidazole is the drug of choice. Any young child presenting with blood in stools and persistent abdominal pain should be suspected to have intussusception and evaluated accordingly.

PERSISTENT DIARRHEA

Persistent diarrhea is an episode of diarrhea, of presumed infectious etiology, which starts acutely but lasts for more than 14 days. It should not be confused with chronic diarrhea which has a prolonged duration but an insidious onset and includes conditions causing malabsorption.

Etiopathogenesis

Although persistent diarrhea starts as acute infectious diarrhea, the prolongation of diarrhea is not entirely due to infection. Various factors that are implicated in pathogenesis include:

- i. The predominant problem is the worsening nutritional status that, in turn, impairs the reparative process in

the gut. This worsens nutrient absorption and initiates a vicious cycle that can only be broken by proper nutrition. Persistent diarrhea is more common in malnourished children. Apart from malabsorption, malnutrition also results from inadequate calorie intake due to anorexia, faulty feeding and improper counseling regarding feeding by doctors. One of the major obstacles to nutritional recovery is secondary lactose intolerance, and in some cases, impaired digestion of other complex carbohydrates due to decrease in brush border disaccharidases.

- ii. Pathogenic *E. coli*, especially the enteroaggregative and enteroadherent types, result in malabsorption by causing persistent infection.
- iii. Associated infections of the urinary tract or another focus of infection (more commonly in malnourished children) contribute to failure to thrive and mortality.
- iv. Prolongation of an acute diarrhea may rarely be a manifestation of cow milk protein allergy. The increased gut permeability in diarrhea predisposes to sensitization to oral food antigens.
- v. The use of antibiotics in acute diarrhea suppresses normal gut flora. This may result in bacterial overgrowth with pathogenic bacteria and/or overgrowth of fungi, resulting in persistent diarrhea and malabsorption.
- vi. *Cryptosporidium* infection is frequently implicated in persistent diarrhea, even in immunocompetent children.

Clinical Features

Majority of patients with persistent diarrhea pass several loose stools daily but remain well hydrated. Dehydration develops only in some patients due to high stool output or when oral intake is reduced due to associated systemic infections. The major consequences of persistent diarrhea are growth faltering, worsening malnutrition and death due to diarrheal or nondiarrheal illness. The presence of secondary lactose intolerance should be considered when the stools are explosive (i.e. mixed with gas and passed with noise) and in presence of perianal excoriation. The stool pH is low and stool test for reducing substances is positive. Unabsorbed dietary lactose once delivered to colon is converted to hydrogen and lactic acid by colonic bacteria. Lactic acid results in decreased stool pH, explosive stools are due to hydrogen and unabsorbed lactose gives positive reducing substances. There is no need for laboratory testing for stool pH and reducing substances when the history is classical and excoriation is marked.

Management

The principles of management are: (i) correction of dehydration, electrolytes and hypoglycemia; (ii) evaluation for infections using appropriate investigations (hemogram, blood culture and urine culture) and their management;

and (iii) nutritional therapy. Two-thirds of patients with persistent diarrhea can be treated on outpatient basis. Patients in need of hospital admission are those with (i) age less than 4 months and not breastfed; (ii) presence of dehydration; (iii) severe malnutrition (weight for height <3SD, mid-upper arm circumference <11.5 cm for children at 6–60 months of age, or bilateral pedal edema); or (iv) presence or suspicion of systemic infection.

Nutrition

Feeding should be started at the earliest. Initially 6–7 feeds are given everyday and a total daily caloric intake of 100 kcal/kg/day is ensured. Caloric intake should be increased gradually over 1–2 weeks to 150 kcal/kg/day in order to achieve weight gain. Tube (nasogastric) feeding may be done initially in children with poor appetite due to presence of serious infection. To ensure absorption and decrease stool output, one may attempt to overcome varying degrees of carbohydrate maldigestion by using diets with different degrees of carbohydrate exclusion in the form of diet A (lactose reduced), diet B (lactose free) and diet C (complex carbohydrate free) diets (Table 12.13).

Initial diet A (reduced lactose diet; milk rice gruel, milk sooji gruel, rice with curds, dalia): This is based on the fact that secondary lactose intolerance exists in children with persistent diarrhea and malnutrition. Clinical trials have shown that reduced lactose diet is tolerated equally well as totally lactose-free diet, without significantly increasing stool output or risk of dehydration. If the patient is fed entirely on animal milk, the quantity should be reduced to 50–60 mL/kg providing not more than 2 g of lactose/kg/day. To reduce lactose concentration in animal milk, it should be mixed with cereals, but not diluted with water as that reduces the caloric content. Milk

cereal mixtures, e.g. milk or curd mixed rice gruel, milk sooji gruel, or *dalia* are palatable, provide good quality proteins and some micronutrients and result in faster weight gain than milk-free diets.

Second diet B (lactose-free diet with reduced starch): About 65–70% of children improve on the initial diet A. The remainder have impaired digestion of starch and disaccharides other than lactose. These children, if free of systemic infection, are advised diet B which is free of milk (lactose) and provides carbohydrates as a mixture of cereals and glucose. Milk protein is replaced by chicken, egg or protein hydrolysate. The starch content is reduced and partially substituted by glucose. Substituting only part of the cereal with glucose increases the digestibility but at the same time does not cause a very high osmolarity.

Third diet C (monosaccharide-based diet): Overall, 80–85% of patients with severe persistent diarrhea will recover with sustained weight gain on the initial diet A or the second diet B. A small percentage may not tolerate a moderate intake of the cereal in diet B. These children are given diet C which contains only glucose and a protein source as egg white or chicken or commercially available protein hydrolysates. Energy density is increased by adding oil to the diet.

The strategy of serial carbohydrate exclusion to varying degrees in plan A, B and C diets are meant to circumvent the problem of carbohydrate malabsorption. In addition green (unripe) banana diet is gaining acceptance for treatment of persistent diarrhea. Fermentation of nondigestible soluble fibers in cooked green (unripe) banana by colonic bacteria generates short chain fatty acids which are absorbed along with sodium in the colon, thereby facilitating water absorption by solvent drag and also conserving dietary nutrients.

Table 12.13: Diets for persistent diarrhea

Diet A (reduced lactose)	Diet B (lactose free)	Diet C (monosaccharide based)
Constituents		
Milk (1/3 katori/50 mL)	Egg white (3 tsp/half egg white)	Chicken puree (5 tsp/15 g) or egg white (3 tsp/half egg white)
Puffed rice powder/cooked rice or sooji (2 tsp/6 g)	Puffed rice powder/cooked rice (3 tsp/9 g)	Glucose (1½ tsp/7 g)
Sugar (1½ tsp/7 g)	Glucose (1½ tsp/7 g)	Oil (1½ tsp/7 g)
Oil (1 tsp/4.5 g)	Oil (1½ tsp/7 g)	Water (1 katori/150 mL)
Water (2/3 katori/100 mL)	Water (¾ katori/120 mL)	
Preparation		
Mix milk, sugar and rice, add boiled water and mix well, add oil.	After whipping the egg white, add rice, glucose and oil and mix well. Add boiled water and mix rapidly to avoid clumping	Boil chicken and make puree after removing bones. Mix it with glucose and oil. Add boiled water to make a smooth flowing feed
Nutrient content		
85 kcal and 2.0 g protein per 100 g	90 kcal and 2.4 g protein per 100 g	67 kcal and 3.0 g protein per 100 g

Constituents

Milk (1/3 katori/50 mL)
Puffed rice powder/cooked rice or sooji (2 tsp/6 g)
Sugar (1½ tsp/7 g)
Oil (1 tsp/4.5 g)
Water (2/3 katori/100 mL)

Preparation

Mix milk, sugar and rice, add boiled water and mix well, add oil.

Nutrient content

85 kcal and 2.0 g protein per 100 g

Diet B (lactose free)

Egg white (3 tsp/half egg white)
Puffed rice powder/cooked rice (3 tsp/9 g)
Glucose (1½ tsp/7 g)
Oil (1½ tsp/7 g)
Water (¾ katori/120 mL)

After whipping the egg white, add rice, glucose and oil and mix well. Add boiled water and mix rapidly to avoid clumping

90 kcal and 2.4 g protein per 100 g

Diet C (monosaccharide based)

Chicken puree (5 tsp/15 g) or egg white (3 tsp/half egg white)
Glucose (1½ tsp/7 g)
Oil (1½ tsp/7 g)
Water (1 katori/150 mL)

Boil chicken and make puree after removing bones. Mix it with glucose and oil. Add boiled water to make a smooth flowing feed

67 kcal and 3.0 g protein per 100 g

Indications for change from the initial diet (diet A) to the next diet (diet B or diet C): The diet should be changed to the next level, if the child shows (i) marked increase in stool frequency (usually more than 10 watery stools/day) at any time after at least 48 hours of initiating the diet; (ii) features of dehydration any time after initiating treatment; or (iii) failure to gain weight gain by day 7 in the absence of initial or hospital acquired systemic infection. Unless signs of treatment failure occur earlier, each diet should be given for a minimum period of 7 days.

Resumption of regular diet after discharge: Children discharged on totally milk-free diet should be given small quantities of milk as part of a mixed diet after 10 days. If they tolerate this and have no signs of lactose intolerance (abdominal pain, abdominal distension and excessive flatulence) then milk can be gradually increased over the next few days. Age appropriate normal diet can then be resumed over the next few weeks.

Supplement vitamins and minerals: Supplemental multivitamins and minerals, at about twice the RDA, should be given daily to all children for at least 2–4 weeks. Iron supplements should be introduced only after the diarrhea has ceased. Vitamin A (as a single dose) and zinc are supplemented as both of them enhance the recovery from persistent diarrhea. A single oral dose of vitamin A should be given routinely, at 2,00,000 IU for children >12 months or 100,000 IU for children 6–12 months. Children weighing less than 8 kg, irrespective of their age, should be given 1,00,000 IU of vitamin A. One should administer 10–20 mg per day of elemental zinc for at least 2 weeks to children between 6 months and 3 years of age.

Additional supplements for severely malnourished infants and children: Magnesium and potassium supplementation is provided to these children. Magnesium is given by intramuscular route at 0.2 mL/kg/dose of 50% magnesium sulfate twice a day for 2–3 days. Potassium is supplemented at 5–6 mEq/kg/day orally or as part of intravenous infusion during the initial stabilization period.

Role of antibiotics: The indiscriminate use of antibiotics in the treatment of acute diarrhea is among the reasons for persistent diarrhea. Hence, the use of empirical antibiotics at admission is to be individualized and reserved for children with either of the following features: (i) severe malnutrition (majority of these children have associated systemic infections and clinical signs of infection may not be obvious); and (ii) evidence of systemic infection. A combination of cephalosporin and aminoglycoside can be started empirically and thereafter changed according to reports of culture/sensitivity. Urinary tract infection is common (seen in 10–15%) and should be treated appropriately.

Monitoring Response to Treatment

Successful treatment is characterized by adequate food intake, reduced frequency of diarrheal stools (<2 liquid

stools/day for 2 consecutive days) and weight gain. Most children will lose weight in the initial 1–2 days and then show steady weight gain as associated infections are treated and diarrhea subsides. All children should be followed regularly even after discharge to ensure continued weight gain and compliance with feeding advice.

Prognosis

Most patients with persistent diarrhea recover with an approach of stepped up dietary management as discussed above. A small subgroup (<5%) may be refractory and require parenteral nutrition and extensive workup. These patients generally have high purge rate, continue to lose weight, do not tolerate oral feeds and require referral to specialized pediatric gastroenterology centers.

CHRONIC DIARRHEA

Chronic diarrhea is a common problem in children. It is defined as an insidious onset diarrhea of >2 weeks duration in children and >4 weeks in adults. The term chronic diarrhea is not synonymous with persistent diarrhea. The approach, etiology and management of chronic diarrhea along with a brief outline of some common causes is discussed.

Approach

Approach to chronic diarrhea must be considered with the following points in mind:

Age of onset: A list of common causes of chronic diarrhea according to age of onset is shown in Table 12.14.

Small or large bowel type of diarrhea: Features in history and examination that help in differentiating small bowel from large bowel diarrhea is shown in Table 12.15. Typically, large volume diarrhea without blood and mucus suggests *small bowel* type of diarrhea and small volume stools with blood and mucus suggest *large bowel* type of diarrhea.

Gastrointestinal versus systemic causes: Diarrhea is most commonly of intestinal origin and sometimes pancreatic, or rarely, hepatobiliary in etiology. Cholestasis due to biliary obstruction or intrahepatic cause can cause diarrhea due to fat malabsorption. Pruritus and malabsorption of fat-soluble vitamins (A, D, E and K) and calcium are commonly associated. Maldigestion due to deficiency of pancreatic enzymes leads to pancreatic diarrhea in cystic fibrosis, Shwachman-Diamond syndrome (cyclic neutropenia and bone abnormalities) or chronic pancreatitis. Other causes include Zollinger-Ellison syndrome, and secretory tumors like VIPoma, carcinoid or mastocytosis. Diarrhea may also be a systemic manifestation of other conditions like sepsis or collagen vascular disorders.

Specific questions in history should include:

- i. Duration of symptoms; nature, frequency and consistency of stools; and presence of blood, mucus or visible oil in stools

Table 12.14: Causes of chronic diarrhea according to age of onset (In order of importance)

Age <6 months	Age >6 months to 5 years	Age >5 years
Cow milk protein allergy	Cow milk protein allergy	Celiac disease
Lymphangiectasia	Celiac disease	Giardiasis
Urinary tract infection*	Giardiasis	Gastrointestinal tuberculosis
Short bowel syndrome**	Toddler diarrhea	Inflammatory bowel disease
Immunodeficiency states	Lymphangiectasia	Immunodeficiency
Cystic fibrosis	Short bowel syndrome**	Bacterial overgrowth
Anatomical defects	Tuberculosis	Lymphangiectasia
Intractable diarrheas of infancy***	Inflammatory bowel disease	Tropical sprue
Microvillous inclusion disease	Immunodeficiency	Immunoproliferative small intestinal disease
Tufting enteropathy	Bacterial overgrowth	Pancreatic insufficiency
Autoimmune enteropathy	Pancreatic insufficiency	
Glucose galactose malabsorption		
Congenital sodium/chloride diarrhea		

* Should be considered in young infants with chronic diarrhea, particularly if fever is noted

** Consider if there is antecedent history of small bowel surgery

*** These rare conditions should only be considered if the diarrhea is very early in its onset (neonate to 3 months) and common conditions have been ruled out

Table 12.15: Differentiating small bowel from large bowel diarrhea

Features	Small bowel diarrhea	Large bowel diarrhea
Stool volume	Large	Small
Blood in stool	No	Usually present
Rectal symptoms, e.g. urgency, tenesmus	No	Yes
Steatorrhea (greasy stools)	Yes	No
Carbohydrate malabsorption	Yes, explosive	No
Protein malabsorption	Yes	No
Pain (if any)	Periumbilical, no reduction after passage of stool	Hypogastric, reduced after passage of stool
Color of stool	Pale	Normal
Smell of stool	Unusually offensive	Normal
Nutrient deficiency	Frequent	Can occur due to blood loss

- ii. Age of onset; relationship of dietary changes, e.g. introduction of milk or milk products and wheat or wheat products, with onset of diarrhea; and any specific dietary preferences, like avoidance of juices
- iii. Family history of atopy (food allergy, asthma or allergic rhinitis), celiac disease, Crohn's disease or cystic fibrosis
- iv. History of abdominal surgery, drug intake, systemic disease, features of intestinal obstruction, pedal edema, anasarca, recurrent infections at multiple sites, previous blood transfusion and coexisting medical problems which predispose the child to diarrhea (e.g. congenital immunodeficiency, diabetes mellitus, hyperthyroidism, cystic fibrosis)
- v. Signs of vitamin or mineral deficiencies (e.g. conjunctival xerosis, Bitot's spots, angular stomatitis, glossitis, cheilitis, rickets, phrynoderma)
- vi. Edema, whether symmetric or asymmetric; pitting or non-pitting (lymphedema)
- vii. Fever and signs of systemic sepsis
- viii. Extragastrintestinal manifestations in eye, skin, joints, oral cavity (suggest inflammatory bowel disease, IBD)
- ix. Inspection of perianal area for fissures, anal tags and fistulae (seen in IBD)
- x. Oral thrush and scars of recurrent skin infections (suggest immunodeficiency)
- xi. Abdominal distention, localized or generalized tenderness, masses, hepatosplenomegaly and ascites.

Important components of physical examination include:

- i. Anthropometry
- ii. Signs of dehydration

Approach based on age of onset: In infants <6 months, cow milk protein allergy and intestinal lymphangiectasia should be considered first. The important clues to each etiology are given in Table 12.16.

Table 12.16: Diagnostic clues to important causes of chronic diarrhea

Cow milk protein allergy	Onset of diarrhea after introduction of cow or buffalo milk or formula Rectal bleeding (due to colitis) Anemia; failure to thrive Family history of allergy or atopy Response to milk withdrawal
Lymphangiectasia	Nonpitting pedal edema suggesting lymphedema Recurrent anasarca Hypoalbuminemia and hypoproteinemia Lymphopenia Hypocalcemia
Cystic fibrosis	History of meconium ileus Predominant or associated lower respiratory tract infections Severe failure to thrive Clubbing History of sibling deaths High sweat chloride (>60 mEq/L)
Immuno-deficiencies	Predominant fever Recurrent infections involving other sites History of sibling deaths Organomegaly Opportunistic infections on stool examination

In young children, celiac disease is the most common cause of chronic diarrhea in North India. *Cow milk protein allergy* usually resolves by 3–5 years; hence, this diagnosis should not be considered in children with onset of diarrhea beyond 5 years. *Toddler diarrhea* is a diagnosis of exclusion after common causes have been ruled out. The onset of diarrhea is between 6 months and 3 years of age. The child passes 3–6 loose stools, mostly during waking hour. Diarrhea worsens with low residue, low fat or high carbohydrate diet. The child is well thriving, there is no anemia or vitamin deficiencies and the diarrhea resolves spontaneously by about 4 years of age. Treatment is with dietary modification; a high (>40%) fat, low carbohydrate diet (especially with decreased intake of juices) and increase in dietary fiber is recommended. *IBD* is less common in this age group as compared to older children. *Giardiasis* can be diagnosed, if multiple fresh stool samples (at least 3 in number) are tested for trophozoites. The laboratory may be asked to use *concentration methods*. Presence of cysts of giardia in immunocompetent patients does not merit a therapy of giardiasis.

Limited etiologies cause chronic diarrhea in older children (Table 12.16). A brief description of common causes of chronic diarrhea is given below.

Celiac Disease

This is an enteropathy caused by permanent sensitivity to gluten in genetically susceptible subjects. It is the most

common cause of chronic diarrhea in children over 2 years of age in North India. High-risk groups include subjects with Type I diabetes mellitus, Down syndrome, selective IgA deficiency, autoimmune thyroid disease, Turner syndrome, Williams syndrome, autoimmune liver disease and first-degree relatives of celiac disease patients. These subjects are at an increased risk of developing celiac disease and thus should be screened.

Presentation: The classical presentation is with small bowel diarrhea, growth failure and anemia. A temporal association of diarrhea and introduction of wheat products at weaning may be present. Onset of diarrhea before introduction of wheat products in diet negates a diagnosis of celiac disease. It may also present without chronic diarrhea as refractory iron deficiency or dimorphic anemia not responding to oral supplements, short stature, delayed puberty, rickets and osteopenia. Examination reveals failure to thrive, loss of subcutaneous fat, clubbing, anemia, rickets and signs of other vitamin deficiencies.

A high index of suspicion for celiac disease is the key to diagnosis.

Diagnosis: The main investigations required for making a diagnosis include:

- i. **Serology:** IgA antibody against tissue transglutaminase (tTG) is an ELISA based test, recommended for initial testing of celiac disease. It has a high sensitivity (92–100%) and specificity (91–100%) in both children and adults. IgA antiendomysial antibody is an equally accurate test (sensitivity 88–100%; specificity 91–100%) but is more difficult to perform. The diagnosis of celiac disease should not be based only on celiac serology as serology may be false positive, false negative and interlaboratory variations are also present.
- ii. **Upper GI endoscopy:** It may be normal or show absence of folds or scalloped folds (Fig. 12.16a). Multiple (4–6 in number) endoscopic biopsies from the bulb and second/third part of duodenum should be taken in all cases.
- iii. **Histology:** The characteristic histological changes in celiac disease are increased intraepithelial lymphocytes (>30/100 enterocytes), increased crypt length, partial to total villous atrophy, decreased villous to crypt ratio and infiltration of plasma cells and lymphocytes in lamina propria (Fig. 12.16b).

Diagnosis of celiac disease (based on the modified criteria of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition, ESPGHAN) require the following:

- i. Clinical features compatible with diagnosis.
- ii. Positive intestinal biopsy as described above with or without serology.
- iii. Unequivocal response to gluten-free diet (GFD) within 12 weeks of initiation of GFD.

A positive serology makes the diagnosis more definite especially in developing countries where other causes of

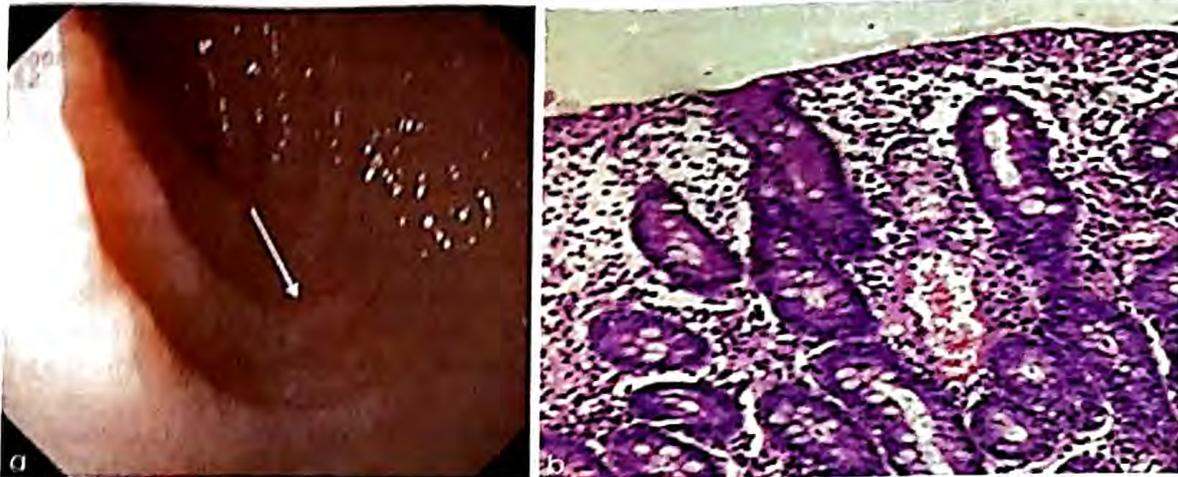


Fig. 12.16: Celiac disease: (a) Upper gastrointestinal endoscopy showing scalloping of duodenal folds (arrow); and (b) Duodenal histology showing total villous atrophy

villous atrophy are common due to intercurrent infections or undernutrition.

The recent ESPGHAN guidelines suggest that in symptomatic patients with tTG >10ULN, the diagnosis of celiac disease may be made without a duodenal biopsy provided that the antiendomysial antibody and HLA DQ2/DQ8 are positive and there is a definite response to gluten-free diet. However, in view of non-availability and cost of antiendomysial antibody and HLA testing and multiple labs reporting tTG as positive/negative only without actual titres this approach is not recommended in our country at present. This is especially important as it is very difficult to confirm or refute the diagnosis of CD after initiation of GFD. Thus all efforts should be made to make a correct diagnosis with full work-up at onset prior to initiation of GFD.

Treatment: The treatment involves lifelong GFD and correction of iron, folate and other vitamin/mineral deficiencies by supplementation. The patient should be assessed at 3 months for response to GFD. After initiation of GFD, all symptoms should subside and weight and height gain should be present. Repeated explanation to patient and parents by doctors is very helpful in sustaining compliance after the child has become asymptomatic.

Cow Milk Protein Allergy

Cow milk protein allergy (CMPA) affects 2 to 5% of all children in the West, with the highest prevalence during the first year of life. In India, CMPA accounts for ~13% of all malabsorption cases in children <2 years of age. A family history of atopy is common in children with CMPA. Nearly 50% children outgrow the allergy by 1 year and ~95% by 5 years of age. It is the most common food allergy in small children who are top-fed but can also occur occasionally in breastfed babies due to passage of cow milk antigen in breast milk.

There are two kinds of reactions to cow milk: (i) *Immediate*, i.e. IgE mediated: It occurs within minutes

of milk intake and is characterized by vomiting, pallor, shock-like state, urticaria and swelling of lips. (ii) *Delayed*, i.e. T cell mediated: It has an indolent course and presents mainly with GI symptoms.

Symptoms: The most common presentation is with diarrhea with blood and mucus. Depending upon the site and extent of involvement, the child may have small bowel, large bowel or mixed type diarrhea. In an Indian study, 40% children presented with bloody diarrhea, 33% watery and 7% with a mixed type of diarrhea. Uncommonly reflux symptoms and hematemesis may be present indicating upper GI involvement. Respiratory symptoms (allergic rhinitis and asthma) and atopic manifestations (eczema, angioedema) may be seen in 20–30% and 50–60% cases, respectively. Iron deficiency anemia, hypoproteinemia and eosinophilia are commonly present.

Diagnosis: In India, non-IgE-mediated CMPA is more common. Sigmoidoscopy (aphthous ulcers and nodular lymphoid hyperplasia as seen in Fig. 12.17a) and rectal biopsy (plenty of eosinophils as seen in Fig. 12.17b) give clue to the diagnosis in >95% cases irrespective of the clinical presentation and should be the first line of investigation in suspected cases. The gold standard for diagnosis of any food allergy is the elimination and challenge test. Typically, the symptoms subside after milk withdrawal and recur within 48 hours of re-exposure to milk.

Treatment: All animal milk/milk products have to be removed from the diet. Soy or extensively hydrolyzed formula, both of which are equally effective in terms of growth and nutrient intake can be used as alternatives. Although soy is more palatable and cheap but it is not recommended in infants <6 months of age. Also 10–15% of CMPA have concomitant soy allergy, thus necessitating use of extensively hydrolyzed formulae. A minority of children may not tolerate the extensively hydrolyzed formulae and need elemental amino acid formulas.

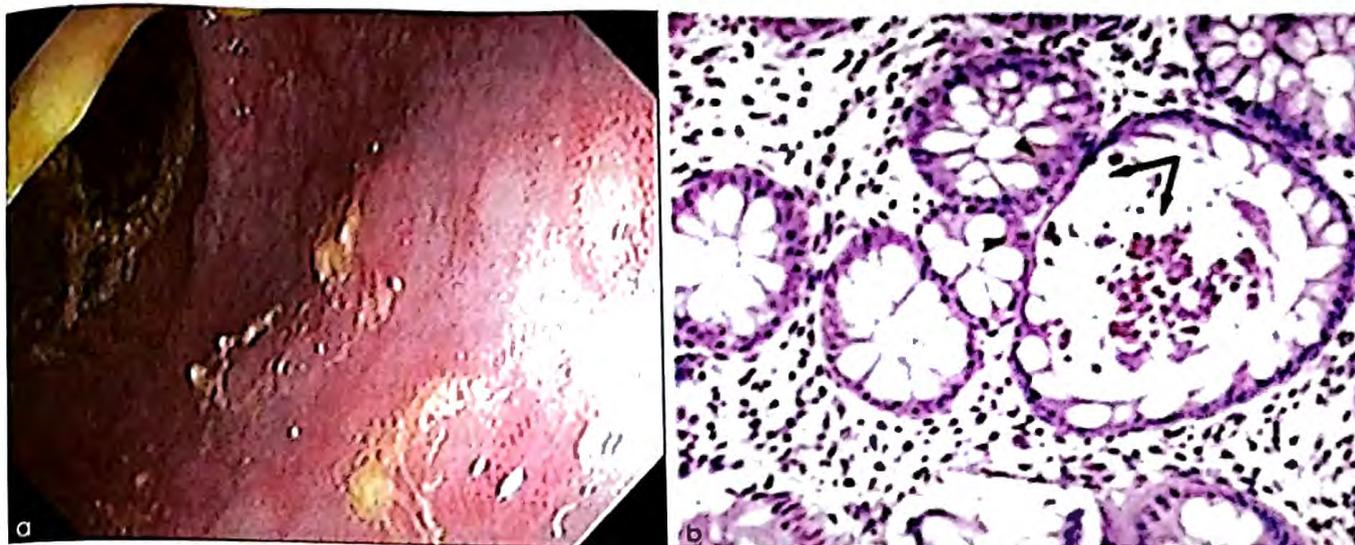


Fig. 12.17: Cow milk protein allergy: (a) Sigmoidoscopy showing aphthous ulcers; and (b) Rectal biopsy showing eosinophilic infiltration with crypt abscess

Parental education regarding diet and calcium supplementation is essential.

Intestinal Lymphangiectasia

It is characterized by ectasia of the bowel lymphatic system, which on rupture causes leakage of lymph in the bowel. The disease is often associated with abnormal lymphatics in extremities. Signs and symptoms include peripheral edema which could be bilateral and pitting due to hypoalbuminemia or asymmetrical and non-pitting due to lymphedematous limb. Diarrhea, abdominal distension and abdominal pain are commonly present. Abdominal and/or thoracic chylous effusions may be associated. Presence of hypoalbuminemia, low immunoglobulins, hypocalcemia and lymphopenia is characteristic of lymphangiectasia. Barium meal follow-through shows thickening of jejunal folds with nodular lucencies in

mucosa. On UGI endoscopy after fat loading with 2 g/kg of butter at bedtime, scattered white plaques or chyle-like substance covering the mucosa may be seen (Fig. 12.18a). Duodenal biopsy reveals dilated lacteals in villi and lamina propria (Fig. 12.18b). The treatment consists of a low fat, high protein diet with MCT oil, calcium and fat-soluble vitamin supplementation. Intravenous albumin is required for symptomatic management and total parenteral nutrition (TPN) is reserved for management of chylous effusions. Resection may be considered, if the lesion is localized to a small segment of intestine.

Immunodeficiency

Both congenital and acquired immunodeficiency can cause chronic diarrhea. It should be suspected, if there is history of recurrent infections at multiple sites (chest/GI/skin) and wasting. The common immunodeficiency conditions

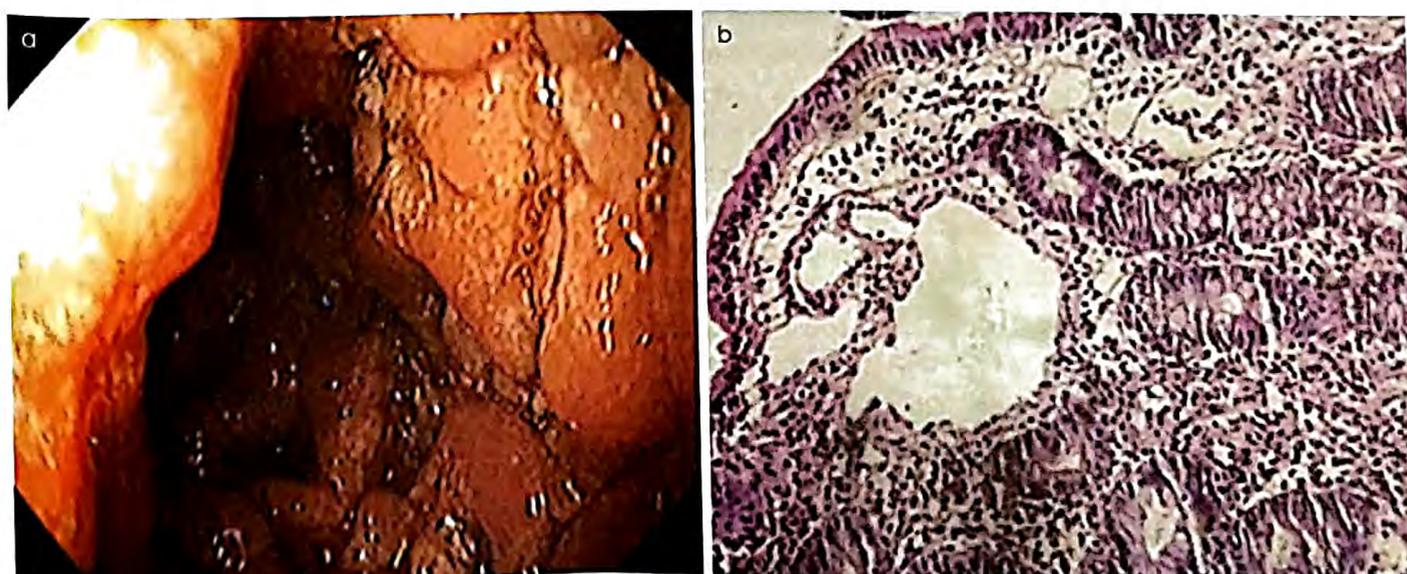


Fig. 12.18: Intestinal lymphangiectasia. (a) Upper gastrointestinal endoscopy showing white deposits; and (b) Duodenal histology shows dilated lacteals

presenting with diarrhea include IgA deficiency, severe combined immunodeficiency (SCID), common variable immunodeficiency (CVID) and chronic granulomatous disease (CGD). There is increased risk of celiac disease (10–20-fold increase) and Crohn's disease in patients with *IgA deficiency*. Diarrhea is either due to enteric infections like giardia, cryptosporidium, CMV, etc. or due to bacterial overgrowth. Diagnosis is made by measuring serum immunoglobulins, T cell counts and functions, phagocytic function (nitroblue tetrazolium reduction test) depending upon the suspected etiology. Treatment involves administration of antimicrobials for bacterial overgrowth and opportunistic infections and therapy for underlying cause (IV immunoglobulins, γ interferon or bone marrow transplantation).

Acquired immunodeficiency syndrome (AIDS): Chronic diarrhea is a common feature in children with AIDS. The impaired mucosal immunity results in recurrent opportunistic infections and the altered maturation and function of enterocytes results in increased permeability and decreased functional absorptive surface with or without bacterial overgrowth. AIDS enteropathy is characterized by chronic diarrhea and marked weight loss in absence of enteric pathogens. The children are often sick with other clinical manifestations but sometimes diarrhea may be the only symptom. Presence of oral thrush, lymphadenopathy, hepatosplenomegaly and parotiditis (10–20% cases) gives clue to the diagnosis. The common infections include:

- i. *Viral*. Cytomegalovirus, herpes simplex, adenovirus, norovirus
- ii. *Bacterial*. *Salmonella*, *Shigella*, *Mycobacterium avium* complex (MAC), *Campylobacter jejuni*, *Clostridium difficile*
- iii. *Fungi*. Candidiasis, histoplasmosis, cryptococcosis

iv. *Protozoa*. *Microsporidium*, *Isospora belli*, *Cryptosporidium*, *Entamoeba histolytica*, *Giardia lamblia*, *Cyclospora*, *Blastocystis hominis*

Multiple stool examinations are required to identify the causative etiology by using special stains and PCR techniques. Colonic/terminal ileum biopsy and duodenal fluid examination are the other ways of diagnosing opportunistic infections. Treatment is with specific antimicrobials (Table 12.17) along with HAART (highly active antiretroviral therapy).

Drug-Induced Diarrhea

Diarrhea can be a side effect of many pharmacologic agents. Altered GI motility, mucosal injury and/or change in intestinal microflora are the main etiologic factors. Antibiotics can cause loose watery stools by altered bacterial flora or bloody stools secondary to *Clostridium difficile* overgrowth and pseudomembranous colitis (PMC). Stopping the offending agent is often enough. If suspicion of PMC is present then stool for toxin assay and sigmoidoscopy is required for confirmation. Metronidazole or oral vancomycin is the drug of choice for PMC.

Inflammatory Bowel Disease (IBD)

IBD is a chronic inflammatory disease of the GI tract and is of two main types, Crohn's disease and ulcerative colitis. In ~10% cases, the findings are non-specific and subjects cannot be classified into one of the above two groups. These cases are labelled as indeterminate colitis. Nearly 25% of all IBD presents in the pediatric age group. Worldwide the incidence of IBD is increasing in children with increase in recent reports of both ulcerative colitis and Crohn's disease from India. The average age of presentation in children is ~10–11 years. Genetics is a very

Table 12.17: Treatment recommendations for infectious diarrhea

Infection causing diarrhea	Drug of choice for treatment
<i>Giardia lamblia</i>	Metronidazole 7.5 mg/kg/dose tds for 5 days
<i>Entamoeba histolytica</i>	Metronidazole 7.5 mg/kg/dose tds for 10 days
<i>Cryptosporidium</i>	Nitazoxanide: In immunocompetent children 1–3 years: 100 mg bd \times 3 days 4–11 years: 200 mg bd \times 3 days
<i>Microsporidium</i>	Oral albendazole (15 mg/kg/day twice a day) for 14 days in immunocompetent. Longer therapy in immunocompromised.
<i>Cyclospora</i>	TMP-SMZ—5/25 mg/kg/day for 7 days
<i>Isospora belli</i>	TMP-SMZ for 7 days
Cytomegalovirus	Gancyclovir 5 mg/kg IV q 12 hrly for 14–21 days
<i>Clostridium difficile</i>	Stop other antibiotics. Oral metronidazole (30 mg/kg/day in 4 divided doses) for 7–10 days for mild disease. Oral vancomycin (40 mg/kg/day in 4 divided doses; maximum, 2 g/day), with or without metronidazole for severe disease
Candidiasis	Fluconazole 6 mg/kg/day oral once a day
Cryptococcus neoformans	Fluconazole for 4 weeks

tds: Three times a day; bd: Twice a day; TMP-SMZ: Trimethoprim-sulfamethoxazole

important risk factor for IBD and up to 30% patients may have a family member with IBD.

Clinical features: Children with ulcerative colitis present with diarrhea and rectal bleeding which raises alarm and leads to early workup and diagnosis. In Crohn's disease, abdominal pain, diarrhea and growth failure are the predominant complaints. The classical triad of Crohn's disease, i.e. pain, diarrhea and weight loss is seen in only 25% cases. Fever, fatigue and anorexia are present in 25–50% cases. The absence of blood in stools and non-specific complaints are responsible for delay in diagnosis of Crohn's disease in children.

Extraintestinal manifestations are seen in 25–30% children with IBD. They can precede, follow or occur concurrently with the intestinal disease and may be related/unrelated to activity of the intestinal disease. Arthralgia/arthritis is the most common extraintestinal manifestation seen in 15–17% cases. Uveitis, erythema nodosum and sclerosing cholangitis are the other extraintestinal manifestations.

Disease distribution: Ulcerative colitis is classified as distal colitis (proctitis/proctosigmoiditis), left side colitis (up to splenic flexure) and pancolitis with majority of children having pancolitis. Majority of patients with Crohn's disease (50–70%) have ileocolonic disease, with isolated colonic involvement in 10–20% and isolated small bowel in 10–15% patients. Upper GI involvement is present in 30–40% cases and perianal disease in 20–25% cases. Crohn's disease is also classified as predominantly inflammatory, fistulizing or stricturing disease based on the clinical features.

As the management and prognosis of Crohn's disease and ulcerative colitis is different, so a correct diagnosis is essential. Table 12.18 lists the main differentiating features between ulcerative colitis and Crohn's disease.

Diagnosis: The initial evaluation of a child with suspected IBD includes a detailed clinical, family and treatment history. A complete examination with growth charting,

perianal and rectal examination for fistulae, tags and fissures is essential. Simple lab tests like hemogram, ESR, C reactive protein, total protein, serum albumin and stool for occult blood helps in screening for IBD and confirming presence of bowel inflammation. Fecal calprotectin is a reliable test for differentiating patients with functional abdominal pain from those with abdominal pain due to inflammatory conditions like Crohn's. It is raised in IBD and normal in FAP.

According to the recommendations of the IBD working group, upper GI endoscopy with biopsy, colonoscopy with ileal intubation and biopsy is essential for all cases (Fig. 12.19). Small bowel evaluation with CT or MR enterography should be done for correct classification into ulcerative colitis or Crohn's disease and to determine the disease extent. Capsule endoscopy may also be used for small bowel evaluation in patients who do not have any suggestion of an obstructive (stricturing) lesion of small bowel.

Treatment: The goal of treatment is to control inflammation, improve growth and ensure a good quality of life with the least toxic therapeutic regimen. As IBD is a chronic disease with remissions and exacerbations, proper counseling of both patient and family at diagnosis is essential. The main drugs used for IBD are 5-aminosalicylates (5-ASA), steroids and immunomodulators (6-mercaptopurine, azathioprine, methotrexate and monoclonal antibodies against tumor necrosis factor, i.e. infliximab). Ensuring proper nutrition with caloric supplementation (~120% of RDA) is a necessity for children with IBD. Calcium and vitamin D supplementation should be given as these children are at an increased risk of osteoporosis.

Surgery is indicated in ulcerative colitis patients with severe acute colitis refractory to medical disease. Uncontrolled hemorrhage, perforation, toxic megacolon, abscesses and obstruction are the other indications for surgery in patients with IBD.

Table 12.18: Differentiation between Crohn's disease and ulcerative colitis

	<i>Crohn's disease</i>	<i>Ulcerative colitis</i>
Distribution	Entire gastrointestinal tract Discontinuous lesions	Colon only Continuous involvement
Bloody diarrhea	Less common	Common
Abdominal pain	Common	Less common
Growth failure	Common	Less common
Perianal disease	Abscess; fistulae	Absent
Serology	<i>Anti-Saccharomyces cerevisiae</i> antibody (ASCA) positive	Perinuclear anti-neutrophil cytoplasmic antibody (p-ANCA) positive
Endoscopy	Deep irregular serpiginous or aphthous ulcers with normal intervening mucosa (skip lesions)	Granularity, loss of vascular pattern, friability and diffuse ulceration
Histopathology	Transmural inflammation with non-caseating granuloma	Mucosal disease with cryptitis, crypt distortion, crypt abscess and goblet cell depletion

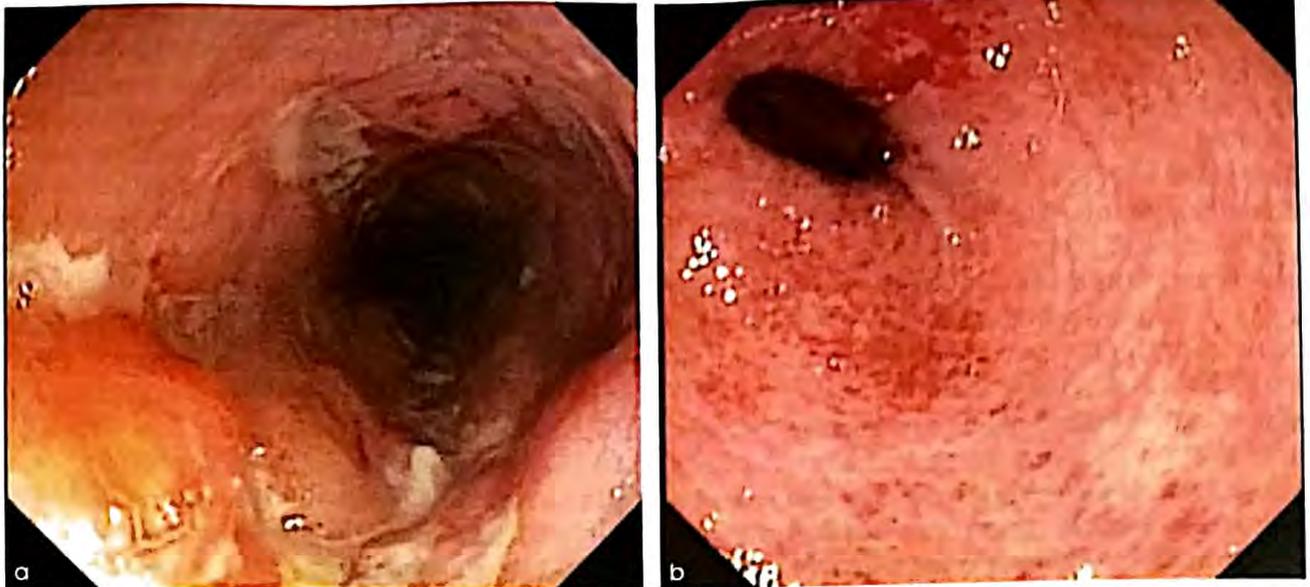


Fig. 12.19: Inflammatory bowel disease: (a) Deep, linear, serpiginous ulcers on colonoscopy in Crohn's disease; and (b) Confluent superficial ulcerations with friability on colonoscopy in ulcerative colitis

Abdominal Tuberculosis

The gastrointestinal tract, peritoneum, lymph nodes and/or solid viscera can be involved in abdominal tuberculosis. The peritoneal involvement is of two types: Wet (or ascitic) and dry (or plastic) type. On the other hand, the intestinal involvement may be ulcerative, hypertrophic or ulcero-hypertrophic type.

The clinical presentation is varied and depends upon the site of disease and type of pathology. Clinical features may include chronic diarrhea, features of subacute intestinal obstruction (abdominal pain, distension, vomiting, obstipation), ascites, lump in abdomen (ileocecal mass, loculated ascites, lymph nodes) and/or systemic manifestations (fever, malaise, anorexia and weight loss).

A high index of suspicion followed by documenting presence of acid-fast bacilli (fine needle aspiration cytology from lymph nodes, ascitic fluid, endoscopic biopsies) on Ziehl-Neelsen staining, PCR or culture leads to a definitive diagnosis. Presence of tubercular granuloma with caseation in the biopsies (endoscopic, peritoneal or liver) also helps make the diagnosis. CT abdomen shows enlarged lymph nodes with central necrosis (Fig. 12.20). An exudative ascites (low serum ascites albumin gradient, SAAG <1.1) with lymphocyte predominance and high adenosine deaminase is typical of tubercular ascites. Colonoscopy classically shows transverse ulcers in ascending colon/caecum, deformed/ ulcerated ileocaecal valve and ulceration/stricture in terminal ileum (Fig. 12.21). In absence of above features, a probable diagnosis of abdominal tuberculosis is made when suggestive clinical features and response to antitubercular therapy is present. It is important to differentiate intestinal TB from Crohn's disease as they mimic each other in clinical presentation but have different treatments.



Fig. 12.20: CT scan showing multiple enlarged lymph nodes with central necrosis in para-aortic and mesenteric regions in abdominal tuberculosis

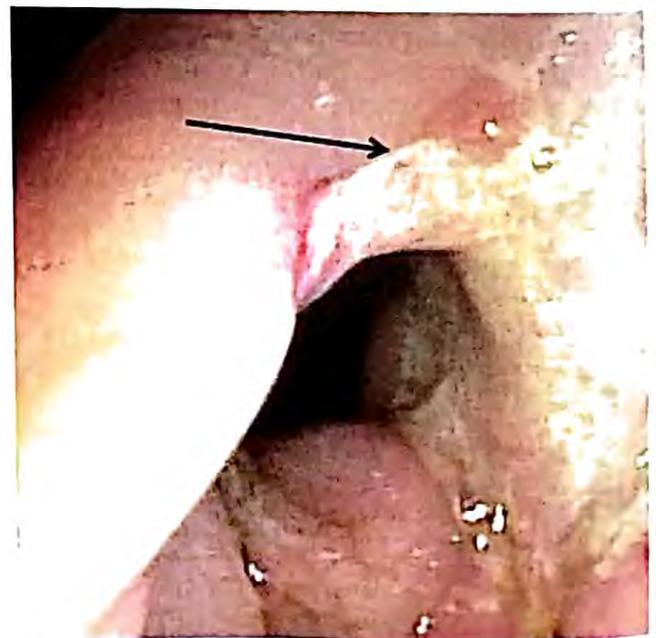


Fig. 12.21: Colonoscopy shows ulceration with gaping ileocaecal valve in a patient with ileocecal tuberculosis

Antitubercular drugs are the mainstay of treatment. Surgery is indicated, if there is bowel perforation, obstruction or massive hemorrhage. One should suspect multidrug resistant tuberculosis in patients with a definite diagnosis of abdominal tuberculosis but a poor response to standard antitubercular therapy.

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GASTROINTESTINAL BLEEDING

Gastrointestinal bleeding is a commonly encountered problem in children. *Upper gastrointestinal bleeding* is defined as bleeding from a site proximal to the ligament of Treitz (at the level of duodenojejunal flexure). *Lower gastrointestinal bleeding* is defined as bleeding from a site distal to ligament of Treitz.

Hematemesis is passage of blood in vomiting and suggests an upper GI site of bleeding. The vomitus may be bright red or coffee-ground in color depending upon the severity of hemorrhage and the duration it stayed in contact with gastric secretions. *Melena* is passage of black tarry stools and suggests an upper GI or small bowel source of bleed. *Hematochezia* is passage of bright red blood in stools.

Hemobilia refers to bleeding from the biliary tree while *pseudo-hemobilia* is bleeding from the pancreas. *Obscure GI bleed* is defined as bleeding from gastrointestinal tract that persists or recurs without any obvious etiology after a diagnostic esophagogastroduodenoscopy and colonoscopy. It accounts for ~5% of all GI bleeds.

Upper GI Bleeding

The causes of hemorrhage from upper GI tract vary in different age groups as shown in Table 12.19. Varices, esophagitis and gastritis are the commonest causes of upper GI bleeding in Indian children.

Painless passage of large amount of blood in vomitus points towards variceal bleeding. One should always look for features of liver disease like splenomegaly, jaundice and ascites. In portal hypertension, the spleen may reduce in size just after a bout of massive hematemesis and is thus missed on examination. In a child with portal hypertension, esophageal varices are the commonest cause of upper GI bleeding (Fig. 12.22a). Gastric varices (Fig. 12.22b), congestive gastropathy and gastric antral vascular ectasia can also present with hematemesis.

Management

General supportive measures, including establishing a good venous access, intake output monitoring, oxygen supplementation (if required) and charting of vital signs are mandatory. Blood transfusion should be given to achieve hemoglobin of 7 g/dL. Short-term antibiotic prophylaxis (third generation cephalosporin for 7 days) may reduce bacterial infection, and variceal rebleeding, and should be administered in children with cirrhosis and variceal bleeding. *Specific treatment* depends upon the patient's condition and expertise of the available personnel. A combination of pharmacologic and endoscopic therapy is preferred. Early administration of vasoactive drugs should be followed by endoscopic therapy within 12 hours of bleed. Following an episode of acute variceal bleeding, all patients should receive secondary prophylaxis to prevent rebleeding.

Table 12.19: Common causes of upper gastrointestinal bleeding

Neonate or infant	Children >2 years
Swallowed maternal blood	Esophagitis due to reflux, medications, infections
Esophagitis	Gastroduodenal erosions/ulceration
Gastroduodenal erosions/ulceration	Portal hypertension
Sepsis/ coagulopathy/stress	Sepsis/ coagulopathy/stress
Hemorrhagic disease of newborn	Caustic ingestion, Mallory-Weiss tear
Esophageal varices (infants >3–4 months)	Henoch-Schönlein purpura
Vascular malformation	Vascular malformation
Foreign body impaction	Foreign body impaction
Bovine milk allergy	Tumors: Leiomyoma, lymphoma, teratoma

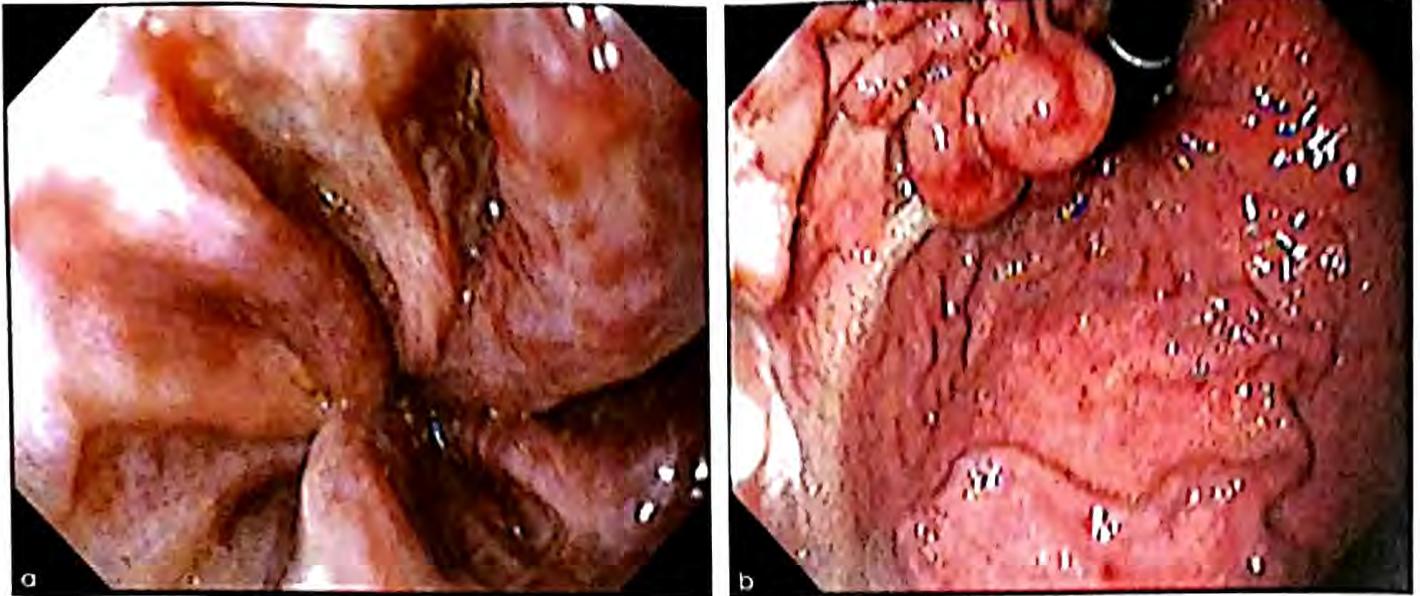


Fig. 12.22: Upper gastrointestinal endoscopy showing (a) Esophageal varicos; and (b) Large gastric varicos

Administration of somatostatin or octreotide decreases the splanchnic and azygous blood flow, thus reducing portal pressures. Both agents are equally effective; limited studies in children have shown control of bleeding in 64–71% children. Infusion should be given for at least 24–48 hours after the bleeding has stopped to prevent recurrence and should not be discontinued abruptly.

Endoscopic sclerotherapy (EST) or variceal ligation (EVL) are the two main methods used to manage esophageal varices. Using a fiberoptic endoscope, the varices are inspected and their location, size and extent are documented. In EST, 2–3 mL of sclerosant (1% ethoxysclerol) is injected into each variceal column. EVL is done with a device called multiple band ligator. The variceal column is sucked into a cylinder attached at the tip of the endoscope and the band is deployed by pulling the trip wire around the varix. Both EST and EVL have 90–100% efficacy in controlling acute bleeding.

12 *Gastric varices* are managed with endoscopic injection of tissue adhesive glue, i.e. N-butyl-2-cyanoacrylate or isobutyl-2-cyanoacrylate. These agents harden within 20 seconds of contact with blood and result in rapid control of active bleeding.

Tamponade of varices is required only when the endoscopic and pharmacologic measures have failed. Sengstaken-Blakemore tube is a triple lumen tube with connection to an esophageal balloon, a gastric balloon and one perforated distal end which helps in aspiration of the stomach contents. The tube is relatively cheap, requires little skill compared to EST and has efficacy of above 75% in controlling acute variceal bleeding.

Transjugular intrahepatic portosystemic shunt (TIPS) involves insertion of a multipurpose catheter through the jugular vein and superior vena cava with the aid of the puncture device. The catheter is passed via hepatic vein into a branch of portal vein through the hepatic

parenchyma. The passage is dilated by a balloon and an expansile metallic mesh prosthesis is placed to maintain the communication directly between the portal vein and hepatic vein. This procedure results in bypassing liver resistance and consequently decreases the portal pressure. Experience of this procedure in children is limited.

Surgical management is required when above measures have failed or when bleeding is from ectopic varices that cannot be effectively controlled by endoscopic procedures. Surgery can be done either in the form of portocaval shunt (selective or nonselective) or devascularization with esophageal staple transection.

Lower Gastrointestinal Bleeding

The causes of lower gastrointestinal bleeding in children are shown in Table 12.20. History and physical examination helps narrow down the differential diagnosis. Increased frequency of stools with blood and mucus with crampy abdominal pain points towards a colitic illness and infectious colitis is by far the commonest cause in children across all ages. A sick preterm with abdominal distension, blood in stools, feed intolerance and systemic instability is likely to have necrotizing enterocolitis. Delayed passage of meconium followed by constipation, abdominal pain and distension is seen in Hirschsprung's disease. Allergic colitis is mostly seen in infants who are top fed with cow milk and present with loose stools mixed with blood and anemia. Onset of bloody diarrhea after antibiotic use points towards pseudomembranous colitis. Presence of extraintestinal manifestations, like aphthous ulcers, joint pains and iritis, gives clue to the diagnosis of inflammatory bowel disease (IBD). History of painful defecation and passage of hard stools with blood streaking of stools is seen in anal fissure. In a patient with history of constipation, straining at stools and digital evacuation, the most likely cause of bleeding is solitary rectal ulcer

Table 12.20: Causes of lower gastrointestinal bleeding

Neonate or infant	Children >2 years
Colitis	
Infectious colitis	Infectious colitis
Cow milk protein allergy	Inflammatory bowel disease
Necrotizing enterocolitis	Tuberculosis
Hirschsprung enterocolitis	Pseudomembranous colitis
Systemic vasculitis	Cow milk protein allergy
	Amebiasis, cytomegalovirus, neutropenic colitis
Others	
Anal fissure	Anal fissure
Intussusception	Polyp or polyposis syndrome
Duplication cyst	Solitary rectal ulcer syndrome
Arteriovenous malformation	Meckel's diverticulum
Rectal prolapse	NSAID-induced ulcer
Meckel's diverticulum	Hemorrhoids, rectal prolapse
Hemorrhagic disease of newborn	Henoch-Schönlein purpura
Coagulopathy	Arteriovenous malformation
	Coagulopathy
	Tumors: Leiomyoma, lymphoma

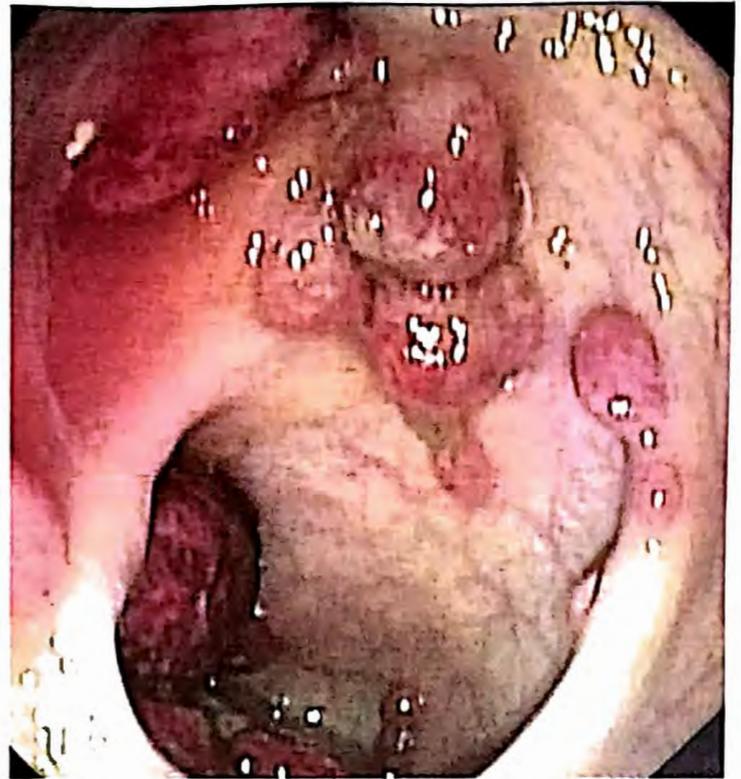


Fig. 12.23: Colonoscopy showing multiple sessile and pedunculated polyps in a child with polyposis coli

syndrome (SRUS). Intussusception is characterized by episodes of abdominal pain, vomiting and red currant-jelly stools, i.e. mixture of blood, mucoid exudates and stool. Painless bleeding is seen commonly in polyps (Fig. 12.23), Meckel's diverticulum (Fig. 12.24), varices (Fig. 12.25), ulcer or vascular anomaly. Presence of typical

cutaneous lesions as seen in blue rubber bleb nevus syndrome often suggests the diagnosis. Children with HIV infection or immunosuppression secondary to chemotherapy can develop CMV enterocolitis or polymicrobial inflammation of cecum (typhlitis), both of which can lead to significant rectal bleeding.



Fig. 12.24: Technetium-99m pertechnetate scan showing Meckel's diverticulum



Fig. 12.25: Colonoscopy showing rectal varix in a patient with EHPVO and lower GI bleeding

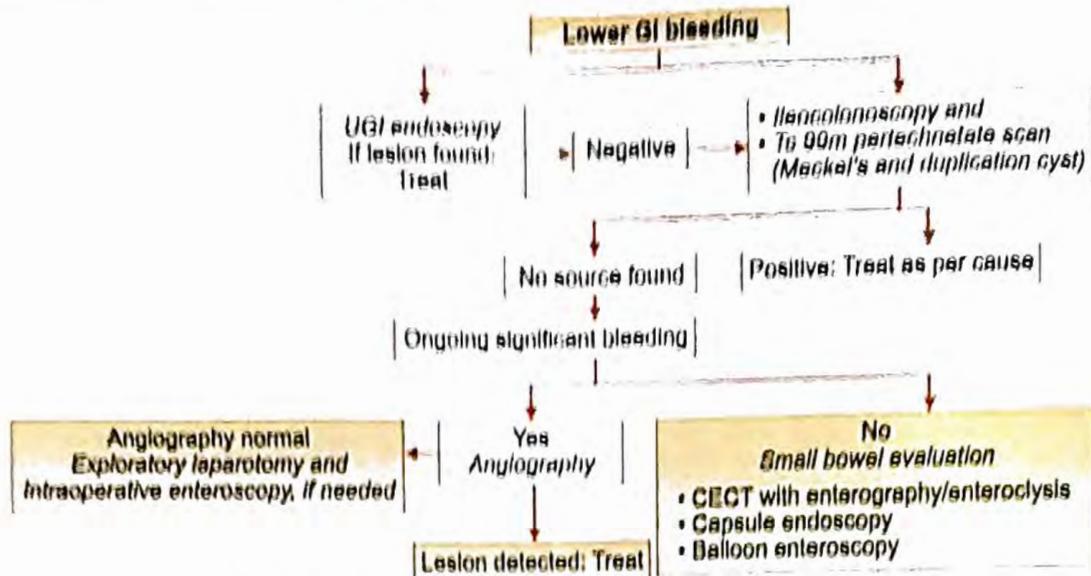


Fig. 12.26: Approach to a child with lower GI bleeding

On examination, presence of fissure and fleshy anal tags suggests Crohn's disease whereas characteristic orobuccal pigmentation is seen in Peutz-Jeghers syndrome. Abdominal examination is useful in detecting sausage-shaped mass in intussusception. A gentle per rectal examination can detect polyps in the rectum and also stool impaction. Presence of palpable purpura in lower limbs with abdominal pain suggests a diagnosis of Henoch-Schönlein purpura. Asking the child to strain will show presence of rectal prolapse.

The aim of investigations in a child with lower gastrointestinal bleeding is to localize the site of bleeding, i.e. small bowel or colon and also to determine the etiology in order to manage it appropriately. The approach is as shown in Table 12.21 and Fig. 12.26. Supportive treatment is similar to that of upper gastrointestinal bleeding and the specific treatment is dependent upon the cause.

Table 12.21: Evaluation for etiology of lower gastrointestinal tract bleeding

Colitic presentation

Hemogram, ESR
Stool examination for trophozoites, culture sensitivity, assay for *Clostridium difficile* toxin
Colonoscopy with biopsy for histology, culture, immunohistochemistry

Noncolitic presentation

Hemogram, ESR, prothrombin time
Colonoscopy and biopsy or polypectomy
Based on presentation
Ultrasound abdomen (intussusception)
^{99m}Tc pertechnetate scan (Meckel's diverticulum, intestinal duplication)
CT angiography (aneurysmal bleed)
Capsule endoscopy, double balloon enteroscopy (obscure bleeding)

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DISORDERS OF THE HEPATOBILIARY SYSTEM

Evaluation

After accurate history and physical examination, a judicious selection of laboratory tests helps in arriving to a definite diagnosis.

Biochemical Tests

Bilirubin: Total and fractionated (unconjugated and conjugated) bilirubin helps to differentiate between elevation caused by hemolysis versus hepatocellular or biliary dysfunction.

Transaminases (aspartate aminotransferase or serum glutamate-oxaloacetate transferase (AST, SGOT) and alanine aminotransferase or serum glutamate pyruvate transferase (ALT, SGPT): ALT is present mainly in liver and in lower concentration in muscle while AST is derived from other organs as well (muscles, kidney, red blood cells). Most marked increase in transaminases occurs with acute hepatocellular injury secondary to inflammation or ischemia, while in chronic liver disease transaminases are mildly or moderately elevated.

Alkaline phosphatase (ALP): Normal values are higher in growing children due to bone isoenzyme fraction. If elevation is associated with increased gamma glutamyl transpeptidase (GGT), it suggests cholestasis. GGT is more specific for hepatobiliary disease. The values are higher in newborns and reach normal adult values by 6-9 months.

Prothrombin time (PT) and international normalized ratio (INR): Deficiency of factors V and vitamin K dependent factors (II, VII, IX and X) occurs in liver disease. PT is a marker of synthetic function of liver. INR is a standardized way of reporting the prothrombin time. It is the ratio of a patient prothrombin time to a normal sample, raised to the power of the international sensitivity index (ISI) value for the analytical system used. ISI ranges between 1.0 and 2.0 and shows how a batch of tissue factor compares to an internationally standardized sample.

$$\text{INR} = (\text{PT test}/\text{PT normal})^{\text{ISI}}$$

The reference range for prothrombin time is usually around 11–16 seconds; the normal range for the INR is 0.8–1.2. A prolongation of PT by >3 seconds is abnormal.

Serum proteins: The half-life of albumin is 20 days; albumin is a marker of liver synthetic functions and is low in chronic liver disease. Gamma globulins are increased in autoimmune hepatitis; the ratio of albumin to globulin is reversed in cirrhosis, particularly in autoimmune liver disease. Low serum albumin and prolonged PT (unresponsive to vitamin K) indicate poor synthetic liver functions, raised ALT and AST indicate inflammation and raised ALP and GGT suggest cholestasis.

Serum ammonia levels: Levels are raised in hepatic encephalopathy.

Cholesterol: Levels are increased in cholestasis.

Liver Biopsy

Biopsy is a useful investigation for making a histologic diagnosis especially in neonatal cholestasis, congenital hepatic fibrosis, storage disorders like glycogen storage diseases and histiocytosis. It is useful for enzymatic estimation in metabolic diseases and for copper in Wilson disease. It is helpful in diagnosis of infectious diseases by immunohistochemistry and monitoring response to therapy. Liver biopsy also helps in understanding the stage of liver disease, e.g. chronic hepatitis or cirrhosis, degree of fibrosis and inflammation (see Chapter 29).

Hepatomegaly

A palpable liver does not always indicate enlargement. It only reflects the relation of the liver to adjacent structures. In normal children, the liver is palpable one cm and in infants up to 2 cm below the costal margin. It is important to measure the liver span to determine the presence of hepatomegaly (Table 12.22). The liver span varies with age: Infants 5–6.5 cm; 1–5 years: 6–7 cm; 5–10 years: 7–9 cm; and 10–15 years: 8–10 cm. The liver is also examined for tenderness, consistency and character of the surface.

Splenomegaly

Common causes of splenomegaly are listed in Table 12.23.

Table 12.22: Causes of hepatomegaly

Chronic liver disease (cirrhosis or chronic hepatitis): Wilson disease, chronic hepatitis B and C, autoimmune liver disease, Budd-Chiari syndrome, cryptogenic

Metabolic or storage disorders: Glycogen storage disease, Gaucher disease, Niemann-Pick disease, progressive familial intrahepatic cholestasis, nonalcoholic fatty liver disease

Infective: Viral hepatitis, liver abscess (pyogenic or amebic), tuberculosis, salmonella, malaria, kala-azar, hydatid disease

Tumors: Lymphoma, leukemia, histiocytosis, neuroblastoma, benign hemangioma, mesenchymal hamartoma, hepatoblastoma, hepatocellular carcinoma

Biliary: Caroli disease, choledochal cyst, congenital hepatic fibrosis, cystic disease of liver; extrahepatic biliary obstruction

Miscellaneous: Congestive heart failure, constrictive pericarditis, sarcoidosis

Table 12.23: Common causes of splenomegaly

Portal hypertension: Cirrhosis, extrahepatic portal venous obstruction; congenital hepatic fibrosis, noncirrhotic portal fibrosis, Budd-Chiari syndrome

Storage disorders: Niemann-Pick disease, Gaucher disease, mucopolysaccharidosis

Hematological malignancies: Leukemia, lymphoma, histiocytosis

Increased splenic function: Collagen vascular disorders, autoimmune hemolytic anemia, inherited hemolytic anemias

Infections: Malaria, enteric fever, viral hepatitis, infectious mononucleosis, kala-azar; congenital infections

Extramedullary hematopoiesis: Osteopetrosis

Liver Abscess

Pyogenic liver abscess is more common than amebic liver abscess in children. The infection reaches the liver by one of the following routes: (i) portal vein, e.g. in intra-abdominal sepsis, umbilical vein infection; (ii) biliary tree obstruction and cholangitis, e.g. choledochal cyst; (iii) systemic sepsis, e.g. endocarditis, osteomyelitis; and (iv) direct inoculation, e.g. in trauma. In children on immunosuppressive medications or with defects of neutrophil function (e.g. chronic granulomatous disease), there is an increased risk of developing abscesses, especially due to *S. aureus*. In children with liver abscess without cholangitis or pyelophlebitis, gram-positive infections are the commonest.

Invasive intestinal amebiasis can lead to **amebic liver abscess** although a history of amebic colitis in the preceding period is not common. Amebic liver abscess is usually solitary and in the right lobe of liver whereas pyogenic abscesses may be multiple (secondary to cholangitis) or single. Nearly three quarters of pyogenic liver abscesses are in the right lobe of liver.

Clinical features: The child presents with fever and right upper quadrant abdominal pain. Jaundice is uncommon.

Examination reveals tender hepatomegaly. Empyema, pneumonia, subphrenic abscess and cholecystitis can have a similar clinical presentation and should be differentiated. Complications include spontaneous rupture into peritoneum, pericardium, pleura or bronchial tree and metastatic spread to lungs or brain.

Diagnosis: Leukocytosis and elevated ESR are usually present. Transaminases and alkaline phosphatase are mildly elevated. X-ray abdomen shows an elevated right dome of diaphragm with or without pleural effusion. Diagnosis is confirmed by imaging; ultrasound provides good details about abscess size, number, rim and liquefaction. Contrast-enhanced CT scan may be required in patients with complications (Fig. 12.27). Amebic serology (indirect hemagglutination test) is positive in >95% children with amebic liver abscess and helps to differentiate it from pyogenic abscess. However, in the developing world, amebic serology may be positive due to prior intestinal amebiasis and thus a negative amebic serology helps exclude amebic liver abscess.

Management: Patients with pyogenic liver abscesses are treated with broad-spectrum antibiotics (against gram-positive—to cover for *Staphylococcus aureus*, gram-negative aerobic and anaerobic bacteria) for 4–6 weeks. Metronidazole is used for 10–14 days in patients with amebic liver abscess. Ultrasound-guided percutaneous needle aspiration and/or catheter drainage is required for abscesses that fail to improve after 3–4 days of antibiotic therapy, large abscess in left lobe and those with impending

rupture (narrow rim <1 cm). Surgery is required for abscesses complicated by frank intraperitoneal rupture or multiseptate abscesses not responding to percutaneous catheter drainage and antibiotics.

Prognosis: The abscess cavity takes 3–6 months to resolve completely. Cure rate following management with antibiotics and percutaneous drainage is excellent.

Liver Tumors

Liver tumors account for ~0.5–2% of all neoplasms in children. Hepatoblastoma, hemangioendothelioma and mesenchymal hamartoma are seen primarily in young children whereas hepatocellular carcinoma, undifferentiated embryonal sarcoma and focal nodular hyperplasia present in the older child. The most common tumors are hepatoblastoma, hepatocellular carcinoma and infantile hemangioendothelioma.

Infantile hepatic hemangioendothelioma is a benign tumor and presents mostly in first 6 months of life with an abdominal mass. Jaundice, skin hemangiomas and congestive heart failure may be associated. The lesion may be single or multiple and is made of thin vascular channels. Observation is recommended for focal lesions. Treatment options for multifocal and diffuse lesions include corticosteroids, propranolol, hepatic artery ligation with or without corticosteroids, hepatic artery embolization, surgical resection or liver transplantation.

Hepatoblastoma is the most common malignant liver tumor in children. It is of two types: Epithelial (fetal or embryonal malignant cells) and mixed (epithelial and mesenchymal elements) and presents with an abdominal mass and anorexia. Weight loss and pain in abdomen usually appear late; metastasis occurs to lungs and lymph nodes and alpha-fetoprotein is raised in the majority of cases. Ultrasound helps to differentiate between malignant and vascular lesions. CT and MRI are used to define tumor extent and resectability (Fig. 12.28). The survival of patients with a hepatoblastoma has markedly improved in recent years by combining surgery with pre- and postoperative chemotherapeutic agents such as cisplatin and doxorubicin. Liver transplantation is an option for unresectable hepatoblastoma following chemotherapy in absence of visible extrahepatic disease.

Hepatocellular carcinoma is usually multicentric. The risk is increased in patients with chronic hepatitis B or C infection, tyrosinemia, glycogen storage disease or prior androgen therapy. The tumor presents as a liver mass with abdominal distension, anorexia and weight loss. Liver functions are usually normal and anemia may be present; alpha-fetoprotein is raised. Imaging with CT/MRI helps in defining tumor extent, resectability and metastasis. Bone scan and CT chest should be done to screen for distant metastasis. Treatment options include surgical resection along with chemotherapy; chemoembolization and liver transplantation.



Fig. 12.27: Computed tomography scan shows a multi-lobulated liver abscess in the right lobe (black arrow) with elevated right dome of diaphragm and ascites. Percutaneous drainage catheter is seen *in situ* (white arrow)



Fig. 12.28: CECT showing a large hepatoblastoma

Suggested Reading

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Jaundice

The term jaundice means a yellow discoloration of skin, sclera and mucous membrane due to increase in the serum bilirubin levels. Nearly 250–300 mg of bilirubin is produced daily, approximately 70% from breakdown of old erythrocytes in reticuloendothelial system. Bilirubin is cleared by the liver in three steps. It is first transported into hepatocytes by specific carriers. Then it is conjugated to 1–2 molecules of glucuronide. Thereafter, the conjugated bilirubin moves to the canalicular membrane where it is excreted into the bile canaliculi by other carrier proteins. Most of the conjugated bilirubin is excreted in the stool and small amount is reabsorbed after deconjugation by colonic bacteria. Colonic bacteria also reduce bilirubin to urobilinogen, which is reabsorbed and excreted in urine.

Serum bilirubin should be >2.5–5 mg/dL for jaundice to be visible. Hyperbilirubinemia is classified as unconjugated (conjugated bilirubin fraction <15% of total bilirubin and normal colored urine) and conjugated hyperbilirubinemia (conjugated bilirubin fraction >20% with high colored urine). Conjugated bilirubin is cleared by kidneys; thus in renal failure, bilirubin levels are increased. Any abnormality of the above steps can cause jaundice (Table 12.24).

Congenital Enzyme Deficiencies

Gilbert syndrome is the most common cause of unconjugated hyperbilirubinemia and affects 3–8% of the

Table 12.24: Causes of jaundice in children

Unconjugated hyperbilirubinemia

Hemolysis: Blood group incompatibility (Rh, ABO), drugs, infection related, glucose-6-phosphate dehydrogenase deficiency, autoimmune hemolysis

Bilirubin overproduction: Ineffective erythropoiesis, large hematoma

Specific conditions in neonates: Physiologic jaundice, breast milk jaundice

Enzyme defects: Gilbert syndrome, Crigler-Najjar syndrome

Miscellaneous: Hypothyroidism, fasting

Conjugated hyperbilirubinemia

Neonatal cholestasis

Infections: Sepsis, acute viral hepatitis, enteric fever, malaria, leptospirosis

Chronic liver disease

Liver tumor: Primary, secondaries

Infiltration: Histiocytosis, leukemia

Enzyme defects: Dubin-Johnson syndrome, Rotor syndrome

Biliary: Choledochal cyst, choledocolithiasis, ascariasis, sclerosing cholangitis

Miscellaneous: Drug toxicity (hepatocellular, cholestatic), total parenteral nutrition, veno-occlusive disease

population. It results from a partial deficiency of the enzyme uridine diphosphate glucuronyl transferase (UDP-GT) and thus, impaired conjugation. Most patients are asymptomatic and exhibit chronic or recurrent jaundice (up to 6 mg/dL) precipitated by intercurrent illness, fasting or stress. Mild fatigue, nausea, anorexia or abdominal pain may be present in some patients. Other liver functions remain normal. No specific treatment is necessary for this disorder.

Crigler-Najjar syndrome (CN) type I is an autosomal recessive disorder characterized by absence of UDP-GT activity. Patients develop severe unconjugated hyperbilirubinemia and die by 18–24 months of age, if untreated. Phototherapy, plasmapheresis and exchange transfusion are required for managing these cases in initial phases. Serum bilirubin levels should be kept below 20 mg/dL during first several months of life to prevent brain damage. Definitive treatment is possible by liver transplantation, preferably auxiliary, if available.

Crigler-Najjar syndrome type II is also known as **Aria syndrome**. There is marked reduction of UDP-GT. In comparison to type I, jaundice is less severe and does not result in kernicterus. The condition responds to drugs like phenobarbitone that stimulate hyperplasia of the endoplasmic reticulum. The bilirubin level significantly decreases in type II CN following administration of phenobarbitone, while no change is seen in type I patients.

Dubin-Johnson syndrome is an autosomal recessive disorder resulting from impaired hepatic excretion of bilirubin and causes conjugated hyperbilirubinemia

(2–6 mg/dL). The transaminases and synthetic liver functions are normal. Most patients are asymptomatic apart from jaundice. Pregnancy and oral contraceptives may worsen jaundice. Liver biopsy is often done for exclusion of other causes and shows brown-black pigmentation.

Rotor syndrome is a rare, autosomal recessive disorder manifesting as mild conjugated hyperbilirubinemia. The primary defect appears to be a deficiency in the intracellular storage capacity of the liver for binding anions. The liver histology is normal.

ACUTE VIRAL HEPATITIS

Viruses can affect the liver, either primarily, e.g. hepatitis A, B, C, E or as part of a systemic involvement, e.g. cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes simplex virus (HSV). In Indian children, hepatitis A is the commonest cause (40–60%) of acute viral hepatitis, followed by hepatitis E (10–20%) and hepatitis B (7–17%). Nearly 8–20% patients have coinfection with more than one virus, HAV and HEV being the commonest. Hepatitis A and E are transmitted by feco-oral route whereas HBV and HCV are transmitted by parenteral or vertical (mother to baby) route (Table 12.25) (see also Chapter 11).

Clinical Features

Following exposure, patients show a prodrome characterized by low grade fever, malaise, anorexia and vomiting, followed by appearance of jaundice. Examination shows icterus, hepatomegaly and splenomegaly (small, soft in 15–20%). Mild ascites may be present in 10–15% cases, which resolves completely on follow-up. Over the next few weeks, the appetite improves, jaundice resolves and the child gets better. In young children, asymptomatic and anicteric presentation of hepatitis A infection can occur.

Differential Diagnosis

The conditions, which mimic the clinical features of viral hepatitis include enteric fever, falciparum malaria,

leptospirosis and viral hemorrhagic fever. Other conditions that need to be differentiated include drug-induced hepatitis, acute presentation of autoimmune liver disease or Wilson disease.

Investigations

Direct hyperbilirubinemia with markedly elevated ALT/AST and normal albumin and prothrombin time are usual. Mild leukopenia with relative lymphocytosis is seen. Ultrasound is not routinely required, but shows mildly enlarged liver with increased echogenicity and edema of gallbladder wall. Viral serologies help determine the etiology of acute viral hepatitis, as shown in Table 12.25.

Complications

These include:

- i. *Acute liver failure.* The appearance of irritability, altered sleep pattern, persistent anorexia and uncorrectable coagulopathy (despite administration of vitamin K) suggests the development of acute liver failure.
- ii. Aplastic anemia
- iii. Pancreatitis
- iv. Serum sickness, vasculitis-like reaction may be seen in hepatitis B infection
- v. Hemolysis (cola-colored urine) with renal failure in subjects with glucose-6-phosphate dehydrogenase deficiency
- vi. *Chronic liver disease:* In patients with acute viral hepatitis due to HBV, repeat testing for hepatitis B surface antigen should be done after 6 months to document clearance or persistence of infection. A majority (95%) clear hepatitis B infection after acute icteric infection.

Management

Maintaining adequate oral intake is essential and intravenous fluids are given, if persistent vomiting and dehydration are present. There is no advantage of enforced bed rest, but vigorous activity should be avoided. No specific dietary modification is recommended. The child

Table 12.25: Epidemiological profile of different hepatitis viruses

Virus	A	B	C	E
Type of virus	RNA	DNA	RNA	RNA
Incubation period, days	15–40	50–150	30–150	15–45
<i>Route of Infection</i>				
Feco-oral	+	–	–	+
Parenteral	Rare	Yes	Yes	–
Others		Perinatal by sexual contact	Perinatal sexual contact	–
Chronic liver disease	–	+	+	–
Vaccine	Available	Available	No	No (being developed)
Diagnostic test	IgM; anti-HAV	HBsAg; IgM anti-HBc	Anti-HCV antibody; HCV RN	IgM anti-HEV

should be monitored for appearance of complications like encephalopathy.

Prevention

Public health measures like sanitation, safe drinking water supply, handwashing and proper food hygiene are of utmost importance, especially in epidemics of hepatitis A or E. Proper screening of blood and blood products and safe injection practices are essential. Universal immunization for hepatitis B is the most effective way of preventing hepatitis B related disease.

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LIVER FAILURE

Liver failure refers to a clinical state resulting from hepatocyte dysfunction or necrosis and not a specific disease etiology. It may occur *de novo* in normal children without any evidence of pre-existing liver disease where it is known as acute liver failure (ALF).

Acute liver failure: An international normalized ratio ≥ 1.5 with hepatic encephalopathy or an international normalized ratio ≥ 2 without hepatic encephalopathy along with biochemical evidence of liver injury in the absence of underlying chronic liver disease is considered as acute liver failure. The presence of hepatic encephalopathy is not essential for diagnosis of ALF in children. All international normalized prothrombin values refer to that measured after 8 hours of parenteral vitamin K administration. This definition has evolved with the understanding that detection of mild grades of hepatic encephalopathy in small children is difficult and any behavioral change or irritability in this age group may not be necessarily due to hepatic encephalopathy.

Patients with chronic liver disease may manifest with features of hepatocellular failure due to progressive worsening of liver function as part of the natural course of the disease or as a sudden dysfunction due to a superimposed hepatic insult resulting in *acute on chronic liver failure (ACLF)*. Superimposed insult can be due to hepatotropic virus (hepatitis A, E, B) infection, hepatotoxic drug intake or sepsis and varies with the geographical area.

ALF in children is a condition associated with high mortality and the etiology varies among different age groups (Table 12.26). Autoimmune liver disease and Wilson disease are two important causes of chronic liver disease in children which may have an acute presentation mimicking ALF. Drugs, especially antitubercular agents (isoniazid, rifampicin, pyrazinamide) and anticonvulsants are a major cause of ALF. In the West, paracetamol poisoning is a common cause of ALF. Herbal medicines and mushroom poisoning are also known to cause ALF. In the neonatal period, liver failure may be a result of metabolic conditions (neonatal hemochromatosis, galactosemia, hereditary fructose intolerance, tyrosinemia type 1, Niemann-Pick disease), infections and hematological conditions like hemophagocytic lymphohistiocytosis. A careful history and rapid investigations are necessary to identify the etiology, which has prognostic and therapeutic implications. However, 30–40% cases are idiopathic.

Clinical Features

The early clinical manifestations of ALF are nonspecific and characterized by lethargy, anorexia, malaise, nausea and vomiting. Central nervous system manifestations include hepatic encephalopathy and cerebral edema with raised intracranial tension. Hepatic encephalopathy is a result of inability of the liver to process and excrete endogenous toxins. Raised levels of ammonia, GABA, false neurotransmitters and proinflammatory cytokines are implicated in its pathogenesis. Hepatic encephalopathy is classified into four stages (Table 12.27). Identification of hepatic encephalopathy in children can

Table 12.26: Causes of acute liver failure in children

Infections	Common: Viral hepatitis (A, B, E) Uncommon: Adenovirus, Epstein-Barr, parvovirus, cytomegalovirus, echovirus, varicella, dengue, herpes simplex virus I and II*
Others	Septicemia*, malaria, leptospirosis
Drugs	Isoniazid with rifampicin, pyrazinamide, acetaminophen, sodium valproate, carbamazepine, ketoconazole
Toxins	Herbal medicines, <i>Amanita phalloides</i> poisoning, carbon tetrachloride
Metabolic	Wilson disease, galactosemia*, tyrosinemia*, hereditary fructose intolerance*, hemochromatosis*, Niemann-Pick disease type C*, mitochondrial cytopathies*, congenital disorder of glycosylation
Autoimmune	Autoimmune liver disease
Vascular	Acute Budd-Chiari syndrome, acute circulatory failure
Infiltrative	Leukemia, lymphoma, histiocytosis*
Idiopathic	

* More common in neonates and infants

Table 12.27: Stages of hepatic encephalopathy in children

Stage	Features	Reflexes
I	Inconsolable crying, inattention to task, not acting like self, disturbed sleep-wake cycle	Normal or hyper-reflexic; asterixis absent
II	Same as in stage I	Normal or hyper-reflexic; asterixis easily elicited
III	Somnolence, stupor, combative	Hyper-reflexic; asterixis present
IV	Comatose, responsive to pain (IVA) or non-responsive to pain (IVB)	Decerebrate or decorticate; asterixis absent

be challenging as in the early stages they present with non-specific findings such as excessive somnolence, reversal of sleep-wake cycle or behavioral and personality changes.

Coagulopathy due to impaired production of coagulation factors results in bleeding. Platelet counts are affected in the setting of infection. The patient may manifest with hypoglycemia, electrolyte imbalance and metabolic acidosis. Infections are common in ALF as the immune system is dysfunctional and invasive procedures are performed commonly. This results in gram-positive, gram-negative and fungal infections. Infection may manifest as hypotension, disseminated intravascular coagulation, worsening metabolic acidosis, worsening encephalopathy, oliguria and azotemia.

Investigations for specific causes, if suspected, are important as specific treatment is needed in these cases (Table 12.28).

Table 12.28: Investigations for cause of acute liver failure

Infectious	IgM anti-HAV (hepatitis A virus)	
	IgM anti-HEV (hepatitis E virus)	
	Hepatitis B surface antigen, IgM core antibody	
	Cytomegalovirus PCR	
	IgM varicella zoster virus, EBV viral capsid antigen	
Metabolic		
	Wilson disease	Ceruloplasmin, Kayser-Fleischer ring, 24 hour urinary copper
	Tyrosinemia	Urinary succinylacetone level
Galactosemia	Urine nonglucose reducing substances, galactose-1-phosphate uridytransferase level	
Autoimmune hepatitis	Anti-liver kidney microsomal antibody; antinuclear antibody; anti-smooth muscle antibody; immunoglobulin levels	
Miscellaneous		
	Hemophagocytosis	Triglyceride, ferritin, fibrinogen and bone marrow biopsy
	Paracetamol poisoning	Plasma levels of paracetamol

Management

The management of liver failure in children is based on: (i) diagnosis of etiology as it influences the prognosis and management; (ii) assessment of severity of liver failure and timely liver transplantation, if indicated; and (iii) anticipation, prevention and treatment of complications. Patients should be treated and monitored closely in an intensive care unit (Table 12.29). Elective intubation and ventilation is beneficial in subjects with stage 3 hepatic encephalopathy or more. The hemodynamics need to be assessed and supported.

Raised intracranial pressure is managed with mannitol 20% (0.5 to 1 g/kg with target osmolality not crossing 320 mOsm/kg) or hypertonic saline (3% to 30%). The target serum sodium should be 145–155 mEq/L to maintain hypertonicity. The head end is kept at 30° elevation in neutral position. Hyperventilation to decrease cerebral edema should be transient. Monitoring intracranial pressure has not been convincingly shown to improve outcomes. Lactulose has not been shown to improve hepatic encephalopathy and outcome. Bowel decontamination by oral nonabsorbable antimicrobials (to decrease ammonia load and to decrease infections) has been tried in ALF but does not alter the survival. Recently it has been shown that N-acetylcysteine does not improve 1-year survival in non-acetaminophen ALF in children. Phenytoin may be used for treating seizures. Normal maintenance intravenous fluids containing dextrose are given and blood glucose is monitored to prevent and treat hypoglycemia. Electrolyte imbalances should be identified and treated early.

Prophylactic antimicrobial regimens do not improve outcome or survival in patients with ALF. Empirical antibiotics are recommended in circumstances with high-risk of sepsis, i.e. surveillance cultures reveal significant isolates, advanced hepatic encephalopathy, refractory hypotension, renal failure or presence of systemic inflammatory response syndrome (temperature >38°C or <36°C, leukocyte count >12,000 or <4,000/mm³, tachycardia). Antibiotic therapy is recommended for

Table 12.29: Monitoring of children with acute liver failure

Pulse rate, respiratory rate, blood pressure, temperature (q 4 hr)
Intake-output charting (q 6 hr)
Liver span, neurological monitoring, grading of coma (q 12 hr)
Blood sugar, electrolytes, pH, bicarbonate, lactate (q 6–12 hr)
Prothrombin time (INR) (daily)
Complete blood counts, CRP (twice a week)
Transaminases, GGTP, alkaline phosphatase, lactate dehydrogenase, total and conjugated bilirubin (twice a week)
Creatinine, calcium, phosphate (twice a week)
Monitor as needed: Evidence of infection on chest X-ray, blood and urine cultures; blood ammonia

Table 12.30: Specific treatment of conditions causing pediatric acute liver failure

Neonatal hemochromatosis	Antioxidants; chelation; prenatal intravenous immunoglobulin in combination with postnatal exchange transfusion
Tyrosinemia	Nitisinone (NTBC); restriction of phenylalanine and tyrosine in diet
Galactosemia	Galactose and lactose free diet
Hereditary fructose intolerance	Fructose free diet
Mitochondrial cytopathies	Coenzyme Q10, vitamin E, carnitine
Amanita poisoning	Penicillin G, silibinin and N-acetylcysteine
Herpes simplex	High dose acyclovir (60 mg/kg/day) for 21 days
Acetaminophen poisoning	N-acetyl-cysteine (see Chapter 27)

patients listed for transplantation. Antimicrobials with coverage against gram-positive and gram-negative organisms (cefotaxime with cloxacillin) along with antifungals are used. Aminoglycosides are avoided to prevent renal dysfunction. Close monitoring and early detection of infection is essential. Coagulopathy does not necessarily warrant transfusion of fresh frozen plasma unless bleeding manifestations are clinically evident or an invasive intervention is planned or INR is >7. Proton pump inhibitors are used for stress ulcer prophylaxis.

In spite of adequate supportive care, the mortality in ALF is as high as 60–70%. Early identification of children who would benefit only from liver transplantation is essential. The King's College criteria are one of the commonly used criteria to identify adult patients requiring liver transplantation. Application of these criteria in developing countries seems to be limited due to variation in etiology other than paracetamol induced liver failure. Young age (≤ 3.5 years), bilirubin ≥ 16.7 mg/dL, prolonged prothrombin time (>40 seconds) and signs of cerebral edema predicted mortality in an Indian study. Table 12.30 lists the specific therapy for common etiologies of ALF.

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CHRONIC LIVER DISEASE

Chronic liver disease (CLD) refers to a spectrum of disorders characterized by ongoing chronic liver damage and a potential to progress to cirrhosis or end stage liver disease. Although a 6-month duration cut off is used for defining chronicity related to hepatitis B and C, it does not apply to the other causes as irreversible liver damage may have already taken place before symptoms of liver disease are recognized.

Cirrhosis is a diffuse liver process characterized by cell injury (necrosis) in response to inflammation/injury and fibrosis and regeneration (nodule formation). When the disease is silent, the patient may have hepatosplenomegaly and abnormal liver function tests and it is termed as compensated cirrhosis. When the patient develops jaundice, gastrointestinal bleed, ascites and/or hepatic encephalopathy, it is known as decompensated cirrhosis.

Etiology

The main causes of CLD in children are listed in Table 12.31. In India, ~25% of CLD is due to metabolic causes (Wilson disease being the commonest), 8–15% are due to hepatitis B and 2–4% due to autoimmune causes. Nearly 40% patients do not have a known etiology, and are labeled cryptogenic.

Clinical Features

The presentation depends on the etiology and pace of disease progression. Patients may present with insidious onset disease with failure to thrive, anorexia, muscle weakness and/or jaundice or abruptly with massive gastrointestinal bleed, acute onset jaundice, along with

Table 12.31: Causes of chronic liver disease

Viral hepatitis	Hepatitis B (common), hepatitis C (uncommon)
Autoimmune liver disease	Autoimmune hepatitis (common), autoimmune sclerosing cholangitis
Metabolic	Wilson disease, glycogen storage disease (IV)*, progressive familial intrahepatic cholestasis*, galactosemia*, NASH related, tyrosinemia*, Indian childhood cirrhosis* (rare), cystic fibrosis, hereditary fructose intolerance*, alpha-1-antitrypsin deficiency, bile acid synthetic defects
Venous obstruction	Budd-Chiari syndrome, veno-occlusive disease, constrictive pericarditis, congestive heart failure
Biliary	Biliary atresia*, choledochal cyst*, primary sclerosing cholangitis, Caroli disease, Alagille syndrome
Rare causes	Niemann-Pick disease, Gaucher disease; drug induced (valproate, carbamazepine)

NASH: Nonalcoholic steatohepatitis

*Causes in infants and young children <5 yr of age

altered sensorium and ascites. Sometimes the patient may be asymptomatic and child is noticed to have hepatosplenomegaly or elevated transaminases on investigations for some unrelated illness. Clinical features on examination that suggest presence of CLD are:

Characteristics of liver: The liver may be firm to hard, nodular or have irregular margins in cirrhosis. Differential left lobe enlargement is a feature of CLD. A small, non-palpable shrunken liver is a feature of post-necrotic cirrhosis.

Stigmata of CLD: These include spider angiomas, palmar erythema, clubbing, leukonychia, muscle wasting, delayed puberty and gynecomastia. Testicular atrophy and parotid enlargement are present in adults with alcoholic liver disease, but not in children.

Portal hypertension: Splenomegaly, ascites, tortuous veins over abdominal wall with flow away from umbilicus, i.e. caput medusae; esophageal varices with/without gastric varices on endoscopy.

Features of hepatic encephalopathy: Asterixis, constructional apraxia or altered sensorium (Table 12.27) may be seen.

Evaluation

Evaluation of patients with suspected CLD is two-pronged: (i) determine etiology of CLD and (ii) assess degree of liver dysfunction and presence of complications (Table 12.32). Based on clinical and laboratory features, liver damage is graded using scores like the CHILD score and pediatric end stage liver disease (PELD) score. Complications of CLD are: (i) hepatic encephalopathy; (ii) portal hypertension with variceal bleeding, portopulmonary hypertension and hepatopulmonary syndrome; (iii) ascites and spontaneous bacterial peritonitis; (iv) hepatorenal syndrome; (v) coagulopathy; (vi) nutrition failure; (vii) increased risk of infections; and (viii) hepatocellular carcinoma.

Hepatic Encephalopathy

Hepatic encephalopathy refers to neuropsychiatric abnormalities that result from liver dysfunction. It is a principal manifestations of CLD and can be graded (Table 12.27). Various factors like gastrointestinal bleed, infection, use of sedatives, dehydration due to aggressive diuresis, constipation and electrolyte imbalance can precipitate encephalopathy. Identification and reversal of the precipitating event is of importance. As ammonia is an important putative metabolite, efforts are targeted towards reducing its production and absorption and facilitating its excretion. Oral antibiotics and synthetic disaccharides have been shown to be effective in minimizing ammonia production in these patients. Neomycin was used in the past but it has serious side effects of deafness and renal toxicity. Rifaximin is a new drug with a better safety profile. Nonabsorbable

Table 12.32: Investigations for chronic liver disease

Common Investigations

Liver function tests	Low albumin, reversal of albumin-globulin ratio and prolonged prothrombin time High conjugated bilirubin suggests liver dysfunction or obstruction Raised transaminases suggest hepatocellular injury; raised alkaline phosphatase and gamma glutamyl transpeptidase suggest biliary disease
Ultrasonography	Nodular liver, mass lesion, dilated portal vein and collaterals, ascites, splenomegaly
Upper GI endoscopy	Portal hypertension: Esophageal or gastric varices
Liver biopsy	Breaking of lamina limitans and lobular inflammation; nodule formation and loss of architecture in cirrhosis; may also aid in diagnosis of specific diseases

Specific to etiology

Viral markers	HBsAg, HBeAg, anti-HBe, anti-HCV, HBV DNA, HCV RNA
Autoimmune hepatitis	Anti-smooth muscle, anti-liver kidney microsomal, antinuclear antibodies
Wilson disease	Ceruloplasmin, Kayser-Fleischer ring; 24 hours urine copper; liver copper
Alpha-1-antitrypsin deficiency	Serum alpha-1-antitrypsin levels; PI type
Galactosemia	Positive nonglucose reducing substances in urine; galactose-1-phosphate uridylyltransferase assay
Cystic fibrosis	Sweat chloride test; genetic analysis
Tyrosinemia	Urinary succinylacetone level
Budd-Chiari syndrome	Doppler ultrasonography for hepatic vein, inferior vena cava
Sclerosing cholangitis	Magnetic resonance cholangiopancreatography; liver biopsy
Storage disorders	Bone marrow, fundus examination; liver biopsy

disaccharides like lactulose and lactitol reach the colon intact and then are metabolized by bacteria into variety of small molecular weight organic acids. It acts by acidifying fecal contents and trapping the diffusible ammonia as ammonium ion in the fecal stream along with alteration in colonic flora (loss of ammonia producing bacteria). In infants and children, protein intake should not be restricted to the point of causing growth failure or compromising overall nutritional status and a target range of 1–2 g/kg/day is often recommended. Vegetable proteins, which are rich in branched chain amino acids are preferred over animal proteins.

Nutrition Failure

Children with end-stage liver disease are at risk for developing nutritional compromise, which increases the disease related morbidity. The etiology of failure to gain weight in children with end-stage liver disease is multifactorial, due to a combination of decreased caloric intake, increased energy expenditure, malabsorption of macro- and micronutrients and altered physiologic anabolic signals. Children with CLD also have reduced levels of liver-derived insulin-like growth factor 1, which mediates the anabolic action of growth hormone and thus a growth hormone-resistant state that negatively impacts growth.

Clinical recognition of malnutrition in infants and children with end-stage liver disease relies on careful monitoring for clinical features like growth failure, loss of muscle mass, delayed motor development or signs of fat-soluble vitamin or essential fatty acid deficiencies (skin rash, peripheral neuropathy, rickets/fractures or bruising). The presence of ascites, edema and organomegaly makes weight an unreliable indicator of nutrition in a child with CLD. So height monitoring, along with assessment of other anthropometric markers of body fat and muscle mass like triceps skin fold and mid-arm circumference should be used.

All patients need increased caloric intake ~120–150% of their estimated daily requirements. Formulas containing medium-chain triglycerides are used to maximize fat absorption in the setting of severe cholestasis. Daily supplements of vitamins and other nutrients like calcium and iron need to be given. For patients who cannot meet the needs by oral feeding, nasogastric tube feedings should be started.

Patients with CLD are especially vulnerable to viral and bacterial infections. Careful attention must be given to ensure that all infants and children with CLD receive all recommended routine childhood vaccinations.

Hepatorenal Syndrome

Hepatorenal syndrome is a functional renal impairment as changes are reversible after liver transplant. It is defined as progressive renal insufficiency in absence of other known causes (prerenal, nephrotoxic drugs) of renal failure in patients with severe liver disease.

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ASCITES

Ascites is the pathologic accumulation of fluid within the peritoneal cavity and it can occur at any age and also *in utero*. The main causes of ascites are given in Table 12.33. Sometimes a large intra-abdominal cyst, i.e. cystic lymphangioma, omental or ovarian cyst can masquerade as ascites; this is known as pseudoascites.

Evaluation: History and examination, imaging studies and paracentesis are required for ascertaining the etiology. Patients present with increased abdominal girth and weight gain. Physical examination reveals abdominal distension, bulging flanks, shifting dullness, fluid thrill and puddle sign. The liver and spleen may be difficult to palpate in patients with tense ascites. Dilated abdominal collaterals and caput medusae may be seen in ascites due to liver disease, while collaterals in flanks and on the back suggest inferior vena cava block. Elevated jugular venous pressure suggests a cardiac origin, e.g. constrictive pericarditis.

Ultrasound is a sensitive imaging technique for the detection of ascites. Free fluid layers in the dependent regions, i.e. the hepatorenal recess (Morrison pouch) and the pelvic cul-de-sac which is detected on ultrasound. Abdominal paracentesis is a simple test for determining the etiology. Diagnostic paracentesis should be done when ascites is first detected, at the time of hospitalization, or when there is clinical deterioration with unexplained fever, abdominal pain or diarrhea. Ultrasound-guided tap is warranted in children with loculated ascites.

Investigations: Ascitic fluid should be evaluated for total and differential cell count, albumin level and culture. Serum albumin is done to calculate the serum ascites albumin gradient (SAAG), i.e. the concentration of albumin in serum minus its concentration in ascitic fluid.

Table 12.33: Causes of ascites

Common

Cirrhosis and portal hypertension
Budd-Chiari syndrome
Nephrotic syndrome
Protein losing enteropathy
Tubercular ascites
Constrictive pericarditis
Cardiac failure

Chylous: Lymphatic obstruction, thoracic duct injury, intestinal lymphangiectasia

Uncommon

Pancreatic: Pancreatitis, pancreatic duct injury

Urinary: Obstructive uropathy, bladder rupture

Hepatobiliary: Bile duct perforation, veno-occlusive disease

Serositis: SLE, eosinophilic enteropathy

Infections: Parvovirus, syphilis, cytomegalovirus

Others: Intestinal perforation, peritoneal dialysis, ventriculo-peritoneal shunt, epidemic dropsy

High gradient ascites (SAAG ≥ 1.1 g/dL) suggests portal hypertension and is seen in cirrhosis, fulminant hepatic failure, Budd-Chiari syndrome and portal vein thrombosis.

Low gradient ascites (SAAG < 1.1 g/dL) occurs in absence of portal hypertension in conditions such as peritoneal carcinomatosis, tuberculous peritonitis, pancreatic ascites, biliary leak ascites, nephrotic syndrome and serositis.

Elevated ascitic fluid level of amylase indicates pancreatitis or intestinal perforation. Polymicrobial infection is consistent with intestinal perforation, whereas monomicrobial infection suggests spontaneous bacterial peritonitis. Uroascites is present when the concentration of urea and creatinine are higher in the ascitic fluid than in serum. In biliary ascites, the ascitic fluid bilirubin is > 6 mg/dL and in chylous ascites the ascitic fluid is milky in appearance and has a triglyceride concentration of > 200 mg/dL.

Treatment

Small amounts of ascitic fluid that do not produce symptoms or clinical sequelae may require little or no treatment. Tense ascites causing respiratory compromise, severe pain, or other major clinical problems should be treated promptly. Treatment largely depends upon the cause, e.g. antitubercular therapy for tubercular ascites, diuretics for chronic liver disease and surgery for bile duct or bowel perforation.

Ascites with Liver Disease

In liver disease, ascites represents a state of excess total body sodium and water. The main postulated pathogenetic mechanisms include: (i) *Underfill theory*: Primarily, there is inappropriate sequestration of fluid within the splanchnic vascular bed as a consequence of portal hypertension that produces decrease in effective circulating blood volume. This activates the plasma renin, aldosterone and sympathetic nervous system, resulting in renal sodium and water retention. (ii) *Overflow theory*: Primary abnormality is inappropriate renal retention of sodium and water in the absence of volume depletion. Basis of this theory is that patients with cirrhosis have intravascular hypervolemia rather than hypovolemia. (iii) *Peripheral arterial vasodilation*: The chief cause of ascites is splanchnic vasodilation, which leads to decrease in effective arterial blood volume. Progressive deterioration of liver functions, portal hypertension, splanchnic arterial vasodilatation and reduced plasma oncotic pressure due to low serum albumin contribute to development of ascites.

Management: For patients with ascites related to liver disease, mobilization of ascitic fluid is accomplished by creating a negative sodium balance until ascites has diminished or resolved; then the sodium balance is maintained so that ascites does not recur. Oral diuretic therapy consists of single morning dose of spironolactone (0.5–3 mg/kg) along with furosemide (0.5–2 mg/kg), that

facilitates maintenance of normokalemia. If weight loss and decrease in abdominal girth are inadequate, the doses of both spironolactone and furosemide should be increased simultaneously. Along with diuretic therapy, patients should be on a sodium restricted diet. One gram of table salt contains 17 mEq of sodium and one gram of sodium approximates 44 mEq of sodium. Restriction of sodium in diet is limited to 1–2 mEq/kg/day for infants and children and 1 to 2 g/day (44 to 88 mEq of sodium/day) in adolescents.

If the ascites is massive or the patient is having respiratory discomfort, large volume paracentesis should be done preferably under cover of albumin infusion. Patients who are resistant to above therapy can be treated with transjugular intrahepatic portosystemic shunting (TIPS) as a temporary measure till orthotopic liver transplantation is done.

Spontaneous Bacterial Peritonitis (SBP)

This refers to bacterial peritonitis not associated with gut perforation or any other secondary cause. Presence of ≥ 250 polymorphonuclear cells/mm³ with a positive culture of ascitic fluid is diagnostic of SBP. The other variants of ascitic fluid infection (AFI) in patients with liver disease are culture negative neutrocytic ascites (≥ 250 polymorphonuclear cells/mm³ with negative culture) and monomicrobial non-neutrocytic ascites (< 250 polymorphonuclear cells/mm³ with positive culture). Patients present with rapid onset abdominal distension, fever, malaise and abdominal pain with tenderness on abdominal examination. However, symptoms may be absent in 30–40% cases with SBP and so patients with new onset ascites and those with unexplained clinical deterioration should be subjected to diagnostic abdominal paracentesis to look for AFI. Third generation cephalosporins, for a total of 5 to 7 days, are recommended for treatment. Long-term administration of oral norfloxacin 5–7.5 mg/kg once a day in patients with cirrhosis and ascitic protein content of < 1 g/dL or prior episode of SBP is recommended. Despite advances in supportive care, bacterial peritonitis is an indicator of poor prognosis.

PORTAL HYPERTENSION

The portal vein is formed by the splenic and the superior mesenteric veins. Normal portal pressure is between 5 and 10 mm Hg and portal hypertension is an increase in portal pressure of > 12 mm Hg. It is a common clinical situation in children and occurs due to increased portal resistance and/or increased portal blood flow. The presence of esophageal varices on endoscopy is the most definite evidence of portal hypertension. The causes of portal hypertension may be either intrahepatic or extrahepatic (prehepatic and posthepatic) (Table 12.34).

The spectrum of portal hypertension in children from developed vs. developing world is different. In the former,

Table 12.34: Causes of portal hypertension

Prehepatic	Portal venous thrombosis, extrahepatic portal venous obstruction (cavernous transformation of portal vein), isolated splenic vein thrombosis
Intrahepatic	Liver cirrhosis (common), congenital hepatic fibrosis, veno-occlusive disease, noncirrhotic portal fibrosis, schistosomiasis, nodular regenerative hyperplasia
Posthepatic	Budd-Chiari syndrome (hepatic vein or inferior vena cava obstruction), constrictive pericarditis

intrahepatic causes of portal hypertension are most common whereas in India, extrahepatic portal venous obstruction (EHPVO) is the commonest cause (50–75%) followed by cirrhosis (25–35%); uncommon causes are congenital hepatic fibrosis, non-cirrhotic portal fibrosis and Budd-Chiari syndrome. Portal hypertension results in development of portosystemic venous channels at different sites giving rise to esophageal, gastric or colonic varices. The main pointers which help in differentiating portal hypertension due to cirrhosis from that due to non-cirrhotic causes are shown in Table 12.35.

Clinical Features

The age of presentation ranges from infants to adults. A majority of patients with EHPVO present with upper gastrointestinal bleeding and splenomegaly. Hematemesis and melena occur due to esophageal or gastric variceal bleeding. The bleed may be recurrent and is well tolerated without development of post-bleed hepatic encephalopathy. Splenomegaly alone is the presentation in 10–20% cases.

Patients with portal hypertension due to cirrhosis have jaundice, ascites, hepatosplenomegaly and less often, upper gastrointestinal bleeding. In Budd-Chiari syndrome, patients present with ascites and hepatomegaly. Tortuous prominent back veins are seen in Budd-Chiari syndrome with inferior vena cava block.

Investigations

The diagnosis of portal hypertension is made by the following investigations:

- i. Ultrasound and Doppler study. The vascular anatomy is defined and any block in portal, splenic or hepatic veins can be detected. Increased size of portal vein is suggestive of intrahepatic portal hypertension. Presence of collaterals, ascites, splenomegaly and liver abnormalities (altered echotexture, size and space occupying lesions) are also seen.
- ii. Endoscopy can reveal varices in esophagus, stomach and congestive gastropathy.
- iii. Colonoscopy is useful in children with lower GI bleeding as it can show presence of rectal varices or colopathy.
- iv. Selective CT and MR portovenography are useful for delineation of vascular anatomy.
- v. Liver function tests are deranged in subjects with cirrhosis. Hemogram may show anemia, leukopenia and thrombocytopenia that suggests hypersplenism.

Complications

The most common complication is GI bleeding secondary to esophageal varices. Hypersplenism usually is not symptomatic. The enlarged spleen is prone to splenic infarcts and accidental rupture with trauma. Other complications like ascites and hepatic encephalopathy occur frequently in children with cirrhosis.

Hepatopulmonary syndrome: The triad of chronic liver disease or portal hypertension, alteration of arterial oxygenation (defined as widened age corrected alveolar arterial oxygen gradient with or without arterial hypoxemia) and evidence of intrapulmonary vascular dilatations defines hepatopulmonary syndrome. Patients with hepatopulmonary syndrome present with dyspnea, platypnea (dyspnea induced in upright position and relieved by recumbency) and orthodeoxia (arterial deoxygenation accentuated in upright position and relieved by recumbency). Examination shows clubbing and cyanosis.

Table 12.35: Differences between cirrhotic and non-cirrhotic portal hypertension

Features	Cirrhotic	Non-cirrhotic
History of jaundice, edema and ascites	Common	Uncommon. Transient ascites may be seen after variceal bleed
Overt hepatic encephalopathy	Common	Not seen
Stigmata of liver disease, e.g. spider angioma, palmar erythema, gynecomastia, etc.	May be seen	Not seen
Splenomegaly	Mild-moderate	Mild-moderate-massive splenomegaly
Synthetic function of liver (prothrombin time/serum albumin)	Deranged	Well preserved
Transaminases (SGOT/SGPT)	Deranged frequently (except in burnt out liver disease)	Usually normal

Contrast echocardiography is the most sensitive test to demonstrate intrapulmonary shunting. The only established effective therapy is liver transplantation.

Portopulmonary syndrome: This is defined as pulmonary arterial hypertension (pulmonary artery pressure >25 mm Hg) associated with severe portal hypertension. Most patients of portopulmonary syndrome have underlying cirrhosis but it can also develop in non-cirrhotic portal hypertension. Symptoms include dyspnea and syncope; echocardiography is required for diagnosis.

Management

This is based on two goals: (i) management of complications like upper gastrointestinal bleeding and ascites, discussed elsewhere in the chapter; and (ii) definitive management that depends on the etiology of portal hypertension. The prognosis is better for children with EHPVO than those with cirrhosis where liver transplantation is the ultimate therapy.

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Extrahepatic Portal Venous Obstruction (EHPVO)

It is the commonest cause of portal hypertension in children in India. It is characterized by obstruction of the main portal vein (PV) with or without involvement of the superior mesenteric vein and splenic vein and with variable involvement of the intrahepatic branches of the PV. The main PV is replaced by a cavernoma that shunts blood across the obstruction along with portosystemic collaterals. Umbilical catheterization/sepsis, pyelophlebitis, procoagulant disorders have been implicated as etiology. However, in vast majority of cases, no cause is identified. These children present with splenomegaly or hematemesis due to variceal bleed. Caput medusa is characteristically absent in these patients as the main PV is thrombosed. With improved endoscopic management, the survival of these children has improved and the long-term complications have become evident. These include poor growth, hypersplenism, portal hypertensive gastropathy/colopathy/enteropathy, rectal varices, ectopic varices, portal biliopathy (compression of biliary system by collaterals) and minimal hepatic encephalopathy due to shunting of blood away from the liver. Meso Rex bypass (shunt across the obstruction from superior mesenteric vein to the left branch of portal vein) can restore the portal flow and alleviate all complications of EHPVO.

Budd-Chiari Syndrome

Budd-Chiari syndrome is caused by the occlusion of the hepatic veins and/or the suprahepatic inferior vena cava. Right heart failure and sinusoidal obstruction syndrome (formerly known as veno-occlusive disease) impair hepatic venous outflow and share features with Budd-Chiari syndrome, but are grouped separately as its etiology and treatment is different. Budd-Chiari syndrome is considered *primary* when obstruction of the hepatic venous outflow tract is result of an endoluminal venous lesion (thrombosis or web). It is considered *secondary* when the obstruction originates from a lesion outside the venous system (tumor, abscess, cysts). The lesion can obstruct outflow by invading the lumen or by extrinsic compression.

The majority of patients with Budd-Chiari syndrome are primary and present with a chronic course; only a small number of patients present with acute or fulminant forms. Acute disorder presents clinically with abdominal pain, ascites, hepatomegaly and rapidly progressive hepatic failure. The chronic form is characterized by hepatomegaly abdominal distension and portal hypertension. In inferior vena cava block, the back veins become prominent, dilated and tortuous with flow from below upwards (Fig. 12.29).

Doppler ultrasound and venography confirm the diagnosis. Investigations should be done to look for presence of hypercoagulable states. Treatment is directed towards restoring the patency of hepatic vein/inferior vena cava by radiological means (angioplasty, stenting or transjugular intrahepatic portosystemic shunt) or surgery (mesoatrial shunt, mesocaval shunt). Orthotopic liver transplant is reserved for patients with end stage liver disease or fulminant failure.



Fig. 12.29: Prominent and tortuous abdominal and flank veins in a child with Budd-Chiari syndrome

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AUTOIMMUNE LIVER DISEASE

Autoimmune liver disease is characterized by hypergammaglobulinemia, presence of circulating autoantibodies, necroinflammatory histology (interface hepatitis, portal lymphoplasmacytic cell infiltration) on biopsy and response to immunosuppressive agents. The condition is common in girls. In children, autoimmune liver disease consists of autoimmune hepatitis, autoimmune sclerosing cholangitis and *de novo* autoimmune hepatitis after liver transplantation. The following two types of autoimmune hepatitis are recognized:

Type 1: Presence of antinuclear antibody and/or anti-smooth muscle antibody; constitutes 60–70% cases.

Type 2: Presence of anti-liver kidney microsomal antibody (LKM); accounts for 20–30% cases.

Clinical Presentation

Children can present in one of the following ways:

- Acute viral hepatitis like presentation (40%) with malaise, nausea, vomiting and jaundice. It may progress to acute hepatic failure particularly in children with type II disease.
- Insidious onset liver disease (30–40%) with progressive fatigue, relapsing or prolonged jaundice lasting for months to years.
- Chronic liver disease and its complications (10–20%) with splenomegaly, ascites, variceal bleeding or hepatic encephalopathy.

Diagnosis

Autoimmune liver disease is a diagnosis of exclusion, based on the following criteria:

- Positive autoantibodies
- Raised gammaglobulins and IgG levels
- Typical histology on liver biopsy
- Absence of known etiology, e.g. viral hepatitis, Wilson disease, drug hepatotoxicity or biliary disease
- Response to immunosuppression confirms the diagnosis.

Management

Steroids and azathioprine are the primary immunosuppressive agents while cyclosporine and mycophenolate mofetil are second line drugs. The endpoint of therapy is normalization of transaminases and histological inflammatory activity with treatment. A majority of patients including those with cirrhosis respond to medical therapy. Liver transplantation is required for patients with

end stage liver stage who are either refractory or intolerant to immunosuppressive therapy. Patients presenting with acute liver failure need liver transplantation, as they are less likely to respond to medical treatment. A high index of suspicion and timely diagnosis of autoimmune liver disease is crucial.

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CHRONIC HEPATITIS B INFECTION

Hepatitis B virus (HBV) infection is a worldwide health problem and may result in AVH, ALF, chronic hepatitis, cirrhosis and hepatocellular carcinoma (HCC). The epidemiology, natural history and evaluation for the infection are discussed in Chapter 11. The age at time of HBV infection affects the outcome, with >90% of infected neonates becoming chronic carriers as compared to 20–25% children infected in preschool age and only 5% adults.

Clinical Features

Chronic HBV infection is defined as persistence of HBsAg for >6 months. Three potentially successive phases have been described in the natural course of chronic HBV infection:

- Immune tolerant phase* is characterized by active viral replication and minimal liver damage. In this phase, serum HBsAg and HBeAg are positive, serum HBV DNA levels are high (in millions), anti-HBe antibody is negative and serum ALT levels are normal.
- Immune clearance phase* occurs years after immune-tolerant phase and is characterized by effort of clearing the chronic HBV infection by the host. In this serum HBV DNA levels are reduced and ALT levels increase. Serum HBsAg and HBeAg are positive and anti-HBe is negative. The patient may become symptomatic in this phase with ALT flares.
- Inactive carrier phase* or nonreplicative phase follows HBeAg seroconversion, i.e. HBeAg is negative and anti-HBe is positive. It is characterized by very low serum HBV DNA levels (<2,000 IU/mL), HBsAg positivity and normal ALT. It may lead to resolution of infection where serum HBsAg becomes undetectable and anti-HBs is present.

Most children with early acquired HBV infection spontaneously clear HBeAg by 15–30 years of age. Majority of the children with chronic HBV infection are asymptomatic during first two decades of life. Cirrhosis develops in 3–10% and hepatocellular carcinoma (HCC) in 1–4% of children with chronic HBV infection.

Management

The recommendations for management of children with chronic HBV include: (i) detailed examination and liver function tests; (ii) serology tests: HBeAg, anti-HBe, HBV DNA (quantitative by PCR), HCV RNA and HIV testing to rule out coinfection in high-risk groups (e.g. following multiple transfusions); (iii) consideration for liver biopsy for grading and staging of liver disease prior to initiation of treatment; and (iv) identifying and treating patients that merit therapy for hepatitis B. The ideal drug for treatment of chronic HBV infection in children is one that is cheap, safe, orally administered, given at all ages for long duration without any risk of viral resistance and capable of interrupting viral replication to undetectable levels. But no such drug is currently available. The drugs licensed for use in children include, interferon (≥ 1 year of age) and oral antivirals (lamivudine and entecavir ≥ 2 years, adefovir and tenofovir >12 years of age).

Children in the nonreplicative phase do not require treatment and there is no effective therapy for patients in the immune-tolerant phase. Treatment is helpful for children in immune-clearance phase with active liver disease and raised transaminases as delayed loss of HBeAg is a risk factor for virus replication and favors development of cirrhosis and hepatocellular carcinoma. Therefore, an attempt at shortening the highly replicative phase by treatment is likely to be beneficial and forms the basis of therapy in children.

The aim of treatment is to achieve sustained loss of HBV DNA, HBeAg seroconversion (HBeAg negative and anti-HBe positive), normal transaminases and improved liver histology and thereby reduced risk of cirrhosis and HCC. Correct patient and therapy selection is the key to successful management. The other aspects of managements include:

- i. Follow-up of all infected children for disease flares and surveillance for hepatocellular carcinoma should be ensured. Risk of cancer in HBV infected subjects is 100-fold more than in HBV negative patient. Alpha-fetoprotein and abdominal ultrasound are used to screen for hepatocellular cancer.
- ii. Educating the child or adolescent regarding avoidance of other hepatotoxic factors, e.g. obesity, alcohol and intravenous drugs, is essential.
- iii. One should screen all family members of HBsAg positive patient for HBsAg. Vaccination of negative members against HBV and evaluating other HBsAg positive members for liver disease is required.

Prevention of Chronic HBV Infection

Prevention is the most effective method of successfully controlling HBV infection and its complications. The hepatitis B vaccine is highly immunogenic with seroconversion rates of $>90\%$ after three doses. Antibody titers (anti-HBs) of >10 mIU/mL signify a response and are protective. The dose in children and adolescents (aged less

than 18 years) is 0.5 mL (10 mg). It is given in 3 doses at 0, 1 and 6 months as an intramuscular injection in the deltoid/anterolateral thigh. For prevention of perinatal infection in HBsAg positive mother, the baby should be given Hepatitis B immunoglobulin (HBIG) along with hepatitis B vaccine within 12 hours of birth, using two separate syringes and separate sites for injection. The dose of HBIG is 0.5 mL IM. The other two doses of hepatitis B vaccine may be given at 1 and 6 months or at 6 and 14 weeks to piggy back it with the DPT vaccination. The efficacy of prophylaxis with both HBIG and hepatitis B vaccine is 90–95%. All infants born to HBsAg positive mothers should be tested for HBsAg and anti-HBs antibodies at 9–15 months of age to identify HBV infected (HBsAg positive, anti-HBs antibody negative) and protected (HBsAg negative, anti-HBs antibody positive) children.

Universal infant vaccination, adequate screening of blood products and use of sterile syringes is a must for controlling chronic HBV infection as prevention is always better and more feasible than cure especially in HBV infection.

HEPATITIS C INFECTION

HCV is an enveloped, single-stranded positive-sense RNA virus of the flavivirus family. Based on phylogenetic analysis of HCV sequences, 6 major HCV genotypes are recognized, designated 1 to 6, with multiple subtypes within each viral genotype. In India, genotype 3 is more prevalent.

Epidemiology

Worldwide prevalence of chronic HCV infection is estimated at 3%, with 150 million chronically infected people. Routes of transmission of HCV are similar to HBV. Mother-to-infant transmission of HCV is the main mode of transmission in children. Hepatitis C affects 4–10% of children born to infected mothers, and 80% of them develop chronic infection. Children are considered infected, if the serum HCV RNA is positive on at least two occasions.

Clinical Presentation

Most children with chronic hepatitis C virus infection are asymptomatic or have mild nonspecific symptoms, with persistent or intermittently elevated or even normal serum transaminases. Hepatomegaly may be present. Severe liver disease may develop 10–20 years after onset of infection, with a less than 2% overall risk during the pediatric age group.

The natural course of HCV infection in children is not clearly understood, but overall advanced liver disease is rare during childhood. In cases with vertical transmission, spontaneous clearance of infection may be seen by 5 to 7 years of age. Children with transfusion-acquired infection may have higher rates of spontaneous HCV clearance than those with vertically acquired HCV infection.

Evaluation

Diagnosis is made by testing for anti-HCV antibody and if positive, confirmed by the presence of HCV RNA. The presence of antibody shows that the patient has been exposed to the virus but does not discriminate between active or resolved infection. The absence of anti-HCV antibody usually indicates that the patient is not infected. The diagnosis of chronic HCV infection is made on the basis of persistently detectable HCV RNA for ≥ 6 months.

Treatment

Combination of interferon (thrice a week of standard IFN subcutaneously or once a week of pegylated IFN) and oral ribavirin (15 mg/kg maximum) daily for a period of 24 weeks for genotype 2 and 3 and 48 weeks for genotype 1 and 4 was the standard therapy for chronic HCV infection. The US FDA has recently approved combined pegylated-IFN- α 2b plus ribavirin for treatment in children >3 years of age. The addition of polyethylene glycol (PEG) increases the half-life of IFN, reduces its volume of distribution and leads to more sustained plasma levels with better viral suppression and allowing once weekly usage. In children the rate of sustained virological response (6 months after completion of drug treatment) indicating resolution of chronic infection varies from 50% in genotype 1 patients, to 90% in genotypes 2 or 3 patients. Multi-transfused thalassemic children with hepatitis C virus infection can also be treated with IFN and ribavirin with a response rate of 60–72%. However, ribavirin-induced hemolysis increases the transfusion requirement during treatment in these children. Newer oral direct acting antiviral agents, like sofosbuvir, have improved the response rates and reduced side effects of therapy in adults with HCV infection of all genotypes. Combination therapy with ledipasvir/sofosbuvir for genotype 1,4,5 and 6 and with sofosbuvir/ribavirin for genotype 2/3 have recently been approved for children above 12 years of age. In younger children the trials with DAA (direct acting antivirals) are ongoing. However, unless clinically indicated, deferring the treatment in view of availability of these drugs in near future in younger children is to be considered.

A frequently overlooked but critical component of the management of children with HCV is to provide information about the virus, including ways to prevent its spread. Adolescents, in particular, need to understand that alcohol accelerates progression of HCV-related liver disease and should abstain from its consumption. The importance of avoiding high-risk behavior such as sharing of intravenous injection needles also needs to be discussed.

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METABOLIC LIVER DISEASE

Metabolic diseases account for up to 15–20% of chronic liver disease in Indian children with Wilson disease being the most frequent and alpha-1-antitrypsin deficiency being rare. The etiology of metabolic liver diseases can be classified based on the primary substrate.

Clinical Features

The clinical features are secondary to hepatocyte injury with development of cirrhosis, storage of lipids or glycogen, or metabolic effects secondary to hypoglycemia or hyperammonemia. Clinical signs and symptoms of most metabolic liver diseases are similar and indistinguishable from those seen in acquired hepatic disorders due to other causes. Presentations can be broadly subdivided into:

- Isolated unconjugated hyperbilirubinemia, e.g. Gilbert syndrome, Crigler-Najjar syndrome types I and II.
- Conjugated hyperbilirubinemia, e.g. progressive familial intrahepatic cholestasis, cystic fibrosis, bile acid synthesis defects.
- Severe liver dysfunction with ascites and coagulopathy, e.g. galactosemia, neonatal hemochromatosis, tyrosinemia.
- Hepatomegaly, hepatosplenomegaly, e.g. glycogen storage disease, lysosomal storage disorders.
- Reye like illness, e.g. mitochondrial hepatopathies, urea cycle defects.
- Chronic liver disease or acute liver failure, e.g. Wilson disease.

The settings in which metabolic liver disease should be suspected include: (i) recurrent episodes of rapid deterioration with minor illnesses; (ii) recurrent unexplained encephalopathy, hypoglycemia, acidosis and hyperammonemia, as in mitochondrial hepatopathies, urea cycle defects, organic acidurias; (iii) consanguinity, sib deaths or positive family history, as in Wilson disease; (iv) specific food intolerance or aversions in childhood, e.g. sugars in hereditary fructose intolerance, protein in urea cycle defects; (v) rickets or unusual urine odors, e.g. tyrosinemia; (vi) developmental delay and multisystem involvement, e.g. mitochondrial hepatopathies; and (vii) fatty liver on ultrasonography or liver biopsy.

Diagnosis

Apart from the high index of suspicion, investigations include complete blood count, arterial blood gases with lactate, electrolytes, glucose, ammonia; plasma and urine amino acids and organic acids; urine for ketones and sugars. Samples of urine and plasma, skin biopsy and liver biopsy are frozen for future evaluation. Liver biopsy provides information about the extent of damage and tissue for estimation of abnormal material (copper, iron

or glycogen) and enzyme assay. Confirmation of the diagnosis requires specific tests like enzyme assay and genetic mutation analysis depending on the suspected etiology.

Management

Management is two pronged; specific treatment of underlying disease and therapy for liver damage. Supportive therapy includes measures like provision of optimal nutrition with vitamin supplementation, antioxidants, correction of hypoglycemia, coagulopathy and ascites, vaccination against infections like hepatitis B and monitoring for hepatocellular carcinoma in high-risk groups like tyrosinemia. Specific therapy is most important and should be given whenever available and affordable, e.g. chelation therapy for Wilson disease and dietary modification for galactosemia. Liver transplantation might be offered to a select group of metabolic liver disorders, in absence of significant multisystem disease.

Wilson Disease

Wilson disease is an inborn error of metabolism due to toxic accumulation of copper in liver, brain, cornea and other tissues.

Clinical Presentation

The age of presentation can vary from 4 to 60 years. Manifestations are more likely to be hepatic in early childhood and neurological in adolescents or adults. The spectrum of hepatic manifestations includes all forms of chronic or acute liver disease, i.e. asymptomatic hepatomegaly, chronic hepatitis, portal hypertension, cirrhosis, 'viral hepatitis' like illness and sometimes acute liver failure. Neurological abnormalities are varied and may present as clumsiness, speech difficulties, scholastic deterioration, behavioral problems, convulsions and choreoathetoid/dystonic movements.

Investigations

Serum ceruloplasmin is decreased (<20 mg/dL) in most patients. In symptomatic patients, the 24 hours urinary copper excretion is more than 100 µg/day. Kayser-Fleischer (KF) ring indicates long-standing disease and severe copper overload. KF rings are more common in children with neurological (96%) than hepatic (60%) and asymptomatic (10–20%) Wilson disease. Hepatic copper is the single best predictive marker and is considered to be the gold standard, with values ≥ 250 µg/g dry weight of liver. Liver biopsy is required for hepatic copper estimation. Mutational diagnosis is difficult because of the occurrence of more than 200 mutations, each of which is rare. Mutational diagnosis is helpful in screening family members of an index patient homozygous for this mutation.

Diagnosis

Wilson disease is strongly suggested by the presence of any two of the following; Low ceruloplasmin, high urinary copper and presence of KF ring. However, hepatic copper content should be estimated if diagnosis is in doubt. All sibs of patients with Wilson's disease should be screened to detect presence of asymptomatic WD.

Treatment

Foods with high copper content like organ meats (liver), chocolates and nuts should be avoided. Continuous life-long pharmacotherapy is essential for management. Treatment entails two aspects: (i) *Induction therapy* aims to reduce copper to subtoxic threshold. This phase usually takes 4 to 6 months (as indicated by urinary copper <500 µg/day and nonceruloplasmin copper <25 mg/dL). D-Penicillamine or trientine is often used as chelation therapy. Ammonium tetrathiomolybdate is the therapy of choice in neurological Wilson disease, but is not easily available in India. (ii) *Maintenance therapy* aims to maintain a slightly negative copper balance so as to prevent its accumulation and toxicity. Penicillamine and trientine have been used for this phase for long periods. Zinc, in view of its low cost and safety profile, can be used for maintenance therapy, especially if there are penicillamine side effects and in asymptomatic sibs.

D-Penicillamine and trientine: Large urinary excretion of copper (2 to 5 mg/day) is observed in the initial months of therapy, falling to 0.1–0.5 mg/day in the maintenance period. Penicillamine has many adverse effects like skin rash, bone marrow depression, nephrotic syndrome or neurological deterioration. Trientine has been used as an alternative chelating agent especially for children intolerant to penicillamine. Trientine is increasingly used as first line drug with good efficacy and a few side effects; both medications are given at a dose of 20 mg/kg/day in two divided doses.

Zinc: Zinc has been used as acetate, sulfate or gluconate salts. Zinc acts by inducing intestinal cell metallothionein, which binds copper to form mercaptides. The metallothionein, with copper is held in the intestinal cells until it is sloughed out. However, zinc is a slow-acting drug that takes longer time to achieve a negative copper balance and is, therefore, effectively used as maintenance therapy.

Liver transplantation is indicated in children with Wilson disease who present as acute liver failure or have decompensated cirrhosis unresponsive to medical therapy.

Glycogen Storage Disorders

Glycogen storage disorders are important metabolic disorders manifesting in childhood with varied clinical picture ranging from asymptomatic hepatomegaly (type VI) to hypoglycemia (type I, III) and decompensated end-stage liver disease (type IV) (see Chapter 24).

Type I glycogen storage disease (von Gierke disease): Inability to convert glucose-6-phosphate to glucose in the liver results in inability to mobilize glycogen. Depending on whether this is due to glucose-6-phosphatase deficiency or translocase deficiency, it is classified as type 1A or 1B.

Hepatomegaly, doll-like facies (Fig. 12.30), hypoglycemia, seizures, growth retardation, hyperuricemia, hypertriglyceridemia and lactic acidosis are main manifestations. Hypoglycemia is more marked after first few months of life as the frequency of feeding decreases. Liver adenoma might develop with risk of bleeding and malignant transformation.

Hepatomegaly and nephromegaly is appreciated on imaging. Platelet dysfunction may be present. Neutropenia is specific to type 1B. There is mild transaminase elevation. Liver biopsy shows hepatocytes with vacuolated cytoplasm and glycogen accumulation (PAS stain positive, diastase sensitive) along with microvesicular steatosis; fibrosis is absent. Definite diagnosis depends on measuring enzyme activity in the liver or mutational analysis.

Management hinges on providing a constant source of glucose in the form of slowly digested complex carbohydrates. This is achieved by frequent daytime feeding, supplementation of uncooked corn starch both in day and specifically at night. As the child grows into adolescence, longer periods of fasting may be tolerated. Since the metabolism of other carbohydrates also yield glucose-6-phosphate, galactose and fructose also need to be restricted. Strict metabolic control with dietary therapy is the key to avoiding complications.

Type III glycogen storage disorder: There is a deficiency of debranching enzyme manifesting as hepatosplenomegaly, hypoglycemia, fibrosis in the liver and elevation

in transaminases. While hypoglycemia and hepatosplenomegaly improve, 80–85% develop a myopathy in type III a disease while the other 15% (type III b) have only liver involvement. These cases are managed with diet similar to that in type I GSD, except that a high protein diet is preferred and there is no need to restrict galactose and fructose.

Type IV glycogen storage disorder: In type IV GSD there is a deficiency of branching enzyme resulting in deposition of an amylopectin like structure in the liver. The presentation is with chronic liver disease, portal hypertension and hepatic decompensation. Most children are symptomatic by 3 years of age. Treatment is largely supportive and liver transplantation is required for patients with advanced disease.

Suggested Reading

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Nonalcoholic Fatty Liver Disease (NAFLD)

This is a common cause of liver disease in children and is closely associated with obesity and insulin resistance. The prevalence is increasing with the expanding prevalence of childhood obesity. NAFLD is a clinicopathological diagnosis characterized by macrovesicular steatosis in hepatocytes, in absence of other causes of chronic liver disease. It ranges from simple steatosis (macrovesicular steatosis in hepatocytes without inflammation) to non-alcoholic steatohepatitis (NASH, macrovesicular steatosis in hepatocytes associated with inflammation and fibrosis) to cirrhosis of liver and hepatocellular carcinoma. Insulin resistance and hyperinsulinemia is regarded as essential to the disease mechanism. Hyperinsulinemia is a response to energy dense diet (rich in saturated fats, sugars and refined carbohydrates). This diet elicits hyperinsulinemia, provides exogenous free fatty acids and drives the liver towards lipogenesis.

Clinical presentation: Most children are asymptomatic. Some have vague abdominal pain; examination shows generalized obesity, cutaneous striae and hepatomegaly. Splenomegaly is uncommon. Acanthosis nigricans, a velvety brown-to-black pigment in skin folds and axillae, typically associated with hyperinsulinemia can be found in 30–50% patients.

Investigations: Typical biochemical abnormalities in NASH include moderately raised serum aminotransferases (with ALT more raised than AST). Metabolic abnormalities include hypertriglyceridemia, elevated fasting serum insulin and hyperglycemia. Other disorders, which may cause fatty liver can be eliminated on basis of



Fig. 12.30: Classical facies with chubby cheeks in a child with glycogen storage disease

clinical and biochemical findings. The diagnosis of NAFLD is suspected when there is raised serum ALT or evidence of fatty liver on radiological studies. Liver histology is required for diagnosis of NASH.

Treatment: The first step in treating NAFLD is to identify it. Besides height and weight, waist circumference provides highly informative data and is a surrogate for visceral obesity. The treatment has two goals—to reverse liver disease and to promote healthy growth. Lifestyle changes aimed at weight reduction are essential. Dietary changes and increased physical activity lead to diminished insulin resistance and are the main stay of therapy. Vitamin E has been shown to be safe and effective in improving NASH histology in children and its use is recommended. Other medications like orlistat, metformin, UDCA and thiozolidinodiones require more data to prove efficacy. The role of bariatric surgery has not been established for childhood obesity. Prevention of overweight and obesity in children is the best strategy to overcome the problem of NAFLD.

Suggested Reading

- Barshop NJ, Sirlin CB, Schwimmer JB, Lavine JE. Review article: epidemiology, pathogenesis and potential treatments of pediatric non alcoholic fatty liver disease. *Aliment Pharmacol Ther* 2008; 28:13–24.
- Mann JP, Goonetilleke R, McKiernan P. Pediatric non-alcoholic fatty liver disease: a practical overview for non specialist. *Arch Dis Child* 2015; 100:673–7.
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Hepatic Manifestations of Systemic Diseases

Apart from disorders that directly involve the liver, a number of disorders affecting other organ systems also have hepatic manifestations. While, in some disorders, these manifestations may be benign, in others the hepatic manifestations might significantly affect the outcome.

Ischemic Hepatitis

Severe shock may lead to hypoperfusion of the liver. This shock may be the result of sepsis, acute cardiogenic shock or severe intraoperative hypoperfusion as in cardiac surgery. It usually manifests as an elevation of transaminases to high levels. The degree of hepatic injury depends on the duration and severity of shock. Thus, coagulopathy as evidenced by prolonged prothrombin time and encephalopathy may result. Jaundice is a late manifestation.

Cardiac Disorders

Apart from an acute cardiogenic shock or intraoperative hypoperfusion in cardiac surgery, liver involvement may be seen as a result of congestion in right heart failure or as part of syndromes that involve both the liver and the heart.

Chronic right heart failure may lead to hepatomegaly, splenomegaly and over long periods result in cardiac cirrhosis. Alagille syndrome, caused by syndromic paucity of intralobular bile ducts results in infantile cholestasis; patients also show peripheral pulmonary stenosis, tetralogy of Fallot and atrial or ventricular septal defects. In biliary atresia, splenic malformation syndrome anomaly, there may be vascular malformations and congenital heart disease.

Sepsis and Systemic Infections

Gram-positive and gram-negative bacterial infections may result in jaundice. Up to one-third of neonatal jaundice has been attributed to sepsis. The mechanism may vary from impaired canalicular bile transport due to defective transporter polarization in hepatocytes without hepatic necrosis to elevated bilirubin load due to hemolysis in clostridium infections and hepatocellular necrosis in pneumococcal infections. Typhoid might result in elevated alkaline phosphatase, transaminases and lactate dehydrogenase. Transaminase elevation and liver dysfunction is also present in dengue hemorrhagic fever and malaria.

Immunological Disorders

Juvenile idiopathic arthritis may be associated with hepatomegaly and elevated transaminases. Systemic lupus erythematosus may be associated with hepatomegaly or autoimmune hepatitis. Transplacental transfer of autoantibodies might lead to neonatal SLE with transient cholestasis, congenital heart block, dermatitis and hematological abnormalities.

Hemolytic Anemias

In thalassemia, the repeated transfusions and the increased iron absorption due to ineffective erythropoiesis leads to chronic iron overload, fibrosis and cirrhosis. Recurrent transfusions increase the risk of acquiring hepatitis B and hepatitis C infections. Sickle cell anemia has a similar risk of transfusion related hepatitis but more specific problems are acute hepatic crisis which is a result of ischemic insult. These individuals are also at higher risk of pigment stones resulting in acute and chronic cholecystitis. These episodes may be difficult to differentiate from acute hepatic crisis.

Malignancies

Leukemias and lymphomas might be associated with hepatic infiltration, presenting as jaundice. Hemophagocytic lymphohistiocytosis, either familial or infection induced, presents with fever, jaundice, hepatosplenomegaly, liver dysfunction and cytopenia. It is an important differential diagnosis for liver failure in the first few months of life. Sclerosing cholangitis may be a complication of Langerhans cell histiocytosis.

Bone Marrow Transplant

Conditioning chemotherapy and total body irradiation may lead to veno-occlusive disease manifesting as weight gain, hepatomegaly, ascites and jaundice. Other causes of liver dysfunction after bone marrow transplant include graft versus host disease (acute or chronic), sepsis, infections hepatitis and drug toxicity.

Endocrine Disorders

Uncontrolled diabetes mellitus presents with hepatomegaly and fatty changes. Hypothyroidism manifests as jaundice in the neonatal period predominantly due to impaired conjugation of bilirubin and partly due to decreased bile flow.

Cellac Disease

Elevated transaminases may be observed, which normalize with gluten-free diet in the majority. Persistent rise of transaminases should lead to evaluation for co-existing autoimmune liver disease.

NEONATAL CHOLESTASIS

Jaundice is common in neonates as physiological jaundice is found in a majority. This jaundice usually resolves by two weeks of age. Also, most pathological causes of unconjugated jaundice are detected and treated by two weeks of age. Though breast milk jaundice can be a cause of unconjugated hyperbilirubinemia beyond two weeks of age, cholestatic jaundice is an important and potentially serious condition that needs evaluation and early treatment. Conjugated hyperbilirubinemia is defined as direct bilirubin value greater than 1 mg/dL if the total bilirubin is less than 5 mg/dL, or a value of direct bilirubin that represents more than 20% of the total bilirubin, if the total bilirubin is >5 mg/dL. Conjugated hyperbilirubinemia presents with high colored urine staining the diapers unlike unconjugated hyperbilirubinemia. *All newborns having jaundice beyond 14 days of age* with dark-colored urine with or without acholic stools should be referred to tertiary health facilities for further investigations and treatment without loss of time after a dose of vitamin K injection. The need for time bound early evaluation and treatment is manifold as mortality and poor outcomes are common in children with metabolic liver diseases and biliary atresia respectively when the referral is delayed. Often, valuable time is lost by work-up in less equipped primary health centres.

Clinical Features

Neonatal cholestasis is characterized by high colored urine along with jaundice. Jaundice is seldom noticed by the parents in the eyes as the sclera is not easily visualized in them. Referral of children with biliary atresia is often delayed as they are healthy looking and gaining weight. Failure to thrive is common in children with metabolic liver diseases. Stool color is best assessed by looking at the core of the stools as otherwise pale stools covered by

bile pigment-stained intestinal epithelial cells may be mistaken for pigmented stools. The presence of pale stools does not necessarily reflect an extrahepatic or obstructive cause as many metabolic liver diseases with significant liver dysfunction present with pale stools. Also intrahepatic diseases with severe paucity of bile ductules or significant canalicular transporter dysfunction may present with pale stools. However, presence of persistently pigmented yellow stools is not seen in biliary atresia. A subset of patients present with signs of coagulopathy like skin or intracranial bleeds (seizures, irritability and bulging fontanel). Hepatomegaly or hepatosplenomegaly is common. Early decompensation is a feature in patients with an underlying metabolic disorder. In a sick infant, one should consider the diagnosis of galactosemia, tyrosinemia, hemochromatosis, herpes and sepsis. Patients with biliary atresia and choledochal cyst are otherwise healthy looking. Bilateral cataract and *E. coli* sepsis is typical of galactosemia, whereas rash (maculopapular or petechial), fever, chorioretinitis, microcephaly and lethargy are suggestive of congenital infections. Triangular facies, pointed chin, prominent ears, cardiac murmurs and butterfly vertebrae are seen in Alagille syndrome. Splenohepatomegaly with cherry-red spot on fundus examination suggests storage disorder.

Diagnosis

Neonatal cholestasis has a multifactorial etiology (Table 12.36). The etiological spectrum in referral western centres is as follows—biliary atresia (25%), PFIC, Alagille syndrome and bile acid synthetic disorders (25%), metabolic (20%), idiopathic neonatal hepatitis (INH, 15%), alpha-1-antitrypsin deficiency (10%), and viral (5%). This data is relevant as the proportion of cases with INH reduces when all necessary investigations especially metabolic tests are done. Also, it warrants mention that this is a western data and that alpha-1-antitrypsin is not as prevalent in India as in European countries. Liver dysfunction, general condition and stool color are important features in the differential diagnosis. These infants need a detailed investigative workup based on a rational approach so as to avoid unnecessary and costly investigations. The etiology and algorithm of evaluation is different in a 'sick' and 'not sick' infant with cholestasis as shown in the flowchart (Fig. 12.31). This approach avoids a battery approach to investigations.

In a non-sick infant with pale stools, the main objective is to quickly establish the diagnosis or rule out biliary atresia. Liver biopsy is an accurate (90–95%) test for differentiating biliary atresia from other causes of neonatal cholestasis. In biliary atresia, portal tract expansion, ductular proliferation and fibrosis is seen, whereas in neonatal hepatitis, there is alteration in lobular architecture, focal hepatocellular necrosis and giant cells formation. Priming with UDCA or phenobarbitone for 3 days before HIDA scan improves the diagnostic efficacy of HIDA. HIDA is more relevant for its negative predictive value (100%) as the presence of excretion into gut rules

Table 12.36: Causes of neonatal cholestasis

Extrahepatic disorders

- Biliary atresia*
- Choledochal cyst*
- Inspissated bile duct syndrome*
- Spontaneous perforation of bile duct

Intrahepatic disorders

- Metabolic:** Galactosemia*, tyrosinemia*, Progressive familial intrahepatic cholestasis (PFIC 1 and 2)*, Niemann-Pick type C disease, mitochondrial hepatopathy and fatty acid oxidation defects*, bile acid synthetic defect, Zellweger syndrome, Wolman disease, cystic fibrosis, alpha-1-antitrypsin deficiency, hereditary fructose intolerance
- Infection:** Sepsis*, urinary tract infection*, TORCH
- Idiopathic:** Neonatal hepatitis *
- Genetic:** Alagille syndrome*, Down syndrome, Trisomy E
- Endocrine:** Hypopituitarism, hypothyroidism
- Anatomic:** Congenital hepatic fibrosis, Caroli disease
- Others:** Neonatal hemochromatosis, total parenteral nutrition related, multifactorial cholestasis of prematurity*

*Common causes

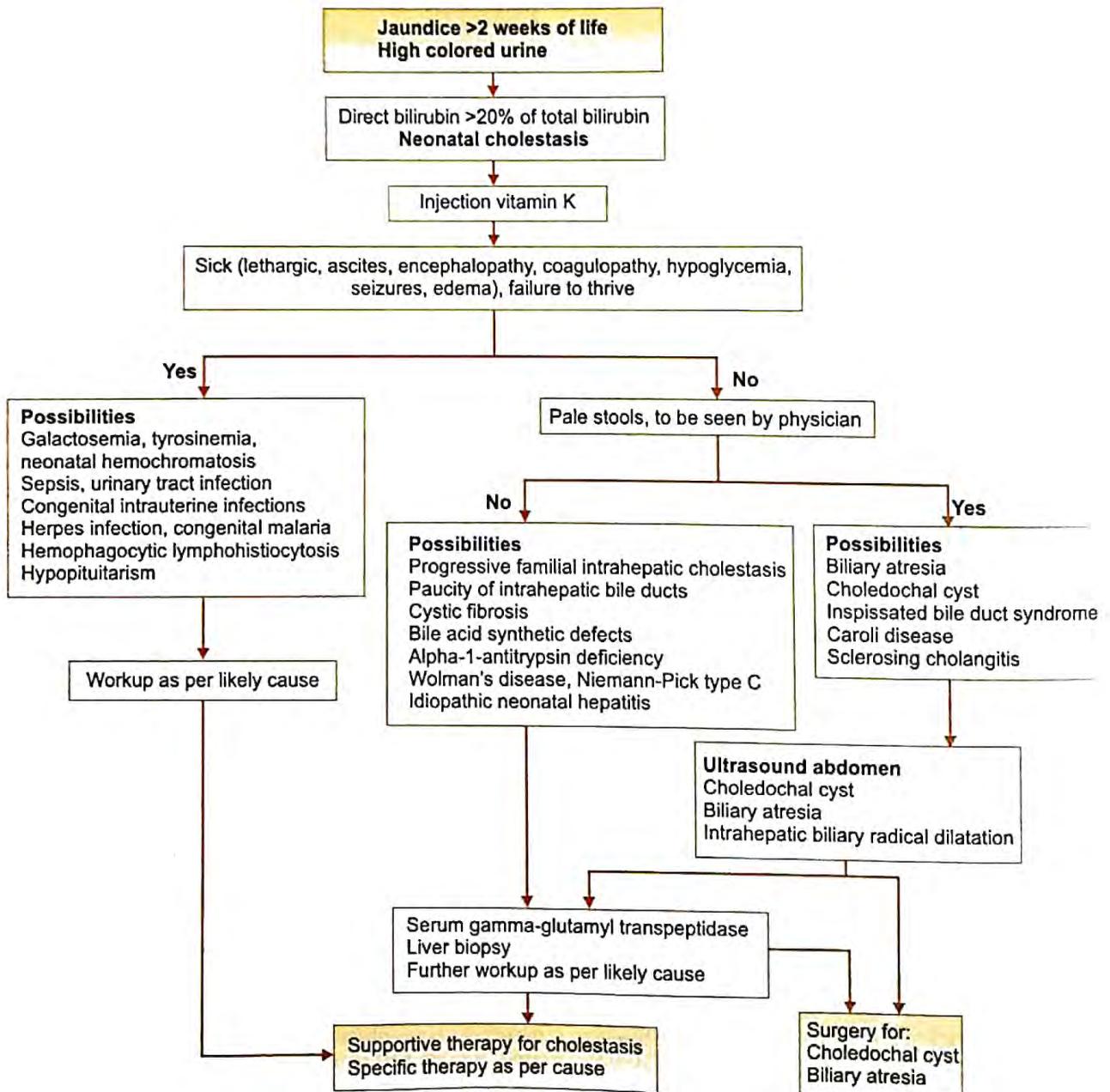


Fig. 12.31: Evaluation of a patient with neonatal cholestasis

out biliary atresia. However, a non-excretory pattern, i.e. no activity in intestine at 24 hours in HIDA scan can be seen in both biliary atresia and severe intrahepatic cholestasis. Thus, the absence of excretion does not necessarily mean biliary atresia. Laparotomy and peroperative cholangiography (POC) may be required in an infant with equivocal biopsy, findings and no excretion on HIDA scan, to evaluate for biliary atresia. In experienced centres, with fast reporting of liver biopsy the histology report is available much before HIDA reports and helps in avoiding a negative laparotomy (patent biliary pathway on POC).

Ultrasound of abdomen is more relevant in determining the presence of dilated CBD/intrahepatic biliary radicle dilatation (seen in choledochal cyst), cysts at the porta (seen in cystic variants of biliary atresia and choledochal cyst), multiple intrahepatic cysts communicating with biliary tree (Caroli's disease), hemangioma (relevant for liver biopsy) and looking for situs inversus (seen in some cases of biliary atresia—relevant for liver biopsy). Even though an absent gallbladder, poorly contractile gallbladder, small gallbladder and triangular cord sign (echogenic density of ≥ 3 mm located immediately cranial to the portal vein bifurcation) are finding associated with biliary atresia, the condition should not be ruled out or diagnosed on the basis of an ultrasound alone. Dilatation of intrahepatic biliary radical is not seen in biliary atresia as it is a pan ductular disease.

In an infant with frankly pigmented stools, intrahepatic causes need to be considered. There is no utility of HIDA in this situation as it will definitely be excretory.

Liver biopsy (light microscopy and immunohistochemistry) is useful in making a specific diagnosis but is not of much use in most situations where a metabolic cause is suspected. A detailed metabolic workup is required for infants with conditions like progressive familial intrahepatic cholestasis types I and II, tyrosinemia, mitochondrial cytopathies and bile acid synthesis defects, etc.

Management

Delayed diagnosis leads to problems of undernutrition, coagulopathy, pruritus (older infants), portal hyper-

tension, ascites and hepatic encephalopathy. The management is begun as soon as the child is seen, parallel to investigations.

General management: This includes the following:

- Nutritional.** Adequate caloric intake (125–150% of RDA based on ideal body weight) with medium chain triglyceride supplementation is necessary. Breast-feeding should be continued and supplementation with high MCT formulae should be done; 2–3% calories should come from long chain triglycerides to prevent deficiency of essential fatty acids. Nasogastric feed is offered to anorexic infants. Supplementation of fat-soluble and water-soluble vitamins is done (Table 12.37). In addition, these infants require supplements of calcium, phosphorus and magnesium and correction of anemia.
- For infants with pruritus, urodeoxycholic acid (UDCA, 10–20 mg/kg/day), rifampicin (5–10 mg/kg/day) and cholestyramine (250 mg/kg/day, max 8 g/day) are used. UDCA is the first agent and others are used in patients with persistent symptoms.
- Management of other complications like ascites, gastrointestinal bleeding and hepatic encephalopathy is discussed in respective sections in the chapter.

Specific management: This is available only for some etiologies as follows:

- Biliary atresia is managed by Kasai procedure (hepatoportoenterostomy). The best results are obtained, if it is done early (<60 days of age) and at centers with expertise. Liver transplantation is indicated in children who fail to drain bile after Kasai procedure or have progressed to end stage cirrhosis either despite surgical treatment or due to late diagnosis.
- Choledochal cyst:** Excision of cyst and hepaticojejunostomy.
- Herpes simplex:** Intravenous acyclovir
- Bacterial sepsis:** Intravenous antibiotics
- Toxoplasmosis:** Pyrimethamine and sulfadiazine with folic acid
- Galactosemia:** Lactose free diet
- Hemochromatosis:** IV immunoglobulins (IVIG) with exchange transfusion may be useful

Table 12.37: Multivitamin supplements for cholestasis

Drug	Dose	Side effects
Vitamin K	2–5 mg IM, repeated monthly Oral: 2.5–5 mg alternate day	Overdose may lead to hemolysis
Vitamin D	Vitamin D ₃ : Oral 1000–2000 IU/day or 30000 IU q monthly	Monitor for hypercalcemia, nephrocalcinosis
Vitamin E	Aquasol E: 50–400 IU/day	Pseudotumor cerebri, hepatotoxicity, hypercalcemia
Vitamin A	Aquasol A: 2500–5000 IU/day Injectable 30,000 IU/IM at diagnosis and 10,000 IU/IM monthly till cholestasis resolves	Pseudotumor cerebri, bone pains
Water-soluble vitamins	Twice the RDA	None

IM: Intramuscular; RDA: Recommended daily allowance.

Doses are provided as a recommended guide and need to be adjusted as per clinical scenario, response and vitamin levels.

There is considerable delay in referral of patients with neonatal cholestasis to higher centers in India. This results in delayed etiologic diagnosis, missed opportunity for corrective biliary atresia surgery in first 60 days and liver decompensation in patients with metabolic etiology. Thus all efforts should be targeted towards early identification of neonates with conjugated hyperbilirubinemia and their referral to centres with expertise.

Suggested Reading

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Liver Transplantation

Liver transplantation is possible for a number of disorders. The graft is obtained either from the cadaver or can be

a split graft (left lateral graft or left lobe) from a living donor. Auxiliary liver transplantation is another method where native liver is not removed and a liver graft from the donor is surgically placed in addition to the native liver. This is usually done for Crigler-Najjar type I or acute liver failure.

The main indications for liver transplantation are biliary atresia, fulminant hepatic failure and chronic liver disease secondary to multiple causes and hepatic tumors. Careful selection of a blood group compatible donor is necessary, including detailed evaluation of liver functions and viral serologies. The recipient's diseased liver is removed and the new liver is transplanted, ensuring vascular and biliary anastomosis. Patients require lifelong immunosuppression using corticosteroids, tacrolimus and mycophenolate mofetil initially and later maintenance therapy with tacrolimus. Rejection and infection are major complications following transplantation. Five-year patient survival rate exceeds 80%.

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- Kamath BM, Olthoff KM. Liver transplantation in children: Update 2010. *Pediatr Clin N Am* 2010; 57:401-14.

Hematological Disorders

Tulika Seth

Hematopoiesis

The hemangioblast is the stem cell from which endothelial and hematopoietic cells develop. Stem cells that give rise to only blood cells are called hematopoietic stem cells. They give rise to two colony-forming units (CFU), one is the common myeloid precursor: Granulocytes, erythrocytes, monocytes and megakaryocytes, also termed CFU-GEMM. The second is the common lymphoid precursor, dedicated to the production of lymphocytes and called CFU-L. The CFU-GEMM gives rise to two progenitors, specific for both the erythrocyte and the megakaryocyte (CFU-EMk), and another for granulocytes and monocytes (CFU-GMo). Each of these develops into specific lineages, the CFU-GMo gives rise to four lineage-specific CFUs, three dedicated to each of the granulocyte lineages (CFU-Eo for eosinophils, CFU-N for neutrophils and CFU-Baso for basophils) and CFU-Mo that is specific for monocytes. The CFU-L gives rise directly to three lymphoid cells: B lymphocytes, T lymphocytes and natural killer cells. This complex and sequential development of hematopoietic cells is driven and regulated by local growth factors and cytokines.

ANEMIA

Anemia is a sign, it is important to investigate the cause of anemia to ensure that it is not due to a serious underlying ailment and to define the correct management approach.

Definition

Anemia is present when the hemoglobin level in the blood is two standard deviations below the mean for the particular age and sex (Tables 13.1, 13.2). The physiologic definition of anemia is a condition in which tissue hypoxia occurs due to inadequate oxygen carrying capacity of blood. According to the National Family Health Survey (NFHS-4) data, the incidence of anemia in urban children is 55.9%, rural is 59.4% and overall is 58.4%.

Physiological Adaptations

Anemia leads to decreased oxygen-carrying capacity of the blood and compensatory physiological adjustments. Tissue hypoxia develops when the enhanced release of oxygen from hemoglobin and increase of blood flow to

Table 13.1: Hemoglobin and hematocrit in infancy and childhood

Age	Hemoglobin (g/dL)		Hematocrit (%)	
	Mean	-2 SD	Mean	-2 SD
Birth (cord blood)	16.5	13.5	51	42
1-3 days (capillary)	18.5	14.5	56	45
1 week	17.5	13.5	54	42
2 weeks	16.5	12.5	51	39
1 month	14.0	10.0	43	31
2 months	11.5	9.0	35	28
3-6 months	11.5	9.5	35	29
0.5-2 years	12.0	10.5	36	33
2-6 years	12.5	11.5	37	34
6-12 years	13.5	11.5	40	35
Girls 12-18 years	14.0	12.0	41	36
Boys 12-18 years	14.5	13.0	43	37

Values two standard deviations below the mean (-2 SD) indicate the lower limit of normal

Table 13.2: Cutoffs for hemoglobin and hematocrit proposed by the World Health Organization to define anemia

Age group	Hemoglobin (g/dL)	Hematocrit %
Children, 6 mo to 5 years	<11.0	<33
Children, 5–11 years	<11.5	<34
Children, 12–13 years	<12.0	<36
Non-pregnant women	<12.0	<36
Men	<13.0	<39

Source: WHO 1997

the tissues is insufficient to meet requirements. The maintenance of blood volume occurs by an increase in the volume of plasma and redistribution of blood flow. Cardiac output increases in anemia as a consequence of increased stroke volume, this high output state increases oxygen delivery to tissues by increasing the flow of blood. Diversion of blood flow occurs from tissues with lesser oxygen requirements to those with greater needs. Thus skin blood flow is reduced, while cerebral and muscle blood flow are increased.

Clinical Features

The hemoglobin level at which symptoms of anemia develop depends on two factors, the rate of development of anemia and state of the cardiovascular system. In general, symptoms occur at a higher hemoglobin level with rapidly developing anemia, e.g. due to acute hemorrhage.

Tiredness, lassitude, easy fatigability and generalized muscular weakness are most frequent and the earliest symptoms of anemia. This presents as poor feeding, irritability and inadequate school performance; pallor is the most prominent and characteristic sign. Pallor of nail beds, oral mucous membranes and conjunctivae are reliable indicators of anemia. Dyspnea on exertion, tachycardia and palpitation are common symptoms. Hemic murmurs become prominent with severity of anemia. These are midsystolic flow murmurs, reflecting increased velocity of blood passing through the valves. They are heard in the pulmonary area, but can be heard in areas corresponding to any of the heart valves. Systolic bruits, postural hypotension and congestive heart failure may be seen in patients with moderate to severe anemia. Nervous system symptoms include dizziness, headache, humming in ears, fainting, tinnitus, lack of concentration and drowsiness; with severe anemia, clouding of consciousness may occur.

Severe anemia is characterized by a high output state with elevated pulse pressure and a 'collapsing' character. Electrocardiographic changes may be found in approximately 30% of patients with hemoglobin of less than 6 g/dL. Findings on ECG are normal QRS waves, depression of the ST segments, and flattening or inversion of T waves.

Approach to Diagnosis

The history may give clues for the etiology of anemia. There may be obstetric history of maternal infections, anemia or collagen vascular diseases, or presence of prematurity, blood loss, jaundice [secondary to ABO or Rh incompatibility, glucose-6-phosphate dehydrogenase (G6PD) deficiency and sepsis], hemangioma or cephalhematoma. History is taken regarding the diet, type and quantity of milk, time of weaning and intake of vitamins and hematinics. Nutritional iron deficiency anemia often occurs between 6 months and 2 years due to inadequate weaning, chronic diarrhea or cow milk allergy. Adolescent growth spurt, menstruating and pregnant teens are at risk for iron deficiency. A vegetarian diet and use of goat milk may result in megaloblastic anemia. History of pica, drug intake, chronic diarrhea, prior surgery, acute and prolonged infections, liver and renal disease, transfusions and age of onset of symptoms should be taken. Thalassemia major usually presents at 4–6 months of age, and 70% present with symptoms by one-year. Diamond-Blackfan (pure red cell) anemia, usually presents at 3-month or earlier and shows a consistently low reticulocyte count and absence of erythroid precursors in the marrow. Fanconi anemia has a variable and later onset, with children presenting at 3–4 years of age or even in adulthood. A family history of anemia, gallstones and requirement for blood transfusions may suggest the diagnosis of chronic hemolytic anemia, including hereditary spherocytosis or G6PD deficiency.

Examination is done for clues to the cause of anemia, e.g. radial limb anomalies (bone marrow failure), splenomegaly (hemolytic anemia, infection, storage diseases), and lymphadenopathy and hepatosplenomegaly (malignancies, malaria, tuberculosis). Petechia, purpura, icterus and bossing also help to diagnose the cause.

Laboratory Investigation

It is important to know the age and detailed history of the child, this information will provide direction to the laboratory investigation. The complete hemogram will reveal, if there is isolated anemia, or if other cell lines are affected. The red cell indices will demonstrate the type of anemia; while the mean corpuscular volume (MCV) denotes the size of the red cells, the mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin content (MCHC) provide information on red cell hemoglobinization (Table 13.3). Using the MCV, anemias can be classified into microcytic/normocytic/macrocytic anemia (Figs 13.1–13.3). Abnormal red cell indices can exist in subjects even when the underlying disorder is not sufficiently severe to cause anemia. In thalassemia minor or iron deficiency, the MCV, MCH and MCHC are low and in megaloblastosis, the MCV is elevated. The red cell distribution width (RDW) gives the size difference in the red blood cells, low RDW means all the red blood cells are small and uniform in size, while a large RDW shows that the cells vary in size greatly. Examination of the

Table 13.3: Red cell indices and serum iron studies in normal children

Red cell indices	Birth	0.5-2 yr	0-12 yr	Girls, 12-18 yr	Boys, 12-18 yr
Mean corpuscular volume (fl)	108	78	80	80	88
Mean corpuscular hemoglobin (pg)	34	27	29	30	30
Mean corpuscular hemoglobin concentration (g/dL)	33	33	34	34	34
Red cell distribution width (RDW)*	12.8 ± 1.2%				
Serum iron	60-170 µg/dL (10-30 µmol/L)				
Serum ferritin, median (range)	100 (15-300) ng/mL (boys); 40 (15-200) ng/mL (girls)				
Total iron binding capacity	250-400 µg/dL (47-70 µmol/L)				
Transferrin saturation**	20-50%				

*RDW = standard deviation (SD) of red blood cell volume × 100/mean corpuscular volume.

**Transferrin saturation = Serum Iron × 100/total iron binding capacity

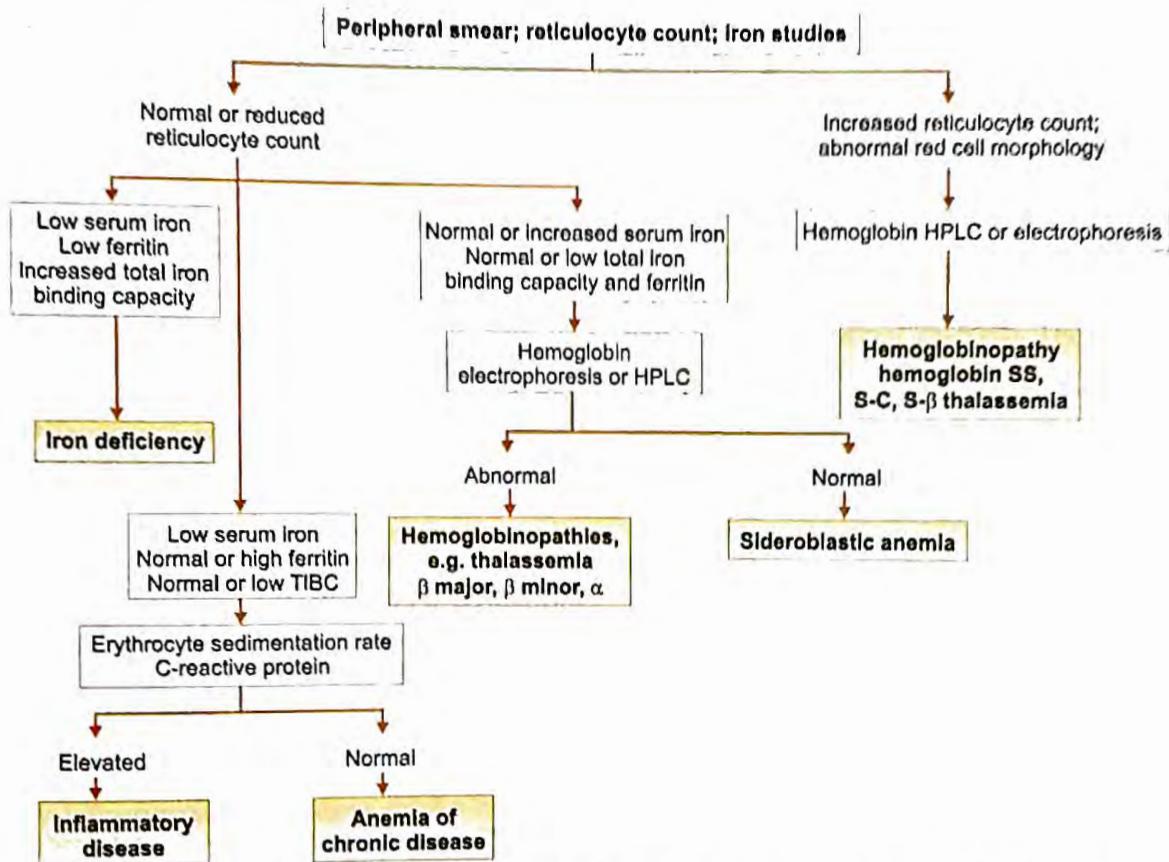


Fig. 13.1: Approach to microcytic anemia. HPLC high performance liquid chromatography

peripheral smear will reveal the red cell morphology, presence of schistocytes, polychromasia, specific red cell morphology or parasites may help in making the diagnosis. The reticulocyte count helps to determine if anemia is caused by red cell destruction or decreased production, the corrected or absolute reticulocyte count is more useful (Table 13.4). When nutritional anemias are suspected, iron status, vitamin B₁₂ and folic acid levels are determined. The reticulocyte count is decreased in bone marrow failure syndromes, transient erythroblastopenia of infancy and infections, e.g. parvovirus. In cases of anemia with increased reticulocyte count, a Coombs test will help to identify, if this is due to immune or hereditary hemolytic anemia.

Table 13.4: Reticulocyte count in evaluation of anemia

Low reticulocyte count

- Congenital or acquired, aplastic or hypoplastic anemia
- Transient erythroblastopenia of childhood
- Pure red cell aplasia
- Parvovirus B19 infection
- Bone marrow infiltration by malignancy, storage disorder

High reticulocyte count

- Hemolysis: Autoimmune hemolytic anemia, hereditary spherocytosis
- Hemorrhage
- Splenic sequestration
- Recovery from vitamin B₁₂, folic acid or iron deficiency
- Sepsis

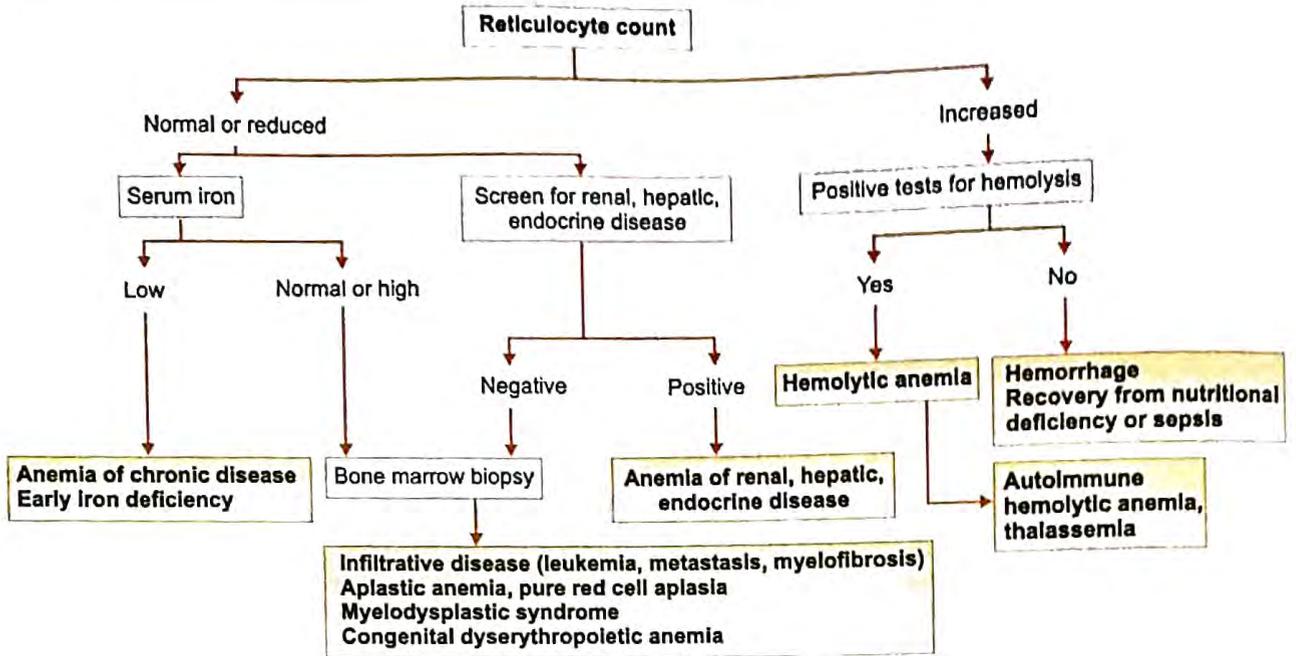


Fig. 13.2: Approach to normocytic anemia

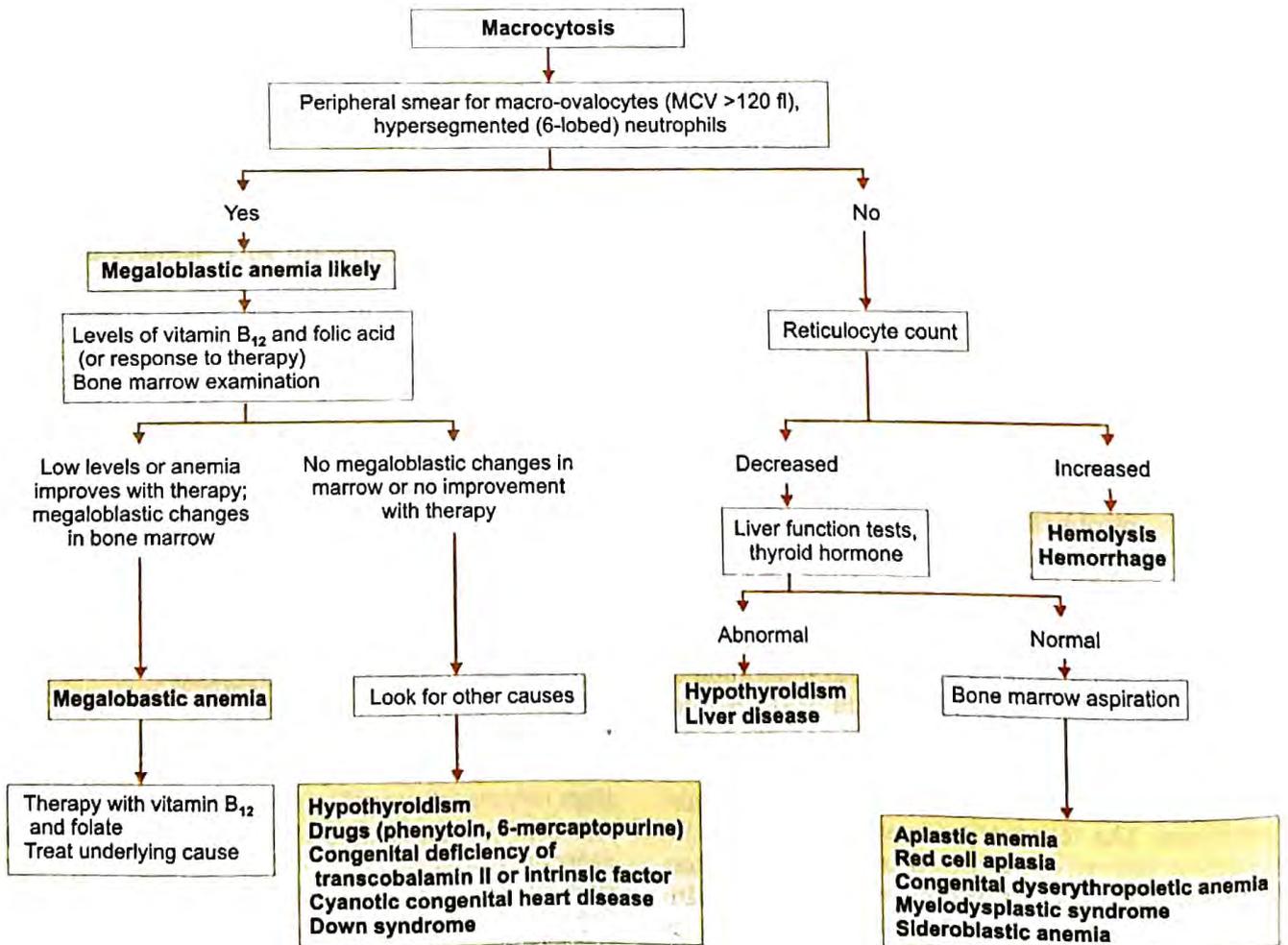


Fig. 13.3: Approach to macrocytic anemia

Suggested Reading

- National Family Health Survey-4 (2017) Government of India, available at <http://rchiips.org>
- Orkin SH, Nathan DG, Ginsburg D, Look AT, Fisher DE, Lux SE (Eds.) (2009) Nathan and Oski Hematology of Infancy and Childhood, 7th edn. Philadelphia: Saunders Elsevier.

IRON DEFICIENCY ANEMIA

Iron deficiency anemia occurs when there is a decrease in total iron body content, severe enough to diminish erythropoiesis and cause anemia.

Pathophysiology

Diminished dietary iron absorption in the proximal small intestine or excessive loss of body iron can result in iron deficiency. Iron is essential for multiple metabolic processes, including oxygen transport, DNA synthesis, and electron transport. In severe iron deficiency, iron-containing enzymes are low and can affect immune and tissue function. Iron deficiency anemia can result in diminished growth and learning and have serious consequences in children. Dietary constituents, e.g. phytates, phosphates and tannates, make non-heme iron unabsorbable.

Healthy newborn infants have a total body iron of 250 mg (~80 parts per million, ppm) that decreases to ~60 ppm in the first 6 months of life. Body iron is regulated carefully by absorptive cells in the proximal small intestine, which alter iron absorption to match body losses of iron. Breast milk iron content is more bioavailable than cow milk. Besides this fact, infants who consume cow milk have more iron deficiency because bovine milk has a higher concentration of calcium, which competes with iron for absorption and they may have gastrointestinal blood loss due to milk allergy. Intercurrent infections and infestations compound the problem.

Clinical Evaluation

Dietary history is important, including intake of milk, weaning foods and supplements. Pica increases the risk of infestations and lead poisoning. Common features of anemia are present in proportion to the severity and rate of development. Behavioral symptoms, such as irritability and anorexia, precede weakness, fatigue, leg cramps, breathlessness and tachycardia. Congestive heart failure and splenomegaly may occur with severe, persistent, untreated iron deficiency. Angular stomatitis, glossitis, koilonychia and platynychia are seen in severe iron deficiency.

Laboratory Diagnosis

The peripheral smear (Fig. 13.4) shows that red cells are microcytic and hypochromic, with anisocytosis, poikilocytosis and increased red cell distribution width (RDW). The MCV and MCHC are reduced. Red cell number is reduced, unlike in thalassemia where it is

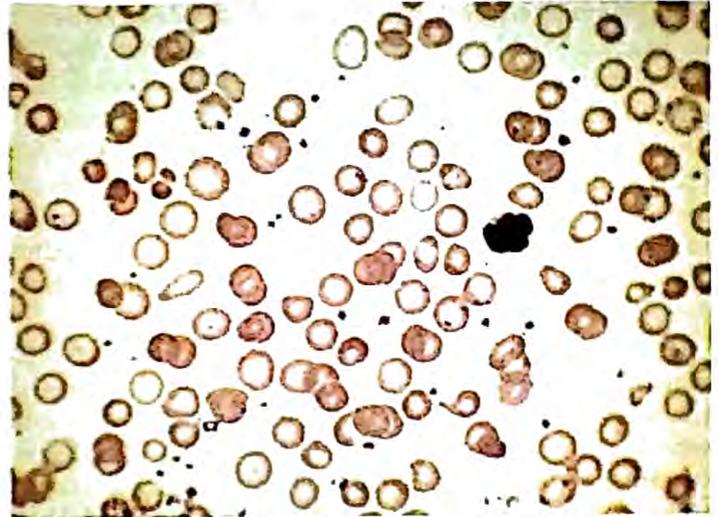


Fig. 13.4: Peripheral smear from a child with iron deficiency anemia, shows microcytosis (the red blood cells are smaller than the small lymphocyte in the field), hypochromia (central pallor >1/3rd of cell diameter), thrombocytosis, and a few ovalocytes and tear drop cells (moderate anisopoikilocytosis). Jenner-Giemsa x1000

increased. Serum iron is reduced, total iron binding capacity (TIBC) is increased and transferrin is reduced to less than 16% (normal 25–50%). The reduction in serum ferritin occurs early, and correlates with total body iron stores. Ferritin, an acute phase reactant, is elevated in inflammatory conditions, and may thus be falsely high in a sick child. High free erythrotoporphyrin (FEP) is seen before anemia develops.

Treatment

The cause of anemia should be identified and corrected. Hookworm infestation is the commonest cause of occult gastrointestinal blood loss in rural India at all ages. Dietary counseling and treatment of any other causative factors are required to prevent recurrence or failure of therapy. Close follow-up is required to assess for adequate response and correction of anemia, this will help to identify iron therapy failure (Table 13.5).

Oral iron preparations should be taken on an empty stomach or in between meals for best absorption. About

Table 13.5: Reasons for non-response to hematinic therapy for iron deficiency anemia

- Poor compliance with therapy
- Poorly absorbed iron preparation, e.g. enteric coated
- Use of H₂ blockers or proton pump inhibitors that cause achlorhydria
- Interaction with food and medications
- Associated vitamin B₁₂ or folic acid deficiency
- Underlying hemolytic anemia, inflammation or infection
- Malabsorption, e.g. celiac disease, giardiasis, *H. pylori* infection
- High rate of ongoing blood loss
- Alternative etiology, e.g. sideroblastic anemia, thalassemias, etc.

10–20% patients develop gastrointestinal side effects such as nausea, epigastric discomfort, vomiting, constipation and diarrhea. Enteric-coated preparations have fewer side effects, but are also less efficacious and more expensive. The most cost-effective oral preparation is ferrous sulfate (20% elemental iron). The dose for treatment of anemia is 3–6 mg/kg/day elemental iron. The reticulocyte count increases within 72–96 hours after initiating therapy. After correction of anemia, oral iron should be continued for 4–6 months to replenish iron stores.

Indications of parenteral iron therapy are limited to conditions such as: (i) intolerance to oral iron, (ii) malabsorptive states, and (iii) ongoing blood loss at a rate where oral replacement cannot match iron loss. Intravenous preparations are preferred over intramuscular; iron sucrose IV preparations are safe and effective. They have been used in children with end stage renal disease on dialysis and inflammatory bowel disease.

Dose Calculation for Parenteral Iron

$$\text{Total dose (mg)} = [\text{Target Hb} - \text{Actual Hb}] \times \text{Weight (kg)} \\ \times 2.4 + [15 \times \text{weight (kg)}]$$

As iron deficiency anemia is readily corrected with medication, blood transfusions should be avoided in young, stable patients. Red cell transfusions are needed in emergency situations, as in patients where the rate of blood loss exceeds the expected rise of hemoglobin, for urgent surgery, hemorrhage or severe anemia with congestive cardiac failure. In very severe anemia with congestive cardiac failure, transfusions must be given very slowly (2–3 mL/kg) with monitoring and diuretic therapy if necessary.

Suggested Reading

- Sachdeva HPS, Gera T, Nestel P. Effect of iron supplementation on mental and motor development in children: systemic review of randomized controlled trials. *Public Health Nutr* 2005; 8: 117–32.
- Shelley E Cray, Katherine Hall, George R Buchanan. Intravenous iron sucrose for children with iron deficiency failing to respond to oral iron therapy. *PBC* 2011;56(4):615–619.
- Kotecha PV. Nutritional anemia in young children with focus on Asia and India. *Indian J Community Med* 2011; 36: 8–16.

MEGALOBLASTIC ANEMIA

Megaloblastic anemia is a distinct type of anemia characterized by macrocytic red blood cells and erythroid precursors, which show nuclear dysmaturity. Common causes are deficiency of vitamin B₁₂ (cobalamin) and folic acid. The incidence varies with dietary practices and socioeconomic patterns. A study has estimated the incidence of folate deficiency as 6.8%, vitamin B₁₂ 32% and combined deficiency as 20% in north Indian children.

Pathophysiology

Megaloblastic changes affect all hematopoietic cell lines with resultant anemia, thrombocytopenia and leukopenia.

DNA synthesis is impaired because of lack of methyl-tetrahydrofolate (a folic acid derivative). Vitamin B₁₂ plays an important role as a cofactor in this reaction, which is necessary for DNA base synthesis.

Etiology

The two most common causes of megaloblastic anemia are vitamin B₁₂ deficiency (cobalamin) and folic acid deficiency. Folate deficiency can be caused by decreased ingestion, impaired absorption (e.g. celiac disease, malabsorption states), impaired utilization (e.g. methotrexate, 6-mercaptopurine, trimethoprim, azathioprine, phenytoin) (Table 13.6) and increased requirement (e.g. infancy, hyperthyroidism, chronic hemolytic disease). Vitamin B₁₂ deficiency can be caused by decreased ingestion, impaired absorption (e.g. intestinal parasites, intrinsic intestinal disease, failure to release vitamin B₁₂ from protein, intrinsic factor deficiency), or impaired utilization (e.g. congenital enzyme deficiencies: orotic aciduria). Folate deficiency can occur during prolonged parenteral nutrition and hemodialysis, as folic acid is lost in dialysis fluid. History of autoimmune disorders may be found in patients of pernicious anemia.

Nutritional deficiency is more common in vegan families (vegetarian with little or no dairy products) and those consuming only goat milk (folate deficient). In infants, it is related to maternal deficiency with inadequate body stores and prolonged exclusive breastfeeding (breast milk is a poor source of vitamin B₁₂ and associated with reduced access to other foods). *Giardia* infection is shown to cause folate malabsorption. *H. pylori* infections are implicated in vitamin B₁₂ malabsorption in adults. Rarely inherited metabolic disorders may cause megaloblastic anemia (Table 13.7).

Clinical Manifestations

A careful dietary history is essential to the diagnosis of megaloblastic anemia. The type and quantity of foods should be documented. Medication intake and history of any other contributing medical disorders and infestation needs to be taken. Anemia, anorexia, irritability and easy fatigability are clinical features common to other causes

Table 13.6: Drugs that cause megaloblastic anemia

<i>Impaired folic acid absorption:</i>	Phenytoin, phenobarbital
<i>Impaired cobalamin absorption:</i>	Proton pump inhibitors
<i>Interference with folate metabolism:</i>	Methotrexate, trimethoprim, pyrimethamine
<i>Interference with cobalamin metabolism:</i>	Metformin, neomycin
<i>Purine analogs:</i>	6-Mercaptopurine, 6-thioguanine, azathioprine
<i>Ribonucleotide reductase inhibitors:</i>	Hydroxyurea, cytarabine, arabinoside
<i>Pyrimidine analogs:</i>	Zidovudine, 5-fluorouracil

Table 13.7: Metabolic causes of megaloblastic anemia**Inborn errors of cobalamin metabolism**

Congenital intrinsic factor deficiency
 Deficiency of transcobalamin I and II
 Cobalamin malabsorption due to defect in intestinal receptor (Imerslünd-Grasbeck syndrome)
 Methylmalonic aciduria
 Homocystinuria

Inborn errors of folate metabolism

Congenital folate malabsorption
 Dihydrofolate reductase deficiency
 N⁵-methyltetrahydrofolate homocysteine methyltransferase deficiency

Other inborn errors

Hereditary orotic aciduria
 Lesch-Nyhan syndrome
 Thiamine responsive megaloblastic anemia

of anemia. Patients should be examined for signs of thrombocytopenia and neutropenia. Features characteristically found in megaloblastic anemia include glossitis, stomatitis and hyperpigmentation of the skin on knuckles and terminal phalanges, enlargement of liver and spleen (30–40% cases). Neurologic signs may precede the onset of anemia. Petechiae and hemorrhagic manifestations have been reported in 25% cases. Pancytopenia and hepatosplenomegaly can make it difficult to differentiate from leukemia. The child should be evaluated for signs of malabsorption such as weight loss, abdominal distention, diarrhea, and steatorrhea. Abdominal scars from ileal resections may be present.

A neurologic examination is mandatory, it may reveal loss of position and vibratory sensation, which are the earliest neurologic signs. Later other posterior and lateral column deficits may be found. Memory loss, confusion and neuropsychiatric symptoms can occur. Persistence of neurological sequelae can be found even after treatment of the deficiency.

Laboratory Evaluation

A complete hemogram with red cell indices shows macrocytosis (>110 fl highly suggestive of megaloblastic anemia) and cytopenias. Hypersegmented neutrophils (nucleus >6 lobes) may be seen. The reticulocyte count should be performed; if available, serum B₁₂ and folate levels are assayed. The Schilling test, which requires radioactive labeled B₁₂, is used to identify pernicious anemia and for evaluation of deficiency states.

Bone marrow evaluation should be performed in any child with more than one abnormal hematological cell line. It can help to rule out other disorders such as leukemia, myelodysplasia, and aplastic anemia. In megaloblastic anemia, the bone marrow will be cellular (Fig. 13.5) and show red blood cell precursor nuclear-cytoplasmic asynchrony. Granulocyte precursors may also be



Fig. 13.5: Peripheral smear of a 12-year-old girl with megaloblastic anemia showing hypersegmented polymorphonuclear cell. Note that the nucleus has more than 5 lobes

abnormal. Serum chemistry may reveal elevated lactic dehydrogenase (LDH) and bilirubin.

Differential Diagnosis

Other causes of macrocytosis should be considered in the differential diagnosis of megaloblastic anemia. These causes include aplastic anemia and other marrow failure syndromes (pure red cell aplasia, Fanconi anemia, transient erythroblastopenia of childhood), congenital dyserythropoietic anemia, chronic liver disease, hypothyroidism, cold agglutinin disease, neoplastic (e.g. myelodysplastic syndromes) and HIV infections.

Treatment

Treatment depends on the underlying cause. If the cause is not identified, therapeutic doses of folate (1–5 mg/day) and vitamin B₁₂ (1000 µg) are administered. Only folate therapy may correct the anemia, but will not correct cobalamin deficiency-associated neurological disorder and result in the progression of neuropsychiatric complications. Folate deficiency due to dietary insufficiency or increased demands is best treated with folate supplements. Folate deficiency due to use of anti-folate medications is managed by reducing or eliminating the implicating agent and supplementation with folic acid. Folate is available as 5 mg tablet and overdose is not associated with any adverse effects; a dose of 1–5 mg/day is recommended for 3–4 weeks.

Parenteral vitamin B₁₂ at a dose of 1 mg (1000 µg) is given intramuscularly; lower doses (250 µg) can be used in infants. A decrease in MCV, reticulocytosis and higher platelet and neutrophil counts is observed within a few days of therapy. In patients with pernicious anemia and malabsorptive states, vitamin B₁₂ (1000 µg) should be given IM daily for

2 weeks, then weekly until the hematocrit value is normal and then monthly for life. Patients with neurological complications should receive 1000 µg IM every day for 2 weeks, then every 2 weeks for 6 months and monthly for life. Oral supplements can be administered; however, absorption is variable and may be insufficient in some patients. In dietary insufficiency, no standard duration of therapy has been defined. Dietary counseling is advised, along with vitamin B₁₂ supplements (oral daily or parenteral dose every 3–12 months).

Suggested Reading

- Devalia V, Hamilton MS, Molley AM. Guidelines for the diagnosis and treatment of cobalamin and folate disorders. *Br J Haematology* 2014; 166:496–513.

HEMOLYTIC ANEMIAS

The term 'hemolytic anemia' is limited to conditions in which rate of red cell destruction is accelerated and ability of the bone marrow to respond to the anemia is unimpaired. Table 13.8 lists important causes. Under maximal stimulation, the normal marrow is capable of increasing its production about 6–8 times its basal level. The reticulocyte count is useful in determining the rate of red cell destruction. The normal reticulocyte count value in the newborn is 3.2±1.4% and in children 1.2±0.7%.

Table 13.8: Causes of hemolytic anemia

Acquired

Mechanical: Macroangiopathic (artificial heart valves, march hemoglobinuria); microangiopathic (disseminated intravascular coagulation, hemolytic uremic syndrome, thrombotic thrombocytopenic purpura)

Infections: Malaria, kala-azar, *Clostridium welchii*

Antibody mediated: Autoimmune hemolytic anemia (warm and cold types)

Transfusion reactions: Immediate and delayed

Hemolytic disease of the newborn

Drugs: Cefotetan, ceftriaxone

Hypersplenism

Cryopathy, e.g. cold agglutinin disease, paroxysmal cold hemoglobinuria

Physical injury, e.g. burns

Chemical injury: Snake bite, lead and arsenic toxicity

Inherited

Hemoglobinopathies, e.g. thalassemia, sickle cell disease

Red cell membrane defect, e.g. glucose-6-phosphate dehydrogenase deficiency

Disorders of the cytoskeletal membrane, e.g. hereditary spherocytosis

Unstable hemoglobins

Lipid membrane defects, e.g. abetalipoproteinemia

Porphyria

Clinical Features

In acute hemolysis, symptoms are related to the rate of fall of hemoglobin. In rapidly occurring hemolysis, the symptoms are more numerous and pronounced. Evidence of anemia as seen by weakness, pallor, fatigue may be seen. In some hemolytic anemias, jaundice is a prominent finding and red urine occurs in intravascular hemolysis. Splenomegaly is seen in autoimmune and many congenital forms of hemolytic anemias. The presence of gallstones and icterus (hereditary spherocytosis), hemolytic/thalassemic facies (thalassemia major, intermedia) (Fig. 13.6), leg ulcers (sickle cell disease) can help lead investigations; confirmatory tests are still required.

Laboratory Manifestations

Laboratory findings in hemolytic anemia are: (i) increased erythrocyte destruction (Table 13.9), (ii) compensatory increase in erythropoiesis (Table 13.10), and (iii) features specific to particular hemolytic anemia. An elevated corrected reticulocyte count may be the only feature of mild hemolytic anemia. The Coombs test is the most

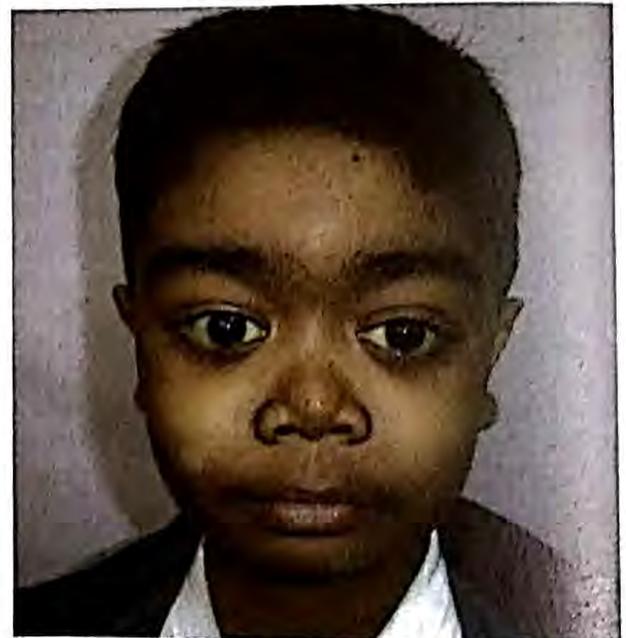


Fig. 13.6: Child with hemolytic anemia, showing hemolytic facies and icterus

Table 13.9: Laboratory signs of accelerated erythrocyte destruction

- Fall in blood hemoglobin level at >1.0 g/dL per week
- Increased serum level of unconjugated bilirubin
- Increased urinary urobilinogen excretion
- Increased serum lactate dehydrogenase
- Reduced haptoglobin and hemopexin
- Reduced glycosylated hemoglobin
- Decreased erythrocyte lifespan (using radioisotope ⁵¹Cr)

Table 13.10: Laboratory signs of accelerated erythropoiesis**Peripheral blood**

Polychromasia or reticulocytosis

Macrocytosis

Increase in nucleated red cells

Bone marrow

Erythroid hyperplasia

Iron kinetic studies

Increased plasma iron turnover

Increased erythrocyte iron turnover

important initially test to perform to define the etiology of hemolysis. A direct antiglobin (direct Coombs) test is positive in most cases of immune hemolytic anemia and implies that the erythrocyte is coated with IgG or C3 component of complement. However, the test may be negative in 2–5% of patients with immune hemolysis.

Haptoglobin and hemopexin are proteins which bind to hemoglobin and heme released from red cells following their destruction. The protein complexes formed after intravascular hemolysis are removed by circulation. Haptoglobin and hemopexin levels are, therefore, low in patients with hemolytic anemia. When haptoglobin is saturated, free plasma hemoglobin can be detected. While the level of indirect bilirubin provides evidence for hemolysis, it is relatively insensitive and is elevated only if the liver function is impaired or when hemolysis is extensive.

Intravascular and Extravascular Hemolysis

Intravascular hemolysis occurs when the released hemoglobin is released into the plasma (hemoglobinemia). A part of the circulating free hemoglobin is converted to methemoglobin, which binds with albumin to form methemalbumin, this confers a brown colour to plasma for several days following hemolysis. When the amount of hemoglobin exceeds the haptoglobin binding capacity it is excreted in the urine (hemoglobinuria), and to some extent is reabsorbed in the proximal renal tubules. The loss of heme-laden tubular cells is seen as hemosiderinuria. In extravascular hemolysis, hyperbilirubinemia is seen, but no free hemoglobin is seen in the plasma. Hence no hemoglobinemia, hemoglobinuria or hemosiderinuria is found in the latter.

A peripheral smear is useful in evaluation of hemolytic anemia. The smear may show malarial parasites, spherocytes (hereditary spherocytosis, following transfusion), bite cells (G6PD deficiency), microcytosis with fragmented red cells (thalassemia) and thrombocytopenia with schistocytes (disseminated intravascular coagulopathy, thrombotic microangiopathy). Specific tests, e.g. hemoglobin electrophoresis, osmotic fragility, enzyme assays (G6PD, pyruvate kinase deficiency), and assay for CD55/59 (paroxysmal nocturnal hemoglobinuria) are required.

Hemolytic disorders may be divided into inherited and acquired varieties. This classification has a pathogenetic significance because the nature of hereditary lesions differs from those acquired. Most intrinsic defects are inherited and the extrinsic are acquired. There are a few exceptions to this generalization; these include paroxysmal nocturnal hemoglobinuria, an acquired disorder characterized by an intrinsic red cell defect.

Management

In an acute attack of hemolysis, it is important to maintain fluid balance and renal output. Shock is managed by standard measures. Blood transfusions, so useful in acute anemia of other types, must be used with caution in patients with acquired anemias. Even with careful blood matching, destruction of transfused blood with increased burden on excretory organs and risk of thromboses may occur. Acute autoimmune hemolytic anemia is treated with steroids (prednisone 1–2 mg/kg/day), gradually tapered over several months, once the patient shows resolution of hemolysis. In chronic hemolysis, the etiology needs to be investigated and treated accordingly.

Hereditary Spherocytosis

Several membrane protein defects are identified in hereditary spherocytosis. Many of these result in instability of spectrin and ankyrin, the major skeletal membrane proteins. The degree of skeletal membrane protein deficiency correlates with the degree of hemolysis. Structural changes lead to membrane instability, loss of surface area, abnormal membrane permeability and reduced red cell deformability. These defects are accentuated by metabolic depletion, demonstrated by increase in osmotic fragility after 24 hours incubation of blood at 37°C. The spleen is the site of destruction of these non-deformable erythrocytes.

Patients have a mild to moderate chronic hemolytic anemia. The MCV is decreased; the MCHC is increased due to cellular dehydration. The red cell distribution width (RDW) is increased due to the presence of spherocytes and increased reticulocytes. Patients often present with jaundice; splenomegaly is seen in ~75% patients and pigment gallstones are frequent.

Patients require lifelong folic acid supplementation (1–5 mg/day) due to high turnover rate of erythropoiesis. Splenectomy does not cure the underlying disorder but reduces the degree of hemolysis, and is considered in patients with severe hemolysis and high transfusion requirement. In children with excessively large spleens, splenectomy may diminish the risk of its traumatic rupture. Splenectomy is performed after 6 years of age, following immunization for *H. influenzae* type b, *S. pneumoniae* and *N. meningitidis*. Prolonged prophylactic therapy with penicillin may be required following splenectomy to reduce the risk of sepsis.

Abnormalities in Red Cell Glycolysis

Glucose is the primary metabolic substrate for erythrocytes. Since the mature red cell does not contain mitochondria, glucose is metabolized by anaerobic pathways, the two chief being the Embden-Meyerhof pump (EMP) and the hexose monophosphate shunt (HMS). EMP accounts for 90% of glucose utilization. The inability to maintain adenosine triphosphate required for cellular functions such as deformability, membrane lipid turnover and membrane permeability results in the shortened red cell life. HMS, responsible for remaining 10% of glucose metabolism, generates substrates which protect red cells against oxidant injury. A defect in the HMS causes oxidized hemoglobin (Heinz bodies), lipids and membrane proteins to collect in the red cell, resulting in hemolysis. The reticulocyte count is raised; bone marrow shows erythroid hyperplasia. A useful screening test is autohemolysis and diagnosis is by specific enzyme assays.

Glucose-6-phosphate Dehydrogenase (G6PD) Deficiency

G6PD deficiency, an X-linked disorder with full expression in affected males, is the most common red cell enzyme deficiency. Variants of the deficiency have been identified, which vary in antioxidant reserve and enzyme levels. After oxidant exposure, hemoglobin is oxidized to methemoglobin and denatured to form intracellular inclusions (Heinz bodies). Heinz bodies attach to the red cell membrane and aggregate intrinsic membrane proteins such as band 3. Reticuloendothelial cells identify these changes as an antigenic site on the red cell membrane, and ingest a part of the red cell shortening its life.

Hallmarks of a hemolytic crisis are pallor, icterus, hemoglobinemia, hemoglobinuria and splenomegaly. Plasma haptoglobin and hemopexin are low. The child may present with jaundice in neonatal period. Peripheral smear shows fragmented bite cells and polychromasia; special stains show Heinz bodies during the initial a few days of hemolysis. The diagnosis of G6PD deficiency is based on family history, clinical and laboratory features, and exposure to oxidants prior to the hemolytic event. Confirmation of the diagnosis is by quantitative enzyme assay or molecular gene analysis. Management consists of supportive care for the acute crisis (hydration, transfusions, if needed, and monitoring) along with folic acid supplements. Counseling to avoid exposure to oxidant drugs is imperative (Table 13.11).

Table 13.11: Drugs that cause oxidant stress and hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency

Sulfonamides: Sulfamethoxazole

Antimalarials: Primaquine, quinine

Analgesics: Aspirin, non-steroidal anti-inflammatory drugs, phenazopyridine (pyridium)

Others: Nitrofurantoin, dapsone, methylene blue, rasburicase, toluidine blue, nalidixic acid, furazolidone, quinidine

Pyruvate Kinase (PK) Deficiency

PK deficiency is the most common EMP defect, inherited in an autosomal recessive manner. The clinical spectrum is variable. Homozygotes show splenomegaly, icterus and hemolytic anemia; heterozygotes are asymptomatic. Management includes splenectomy and folate supplements to prevent megaloblastic complications.

Autoimmune Hemolytic Anemia

This arises as an autoimmune phenomenon targeting red cells, which might be isolated or complication of an infection (hepatitis B, upper respiratory infections, mononucleosis, cytomegalovirus infection), systemic lupus or other autoimmune syndromes, immunodeficiency states and malignancies. The disease has an acute onset, manifested by weakness, pallor and fatigue. Jaundice is a prominent finding and splenomegaly is often present. Some cases are chronic. Evidence of an underlying disease (e.g. lupus, HIV) may be present. The anemia may be severe and result in cardiovascular collapse, requiring emergency management.

The anemia is normochromic and normocytic, which may vary from mild to severe (hemoglobin level <5 g/dL); reticulocyte count is usually increased. Spherocytes and nucleated red cells may be seen on the peripheral smear. Other findings include increased lactic dehydrogenase, indirect and total bilirubin, aspartate aminotransferase and urinary urobilinogen. Intravascular hemolysis is indicated by hemoglobinemia or hemoglobinuria. Examination of the bone marrow shows erythroid hyperplasia, but is seldom required.

In almost all cases, the direct antiglobulin (direct Coombs) test is positive. Further evaluation allows distinction into one of three syndromes.

- i. Presence of IgG on patient red blood cells, maximal in vitro antibody activity at 37°C, specificity for Rh-like antigen constitute warm autoimmune hemolytic anemia with extravascular destruction by the reticulo-endothelial system. This can also be due to many drugs causing hapten or autoantibody type hemolysis.
- ii. Detection of complement alone on red blood cells, optimal reactivity in vitro at 4°C, i or I antigen specificity are diagnostic of cold autoimmune hemolytic anemia with intravascular hemolysis. This condition is usually seen only in adults. In children, Donath Landsteiner hemolytic anemia, associated with an acute viral syndrome and mediated by cold hemolysin occurs frequently. Paroxysmal cold hemoglobinuria is identical to cold autoimmune hemolytic anemia, except for P-antigen specificity and in vitro hemolysis. Paroxysmal cold hemoglobinuria is associated with significant infections, such as mycoplasma, Epstein-Barr virus and cytomegalovirus.
- iii. Occasionally, IgG and complement associated hemolytic anemia due to warm antibody or rarely drug associated autoimmune hemolytic anemia.

Treatment

Medical management of any underlying disease is important in symptomatic cases. Most patients with warm autoimmune hemolytic anemia (where hemolysis is extravascular), respond to therapy with prednisone (1 mg/kg for 4 weeks, or till hemoglobin is stable). After initial treatment, the dose of steroids is tapered over 4–6 months. In severe cases, other immunosuppressive agents such as cyclophosphamide, azathioprine, cyclosporine and danazol may be tried alone or in combination with corticosteroids. Some patients may respond to intravenous immunoglobulin (IVIg; 1 g/kg/d for 2 days), although the response is not sustained. Although the rate of remission with splenectomy is as high as 50% particularly in warm autoimmune hemolytic anemia, the procedure should be withheld until other treatments have failed. Refractory cases may respond to rituximab or hematopoietic stem cell transplantation.

Patients with cold autoimmune hemolytic anemia and paroxysmal cold hemoglobinuria are less likely to respond to corticosteroids or IVIG. These syndromes are associated with infections and have an acute, self-limited course. Supportive care including transfusion of compatible blood may often be necessary, but should be monitored closely. In most patients, crossmatch compatible blood will not be found, and the least incompatible unit should be identified by the blood bank. Transfusions must be conducted carefully, beginning with a test dose.

Prognosis

Children with warm autoimmune hemolytic anemia are at higher risk for more severe and chronic disease with higher morbidity and mortality. Hemolysis and the positive antiglobulin tests may continue for months or years. Patients with cold autoimmune hemolytic anemia or paroxysmal cold hemoglobinuria are more likely to have acute self-limited disease (<3 months).

Suggested Reading

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- Gupta N, Sharma S, Seth T, et al. Rituximab in steroid refractory autoimmune hemolytic anemia. Indian J Pediatr 2012; 79: 803–805.

THALASSEMIAS

Thalassemia is a Greek term derived from *thalassa*, which means “the sea” (Mediterranean sea) and *emia*, which means “related to blood”. It occurs due to globin gene defects, one of the commonest monogenic diseases. Molecular biology and genetics of thalassemia syndromes have revealed more than 200 mutations, across populations from Southeast Asia to Africa. Carrier rates for thalassemia reported in North Indians, varies in different ethnic groups from 3–17%.

The major hemoglobin in children after 1 year of age, HbA constitutes approximately 90%, and a minor component, HbA₂ accounts for 23%. The main hemoglobin in fetal life is HbF of which only traces remain after 1 year of life.

Pathophysiology

Thalassemias are inherited disorders of hemoglobin synthesis that result from alteration in the rate of globin chain production. A decrease in the rate of production of a globin (α , β , γ , δ) impedes hemoglobin synthesis and creates an imbalance with normally produced globin chains. Because two types of chains (α and non- α) pair with each other at a ratio close to 1:1 to form normal hemoglobin, an excess of the normally produced type is present and accumulates in the cell as an unstable product, leading to early destruction of the red cell.

The type of thalassemia usually carries the name of the under produced chain or chains. The reduction may vary from a slight decrease to a complete absence. When β chains are produced at a lower rate, the thalassemia is termed β^+ , whereas β^0 thalassemia indicates a complete absence of production of β chains from the involved allele. The disease is inherited in a Mendelian recessive fashion. Advances in knowledge of molecular genetics have led to considerable progress in control of thalassemias. Carriers are relatively easy to identify and screen. Prenatal diagnosis and genetic counseling programs in many countries have led to a dramatic reduction in the frequency of births of children with thalassemias major. Awareness is required amongst health professionals and the public to control this disease in India.

Presentation

Thalassemia should be considered in any child with hypochromic, microcytic anemia that does not respond to iron supplementation. Children with thalassemia major usually demonstrate no symptoms until about 3–6 months of age (when chains are needed to pair with chains to form HbA, after chains production is turned off). The condition may not be recognized because of the delay in cessation of HbF production till 3–5 years of age in some cases. Severe pallor and hepatosplenomegaly are almost always present. Icterus is usually not seen but mild to moderate jaundice may be found due to liver dysfunction from iron overload and chronic hepatitis.

Features of severe anemia, including intolerance to exercise, irritability, murmur or signs of heart failure may be present. Bony abnormalities, such as frontal bossing, prominent facial bones and dental malocclusion are usually present (Fig. 13.6). Ineffective erythropoiesis creates a hypermetabolic state associated with fever and failure to thrive. Hyperuricemia may be present.

Spectrum of β Thalassemias

β thalassemia trait: Patients have mild anemia and abnormal red cell indices; high performance liquid chromatography (HPLC) or hemoglobin electrophoresis shows elevated levels of HbA₂ or HbF, or both. Peripheral blood film examination shows marked hypochromia, microcytosis (without anisocytosis, which is found with iron deficiency) and target cells.

Thalassemia intermedia: This condition, found in compound heterozygous state, presents with anemia of varying severity, which may or may not require regular blood transfusions. Icterus and splenomegaly are present. These patients require monitoring over time to understand the spectrum of the disease.

Thalassemia major: The condition is characterized by transfusion dependent anemia, splenomegaly, bony deformities, growth retardation and hemolytic facies in untreated or inadequately treated individuals. Blood smear shows hypochromia, microcytosis, marked anisocytosis, fragmented and nucleated red cells, polychromasia and occasionally immature leukocytes. Organomegaly is reduced in well-transfused patients, but is marked in patients receiving irregular or inadequate transfusion support.

β thalassemia with β chain structural variants: The most significant condition in this group is HbE. Patients with HbE/ β thalassemia may show severe symptoms identical to patients with thalassemia major or a milder course similar to thalassemia intermedia or minor. The variation in severity can be explained because of different genotypes, (i.e. β^+ or β^0), the co-inheritance of α thalassemia gene, level of HbF and presence of other modifying genes.

Laboratory Studies

Complete blood count and peripheral blood film results are sufficient to suspect the diagnosis. In thalassemia major and intermedia, the hemoglobin level ranges from 2–8 g/dL; MCV and MCH are significantly low. Reticulocyte count is elevated to 5–8% and leukocytosis is usually present. A shift to the left is also encountered, reflecting the hemolytic process. The platelet count is usually normal, unless the spleen is markedly enlarged and causing hypersplenism.

Peripheral blood film reveals hypochromasia and microcytosis, polychromatophilia, nucleated red blood cells, basophilic stippling and occasional immature leukocytes (Figs 13.7 and 13.8). An HPLC sample must be sent prior to the first blood transfusion to confirm the diagnosis of thalassemia that shows absence of HbA and high levels of HbF. Elevated HbA₂ is characteristic of thalassemia trait.

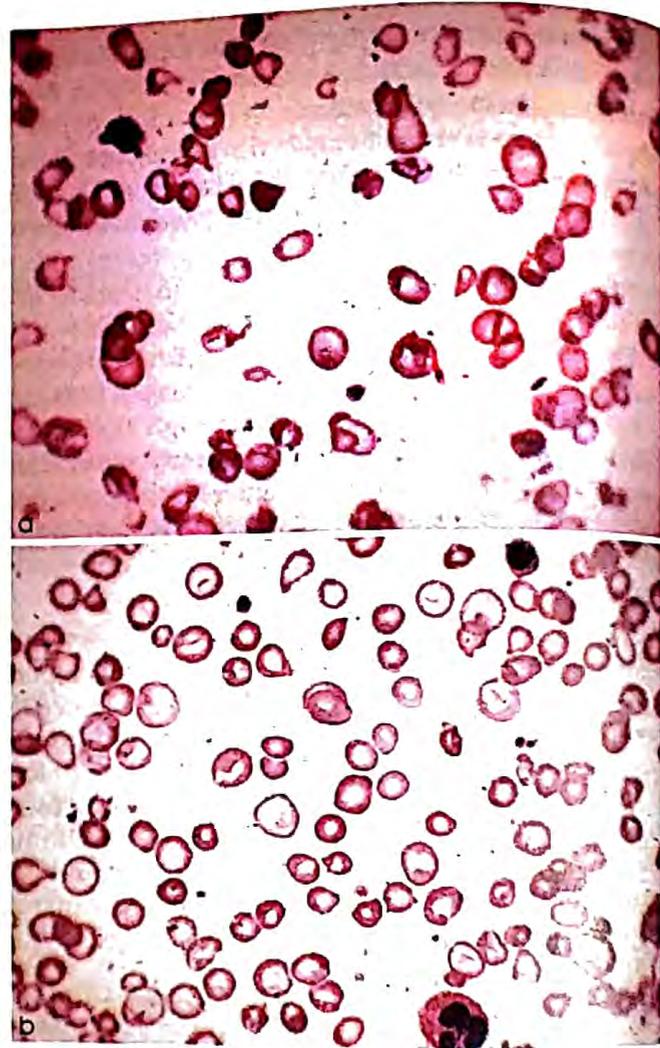


Fig. 13.7: Peripheral smears from a transfusion dependent patient with beta thalassemia major showing marked anisopoikilocytosis, microcytosis, hypochromia, polychromatophilia, nucleated red blood cells and a few fragmented erythrocytes. Jenner-Giemsa $\times 1000$

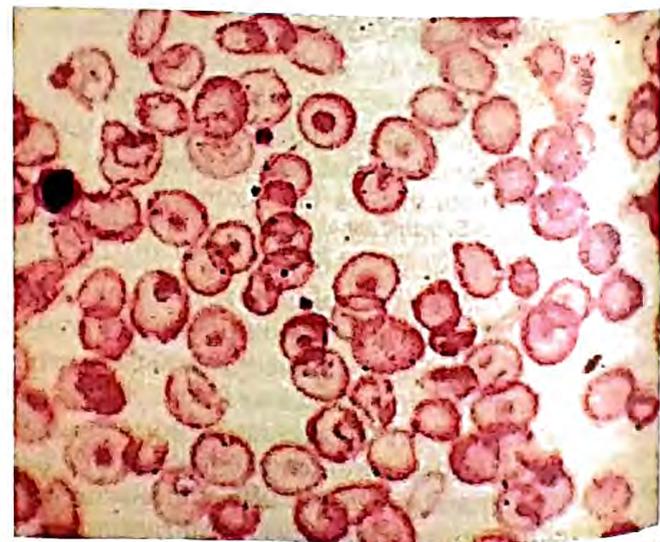


Fig. 13.8: Peripheral smear from an asymptomatic patient with hemoglobin E disease, showing microcytosis, hypochromia, target cells and nucleated red blood cells. Jenner-Giemsa $\times 1000$

Management

Genetic counseling is needed for the couple and their family to prevent the birth of other children with thalassemia major. Prenatal testing is available to ensure the second child of the afflicted family does not have thalassemia major. The availability of hematopoietic stem cell transplantation offers the possibility of cure in severe forms of thalassemia.

Patients with thalassemia major require medical supervision to monitor for complications. Blood transfusion should be initiated at an early age when the child is asymptomatic and attempts should be made to keep pretransfusion hemoglobin level at 9–10 g/dL (to promote growth and prevent deformities). Chelation therapy for the accumulated iron overload is necessary to prevent organ dysfunction. A normal diet is recommended, with the following supplements: Folic acid, small doses of ascorbic acid (vitamin C), and alpha-tocopherol (vitamin E). Iron preparations as hematinics or dietary supplements should not be given. Drinking tea with meals has been shown to decrease absorption of iron in the gut.

Blood Transfusions and Infections

After multiple transfusions, patients often develop transfusion reactions or alloimmunization to red cell antigens. These complications can be minimized by using leukocyte filters during transfusion or having blood banks prepare leuko-poor packed red cells. Administration of acetaminophen and diphenhydramine hydrochloride before transfusion(s) minimizes febrile or allergic reactions. The major complications are those related to transmission of blood-borne viral infections. Hepatitis B vaccination and regular assessment of hepatitis C and HIV status are part of routine care. Folate supplements are required; ferritin levels are used to monitor iron overload.

Lactoferrin, a prominent component of granules of polymorphonuclear leukocytes, is bacteriostatic for many pathogens. Very high transferrin saturation in patients with iron overload affects the bacteriostatic properties of the protein, resulting in increased risk of infections with *Y. enterocolitica* that presents with fever and diarrhea. Other important infections which may occur are mucormycosis and *Listeria monocytogenes*.

Iron Overload

Iron overload is a major cause of morbidity. The excessive load of iron is due to increased gastrointestinal iron absorption as well as repeated transfusions. Patients show signs of endocrinopathy affecting pancreas, thyroid and parathyroid glands, decreased growth and lack of sexual maturation. The simplest method for monitoring iron status is by estimating serum ferritin. Other investigations include liver biopsy, liver MRI and echocardiography. An accurate and noninvasive tool to assess cardiac iron status is cardiac T_2^* magnetic resonance (CMR).

Chelation Therapy

The introduction of chelating agents capable of removing excess iron from the body has dramatically increased life expectancy. The cost, however, has resulted in poor compliance and inadequate dosing of iron chelators in many Indian patients. Combination therapy may be needed in children not adequately controlled by appropriate use on a single iron chelator.

Deferoxamine (DFO) is administered by subcutaneous infusion pump (40–60 mg/kg/day over 8–12 hours for 5–6 days/week). Higher doses of DFO may be administered IV when serious iron overload such as cardiac failure occurs. Eye examinations, hearing tests and renal function tests are required to monitor the effects of DFO therapy. Deferasirox is an oral chelating agent, which binds iron with high affinity and is excreted in bile and via the feces. This chelator is highly selective for iron and chelates both intracellular and extracellular excess iron. The dose is 30 mg/kg dissolved in water and taken daily. Deferiprone is an oral chelating agent, which is less effective than DFO in preventing organ damage. It is administered at a dose of 75 mg/day, but should be given under supervision for side effects including arthritis, neutropenia and agranulocytosis.

Splenectomy

The spleen acts as a store for nontoxic iron, protecting the body from extra iron thus early removal of the spleen may be harmful. Splenectomy is justified only in hypersplenism, leading to excessive destruction of erythrocytes and thus increasing the need for frequent blood transfusions, resulting in further iron accumulation. Patients who require more than 200–250 mL/kg of packed red blood cells per year to maintain hemoglobin may benefit from this procedure. Pre-splenectomy immunizations and prophylactic antibiotics have significantly decreased infections in splenectomized children. The procedure is delayed until the child is aged 5 years old. This is rarely required in children receiving adequate transfusion therapy.

Other Complications

Bone problems: The classic "hair on end" appearance of the skull, results from widening of the diploic spaces and the maxilla may overgrow, resulting in maxillary overbite and prominence of the upper incisors. These changes contribute to the classic hemolytic/chipmunk facies observed in patients with thalassemia major. Osteoporosis and osteopenia may result in fractures; the child may need treatment with calcium, vitamin D and bisphosphonates to improve bone density.

Extramedullary hematopoiesis: This usually occurs in patients with thalassemia intermedia who are not receiving transfusion therapy. They may cause neuropathy or paralysis from compression of the spine or peripheral

nerves. Compression fractures and paravertebral expansion of extramedullary masses, which behave like tumors, are seen during the second decade of life.

Psychosocial: As these children survive into adulthood, problems related to employment, marriage and having families, as well as the stress of chronic illness will need to be addressed.

Cure of Thalassemia Major

Hematopoietic stem cell transplantation (HSCT) is the only known curative treatment for thalassemia. Poor outcome of HSCT occurs in patients with hepatomegaly, portal fibrosis and inadequate chelation prior to transplant. The event-free survival rate for patients who have all three features is 59%, compared to 90% for those who do not.

Management of Other Thalassemia States

Thalassemia intermedia patients require monitoring to assess the need for transfusion as persistently low hemoglobin may retard growth. Hydroxyurea at a dose of 15–20 mg/kg/day may be used in an attempt to increase HbF production and reduce the need for transfusions. This therapy is most effective in those children with *XLM1* mutation.

Patients with thalassemia trait do not require medical follow-up after the initial diagnosis; iron therapy should not be used unless definite deficiency is confirmed. Genetic counseling is indicated to create awareness and prevent thalassemia major in subsequent offspring.

Suggested Reading

- Nadkarni A, Gorakshakar AC, Krishnamoorthy R, et al. Molecular pathogenesis and clinical variability of beta thalassemia syndromes among Indians. *Am J Hematol* 2001; 68: 75–80.
- Prevention and control of hemoglobinopathies in India: Thalassemias, sickle cell disease and other variant hemoglobins. National Health Mission, Government of India. nhm.gov.in/nrhm-components

SICKLE CELL ANEMIA

13 Sickle cell anemia, which occurs in India with a gene frequency of 4.3%, is relatively common in multiple states including Odisha, Maharashtra, Madhya Pradesh, Jharkhand and Gujarat.

Pathophysiology

Sickle cell anemia, an autosomal recessive disease, results from the substitution of valine for glutamic acid at position 6 of the beta-globin gene. Sickled red cells are less deformable, and obstruct the microcirculation, resulting in tissue hypoxia that perpetuates sickling. Deoxygenation of the heme moiety of sickle hemoglobin (HbSS) leads to hydrophobic interactions between adjacent molecules that aggregate into larger polymers. The affected cells are rapidly hemolyzed and have a lifespan of ~10–20 days (normal 120 days). Patients who are homozygous for the

sickle cell gene have sickle cell disease; those who are heterozygous have the sickle trait.

Clinical Evaluation

History is taken for the site, character, frequency, duration, and severity of pain, and precipitating or relieving factors. Pain is the most common presentation of a vaso-occlusive crisis. Shortness of breath or dyspnea is suggestive of acute chest syndrome. Neurological symptoms, such as unilateral weakness, aphasia, paresthesias, and visual symptoms (retinal hemorrhage) may suggest stroke or infarct. Sudden increase in pallor, syncope or sudden pain or increase in left-sided abdomen mass may indicate a splenic sequestration crisis.

Icterus (unconjugated bilirubin), pallor and mild splenomegaly in a young child are the usual presentations. The disease may manifest as a febrile episode as patients are prone to pneumococcal, *Salmonella* and other bacterial infections. Each episode of fever should be screened for a focus of infection and treated promptly. Tachypnea suggests pneumonia, congestive heart failure or acute chest syndrome. Hypoxia is commonly seen in patients with acute chest syndrome. Severe anemia may occur with aplastic crisis; patients may have signs of congestive heart failure. Hypotension and tachycardia are signs of septic shock or sequestration crisis. Growth retardation and gallstones are common and need medical attention. The spleen undergoes autoinfarction and is usually not palpable beyond 6 years of age.

Types of Crisis

- Vaso-occlusive crisis:** This crisis occurs when the microcirculation is obstructed by sickled red cells, resulting in ischemic injury. Pain is the chief complaint; bones (e.g. femur, tibia and lower vertebrae) are frequently involved. Vaso-occlusion may present as dactylitis or as hand and foot syndrome (painful swollen hands and/or feet in children). Vaso-occlusion may mimic an acute abdomen. The spleen develops autoinfarcts and becomes fibrotic. In the kidney, it results in papillary necrosis, which results in isosthenuria (inability to concentrate urine). Vaso-occlusive crises can involve the lungs and cause acute chest syndrome; retinal hemorrhages in the eye and involvement of corpus cavernosum, leading to priapism. Involvement of the femoral head results in avascular necrosis. Cerebrovascular accidents may occur in children, and tend to be recurrent.
- Acute chest syndrome:** This is a vaso-occlusive crisis, with chest pain, cough, tachypnea, dyspnea, hypoxemia and fever. The condition requires hospitalization with need for IV fluids, oxygen, bronchodilators and antibiotics (including for *Mycoplasma* and *Chlamydia*).
- Sequestration crisis:** Sickled cells block splenic outflow and pooling of blood in the engorged spleen, resulting in splenic sequestration.

- iv. **Risk of infections:** Patients are susceptible to infection with encapsulated organisms (*H. influenzae*, *S. pneumoniae*) and other microbes (*Salmonella*, *Mycoplasma*, *S. aureus*, *E. coli*).
- v. **Aplastic crisis:** Aplastic crisis occurs when the bone marrow stops producing red blood cells, following an infection (often parvovirus B19) or associated with folate deficiency. The condition is self-limited; supportive care and packed red cell transfusions are required.

Laboratory Studies

Anemia and thrombocytosis are commonly found. While leukocytosis is common, white cell count $>20000/\text{mm}^3$ with a shift to the left indicates infection. On peripheral smear, sickle-shaped red cells are found along with target cells. Presence of Howell-Jolly bodies indicates functional asplenia. The indirect bilirubin level may be elevated because of hemolysis. If the diagnosis of sickle cell anemia has not been made, the sickling test establishes the presence of HbS. Hemoglobin electrophoresis differentiates individuals who are homozygous from the heterozygous. The former will have high levels of HbSS (80–90%); carriers have lower levels (35–40%). These samples should be taken before blood transfusion.

Assessment during Acute Illness

In a sick child, blood type and crossmatch is required for probable transfusion. X-ray of the chest and bones, and blood culture may be indicated. Monitoring of oxygen saturation and arterial blood gases should be advised in patients in respiratory distress. A drop in hemoglobin exceeding 2 g/dL from baseline indicates splenic sequestration or aplastic crisis; the reticulocyte count and examination of spleen size help differentiate these conditions. An electrocardiogram is performed, if patient has chest pain and/or irregular pulse.

Hospital Management

Hydration and analgesia are the mainstays of treatment in pain crisis. Oral hydration is preferred, if the patient is not vomiting and can tolerate oral fluids. Narcotic analgesia is frequently used. Patients with severe dehydration should receive IV fluids. Blood transfusion is required in patients with aplastic and sequestration crisis.

Oxygen supplementation is advised in patients with hypoxia. Intubation and mechanical ventilation may be required, if cerebrovascular accidents have occurred, or with acute chest syndrome. Exchange transfusion consists of replacing the patient red cells by normal red cells, decreasing sickle hemoglobin (HbS) $<30\%$. Exchange transfusions are indicated in patients with cerebrovascular accidents and acute chest syndrome. They may be effective in patients with acute sequestration crisis or in priapism that does not resolve after adequate hydration and analgesia.

Preventive Care

All children require prophylaxis with penicillin/amoxicillin, at least until 5 years of age. They should receive the pneumococcal, meningococcal and hemophilus vaccines. They should also receive lifelong folate supplements. Hydroxyurea, that increases HbF and reduces episodes of pain crises, stroke and acute chest syndrome, is recommended to be given at a daily dose of 10–15 mg/kg/day. Children on hydroxyurea should be monitored with complete blood counts. Patients need to be screened for gallstones and stroke. Genetic counseling and testing should be offered to the family. Parents need to learn to identify complications.

Suggested Reading

- Steinberg MH. Management of sickle cell disease. *N Engl J Med* 1999; 340(13): 1021–1030.
- Prevention and Control of Hemoglobinopathies in India: Thalassemias, Sickle cell disease and other Variant hemoglobins.

APLASTIC ANEMIA

Aplastic anemia is a group of inherited or acquired disorders of the hematopoietic stem cells that involve one or more cell lines (erythroid, myeloid, megakaryocytic). The prevalence of bone marrow failure resulting from hypoplastic or aplastic anemia is 2–6 cases per million in Western literature. In India, the prevalence is higher, although exact data is not available.

Etiopathogenesis

Hematopoietic stem cells are damaged by various mechanisms: (i) Acquired stem cell injury from viruses, toxins or chemicals; (ii) abnormal cellular control of hematopoiesis; (iii) abnormal marrow microenvironment; (iv) immunologic suppression of hematopoiesis (due to antibodies, cytotoxic T cells); and (v) mutations in genes, resulting in inherited bone marrow failure.

Differential Diagnosis

Family and past medical history helps distinguish inherited from acquired causes. Inherited bone marrow failure syndromes are usually diagnosed in childhood or young adults. They may have characteristic physical anomalies, familial incidence or thrombocytopenia at birth. Acquired aplasia can occur due to exposure to toxins, drugs like chloramphenicol, environmental hazards and viral infections (hepatitis B and C). Single lineage cytopenias may occur and need to be differentiated from transient erythroblastopenia of childhood (Table 13.12).

Clinical Features

Physical examination shows pallor and/or signs of congestive heart failure. Ecchymoses, petechiae, gum bleeding and epistaxis are associated with thrombo-

Table 13.12: Congenital syndromes associated with bone marrow failure

Syndrome	Inheritance	Associated features	Risk of malignancy
Associated with pancytopenia			
Fanconi anemia	ARI	Absent thumbs, absent radius, microcephaly, renal anomalies, short stature, café-au-lait spots, skin pigmentation	High risk of acute myeloid leukemia, myelodysplasia, oral or liver cancer
Dyskeratosis congenita AD, ARI	X-linked recessive	Dystrophic nails, leukoplakia	Skin (squamous cell) cancer, myelodysplasia
Single lineage cytopenias			
Amegakaryocytic thrombocytopenia	ARI	None	None
Diamond-Blackfan syndrome (pure red cell aplasia)	AD, ARI	Short stature, congenital anomalies in one-third, macrocytosis, high fetal hemoglobin, raised adenosine deaminase	Leukemia, myelodysplasia, other cancers
Thrombocytopenia with absent radii (TAR)	ARI	Absent radius	None

ARI: Autosomal recessive; AD: Autosomal dominant

cytopenia. Fever, pneumonia and sepsis are due to neutropenia. The child should be evaluated for stigmata of congenital marrow failure syndromes (Table 13.12, Figs 13.9 and 13.10). However, Fanconi anemia may be present even without any abnormal phenotypic features.

Laboratory Studies

Hematological features of marrow failure include single cytopenia, as in pure red cell aplasia and amegakaryocytic



Fig. 13.10: Radial ray defects present in a wide spectrum and include absent or hypoplastic thumbs. Thenar hypoplasia may be missed unless carefully examined



Fig. 13.9: Child with Fanconi anemia. The child had hyperpigmentation, microcephaly and microphthalmia. She also had radial ray defects and growth retardation

thrombocytopenic purpura, and aplastic anemia where pancytopenia or bilineage involvement is present. Peripheral smear shows anemia, occasionally with macrocytosis (>110 fl), thrombocytopenia and agranulocytosis. Corrected reticulocyte count $<1\%$ indicates reduced red cell production. Bone marrow aspirate and biopsy are essential for diagnosis and evaluation of marrow cellularity (Fig. 13.11). The marrow is replaced with fat cells and lymphocytes, with a few hematopoietic cells.

Special Tests

The Ham test or sucrose hemolysis test may be positive in patients with *paroxysmal nocturnal hemoglobinuria* (red cells lysed by patient acidified sera) and type II

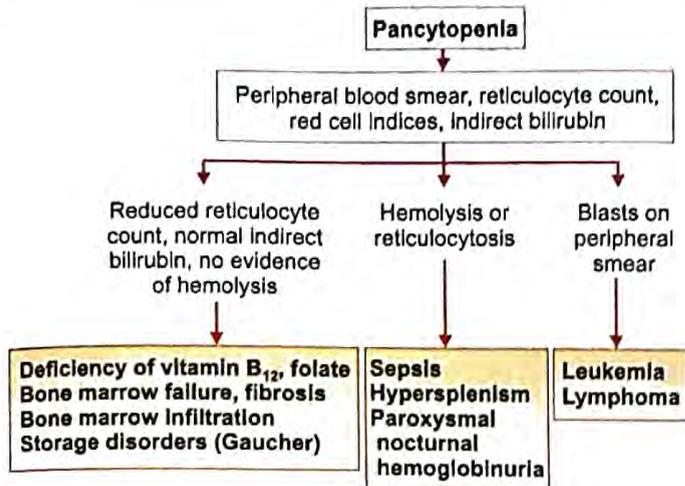


Fig. 13.11: Algorithm for evaluation of pancytopenia

congenital dyserythropoietic anemia (red cells lysed by other acidified sera but not patient sera). A recent transfusion with packed red cells may induce a false-negative test result. A specific test for paroxysmal nocturnal hemoglobinuria is assay for two complement regulatory proteins normally present on red cells, CD55 (decay accelerating factor, DAF) and CD59 (membrane inhibitor of reactive lysis, MIRL). Deficiency of CD55/59 on red cells is the hallmark of the disease. Peripheral blood cells in *Fanconi anemia* show characteristic hypersensitivity and chromosomal breakage with cross-linking agents (mitomycin C and diepoxybutane). The chromosomal fragility is seen even in patients who lack physical stigmata of the disease.

Treatment

Supportive care such as packed red cells for anemia, platelets for thrombocytopenia and antibiotics for infection is needed. Hematopoietic stem cell transplant (HSCT) is the only curative therapy. Criteria for referral for HSCT is: (i) patients who are young, (ii) severe aplastic anemia, and (iii) a matched related sibling donor. Patients with severe acquired aplastic anemia who cannot undergo HSCT may benefit from therapy with antithymocyte globulin (ATG) or anti-lymphocyte globulin (ALG) and cyclosporine. Granulocyte colony-stimulating factor (G-CSF) is indicated in patients with neutropenia with infection. If the neutrophil count does not increase, this therapy should be discontinued after 7 days, because of the risk of malignancy.

Therapy with ATG or cyclosporine is contraindicated in patients with Fanconi anemia. The only curative treatment for them is HSCT. However, this will neither cure the physical and renal manifestations of the disease, nor prevent the risk of cancer. Palliative therapy with oral androgens has been used in patients of Fanconi anemia who cannot undergo HSCT.

Prognosis

Severe anemia can result in high-output cardiac failure, neutropenia can lead to bacterial and fungal infections; severe bleeding can occur due to thrombocytopenia. The severity and extent of cytopenia determine prognosis. With current HSCT regimens, most patients with severe aplastic anemia show 60–70% long-term survival; better survival is reported in favorable subgroups.

Suggested Reading

- Mahapatra M, Singh PK, Agarwal M, et al. Epidemiology, clinical and hematological profile and management of aplastic anemia: AIIMS experience. *JAPI* 2015; 63: 30–35.

HEMATOPOIETIC STEM CELL TRANSPLANTATION

Bone marrow transplantation (BMT) is more correctly called hematopoietic stem cell transplantation (HSCT). This is an established life-saving procedure for a number of malignant and non-malignant diseases. The hematopoietic stem cell transplants are of the following types: (1) Autologous transplant—when the source of stem cells is harvested from the patient and (2) Allogeneic transplant—when stem cells are collected from a human leukocyte antigen (HLA) matched sibling or unrelated donor. The commonly used sources of hematopoietic stem cells are cytokine mobilized peripheral blood, bone marrow and umbilical cord blood.

Indications

The indications for hematopoietic stem cell transplantation can be conveniently divided into two groups (Table 13.13): (a) Malignant disorders—here the cure is by the high doses of chemotherapy or radiation therapy, while the transplant serves to rescue the patient from the myelotoxic effects of the anti-cancer therapy. In allogeneic type of transplants, there is an additional benefit of the immunological response of 'graft versus cancer effect', which contributes to controlling the disease. (b) Non-malignant diseases—in these conditions the abnormal marrow is destroyed and replaced by the healthy unaffected donor marrow. This

Table 13.13: Indications for stem cell transplantation

Malignant disorders	Non-malignant disorders
Acute myeloid leukemia	Thalassemia
Chronic myeloid leukemia	Aplastic anemia
Acute lymphoblastic leukemia (high risk)	Fanconi anemia
Hodgkin disease	Immunodeficiency syndromes
Non-Hodgkin lymphoma (relapsed or refractory)	Inborn errors of metabolism
Neuroblastoma	Autoimmune diseases (rare)
Ewing sarcoma	
Myelodysplastic syndromes	
Gliomas	
Other solid tumors	

corrects genetic or acquired disease of blood and bone marrow.

Allogeneic Hematopoietic Bone Marrow Transplant

Donor Requirement

For an allogeneic transplant, a human leukocyte antigen (HLA) identical sibling is the ideal donor. In spite of HLA identity, there is always variation in minor histocompatibility loci, which may lead to graft rejection or graft versus host disease. It is possible to have a successful transplant using a partially matched sibling as a donor, or an unrelated HLA identical donor, but complications of graft versus host disease and graft rejection are severe. Most centers in India do not conduct unrelated transplants. Unlike other organ transplants, ABO blood group compatibility is not essential. After successful hematopoietic transplantation, the blood group of the recipient will change to that of the donor.

Conditioning Procedure

Myeloablative conditioning: The standard preparatory regimens given prior to hematopoietic transplantation are myeloablative (suppression of bone marrow). Patients receive extremely high doses of chemotherapy. The aim is threefold: (a) eradication of malignant cells or abnormal clone of cells, (b) suppression of the immune system of the host so that the allograft is not rejected, and (c) clearing a "physical space" to allow adequate growth of donor stem cells.

Non-myeloablative conditioning: This aims to suppress the immunity of the recipient sufficiently to allow allogeneic engraftment, without destroying the recipient marrow. These regimens have less toxicity, but higher risk of relapse.

Technical Aspects

The donor marrow is harvested by repeated aspiration from the posterior iliac crests, under general anesthesia (though now chiefly collected as peripheral blood stem cells by apheresis after G-CSF mobilization). The hematopoietic stem cells (HSC) are collected in a bag with anticoagulant. The number of stem cells (CD34+) required for successful engraftment is estimated to be about 3×10^6 per kg of recipient body weight. Transfused through the veins, the stem cells home into the recipient marrow space and start engrafting. Engraftment is considered established when the peripheral neutrophil count reaches $500/\text{mm}^3$ on 3 successive days.

Supportive Care

Protective isolation: After transplantation, it takes about 2–3 weeks before engraftment occurs, that is the time when the stem cells start producing adequate number of neutrophils, platelets and erythrocytes. During this period, very intensive support is required.

Venous access: A long-term, silastic, multi-lumen catheter is needed for IV medications, infusion of stem cells, blood sampling, and administration of blood components and nutrition.

Infections: Bacterial and fungal infections are a major complication in early and late post-transplant period. Prompt institution of appropriate antibiotics is needed. Later, viral infections assume increasing importance, the chief being cytomegalovirus, herpes simplex virus and varicella zoster. Bacterial infections with encapsulated organisms can occur after 3–6 months.

Blood components: Patients require multiple red cell and platelet transfusions during the period of pancytopenia, until engraftment occurs. Patients are immunosuppressed and at risk of developing transfusion associated—graft versus host disease. To prevent this, all cellular blood products should be irradiated prior to transfusion, to inactivate donor lymphocytes.

Growth factors: Hematopoietic growth factors, such as granulocyte colony-stimulating factor, are administered to reduce the duration of neutropenia.

Failure of Engraftment

Failure to engraft after HSCT (graft dysfunction) or inability to sustain graft (graft rejection) is an uncommon but serious complication. Causes include insufficient stem cell dose, infections, graft-versus-host disease and other immunological processes. The incidence is higher in unrelated donor and HLA mismatched transplant.

Graft Versus Host Disease

Graft versus host disease (GVHD) may be acute or chronic. Acute GVHD occurs within the first 3 months after transplant and affects 3 tissues: Skin, gut and liver and may be accompanied by fever. The severity is graded based on the extent of skin involvement, degree of jaundice and severity of diarrhea. Chronic GVHD develops later than 100 days after transplant and often follows acute GVHD, but may also develop de novo. Clinically, it resembles autoimmune disorders like scleroderma with skin rash, sicca complex, sclerosing bronchiolitis and hepatic dysfunction. The mortality varies from 20–40%. Management is with immunosuppressive agents.

Autologous Stem Cell Transplantation

Autologous bone marrow or peripheral blood stem cell transplantation is a procedure similar to allogeneic bone marrow transplant, the major difference being that the patient's own stem cells are used for engraftment. The concept of performing autologous stem cell transplant is to permit administration of very high doses of chemotherapy which would otherwise be fatal, due to severe myelosuppression. First the patient's marrow or stem cells are collected prior to chemotherapy, they are

then used to 'rescue' the patient from the myelotoxicity after the chemotherapy. The procedure is only indicated for malignancies which are chemo- or radiosensitive, e.g. leukemia, lymphoma, neuroblastoma and other solid tumors.

Peripheral blood stem cell transplantations (PBSCT) have virtually replaced bone marrow for autologous stem cell transplantation. Engraftment takes place more rapidly when peripheral stem cells are used instead of bone marrow cells. The advantage of autologous transplant over allogeneic transplant is that there is no graft versus host disease, and once engraftment occurs then graft rejection is unlikely.

Peripheral Blood Stem Cell Transplantation (PBSCT)

The procedure is similar to bone marrow transplant except for differences in the method of collection of stem cells and slight changes in the engraftment potential. Peripheral blood contains 0.1% stem cells; this number is increased by administration of colony-stimulating factors. For allogeneic PBSCT, administration of G-CSF for 4–5 days results in higher number of circulating stem cells, which can be collected by apheresis. The donor is spared the pain of marrow aspiration. For autologous PBSCT, stem cells are collected similarly, but chemotherapy is given prior to the harvest to reduce tumor contamination and yield higher proportion of stem cells.

Cord Blood Stem Cell Transplantation

Placental blood, which is routinely discarded in clinical practice, is a rich source for allogeneic hematopoietic stem cells. The main limitation of cord blood transplants is the limited number of nucleated cells available in a single unit. As compared to bone marrow transplantation, the time for engraftment in cord blood transplantation is much longer, taking a month for neutrophil engraftment and >50 days for platelet engraftment. There is also a higher incidence of non-engraftment, leading to high morbidity and mortality. The main advantage is a lower incidence and severity of GVHD.

Suggested Reading

- Seth S, Kanga U, Sood P, et al. Audit of peripheral stem cell transplant for aplastic anemia in multi-transfused and infected patients. *Transplant Proc* 2012; 44: 922–24.
- Kumar R, Prem S, Mahapatra M, et al. Fludarabine, cyclophosphamide and horse antithymocyte globulin conditioning regimen for allogeneic peripheral blood stem cell transplantation performed in non-HEPA filter rooms for multiply transfused patients with severe aplastic anemia. *Bone Marrow Transplant* 2006; 37: 745–9.

DISORDERS OF HEMOSTASIS AND THROMBOSIS

Approach to a Bleeding Child

An important initial step is to stabilize the bleeding patient. Assessment of vitals provides a clue to the severity of the

disorder and magnitude of blood loss. Administration of replacement fluids/blood is necessary. Following this, the child should be evaluated for the etiology of bleeding, which may be due to platelets (Tables 13.14 and 13.15), coagulation defects (Table 13.16) or dysfunctional fibrinolysis. Clinical assessment (including type of bleeding and antecedent events) and results of initial screening help to rapidly identify the cause, and enable specific management.

Table 13.14: Causes of thrombocytopenia

Idiopathic thrombocytopenic purpura

Infections: Disseminated intravascular coagulation, malaria, kala-azar, dengue hemorrhagic fever, hepatitis B and C, HIV, congenital (TORCH) infections, infection associated hemophagocytosis syndrome

Medications: Valproate, penicillins, heparin, quinine, digoxin

Thrombotic microangiopathy: Thrombotic thrombocytopenic purpura; hemolytic uremic syndrome

Malignancies: Leukemia, lymphoma, neuroblastoma

Autoimmune or related disorders: Systemic lupus erythematosus, Evans syndrome, antiphospholipid syndrome, neonatal immune thrombocytopenia

Immunodeficiency: Wiskott-Aldrich syndrome, HIV/AIDS

Bone marrow failure: Thrombocytopenia with absent radii, Fanconi anemia, Shwachman-Diamond syndrome

Marrow replacement: Osteopetrosis, Gaucher disease

Others: Hypersplenism, Kasabach-Merritt syndrome

Table 13.15: Qualitative disorders of platelet function

Inherited disorders

Glanzmann thrombasthenia (GP Ib deficiency)

Bernard-Soulier syndrome (GP IIb-IIIa deficiency)

Gray platelet syndrome

Dense body deficiency

Acquired disorders

Medications

Chronic renal failure

Cardiopulmonary bypass

Table 13.16: Common coagulation disorders

Inherited disorders

Hemophilia A and B

von Willebrand disease

Specific factor deficiencies

Factor VII, X, XIII deficiency

Afibrinogenemia

Acquired disorders

Liver disease

Vitamin K deficiency

Warfarin overdose

Disseminated intravascular coagulation

Pathogenesis

The process of hemostasis is divided into cellular and fluid phases. The former involves platelets and the vascular wall, while the latter involves plasma proteins. The physiology of hemostasis is complex, involving a fine balance between flow of blood and local responses to vascular injury. The fluid phase is divided into three processes: (i) multiple-step zymogen pathway that leads to thrombin generation, (ii) thrombin-induced formation of fibrin clot, and (iii) complex fibrinolytic mechanisms that limit clot propagation.

The physiology of hemostasis includes the generation of insoluble fibrin and activation of platelets to form a hemostatic plug. Pro- and anticoagulant pathways, platelet number and their function, and vascular factors control this process. The coagulation cascade is often depicted as involving two pathways: Intrinsic and extrinsic. The extrinsic pathway, the primary initiating pathway for coagulation, is measured by prothrombin time (PT). The intrinsic system that works as a regulatory amplification loop is assessed by activated partial thromboplastin time (aPTT) (Fig. 13.12).

Clinical Evaluation

The age at onset of bleeding, type and sites of bleeding (mucosal, skin, deep in joints or muscle), spontaneous or after intervention (dental extraction, surgery, circumcision), duration, frequency and the measures required for control assist in defining the etiology (Table 13.17). In case of recent onset bleeding, history of antecedent infections, rash (Henoch-Schönlein purpura, varicella), and preceding icterus, diarrhea or dysentery needs to be elicited. Important medications that may commonly cause bleeding are anticonvulsants, penicillin, warfarin, aspirin, non-steroidal anti-inflammatory drugs and heparin. History of blood transfusions helps assess the severity of bleeding. Family history is important; documentation of sex of affected members and details of bleeding manifestations is done. The pedigree should include the sex of any stillborn or dead children as well. An illness limited to boys suggest an X-linked disorder (e.g.

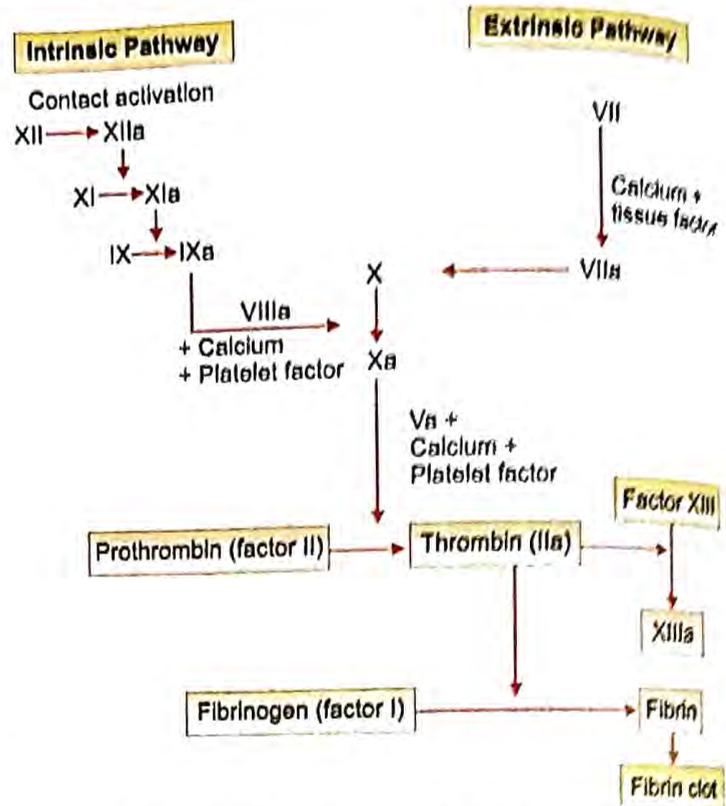


Fig. 13.12: *In vivo* coagulation cascade

hemophilia), females with bleeding conditions are seen in autosomal dominant conditions (von Willebrand disease). Specific types of bleeding may assist in diagnosis, e.g. poor wound healing and prolonged bleeding from the umbilical stump suggests factor XIII deficiency.

An examination is done, noting the anemia, fading and new ecchymoses (Fig. 13.13). The presence of petechiae, vascular malformations and rashes is documented. Splenomegaly suggests infections, malignancy, collagen vascular disorders or hypersplenism rather than a primary bleeding defect. Rashes may be seen due to petechiae, post-drug exposure, infections, collagen vascular disorders, Langerhans cell histiocytosis and Wiskott-Aldrich syndrome. The mouth and nose are examined for local causes of bleeding. Hemangiomas and telangiectasias lead to mucocutaneous bleeding in Kasabach-Merritt syndrome and hereditary telangiectasia.

Table 13.17: Differences in bleeding patterns between platelet disorders and coagulation disorders

	Platelet disorders	Coagulation disorder
Site of bleeding	Skin, mucous membranes (mucosal bleeds: epistaxis, oral, gastrointestinal tract)	Soft tissues, joints, muscles (deep bleeds)
Petechiae	Yes	No
Ecchymoses	Small, superficial	Large, deep
Hemarthrosis, muscle bleeding	Extremely rare	Common
Bleeding after minor trauma	Yes	No
Bleeding after surgery	Immediate; usually mild	Delayed (1–2 days); often severe
Example	von Willebrand disease, idiopathic thrombocytopenic purpura	Hemophilia



Fig. 13.13: Large ecchymotic patch on the upper limb of a young girl with von Willebrand disease

Laboratory Investigations

A hemogram is done for platelet count, morphology of platelets and red cells, and screen for microangiopathic hemolysis. The peripheral smear is made from a fresh finger stick, avoiding artefactual errors due to EDTA anticoagulation. Initial screening tests are PT and aPTT (Fig. 13.14). Specific factor assays are done to identify and grade factor deficiencies. The aPTT is used for monitoring heparin therapy; PT and ratio of PT to an international normalized standard (INR) are used to assess therapeutic warfarin affect.

Bleeding time is rarely used due to the problems of reproducibility and reliability. This test is abnormal if the platelet count is below 100,000/ μL (Table 13.14). In systemic vasculitic disorders (Henoch-Schönlein purpura) and

connective tissue defects (Ehlers-Danlos syndrome), the bleeding time is also prolonged (Table 13.18). Bleeding time is largely being replaced by platelet aggregation studies for inherited and acquired platelet dysfunctions. For evaluation of von Willebrand disease (vWD), the tests required are: vW cofactor and antigen assays, factor VIII assay, ABO blood group (vW antigen levels vary with blood group) and electrophoretic analysis of vW multimers. Sick patients require evaluation for disseminated intravascular coagulopathy.

Suggested Reading

- Clinical and laboratory approach to the patient with bleeding. In: Nathan and Oski's Hematology of Infancy and Childhood, 6th edn. Nathan DG, Orkin SH, Ginsburg D, Look AT. Lusher JM, eds. WB Saunders: Philadelphia; pp 1515–1526.

Idiopathic Thrombocytopenic Purpura (ITP)

ITP continues to carry its acronym, although the condition is no longer idiopathic, and is considered to have an immune basis. This is the commonest bleeding disorder presenting in children between 1 and 7 years of age. It is important to correctly diagnose this entity and differentiate it from other ominous conditions. Thrombocytopenia lasting less than 6 months is termed acute, and greater than 6 months is termed chronic. The majority of children (60–75%) are likely to have acute ITP that resolves within 2–4 months of diagnosis, regardless of therapy.

Pathogenesis

Normal platelet counts vary between 150 and 400 $\times 10^3/\text{mm}^3$ in children above one week of age. ITP is believed to have an immune pathogenesis, against the platelet glycoprotein IIb/IIIa complex. Platelets with surface antibodies are trapped in the spleen, and removed by macrophages. The

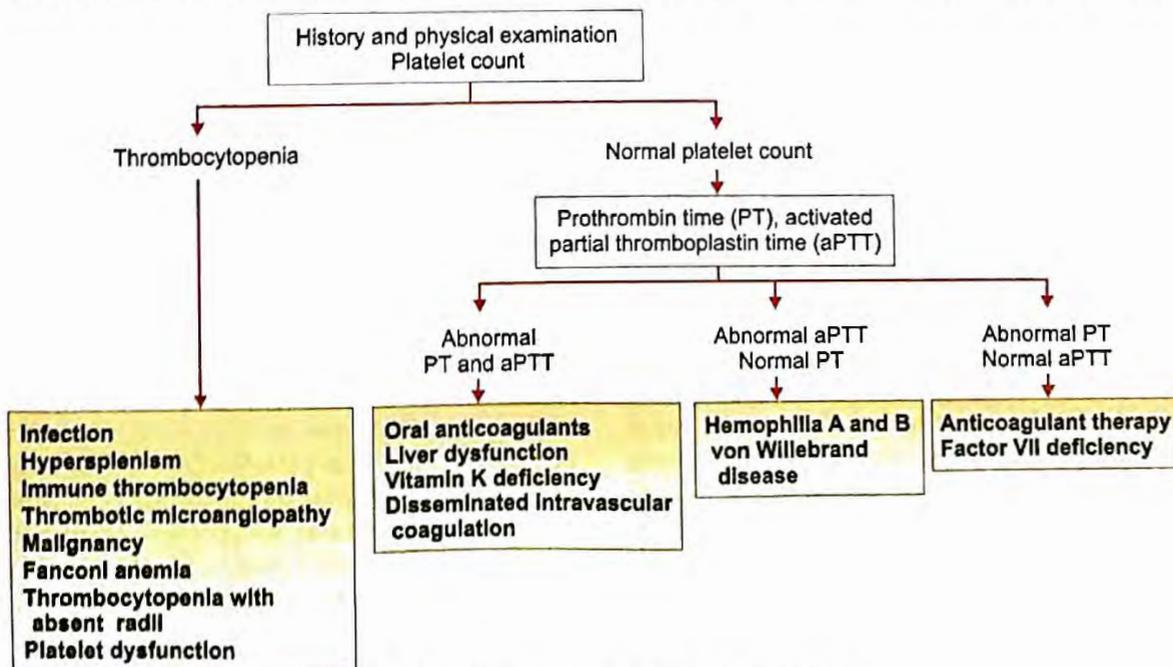


Fig. 13.14: Work-up in a child with bleeding

Table 13.18: Vascular causes of bleeding

Henoch-Schönlein purpura
Vasculitis in systemic lupus erythematosus
Ehlers-Danlos syndrome
Scurvy
Prolonged steroid use; Cushing disease
Hereditary hemorrhagic telangiectasia

pathogenesis of these antibodies is not known. The antibodies may be directed towards viral antigens, which then cross-react with platelet antigens. Recent data describes a TH1 dominant proinflammatory cytokine state. While increased megakaryocyte number in the bone marrow is the hallmark of immune-mediated platelet destruction, a relative decrease in megakaryocyte production due to specific anti-platelet autoantibodies is also implicated in the pathogenesis.

Clinical Evaluation

There is often an antecedent history of febrile illness, but the child on presentation is afebrile. There is a seasonal clustering of cases, more frequent during change of seasons. Children present with a sudden appearance of bruises and mucosal bleeding: Epistaxis, oral oozing and prolonged bleeds with superficial trauma. It is important to estimate the duration of symptoms, and confirm if this is the initial episode or if there have been prior events, as in the chronic ITP. The patient is examined for features of marrow failure (Fanconi anemia: Hypoplastic or absent thumb, short stature and hyperpigmentation; thrombocytopenia with absent radii) and large hemangiomas.

Bleeding is mild unless the platelet counts are below 20,000/ μ L. With counts from 20,000–50,000/ μ L, petechiae and ecchymoses are observed following mild trauma. The presence of splenomegaly or lymphadenopathy should raise suspicion of infection, malignancy or collagen vascular disorder, rather than ITP. Hypersplenism and hepatitis C may also cause thrombocytopenia.

Laboratory Evaluation

Complete blood count shows that only the platelet count is diminished; other hematological parameters are normal. A peripheral smear will help screen for abnormal cells such as blasts, malarial parasites, estimate the platelet count, and exclude spurious thrombocytopenia. It will also help to assess platelet size: Larger platelets are young and an indicator of platelet production. Liver and renal function tests and lactic dehydrogenase is done to rule out the possibility of hepatitis, occult malignancy, hemolysis and hemolytic uremic syndrome. If the child is febrile and ill, then appropriate evaluation is required; this includes chest X-ray, blood culture, tests for malaria or dengue serology. Screening tests for disseminated intravascular coagulopathy should be done, if sepsis is suspected. A bone marrow will show increased

production of megakaryocytes and help exclude marrow infiltration or bone marrow failure.

Management

Platelet transfusions need to be avoided. Minimizing the risk of hemorrhage and decreasing the long-term side effects of treatment are the goals of therapy. In a child with a few scattered petechiae or bruises, platelet count above 20,000/ μ L and no bleeding, only close observation is required. For children with bleeding, treatment includes intravenous immunoglobulin (IVIG) 1 g/kg/day for 1–2 days; or anti-D immunoglobulin 50–75 mg/kg only in Rh positive children. Steroids are administered after hematological malignancy is excluded. Dexamethasone 20 mg/m² (total dose) for 4 days every three weeks for 4–6 courses, or prednisone 1–2 mg/kg/day for 2–3 weeks or 4 mg/kg/day for 7 days and then tapered have been used. If serious hemorrhage occurs, platelet transfusions may be used under cover of steroids. Therapeutic options for chronic ITP include alternate day low dose steroids, splenectomy and various combinations of danazol, vincristine, cyclosporine, azathioprine or rituximab.

Suggested Reading

- Nugent D. ASH education book 2006. www.asheducationbook.org/cgi/reprint/2006/1/97/pdf.
- Sharma SK, Gupta N, Seth T, Srinivas M, Mishra P, Mahapatra M. Successful management of refractory chronic immune thrombocytopenia with intracranial hemorrhage by emergency splenectomy. *Indian J Pediatr* 2012; 79: 397–399.

Neonatal Alloimmune Thrombocytopenia

Thrombocytopenia in the neonate has varied causes; a sick newborn may have sepsis, meconium aspiration, and TORCH infection. In a well looking infant, the causes may be medications taken by the mother or immunologic causes like maternal lupus erythematosus or neonatal alloimmune thrombocytopenia. In neonatal alloimmune thrombocytopenia, the fetal platelets are destroyed by passage of maternal antibodies against paternally inherited antigens present on fetal platelets. Many platelet antigens, like HPA-1a and HPA-5b, have been identified. No prior pregnancy is required to sensitize the mother; hence 50% of cases may occur with the first pregnancy. A high index of suspicion is required, since the entity can result in intracranial hemorrhage. As there are a few specific tests for its diagnosis, it is primarily a diagnosis of exclusion. Postnatal management requires transfusion of washed, maternal platelets (irradiated, if facilities are available) and monitoring until platelet counts normalize. The risk for neonatal alloimmune thrombocytopenia increases in subsequent pregnancies. The fetus might need serial ultrasound examinations to screen for intracranial hemorrhage. The mother may receive therapy with IV immunoglobulin (IVIG 1 g/kg repeated every 4-monthly) and oral dexamethasone.

Hemophilia

Hemophilias are the commonest hereditary clotting deficiency. They are X-linked recessive disorders. Hemophilia A is due to factor VIII deficiency and hemophilia B is due to insufficient factor IX. The clinical features of hemophilia A and B are indistinguishable. The presentation depends on the level of factor present. In mild cases the factor level is enough to prevent minor spontaneous bleeds and the children only manifest, if they have surgery or severe trauma. In severe cases where factor levels are less than 1%, repeated, spontaneous, debilitating joint bleeds (Fig. 13.15) lead to severe handicap and intracranial bleeds can be life-threatening. Treatment requires appropriate factor replacement, judicious physiotherapy to prevent chronic joint disease, counseling for injury prevention and monitoring for inhibitor development. Children with hemophilia should be managed in centers equipped for their special needs.

Replacement therapy for children with hemophilia with concentrates of factor VIII or IX is available and recommended. As FFP is frozen, it retains all factors at their hemostatic levels including the labile factors V and VII. Each unit of factor VIII/kg increases the level by 1%. To achieve a target of 30% factor VIII, required for management of most hemarthroses, a dose of 15 U/kg every 12–24 hours for 1–2 days is required. In a major bleed, e.g. intracranial hemorrhage, the target factor level is 80–100% correction; the dose needed to achieve this is 40–50 U/kg every 8–12 hours for 7–14 days. Lower doses can be used in case of financial constraints, as some factor support is better than no factor replacement. Aminocaproic acid (Amicar) and tranexamic acid are effective adjunct therapy in mild hemophilia. The principles of therapy of hemophilia B are similar, except that factor IX is used for replacement and 1-unit of factor IX/kg raises factor level by 2%. In emergencies when factor IX is unavailable, only FFP is used as cryoprecipitate does not contain factor IX.



Fig. 13.15: Child with hemophilia with knee hemarthrosis with severe pain and signs of inflammation

Primary prophylaxis is a better mode of management. Patients with severe hemophilia (<1% measurable level), are given factor replacement 2–3 times a week to reduce the risk of bleeds, enable more activity and less deformities. All children should receive hepatitis B immunizations, vaccines can be given by the subcutaneous route and the parents should be counseled regarding injury prevention. Genetic counseling is required and families should be informed of the availability of prenatal diagnosis. Evaluation for development of inhibitors is essential during first 30 exposure days.

Suggested Reading

- Roberts HA, Escobar M, White II GC. Hemophilia A and hemophilia B. In: Williams Hematology, 7th edn. Lichtman, Beutler, Kipps, Seligsohn, Kauchansky, Prchal, eds. McGraw-Hill: New York 2006; pp 1867–86.

Vitamin K Deficiency

Phytomenadione or vitamin K₁ is an essential lipid-soluble vitamin that plays vital role in the production of vitamin K dependent coagulation factors. These are factors II (prothrombin), VII, IX, X, protein C and S. Vitamin K is found in green leafy vegetables, oils such as soybean and canola and is synthesized by the colonic bacteria. Deficiency frequently occurs in newborns due to the low transmission of vitamin K across the placenta, paucity in the breast milk, sterile intestines and a premature liver. Classic vitamin K deficiency bleeding occurs in 0.25–1.7% of infants. The prevalence of late vitamin K deficiency bleeding in breastfed infants without prophylaxis is 20 cases per 100,000 live births. Later in life, vitamin K deficiency occurs due to antibiotic use, parenchymal liver disease, prolonged total parenteral nutrition and malabsorption. Deficiency of vitamin K dependent factors leads to a prolonged prothrombin (PT) and activated partial thromboplastin time (PTT). Precise diagnosis is made by assay of proteins in vitamin K absence (PIVKA).

For prophylaxis against hemorrhagic disease of the newborn, administration of vitamin K as a single subcutaneous dose of 1 mg of vitamin K is required. In treatment of babies who did not receive prophylaxis or suffer from anticoagulant overdose, larger doses of vitamin K (2–10 mg) can be given and repeated till coagulation studies are normal. Fresh frozen plasma can be used, if there is overt bleeding, or liver dysfunction is suspected. Prophylaxis with vitamin K is safe and fears of leukemia are unsubstantiated.

Suggested Reading

- Controversies concerning vitamin K and newborn. American Academy of Pediatrics Committee on Fetus and Newborn. Pediatrics 2003; 112: 191–2.

Disseminated Intravascular Coagulopathy (DIC)

DIC is an acquired disorder of dysregulation of hemostasis. The presentation ranges from isolated derangement of

laboratory parameters to bleeding from multiple sites, with high mortality. DIC is triggered by a variety of conditions all of which result in activation of the clotting cascade, deposition of fibrin in the microcirculation and consumption of platelets and clotting factors. The diagnosis of DIC is clinical (Fig. 13.16); laboratory tests provide confirmatory evidence.

Pathophysiology

Three chief pathologic processes are involved.

- i. **Initiation of fibrin deposition:** Thrombin generation in DIC is mediated by the extrinsic (tissue factor) pathway. The tissue factor accumulates on activated platelets by binding to platelet P-selectin which results in thrombin generation.
- ii. **Amplification role of thrombin:** Thrombin generated amplifies inflammation and clotting by activation of platelets, activation of factors V, VIII and IX leading to more thrombin production. Activated factor XIII leads to it cross-linking with fibrin clots making them insoluble, while thrombin activable fibrinolysis inhibitor makes these clots resistant to fibrinolysis.
- iii. **Propagation of fibrin deposition:** Fibrinolysis is suppressed secondary to increase in plasma levels of plasminogen-activator inhibitor-1 (PAI-1).

Following injury, infection or other precipitating factors, there is release of cytokines (TNF- α , IL-1, IL-6) that changes the endothelium from an anticoagulant to a procoagulant surface and interferes with fibrinolysis. Effects of DIC, like hypotension or acute lung injury, are due to these cytokines. As DIC continues, fibrinogen, prothrombin, platelets and other clotting factors are consumed beyond the capacity of the body to compensate and bleeding ensues. Activated protein C has anti-inflammatory effect, downregulates tissue factor and decreases calcium ion flux.



Fig. 13.16: An ill child with disseminated intravascular coagulation shows ecchymoses, purpura and subconjunctival hemorrhage

Causes

The main groups of illnesses causing DIC are: Infections, malignancy, tissue necrosis, ABO incompatible blood transfusion and snakebites (Table 13.19). Acute DIC is the most common form; bleeding manifestations predominate and the patient is critically ill. Chronic DIC occurs due to a weak or intermittent activating stimulus, e.g. giant hemangiomas, certain vasculitic disorders and in some solid tumors.

Laboratory Features

Screening tests: Peripheral blood film examination and hemogram reveal schistocytes and thrombocytopenia. Prothrombin time, activated partial thromboplastin time and thrombin time are prolonged, and fibrinogen level is low.

Supportive tests: Increase in fibrin degradation products or D-dimers are characteristic. A 50% fall in platelets and fibrinogen level are most sensitive in making a laboratory diagnosis. A DIC scoring system is proposed by the International Society on Thrombosis and Hemostasis (Table 13.20). An underlying disorder known to be associated with DIC is a prerequisite for the use of this algorithm; score of >5 is significant.

Table 13.19: Disorders which cause disseminated intravascular coagulopathy (DIC)

Acute DIC	Chronic DIC
Medical conditions	
Septicemia or infections*	Solid tumors
Fulminant hepatic failure	Kasabach-Merritt syndrome
Heat stroke, hyperpyrexia	Liver cirrhosis
Severe burns	
Acute promyelocytic leukemia, neuroblastoma	
Snakebite	
Collagen vascular disorders	
Surgical conditions	
Severe trauma—crush injury, multiple fractures with fat emboli	Vascular tumors
Major operations	Aortic aneurysm
Severe renal allograft rejection	
Iatrogenic	
Hemolytic transfusion reaction; massive transfusion	Artificial surfaces
Heparin-induced thrombosis	

*Include the following infections:

Bacterial: Meningococcus, gram-negative bacteria, group B Streptococcus

Viral: Arboviruses, varicella, variola, rubella, paramyxoviruses, HIV, Ebola virus

Parasitic: Malaria

Mycotic: Candida, Aspergillus

Rickettsial: Rocky Mountain spotted fever

Table 13.20: Algorithm for diagnosis of disseminated intravascular coagulation (DIC) using the DIC score**Risk assessment**

Does the patient have an underlying disorder known to be associated with disseminated intravascular coagulopathy? (If yes, proceed. If no, do not use this algorithm).

Order global coagulation tests

Platelet count; prothrombin time, fibrinogen, soluble fibrin monomers or fibrin degradation products

Score test results	Score
(a) Platelet count >100,000/mm ³	0
50,000–100,000/mm ³	1
<50,000/mm ³	2
(b) Elevated fibrin-related marker (soluble fibrin monomers or fibrin degradation products)*	
No increase	0
Moderate increase	2
Strong increase	3
(c) Prothrombin time	
<3 sec	0
>3 but <6 sec	1
>6 sec	2
(d) Fibrinogen level	
>1 g/L	0
<1 g/L	1

Calculate score

Score ≥5: Compatible with overt DIC; repeat daily

Score ≤5: Suggestive of non-overt DIC; repeat in 1–2 days

* Values of D-dimer above the upper limit of normal are moderately elevated; values above 5 times the upper limit of normal are strongly increased.

Treatment

Treatment of underlying cause and general care: The underlying disease must be managed appropriately (e.g. with use of antibiotics and anti-snake venom, as required). Tissue perfusion and respiratory function must be maintained by IV fluids and oxygen support, respectively. DIC may be compounded by vitamin K deficiency.

Hemostatic support (replacement therapy): In patients with low levels of platelets, fibrinogen and other clotting factors, replacement of deficient components is useful. Replacement therapy is not indicated, if there is no clinical bleeding and if no invasive procedures are planned. Monitoring is essential for guiding management and checking adequacy of replacement. The different blood components available are fresh frozen plasma (FFP), cryoprecipitate, platelet concentrates and packed red cells (Table 13.21). The initial doses given are merely guidelines; required doses depend on rate and degree of consumption. Replacement therapy is halted when stabilization in platelet counts, fibrinogen levels and a fall in fibrin degradation products are observed.

Heparin therapy: For a patient who is actively bleeding, heparin aggravates the bleeding. In most cases of acute DIC (>95% patients), heparin therapy is not useful. Heparin is recommended only in a minority of patients with arterial or large vessel venous thrombosis. Careful monitoring of platelet counts, fibrinogen levels and PT, aPTT and TT is necessary.

Table 13.21: Types of blood component therapy, their constituents and guidelines for use

Component	Constituents	Indication	Dose	Precautions
Fresh frozen plasma (FFP)	All coagulation factors as in normal plasma; contains 0.7–1.0 U/mL of factors II, V, VII, VIII, IX, X, XI, XII, XIII and 2.5 mg/mL fibrinogen	Coagulation factor deficiencies with prolonged prothrombin time; thrombotic thrombocytopenic purpura	15 mL/kg or 1 bag per 10 kg (constitutes 25–30% replacement therapy for coagulation factors)	Infuse soon after thawing; need ABO compatible units; may cause fluid overload
Cryoprecipitate	Fibrinogen 150 mg/bag, factor VIII 80–120 units/bag, factor XIII and vWD (does not contain factor IX)	Fibrinogen deficiency or consumption; factor VIII deficiency (hemophilia A), vWD disease; factor XIII deficiency	1 bag per 5 kg will raise fibrinogen levels by 70 mg/dL	
Random donor platelets (RDP)	Platelets; ≥5.5 × 10 ¹⁰ platelets per bag	Thrombocytopenia	One unit raises platelet counts by 5000–10,000/mm ³ ; 1 unit every 10 kg raises counts by 30,000–50,000/mm ³	Infuse rapidly; do NOT refrigerate prior to transfusion
Single donor platelets (SDP)	Platelets; contains at least 3 × 10 ¹¹ platelets	Thrombocytopenia	One collection is equivalent to approximately 6 units of random platelets	Precautions as above
Fresh blood	All components of blood	To replace acute and massive blood loss	Only to be used in severe trauma	Not a good source for platelets or coagulation factors

Novel therapies: Supplementation with activated protein C has shown promise in critically ill patients. High-dose therapy with antithrombin III has shown benefit in some neonatal studies.

Suggested Reading

- BCSH Secretary, British Society for Hematology. Guidelines for diagnosis and management of disseminated intravascular coagulation. *Br J Haematol* 2009; 145: 24–33.

THROMBOTIC DISORDERS

The incidence of thrombosis is lower in children than adults; thrombosis related morbidity is, however, significant. Children till 6-month-old have lower levels of the vitamin K dependent coagulation factors II, IX, and X, compared to adults. Levels of thrombin inhibitors, such as antithrombin and heparin cofactor II, plasminogen, protein C and S are low at birth. Protein S levels approach adult values by the age of 3–6 months, but protein C levels are low even into childhood. Thrombin generation is decreased (low prothrombin levels) and delayed in newborns compared to adults. The incidence of thrombosis is highest in infants and in adolescence.

Clinical Evaluation

Conditions associated with arterial thrombosis include congenital heart disease, recent cardiac catheterization, fever, recent surgery, trauma, central venous catheter use, and underlying nephrotic syndrome, collagen vascular disease and dehydration (Table 13.22). The age at which thrombosis occurred and type of thrombosis (deep vein, arterial or stroke) should be documented.

Table 13.22: Factors which increase risk of thrombosis in children

Acquired conditions

Infections: Viral, bacterial sepsis
 Disseminated intravascular coagulation
 Dehydration
 Central venous catheter
 Surgery, trauma
 Cyanotic congenital heart disease
 Antiphospholipid antibody syndrome
 Acute lymphoblastic leukemia; therapy (L-asparaginase and steroids)
 Nephrotic syndrome

Inherited prothrombotic disorders

Resistance to activated protein C
 Factor V Leiden
 Protein C deficiency
 Protein S deficiency
 Antithrombin deficiency
 Prothrombin gene *G20210A* mutation
 Elevated lipoprotein (a) level
 Hyperhomocysteinemia

Symptoms due to deep vein thrombosis include pain and swelling of the limb; erythema and tenderness on foot dorsiflexion (Homan sign) may be seen. Pulmonary embolism may present with anxiety, breathlessness, pleuritic chest pain, fever and cough. Symptoms of central nervous system thrombosis include headache, vomiting, lethargy, seizures, focal weakness or hemiplegia. Strokes may occur *in utero*; the newborn may then present with seizures and lethargy. Precipitating factors like infection, dehydration and trauma are common. Patients with renal vein thrombosis show flank pain and hematuria. Signs of arterial thrombosis include diminished or absent peripheral pulses and cool extremities.

Laboratory Evaluation

Since clotting factors are consumed in an acute thrombosis, their low level may be the result of the pre-existing thrombosis. The child should be evaluated to rule out DIC with complete blood count, peripheral smear, D-dimer, prothrombin time (PT), activated partial thromboplastin time (aPTT) and fibrinogen level.

Imaging studies include: (i) Color Doppler imaging. Signals are absent in thrombosed vessels and the lumen cannot be compressed with direct pressure. However, this may not be sufficiently sensitive to detect thrombosis in vessels such as subclavian veins, superior vena cava or brachiocephalic veins; (ii) Echocardiography. This is useful for vena cava and proximal subclavian vein thrombosis; (iii) Computerized tomography. Useful for detecting venous sinus thrombosis; however, both MRI and MRA are better at detecting early arterial ischemic strokes; (iv) Chest radiography. Reveal findings of pulmonary embolism which include small pleural effusions with wedge-shaped pleural-based opacity of pulmonary infarction; (v) Ventilation-perfusion (V/Q) scan. Sensitive procedure for detecting pulmonary embolism.

Management

Urgent stabilization is required. If respiratory distress or neurological problems exist, management in an intensive care unit is required. If possible, screening tests for hypercoagulable state should be sent prior to initiating anticoagulation therapy. Children with lower extremity deep vein thrombosis can be fitted for compression stockings. Initial therapy requires heparin (unfractionated, low molecular weight) followed by oral warfarin therapy. While underdosing hampers resolution of the thrombus, close monitoring is required to prevent overdose and risk of bleeding. The international normalized ratio (INR), which is PT of patient compared to an international standard, is kept in the therapeutic range ~2–3. The duration of therapy depends on the risk of recurrence; this can be assessed by testing for thrombophilia status, best done 3 months after the event and after stopping anticoagulants.

Recurrent Thrombosis

Children with no adverse genetic factors have ~5% recurrence rate; the risk is higher with single risk factor (17.6%) and with two or more risk factors (~50%). Recurrent thrombosis can be due to inadequate anticoagulation therapy.

Suggested Reading

- Tormene D, Gavasso S, Rossetto V, Simioni P. Thrombosis and thrombophilia in children: a systematic review. *Semin Thromb Hemost* 2006; 32: 724–8
- Seth T. Thrombosis in neonates and children. *Eastern J Med* 2009; 14: 36–45

DISORDERS OF WHITE BLOOD CELLS

Evaluation of quantitative and qualitative changes in lymphocytes and myeloid series will help diagnose many infectious, immunologic, malignant and even endocrine disorders. A detailed history and examination that provides information regarding onset, duration, fever, rashes, lymphadenopathy and organomegaly must be obtained.

Quantitative changes (more than +2 SD) in counts are the most frequent anomaly on a report. The percentage increase over normal range is important, very high counts are indicative of leukemoid reaction or leukemia. Absolute count is rarely required, e.g. absolute eosinophil count (AEC) for hypereosinophilic syndromes and absolute neutrophil count for degree of marrow suppression. The morphology of cells may reveal abnormal size, immaturity, nuclear-cytoplasmic ratio, inclusions and abnormal granules. Howell-Jolly bodies are found in cases of absent splenic function (asplenia, post-splenectomy), toxic granulations and left shift suggests sepsis, Epstein-Barr virus infection results in large monocytoïd cells (confused as blasts in peripheral smear).

Leukocytosis

Neutrophils: Chief causes include acute bacterial infections, blood loss, hemolysis and diabetic ketoacidosis (Table 13.23). Leukocyte alkaline phosphatase (LAP) is an enzyme in mature neutrophils that stains blue when positive. LAP is increased in infections and leukemoid reaction (very high leukocyte response to infection; may be confused with leukemia). In chronic myeloid leukemia the neutrophils are LAP deficient, and score is low compared to normal.

Monocytosis: Monocytes are circulating tissue macrophage precursors. These cells migrate to different tissues and transform into macrophages, e.g. Kupffer cells in liver. These cells are important for ingestion and killing of many pathogenic bacteria and parasites, e.g. *M. tuberculosis*, *Leishmania*. Monocytes are the first granulocytic cells to recover in post-chemotherapy states when leukocyte counts recover. Abnormality of macrophage activation leads to disorders like familial hemophagocytic syndrome.

Table 13.23: Common causes of neutrophilia

Acute

Acute bacterial infections
Epinephrine, corticosteroids, granulocyte colony-stimulating factor
Hemorrhage; hemolysis
Hypoxia
Trauma, burns, exercise, heat stroke
Renal failure, diabetic ketoacidosis, hepatic failure
Hodgkin lymphoma

Chronic

Chronic myeloid leukemia
Rheumatological and inflammatory diseases
Hemolytic anemias; sickle cell anemia
Post-splenectomy
Chronic blood loss
Thyrotoxicosis
Chronic idiopathic neutrophilia

Genetic causes or syndromes

Down syndrome
Asplenia
Leukocyte adhesion defects

Langerhans cell histiocytosis is a clonal proliferative disorder of histiocytes.

Basophilia: Basophilia usually occurs due to hypersensitivity reactions, but can be found in many other disorders such as chronic myeloid leukemia, Hodgkin lymphoma, varicella infection, nephrotic syndrome, hypothyroidism and use of antithyroid medications.

Eosinophilia: This occurs in allergic disorders (atopic dermatitis, asthma), systemic inflammatory conditions (inflammatory bowel disease, rheumatoid arthritis) and malignancies (Hodgkin lymphoma). Parasites which invade tissue (*Toxocara* spp. that causes visceral larva migrans) are likely to cause eosinophilia (Table 13.24). Elevated and sustained eosinophil counts are associated with cardiac toxicity. Moderate elevated absolute eosinophil count are above 1500–5000 cell/μL and severe eosinophilia is >5000 cells/μL.

Lymphocytosis Lymphocytosis is a feature of many pediatric infections (Table 13.25). It is important to differentiate reactive from neoplastic lymphocytosis.

Leukopenia

Important causes of leukopenia that need to be evaluated include: Aplastic anemia, megaloblastic anemia, bone marrow replacement or infiltration (malignancy, Gaucher disease, osteopetrosis) and hypersplenism.

Neutropenia: Neutropenia is the presence of neutrophil count that is 2SD below the normal. Severe neutropenia is absolute neutrophil count <500/μL. Neutropenia can be due to infections, inflammatory conditions, bone

Table 13.24: Common causes of eosinophilia**Acute**

Allergic disorders: Asthma, atopic dermatitis, urticaria, drug hypersensitivity, pemphigoid

Parasitic infestations: Toxocara, ascaris, amebiasis, strongyloidiasis, filaria, toxoplasmosis, trichinosis, schistosomiasis, malaria, scabies

Fungal infections: Bronchopulmonary aspergillosis, coccidiomycosis

Malignancy: Hodgkin lymphoma, T cell lymphoma, acute myelogenous leukemia, myeloproliferative syndrome

Hypereosinophilic syndrome

Chronic

Allergic disorders: Pemphigus, dermatitis herpetiformis

Autoimmune disorders: Inflammatory bowel disease, rheumatoid arthritis

Myeloproliferative syndrome, hypereosinophilic syndrome
Loeffler syndrome

Immunodeficiency syndromes: Hyper-IgE, Wiskott-Aldrich syndrome; Omenn syndrome; graft versus host reaction

Miscellaneous: Thrombocytopenia with absent radii; renal allograft rejection; Addison disease

Table 13.25: Common causes of lymphocytosis

Infections: Infectious mononucleosis, infectious hepatitis, cytomegalovirus, tuberculosis, pertussis

Endocrine: Thyrotoxicosis, Addison disease

Malignancy: Acute lymphoblastic leukemia, lymphoma

marrow failure, malignancy or its treatment. It can also be due to rare metabolic disorders like glycogen storage disease type 1b, Shwachman-Diamond syndrome and Kostmann syndrome (Table 13.26).

Lymphopenia: The condition is frequent in inherited immunodeficiency syndromes due to decreased production of B or T lymphocytes, and in Wiskott-Aldrich syndrome. Lymphopenia is also found in acquired immunodeficiency syndrome, systemic lupus erythematosus, protein losing enteropathy and following treatment with anti-thymocyte globulin and corticosteroids.

Qualitative Defects

Chediak-Higashi syndrome is identified by characteristic giant lysosomes in granulocytes and oculocutaneous albinism. The condition is due to defect in *CHS1* gene that encodes for lysosomal trafficking, resulting in ineffective granulopoiesis, delayed degranulation and defects in

Table 13.26: Common causes of neutropenia**Acute**

Infections: Severe sepsis; tuberculosis, Shigella, brucellosis; dengue, varicella, Epstein-Barr virus, cytomegalovirus, HIV; kala-azar, malaria; rickettsia

Drugs: Sulfonamides, phenytoin, phenobarbital, penicillin, phenothiazines

Bone marrow infiltration: Leukemia, lymphoma, neuroblastoma

Hypersplenism

Chemotherapy: Busulphan, cyclophosphamide, radiation

Chronic

Aplastic anemia: Acquired; inherited (Fanconi anemia)

Autoimmune diseases: Systemic lupus erythematosus, Crohn disease, rheumatoid arthritis

Vitamin B₁₂ or folate deficiency

Bone marrow infiltration: Myelodysplasia, chronic myelogenous leukemia, chronic idiopathic neutropenia

Paroxysmal nocturnal hemoglobinuria

Inherited disorders: Cyclic neutropenia; severe congenital neutropenia; chronic benign neutropenia; Kostmann syndrome; Shwachman-Diamond syndrome; dyskeratosis congenita; Chediak-Higashi syndrome; glycogen storage disease type 1B

Associated with immunodeficiency: Hyper-IgM syndrome; HIV

chemotaxis leading to increased bacterial infections. In the accelerated phase, there is lymphohistiocytic infiltration of organs.

Leukocyte adhesion defect has deficiency of CD11 and CD18 on the neutrophils, resulting in defects in adhesion, chemotaxis and C3bi-mediated phagocytosis. This causes delayed umbilical cord separation in the newborn and leads to repeated, severe infections and periodontitis later in life.

Chronic granulomatous disease is an X-linked or rarely autosomal recessive defect of the respiratory burst oxidase in the granulocytic cells. It results in infections in the lungs, skin and gastrointestinal tract due to *S. aureus*, *Aspergillus* spp., and *Serratia marcescens*, which lead to deep-seated granulomatous lesions. Other immunodeficiencies have quantitative defects in T, B or both lymphocyte subsets with maturation or functional defects, which may lead to life-threatening infections.

Suggested Reading

- The phagocytic system and disorders of granulopoiesis and granulocyte function. In: Nathan and Oski's, Hematology of Infancy and Childhood, 7th edn. Eds. Orkin SH, Nathan DG, Ginsburg D, Look AT, Fisher DE, Lux SE. WB Saunders, Philadelphia, 2009; pp 1109–1220.

Otorhinolaryngology

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DISEASES OF THE EAR

Acute Otitis Media

Otitis media is a common early childhood morbidity that refers to viral or bacterial infection of the 'middle ear cleft'. The middle ear cleft is a term that includes the pneumatic spaces of the middle ear cavity medial to the tympanic membrane, the attic superiorly, the mastoid antrum posterior to the attic, and pneumatized air cells in temporal bone that surround the mastoid antrum and extend to the petrous apex. Anatomic features that predispose a young child to ear infections include a shorter, more horizontal and compliant eustachian tube, and bacterial carriage in the adenoids. Risk factors include exposure to cigarette smoke, overcrowding, bottle feeding, use of pacifier, day care center attendance, cleft palate, Down syndrome, allergy, immune dysfunction and gastroesophageal reflux.

Incidence: The peak incidence of acute otitis media in childhood is in infancy and decreases with advancing age. Acute otitis media is uncommon beyond the age of 7 years.

Etiology: The most common causative organisms are *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* in ~75% cases; less common pathogens include *S. pyogenes*, *S. aureus* and *Pseudomonas aeruginosa*; viruses may be the sole pathogen in 15% of cases.

Diagnosis: The condition is characterized by rapid onset of symptoms such as otalgia or ear tugging, fever, crying

and irritability. Older children may report impaired hearing. History of recent upper respiratory tract infection is common. Otoscopy reveals a red and bulging tympanic membrane or perforation of the tympanic membrane with otorrhea (opaque, yellow-green or reddish-brown fluid). Cleaning of the fluid reveals an intact drum, as the rupture is small and closes promptly after spontaneous perforation. The diagnosis of otitis media is considered in the presence of the following criteria: Rapid onset of symptoms, signs of middle ear effusion and signs and symptoms of middle ear inflammation.

Treatment: Antimicrobial therapy is recommended in all patients except a few who may qualify for a trial of observation (Table 14.1). Amoxicillin is the first choice of therapy. Higher doses (80–90 mg/kg/day) are considered where streptococcal resistance is endemic. Coamoxiclav, cefaclor, cefuroxime and newer generation cephalosporins are useful second-line drugs. Macrolides are considered in patients allergic to penicillin and/or cephalosporins. Antibiotic therapy is continued for at least 7 days. Otoscopy should be repeated after 3–4 days and at 3 weeks. Adjuvant treatment with oral and topical decongestant agents is not necessary. Antihistaminic agents, which contribute little to resolution of otitis media and may precipitate sinus infections by drying mucosal secretions, are not recommended.

Table 14.1: Recommendations for initial management for uncomplicated acute otitis media

Age, months	Severe symptoms*, otorrhea or uncertain access to follow-up		No severe symptoms* or otorrhea; follow-up assured	
	Unilateral	Bilateral	Unilateral	Bilateral
6–23	Antibiotic therapy	Antibiotic therapy	Treat or observe**	Antibiotic therapy
≥24	Antibiotic therapy	Antibiotic therapy	Treat or observe**	Treat or observe**

Clinical practice guideline: Diagnosis and management of acute otitis media. Pediatrics 2013; 131:e964–99

*Include toxic-appearance; otalgia persisting for >48 hours; temperature >39°C (102.2°F) in last 48 hours

**If observation is offered, follow up must be ensured and antibiotics are begun if the child worsens or fails to improve within 48 to 72 hours of onset of symptoms

made by visualization of keratin debris/flakes in the middle ear or pars flaccida. CT temporal bone outlines the extent of cholesteatoma in the middle ear and mastoid and its intracranial extension, and helps plan the management.

Treatment: Patients with otitis media and cholesteatoma require mastoidectomy and removal of the cholesteatoma. The goal of therapy is to create a safe ear by removing the cholesteatoma. Hearing restoration is a secondary goal.

Complications of Otitis Media

Untreated otitis media may cause serious complications that are classified as extracranial or intracranial (Table 14.2). Complications of acute otitis media usually occur in young children, while complications of chronic otitis with cholesteatoma are common in older children.

Hearing loss is the most common complication of chronic otitis media. Hearing loss is usually conductive and results from tympanic membrane perforation, ossicular discontinuity and discharge in middle ear. Sensorineural hearing loss may occur, either due to cholesteatoma eroding the labyrinth or following entry of inflammatory toxins or ototoxic ear drops into the inner ear. Bilateral hearing loss affects speech and language development and school performance.

Acute coalescent mastoiditis results from spread of infection into the mastoid air cells and erosion of bony septations. It presents with post-auricular erythema, tenderness and edema, with the auricle displaced inferiorly and laterally. The entity should be differentiated radiologically from fluid effusion within mastoid air cells that is commonly associated with acute or chronic otitis media and leads to opacification on computed tomography (CT), mistakenly reported as mastoiditis. Untreated coalescent mastoiditis may erode the mastoid cortex, leading to subperiosteal abscess in postauricular, temporal or zygomatic area (Fig. 14.4). The ruptured subperiosteal abscess may track along neck muscles leading to deep neck abscesses. Findings on CT include fluid in the mastoid air cells and loss of bony septa between these cells. Initial therapy should be with parenteral antibiotics; therapy against Gram-negative and anaerobic pathogens is added, if mastoiditis is superimposed on a chronically draining ear. Cortical mastoidectomy with/without



Fig. 14.4: An 8-year-old boy with left-sided chronic suppurative otitis media associated with post-auricular abscess (arrow mark). Note the swelling at the root of zygoma and periorbital puffiness

tympanostomy tube insertion is indicated in patients with unsatisfactory response to parenteral antibiotics, subperiosteal or neck abscesses, intracranial complications and for mastoiditis.

Labyrinthine fistula may form due to inner ear erosion by cholesteatoma, and presents with vertigo and sensorineural hearing loss. Cholesteatoma-induced labyrinthine fistula and labyrinthitis (inflammation or infection of the inner ear) requires urgent surgical intervention in the form of mastoidectomy.

Facial nerve paralysis secondary to otitis media is treated with antibiotics, but surgery is often indicated. During the early phase of acute otitis media, myringotomy to release pus from the middle ear may suffice, whereas cases presenting later with accompanying mastoiditis require cortical mastoidectomy and facial nerve exploration. Facial nerve paralysis secondary to cholesteatoma requires modified radical mastoidectomy and facial nerve decompression.

Meningitis is the most common intracranial complication of both acute and chronic otitis media. Acute otitis media is also the chief cause of secondary meningitis and pneumococcal meningitis is the most common cause of acquired sensorineural hearing loss in children. The morbidity and mortality associated with secondary meningitis has decreased significantly following use of appropriate antibiotics, and in the developed world, with use of pneumococcal vaccines.

Brain abscess is a potentially lethal complication. Unlike meningitis, which is more commonly associated with acute otitis media, brain abscesses is almost exclusively a complication of CSOM. Therapy with broad-spectrum parenteral antibiotics is begun immediately and surgical drainage is considered.

Thrombosis of the sigmoid or transverse sinus is an important intracranial complication. Patients present with

Table 14.2: Complications of otitis media

Extracranial	Intracranial
Acute coalescent mastoiditis	Meningitis
Subperiosteal abscess	Epidural abscess
Facial nerve paralysis	Dural venous (sigmoid sinus) thrombosis
Labyrinthitis or labyrinthine fistula	Brain or subdural abscess
	Otitic hydrocephalus

headache, malaise and high spiking fever. Treatment is with parenteral antibiotics and drainage of the mastoid.

Otitis Externa

Acute otitis externa (swimmer's ear) presents with itching, pain and fullness of the ear, with or without otorrhea. Erythema and edema of the ear canal and tenderness on moving the pinnae or tragus are diagnostic. Risk factors include swimming, impacted cerumen, use of hearing aid, eczema and trauma from foreign objects. Chief pathogens include *P. aeruginosa*, *Staphylococcus*, *Proteus*, *E. coli* and *Aspergillus* or *Candida* sp. Management with aural toileting and topical antibiotic drops is associated with clinical cure rates of up to 80%. If edema is significant, a ribbon gauze or wick may be placed in the external auditory canal to keep it patent and allow delivery of topical ear drops. Oral antibiotics are reserved for cases who fail to improve and complicated cases.

Otomycosis or *fungal otitis externa* is common in humid weather or following treatment of a bacterial infection. Patients present with ear pain and pruritus; *Aspergillus* and *Candida* spp. are common pathogens. Otoscopy reveals thick cream-colored discharge associated with fungal spores and filaments. The condition is managed with aural toilet and topical antifungal (e.g. clotrimazole) drops.

Otic furunculosis is a very painful, superficial abscess in the outer portion of the ear canal, typically due to *S. aureus*. Oral antibiotics and analgesics ensure relief; incision and drainage is rarely required.

Eczematous or *psoriatic otitis externa* refers to inflammatory conditions characterized by ear discharge, pruritis and/or scaling of skin of the ear canal. Contact, atopic or seborrheic dermatitis is usually present.

Hearing Loss

Hearing loss in children may be congenital or acquired. Based on pathology, hearing loss is categorized as conductive, sensorineural or mixed. Early detection of hearing loss in children is important as untreated hearing loss interferes with development of speech, language and cognitive skills.

Conductive Hearing Loss

Any pathology that interferes with the conduction of sound through the ear canal, tympanic membrane or middle ear ossicles may cause conductive hearing loss. Hearing loss is usually acquired and mild to moderate in severity. Common causes include otitis media with effusion, tympanic membrane perforation, tympanosclerosis and cholesteatoma. Less commonly, conductive hearing loss is congenital, associated with congenital ossicular fixation or discontinuity and atresia of the ear canal. Hearing loss may be associated with middle ear abnormalities, e.g. Apert, Crouzon and Treacher Collins syndromes.

Sensorineural Hearing Loss

Sensorineural hearing loss is caused by pathology in the cochlea, auditory nerve or central auditory pathway. Congenital and acquired hearing loss is equally prevalent. The most common cause of acquired sensorineural hearing loss is meningitis; other causes are prematurity, hyperbilirubinemia, perinatal hypoxia, acquired immunodeficiency syndrome, head trauma and medications (e.g. aminoglycosides, loop diuretics). The chief etiology of congenital hearing loss is intrauterine infections (e.g. TORCH, syphilis). Almost 30% of congenital hearing loss is associated with one of 300 inherited disorders, including Pendred syndrome (euthyroid goiter), Jervell and Lange-Nielsen syndrome (prolonged QT waves, syncope), Usher syndrome (retinitis pigmentosa and blindness), Alport syndrome (microscopic hematuria and renal failure), branchio-oto-renal syndrome, neurofibromatosis and Waardenburg syndrome. Over 65 genes are associated with inherited hearing defects. Mutations in *GJB2*, encoding for connexin 26 (expressed in the inner ear and involved in cochlear homeostasis) account for one-half of patients with autosomal recessive non-syndromic hearing loss.

Screening for Hearing Loss

Significant hearing loss is present in 1–3 per 1000 newborns, particularly in babies requiring neonatal intensive care. Hearing loss has significant implications for development of speech, language and cognitive skills. Effective hearing aids and cochlear implants are now available that, if applied early in life and supplemented with auditory training, can lead to near-normal hearing, good acquisition of speech and language, and integration into normal schooling. Hence, most countries as well as the Indian Academy of Pediatrics recommend universal screening for hearing loss in newborn period. An important initiative in infant hearing screening and intervention program is the '1-3-6' guideline. This recommends screening all newborns for hearing loss by 1 month of age, completing secondary diagnostic testing for infants who fail the first screening by 3 months, and ensuring early intervention for diagnosed hearing loss by 6 months, enabling language and social development in line with physical development. However, some forms of early-onset hearing loss are not apparent at birth. The American Academy of Pediatrics Joint Committee on Infant Hearing lists risk factors that should prompt continued monitoring of hearing status, even if the initial screening is normal (Table 14.3).

Screening in Older Children

Indications for hearing screening in older children are parental concern for hearing or speech, poor language development or decline in language skills, ear infections, difficulty in understanding conversation or inappropriate response to commands. Examination includes otoscopy

Table 14.3: Indications for continued hearing monitoring despite normal hearing on neonatal screening

Caregiver concern regarding hearing, speech, or developmental delay
Family history of childhood hearing loss
Neonatal intensive care for >5 days or any of the following: Extracorporeal membrane oxygenation; assisted ventilation; exposure to ototoxic antibiotics or loop diuretics; hyperbilirubinemia requiring exchange transfusion
<i>In utero</i> infections (CMV, rubella, syphilis, herpes, toxoplasmosis)
Findings of a syndrome associated with hearing loss
Postnatal infection known to cause hearing loss (e.g. meningitis)
Syndromes associated with progressive hearing loss (e.g. neurofibromatosis)
Neurodegenerative disorders (e.g. Hunter syndrome, Friedreich ataxia)
Head trauma
Recurrent or persistent (≥3 months) otitis media with effusion
Chemotherapy or radiation to head and neck

with attention to middle ear pathology. Doubtful cases require referral for audiologic evaluation. Techniques that assess hearing sensitivity are selected based on child's age and ability to cooperate with testing (Table 14.4).

Management of Hearing Loss

Management of hearing loss is based on the extent of deficit and the underlying pathology. For mild to moderate conductive hearing loss, options include tympanostomy tube for otitis media with effusion, tympanoplasty for tympanic membrane perforations, mastoidectomy and tympanoplasty for cholesteatoma and canaloplasty for canal atresia. Conventional hearing aid, bone conduction hearing aid or middle ear implant are considered in patients with conductive hearing loss, if the pathology cannot be surgically corrected. Treatment of mild sensorineural hearing loss may consist simply of preferential seating in school. Unilateral or bilateral hearing aid usage is advised for mild to moderate sensorineural hearing loss, while children with severe to profound loss who do not benefit significantly from

hearing aid are considered for cochlear implantation. Patients in whom cochlear implants are not feasible are taught sign language and enrolment in deaf education programs.

Pediatric Cochlear Implantation

A cochlear implant directly stimulates the residual cochlear nerve cells in the spiral ganglion (cochlea). The US FDA approves cochlear implantation in adults with bilateral severe to profound (>70 dB hearing loss) sensorineural hearing loss who have poor speech discrimination and fail hearing aids. Decisions are tougher in children as audiological testing is less reliable. Similar to adults, cochlear implantation is advised for children with severe to profound sensorineural hearing loss with unsatisfactory benefit from a trial of hearing aid use for 3–6 months. As early introduction of sound is crucial to develop processes for sound awareness and speech development in the auditory cortex, hearing should be aided as early as possible. Evaluation before surgery includes computed tomography and magnetic resonance imaging to assess anatomic anomalies and confirm the presence of cochlear nerve. Multielectrode implants that provide information across various frequencies are positioned sequentially along the cochlea to allow sound to be coded and transmitted for the entire sound spectrum (Fig. 14.5).

Suggested Reading

- Joint Committee on Infant Hearing of the AAP, Muse C, Harrison J, Yoshinaga-Itano C, et al. Supplement to the JCIH 2007 position statement: Principles and guidelines for early intervention after confirmation that a child is deaf or hard of hearing. *Pediatrics* 2013; 131:e1324–49.
- Liming BJ, Carter J, Cheng A, et al. International Pediatric Otolaryngology Group consensus recommendations: Hearing loss in the pediatric patient. *Int J Pediatr Otorhinolaryngol* 2016; 90: 251–258.
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- Siddiq S, Grainger J. The diagnosis and management of acute otitis media: American Academy of Pediatrics Guidelines 2013. *Arch Dis Child Educ Pract Ed* 2015; 100:193–7.

Table 14.4: Tools to screen hearing

Test	Principle	Age of child
Automated otoacoustic emissions	Evaluates cochlear function; also affected by ear canal obstruction or middle ear effusion	Any age; neonatal screening
Automated auditory brainstem response	Measures integrity of cochlea, auditory nerve and brainstem	Any age; neonatal screening
Visual reinforced audiometry	Sound booth based conditioned hearing	8 months to 2.5 years
Play audiometry	Play/game reinforced hearing evaluation	>2.5 years
Audiometry	Ear and frequency specific hearing assessment	>4 years



Fig. 14.5a: X-ray (modified Stenver view) of the mastoid showing cochlear implant with multichannel stimulating electrodes along the cochlear turn (arrow). Note the receiver stimulator component placed posterosuperiorly and the ball/ground electrode located superiorly



Fig. 14.5b: Cochlear implantee in a rehabilitation session. Note the external component, including a microphone behind the pinna and a transmitter superiorly over the mastoid that transmits amplified sound to the internal receiver stimulator complex transcutaneously

DISEASES OF NOSE AND SINUSES

Rhinitis

Inflammation of mucosa lining the nose may occur alone (rhinitis) or with paranasal sinuses (rhinosinusitis).

Viral Rhinitis

Viral rhinitis (common cold) is the most frequent cause of nasal obstruction and rhinorrhea in children, occurring up to 6–8 times a year, usually due to infection with rhinovirus, influenza or adenovirus. Symptoms include malaise, low to moderate grade fever, nasal congestion and rhinorrhea, with or without sore throat. Antipyretics, saline nasal drops, oral decongestants and antihistamines provide symptomatic relief. Annual influenza vaccination reduces the incidence of severe cases. Less than 5% affected children develop superimposed bacterial rhinosinusitis and suppurative otitis media.

Allergic Rhinitis

The condition is due to an IgE-mediated reaction to specific allergens, commonly inhaled house dust mite, pollen and spores. Coexisting atopic dermatitis and asthma are common. Presentation is with sneezing, itching, nasal obstruction and clear rhinorrhea that are seasonal (hay fever) or perennial with intermittent exacerbations. Examination shows pale nasal mucosa, hypertrophied nasal turbinates and thin mucoid rhinorrhea with or without conjunctival itching and redness. Diagnosis is clinical; supportive tests such as eosinophilia on nasal

smear, skin tests for common allergens and increased serum total or allergen-specific IgE are not essential. Further, skin tests may be negative in children during the first 1–2 years of illness while the sensitization is confined to nose and sinuses. Differential diagnosis includes food allergy (egg protein, cow milk, sea food). Management comprises of allergen avoidance. Topical corticosteroid sprays provide symptomatic relief. Topical decongestants are discouraged due to the risk of rebound congestion and rhinitis medicamentosa.

Bacterial Rhinosinusitis

Four pairs of paranasal sinuses surround the nose and help humidify inspired air. The maxillary and ethmoid sinuses are present at birth and get easily infected in childhood. Sphenoid and frontal sinuses develop at approximately 9–10 months and 7–8 years of age, respectively, and rarely get infected alone.

Acute bacterial rhinosinusitis: Rhinosinusitis is termed acute, if symptoms are for less than 12 weeks. It usually follows viral rhinitis, but may develop *de novo* and recurrently in the presence of predisposing factors such as allergic rhinitis, adenoid inflammation and hypertrophy, cystic fibrosis, immunodeficiency, ciliary dyskinesia, daycare attendance, exposure to tobacco smoke and gastroesophageal reflux. Viral infections cause mucosal edema and ciliary hypoactivity causing obstruction of sinus ostia (openings of sinuses into the nasal cavity) and stasis of secretions. Obstructed sinuses are likely to get infected by bacteria from the nasopharynx, usually *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*.

Persistent fever, facial pain or heaviness, nasal obstruction or purulent discharge, cough, dental pain and earache or fullness beyond 7–10 days of upper respiratory tract infection suggest the diagnosis of infective rhinosinusitis. Periorbital edema, proptosis, diplopia, severe headache, vomiting, seizures or focal neurological deficits suggest ocular or central neurological system involvement, meriting computed tomography.

Orbital extension, contributing to 90% of complications, follows direct extension of infection from the ethmoid sinuses, and is classified as inflammatory edema, orbital or preseptal cellulitis, subperiosteal abscess, orbital abscess and cavernous sinus thrombosis (Fig. 14.6).

Ophthalmoplegia, vision loss and toxemia indicate infection of cavernous sinuses. Intracranial complications, including meningitis and brain abscesses, are common with frontal and sphenoid sinusitis.

While a proportion of cases resolve spontaneously, therapy with oral antibiotics (amoxicillin, coamoxiclav for 10–14 days) is preferred. Longer courses and/or second-line antibiotics may be indicated based on organism sensitivity and nature of illness. Measures, such as oral or topical decongestants, mucolytics and nasal saline provide early symptomatic relief. Patients with complications may require parenteral antibiotics with or without endoscopic sinus surgery and abscess drainage.

Chronic bacterial rhinosinusitis: When symptoms of rhinosinusitis persist for >12 weeks, infection with *S. aureus*, anaerobes and even fungi should be considered apart from usual bacterial pathogens. Nasal obstruction, purulent discharge, chronic cough, facial heaviness, dental pain, malaise and headache are common features. Young children may be just irritable. Prolonged inflammation causes formation of polyps in paranasal sinuses, ethmoid sinuses being most commonly affected.

Chronic bacterial rhinosinusitis is treated with a broad-spectrum antibiotic (coamoxiclav, broad-spectrum cephalosporin or fluoroquinolone) for 3–6 weeks. Oral decongestants and topical corticosteroid sprays (e.g. mometasone or fluticasone) hasten symptomatic relief by reducing mucosal edema, improving patency of sinus

ostia. Nasal steroid sprays are safe and do not impact facial or body growth. Saline irrigation decreases mucosal edema and improves mucociliary clearance of the nose and paranasal sinuses. Managing underlying gastroesophageal reflux with proton pump inhibitors may defer the need for surgery. Computed tomography and referral to a specialist is recommended in patients refractory to 3–6 weeks of medical management and those with complications.

Allergic Fungal Rhinosinusitis

Allergic fungal rhinosinusitis is increasingly recognized in atopic immunocompetent children, chiefly adolescents, but is less common than in adults. It is caused by hypersensitivity to fungal antigens. Patients present with nasal obstruction, discharge and headache. Evaluation shows unilateral or bilateral nasal polypi. Proptosis and telecanthus suggest extensive disease with expansion of the ethmoid (lateral displacement of orbit) or frontal sinuses (inferolateral displacement of orbit). CT imaging shows characteristic non-erosive expansion of sinuses with opacification and intermittent hyperdensities. Management consists of endoscopic removal of polypi and widening of sinus ostia. Topical steroid sprays reduce mucosal edema and prevent as well as delay recurrences.

Nasal Obstruction

Apart from chronic rhinosinusitis, common and important causes of chronic nasal obstruction are adenoid hypertrophy, deviated nasal septum and choanal atresia.

Adenoid Hypertrophy

Adenoids are the lymphoid tissue located in the roof and posterior wall of nasopharynx that protects the upper aerodigestive tract against inhaled antigens. Adenoids usually grow until the age of 5-years due to heightened immunologic activity, often causing some airway obstruction following which it gradually shrinks. Chronic bacterial infection, gastroesophageal reflux and passive smoking may cause persistent adenoidal hypertrophy, leading to nasopharyngeal obstruction. An obstructed nasopharyngeal airway leads to chronic mouth breathing and dental malocclusion, while dysfunction of eustachian tube causes otitis media with effusion and conductive hearing loss. When associated with tonsillar hypertrophy, patients may show features of obstructive sleep apnea. Diagnosis is based on examination and endoscopic evaluation. Lateral radiograph of the neck reveals enlarged soft tissue in nasopharynx, occluding the airway (Fig. 14.7).

Pubertal growth of the midface and regression of adenoids provide symptomatic relief of adenoid-related nasal obstruction beyond the age of 9 years. Medical management of symptomatic adenoid hypertrophy includes courses of antibiotics, prolonged use of aqueous nasal steroid spray and treatment of gastroesophageal



Fig. 14.6: Acute bacterial rhinosinusitis with orbital cellulitis. Note the marked lid edema, congestion and proptosis

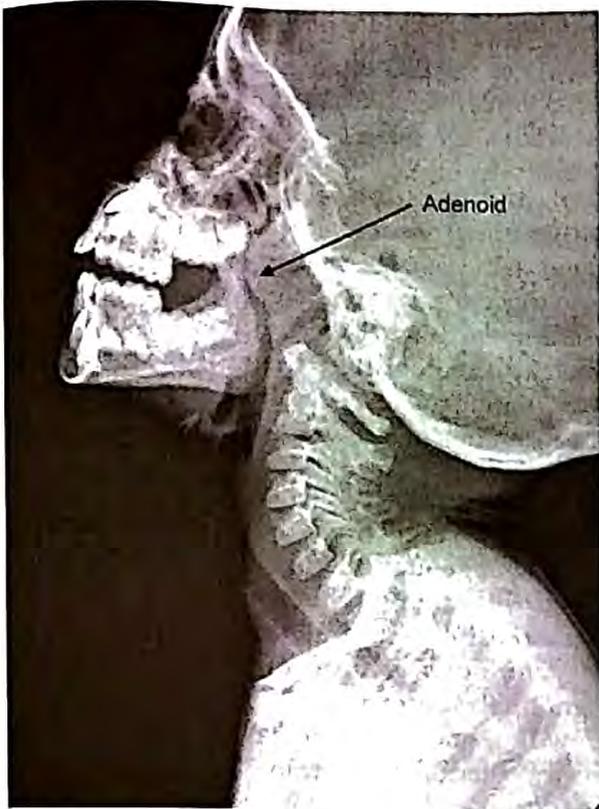


Fig. 14.7: Lateral radiograph of the neck showing adenoid hypertrophy occluding the nasopharyngeal airway in a 6-year-old boy (Courtesy: Textbook of ENT, Hazarika)

reflux with proton pump inhibitors. Adenoidectomy is recommended in the presence of adenoid hypertrophy that is associated with persistent or recurrent otitis media with effusion, failure of medical management for obstructive sleep apnea, chronic adenoiditis, craniofacial growth abnormalities due to prolonged airway obstruction and chronic rhinosinusitis. Adenoidectomy is also done for patients with concomitant cleft palate or submucous cleft palate so as to avoid uncovering symptoms of velopharyngeal insufficiency, such as nasal regurgitation of fluids and hypernasal speech that are masked due to compensation by hypertrophied adenoids.

Deviated Nasal Septum

Deviation of septum (bony, cartilaginous or both) may be developmental or following trauma at birth or in later life. The space in nasal cavity is reduced on the convex side. Patients may experience bilateral nasal obstruction due to compensatory inferior turbinate hypertrophy on the concave side and/or rhinitis.

Choanal Atresia

This term refers to congenital failure of the nasal cavities to open into the nasopharynx. Unilateral or bilateral choanal atresia or stenosis is hypothesized to be caused by complete or partial persistence of buccopharyngeal membrane (separating oral cavity from pharynx) or nasobuccal membrane (separating nose from oral cavity)

or due to abnormal neural crest cell migration. As infants are obligate nasal breathers, patients with bilateral choanal atresia present immediately after birth with respiratory distress and intermittent cyanosis, precipitated by suckling that improves when the child cries. Bilateral atresia can be associated with CHARGE syndrome (coloboma, heart abnormalities, choanal atresia, retardation of growth and development, genitourinary defects and ear anomalies). The presentation of unilateral atresia is less dramatic and usually delayed. Patients present with persistent unilateral nasal discharge or blockage, typically when the opposite nasal passage is blocked due to rhinitis or adenoid hypertrophy.

The diagnosis of choanal atresia is considered when a 6F feeding catheter cannot be passed through the nose into the nasopharynx at birth. Flexible nasal endoscopy and CT confirm the diagnosis (Fig. 14.8). Patients with bilateral atresia require facilitation of oral breathing by keeping the mouth open and pulling the tongue forward manually by oral digital manipulation, followed by placement of plastic oropharyngeal airway or McGovern open-tip nipple.

Epistaxis

Bleeding from the nose is frequent in children and usually follows injury to the anterior portion of the nasal septum in Little's area, the location of Kiesselbach arterial plexus. Bleeding follows local trauma, especially by nose picking during hot summer days, when reduced ambient humidity causes crusting in the anterior nasal cavity. Examination reveals prominent vessels that bleed promptly when touched with a cotton-tipped probe or a dried clot over Little's area. Avoidance of nose picking, use of lubricating ointment and pinching the nose to stop the bleeding are taught to the child and parents. Refractory cases require chemical- (topical silver nitrate) or electro-

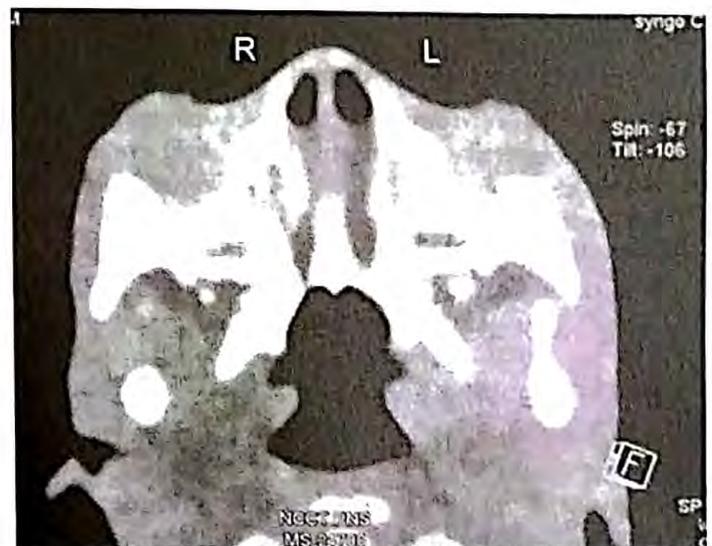


Fig. 14.8: Axial computed tomography of paranasal sinuses showing right (R)-sided bony and membranous choanal atresia and left (L)-sided complete bony atresia

cauterization. Coagulopathy should be ruled out in children with family history, bleeding from other sites or refractory or severe epistaxis. Uncommon causes of recurrent epistaxis include juvenile nasopharyngeal angiofibroma and hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome), the latter presenting with severe recurrent epistaxis, gastrointestinal bleeding and pulmonary hemorrhage.

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DISEASES OF ORAL CAVITY AND PHARYNX

Inflammatory Disorders

Recurrent aphthous stomatitis presents as variably-sized painful white ulcers with surrounding erythema, located on the oral mucosa and/or tongue. The precise etiology is unknown. Minor (<1 cm) ulcers resolve spontaneously over several days. Major ulcers (>1 cm) are less common, may affect the soft palate or tonsils, and heal slowly (4–6 weeks) sometimes with scarring. Though most cases are idiopathic, recurrent ulcers are seen in Behcet disease and cyclic neutropenia. Symptomatic management includes local application of protective and analgesic pastes or anesthetic gels, failing which topical or, rarely, systemic steroids may be tried.

Herpetic stomatitis caused by herpes simplex virus type 1 is highly contagious. Erythematous gingiva and mucosal hemorrhage are associated with clusters of painful vesicles, evolving to gray pseudomembranous mucosal ulcers. Symptomatic treatment includes analgesics and oral or intravenous hydration. While oral acyclovir hastens recovery, lesions usually heal spontaneously in 10–14 days.

Oral candidiasis (thrush) caused by *Candida* appears as small white curd-like lesions on tongue and oral mucosa. While common in infants <6 months of age, the condition is often seen in patients receiving prolonged antibiotics or corticosteroids. Other risk factors include poor oral hygiene, xerostomia, diabetes, leukemia or immunodeficiency. Topical nystatin or oral fluconazole are effective.

Congenital Disorders

Ankyloglossia (tongue tie) refers to limitation of anterior tongue mobility due to congenitally short lingual frenulum. Mild forms are common, do not affect speech and improve as the patients grow. A very short and tight frenulum might restrict tongue protrusion beyond the lips, may be associated with clefting of the tongue tip, and interfere with feeding and speech.

Cleft lip and cleft palate occur due to incomplete fusion of the developing maxillary and nasal processes. Cleft lip may be unilateral or bilateral, and incomplete (when only the lip is bifid) or complete (associated with cleft in the alveolar ridge). Likewise, cleft palate may be unilateral or bilateral, and incomplete (cleft in palate posterior to incisive foramen) or complete (cleft involving entire length of palate). 40% cases of cleft lip or palate are associated with other congenital anomalies; syndromic associations include Goldenhar and Treacher Collins syndromes. Cleft palate leads to feeding difficulty, abnormal nasal breathing, abnormal speech, hearing impairment and impaired dentofacial growth. Staged surgical reconstruction of the lip and palatal defects is performed.

Micrognathia refers to a disproportionately small mandible. Congenital micrognathia may be isolated or associated with Pierre Robin sequence (with cleft palate and glossoptosis). Unilateral mandibular hypoplasia may present with other features of hemifacial macrosomia. Micrognathia may cause difficulty in feeding, dental overcrowding and in severe cases where the tongue is displaced posteriorly, breathing difficulty. Milder cases resolve spontaneously. Neonates with breathing difficulty require prone nursing and/or oropharyngeal airway. Severely symptomatic patients require surgical procedures like tongue advancement, mandibular distraction osteogenesis or tracheotomy.

Macroglossia refers to disproportionately large tongue compared to other structures of the oral cavity. Cases may be idiopathic or syndromic, associated with Down or Beckwith-Wiedemann syndromes, neurofibromatosis or congenital hypothyroidism. Macroglossia may be acquired, due to infections, trauma, tumor or vascular malformation. The condition may lead to drooling, speech impairment, feeding difficulty, abnormal growth of alveolus and dentition, or airway obstruction. Speech rehabilitation and/or surgical reduction may be needed.

Stuttering, Stammering

Stuttering is dysfluency of speech characterized by abnormal repetition of syllables and prolonged interruptions. The most common pattern is developmental stuttering, appearing usually at 3–4 years, when there is inappropriate stuttering for the level of language development. Acquired stuttering is uncommon and may follow emotional trauma or neurological illness. Stuttering is usually not associated with structural orofacial anomalies like tongue tie or adenotonsillar hypertrophy. Surgical intervention for these abnormalities is not useful. Mild forms of dysfluency improve spontaneously; persistent stammering requires speech and language therapy starting in preschool years. Delayed intervention is associated with persistent stammering into adulthood and significant psychosocial morbidity.

Sore Throat

Viral pharyngitis is common and caused by rhinovirus, influenza or parainfluenza virus, adenovirus or coxsackie virus. Patients present with fever, sore throat, dysphagia, rhinorrhea, nasal obstruction, cough and bodyache. Examination shows non-exudative erythema of pharynx and tonsils and tender cervical lymphadenopathy. Supportive treatment with analgesics, saline gargles and saline nasal drops is sufficient. Antibiotics are required in cases of secondary bacterial infection.

Infectious mononucleosis, caused by Epstein-Barr virus, affects teenagers and is transmitted via body fluids, commonly saliva. Patients present with fatigue, high fever, malaise, sore throat, dysphagia and odynophagia. Examination shows enlarged tonsils, edema of soft palate, palatal petechiae, significant cervical lymphadenopathy, hepatosplenomegaly, and a fine rash over arms or trunk. Differential leukocyte count indicates that over 50% are lymphocytes and more than 10% lymphocytes have an atypical appearance. Monospot or Paul-Bunnell tests are useful for screening; presence of anti-VCA IgM antibody confirms the diagnosis. Management is supportive, comprising of hydration, bed rest, analgesics and antipyretics. Patients with respiratory difficulty or extreme dysphagia due to severely enlarged tonsils may require corticosteroids. Ampicillin may cause generalized itchy maculopapular rash and should be avoided. Severe airway obstruction may necessitate tonsillectomy or tracheotomy.

Diphtheria: Though its incidence has declined significantly following immunization, early diagnosis of this potentially lethal condition is critical. The patient appears ill and toxic. Examination shows exudative tonsillopharyngitis with a thick gray membrane over the tonsils extending to the palate, pharynx and occasionally larynx that bleeds when removal is attempted. Cervical lymphadenopathy is common. Gram staining and culture confirms infection with the causative Gram-positive bacillus *Corynebacterium diphtheriae*. Clinical suspicion is enough to warrant immediate treatment with diphtheria antitoxin without awaiting microbiological confirmation. Therapy is with high dose penicillin or erythromycin. Airway obstruction is managed with tracheotomy.

Acute bacterial pharyngotonsillitis is usually caused by group A β -hemolytic streptococci. Less common pathogens include non-group A streptococci, *S. aureus*, *H. influenzae*, *M. catarrhalis*, diphtheria, gonococci, *Chlamydia* and *Mycoplasma* spp. Pharyngitis presents with fever, throat pain, odynophagia and occasionally, headache, abdominal pain, nausea and vomiting. Enlarged erythematous bilateral tonsils with yellow follicles are typical (Fig. 14.9). Severe cases show purulent exudation with or without membrane formation on tonsils, and cervical lymphadenopathy. A rapid strep test helps distinguish viral from streptococcal pharyngotonsillitis; negative results should be confirmed by throat culture. If



Fig. 14.9: Acute staphylococcal pseudomembranous tonsillitis with unilateral hypertrophy of the right tonsil. This condition has to be differentiated from other causes of white patch on the tonsil (Courtesy: Textbook of ENT, Hazarika)

strongly suspected, therapy against *Streptococcus* should begin without awaiting microbiological confirmation. Initial therapy is with penicillin or a first generation cephalosporin for 10 days. Coamoxiclav, clindamycin or erythromycin and metronidazole are considered in refractory cases. Complications include peritonsillar, parapharyngeal or retropharyngeal abscesses; non-suppurative complications are scarlet fever, acute rheumatic fever and poststreptococcal glomerulonephritis.

Tonsillectomy

Indications for tonsillectomy include adenotonsillar hypertrophy causing obstructive sleep apnea, speech defects, craniofacial growth abnormality, dysphagia, failure to thrive or cor pulmonale. Other indications for tonsillectomy are recurrent acute tonsillitis, recurrent tonsillitis associated with valvular heart disease or recurrent febrile seizures, recurrent peritonsillar abscess, infectious mononucleosis with severely obstructing tonsils refractory to medical management, and suspected tonsillar neoplasia.

Obstructive Sleep Apnea

Obstructive sleep apnea is characterized by partial or complete upper airway obstruction during sleep. The chief etiology is adenotonsillar hypertrophy. Disease associations include obesity, allergic rhinitis, laryngomalacia, mucopolysaccharidoses, Down syndrome, craniofacial syndromes, cerebral palsy, hypothyroidism and nasal masses. Sequelae of obstructive sleep apnea are hypoxemia, hypercapnia and acidosis that contribute to behavioral and neurocognitive impairment with poor learning, attention deficit and hyperactivity, cardio-

vascular sequelae (systemic and pulmonary hypertension and cor pulmonale), and metabolic complications such as reduced insulin sensitivity, failure to thrive and dyslipidemia.

Parents complain of the child snoring, choking, holding breath, sleeping restlessly, frequent arousals, excessive daytime sleepiness, morning headaches and/or enuresis. Other daytime symptoms include hyperactivity and inattention, moodiness and poor scholastic performance. Examination reveals obesity, sleepiness, adenotonsillar hypertrophy, high arch palate, large tongue, long face and/or retrognathia. The diagnosis is ascertained by polysomnography (sleep study) that analyzes electroencephalography, electro-oculography, electromyography, oral and/or nasal airflow, electrocardiography, pulse oximetry, respiratory efforts, end tidal or transcutaneous CO₂, sound recordings (for snoring) and continuous video monitoring during night's sleep in the sleep laboratory. The Apnea-Hypopnea Index, that estimates the number of apnea and hypopnea events per hour of sleep, indicates the severity of sleep apnea; value >10 suggests severe obstructive apnea. Sleep study also helps differentiate between this condition and central apnea, periodic breathing and central hypoventilation syndromes.

Adenotonsillectomy is the treatment of choice for severe obstructive sleep apnea. Tracheotomy may be considered in the most severe cases. Children younger than 3 years and those with severe apnea, obesity, cardiac complications or neuromuscular disorders require careful monitoring postoperatively.

DISEASES OF THE LARYNX AND TRACHEA

Stridor

The term stridor refers to audible respiratory noise produced by turbulent airflow through an obstructed upper airway. It should be differentiated from stertor that refers to snoring-like noise produced from obstructed nasopharynx or oropharynx.

X-ray of chest or lateral neck may suggest retropharyngeal abscess, epiglottitis, croup or tracheal stenosis. Computed tomography may be required to rule out extrinsic vascular compression, but is rarely required in an acute scenario. Flexible endoscopy helps assess nasal cavity, nasopharynx, oropharynx, supraglottis and glottis during dynamic respiration without need for general anesthesia, but is *avoided, if acute epiglottitis is suspected*. Rigid laryngotracheobronchoscopy, performed under general anesthesia, is the gold standard when evaluating a child with stridor. Apart from enabling diagnosis, it may be therapeutic, allowing removal of foreign body, release of a web or excision of papilloma. Common etiologies of airway obstruction and stridor are discussed below.

Infections

Acute laryngotracheobronchitis (croup) is a viral upper respiratory tract infection that affects children, 6 months to 3 years of age. Patients present with biphasic stridor, barking cough and low-grade fever after an episode of common cold. Symptoms may evolve over several days. Chest X-ray reveals characteristic narrowing of the subglottic region, known as the 'steeply' sign (Fig. 14.10). Most cases of croup are mild and resolve in 1–2 days with conservative management, including reassurance, cool mist and oral hydration. Nebulized epinephrine (1:1000, in doses of 0.1–0.5 mL/kg, to a maximum of 5 mL) provides symptomatic relief. A single dose of dexamethasone (0.3–0.6 mg/kg, intramuscular) reduces severity, if given within the first 24 hours. Inhaled budesonide (1 mg twice a day for two days) also shows satisfactory results. Antibiotics against *Staphylococcus* and *H. influenzae* are indicated, if the child fails to improve and/or purulent secretions are present.

Acute epiglottitis (supraglottitis), due to infection with *H. influenzae* type B, is less common but a more severe illness than croup. The incidence has declined following improving immunization against *Haemophilus*. Patients, usually 3–6 years of age, present with acute sore throat, high fever, muffled voice, inspiratory stridor, marked dysphagia and drooling. Unlike croup, cough is usually absent. The patient looks toxic and prefers to sit in a leaning forward, 'tripod' position that helps them breathe better. Lateral neck X-ray reveals a characteristic thickening of the epiglottis ('thumbprint' sign). Maneuvering of the oropharynx or larynx is not advised as it might precipitate fatal laryngospasm. Rapid airway management is crucial and includes intubation by skilled personnel or rigid bronchoscopy followed by tracheotomy. In atypical presentations, a skilled physician might try flexible endoscopy, which shows significant edema and erythema of the supraglottic structures compromising the airway. IV, cefotaxime or ceftriaxone are administered for 7 days.

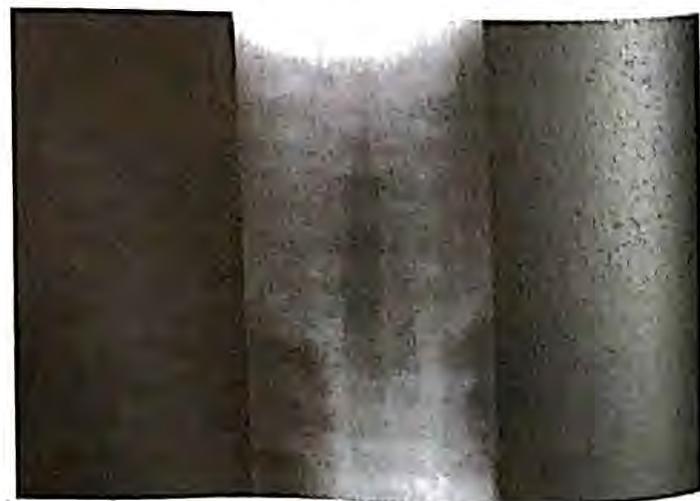


Fig. 14.10: Laryngotracheobronchitis (croup). 'Steeply sign'

Bacterial tracheitis typically caused by *S. aureus*, affects younger children and follows a viral upper respiratory tract infection. The child appears toxic and has brassy cough with biphasic or expiratory stridor. X-ray neck shows an irregular tracheal wall. Bronchoscopy is diagnostic and allows culture and removal of purulent tracheal secretions.

Retropharyngeal abscess is a suppurative complication of bacterial pharyngitis or dental infection, with abscess formation in lymph nodes between the pharynx and prevertebral fascia. Patients appear toxic with high fever, stridor, drooling and reduced neck mobility. Spread of infection into the mediastinum can be fatal. The diagnosis is confirmed by lateral neck radiograph and contrast CT. Management comprises parenteral antibiotics and surgical drainage of abscess by transoral or transcervical approach. Tracheotomy may be necessary to secure the airway.

Congenital Causes

Laryngomalacia is the most frequent congenital laryngeal anomaly and the chief cause of chronic stridor in infancy. The condition is characterized by inspiratory stridor that increases when the child is supine or crying, and decreases in a prone position. Flexible endoscopy reveals omega-shaped epiglottis, short aryepiglottic folds and partial collapse of a flaccid supraglottic airway with inspiration. Laryngomalacia is generally benign and self-limited, with most cases resolving by 18 months of age. Concomitant gastroesophageal reflux should be managed medically. Surgical intervention, in form of supraglottoplasty or temporary tracheostomy, is advised, if respiratory distress is significant.

Vocal cord paralysis is the second most common congenital laryngeal anomaly. Bilateral vocal cord paralysis presents with high-pitched inspiratory stridor and cyanosis. It is usually caused by palsy of the recurrent laryngeal nerve due to excessive stretching of the neck during vaginal delivery. The condition may be idiopathic or associated with Arnold-Chiari malformation, hydrocephalus or hypoxia. Unilateral vocal cord paralysis, in contrast, presents with mild stridor or weak cry. Aspiration may occur, if cord immobility is due to vagus nerve paralysis, as the superior laryngeal nerve (that carries laryngeal mucosal sensation) is also affected. Iatrogenic injury to the left recurrent laryngeal nerve during ligation of patent ductus arteriosus may be a cause. Diagnosis is made on fiberoptic laryngoscopy, which reveals bilateral or unilateral vocal cord immobility. Unilateral cord palsy without aspiration does not need active treatment in most cases as hoarseness improves with time. Tracheotomy might be required to secure the airway in bilateral cord paralysis.

Iatrogenic Causes

Acquired subglottic stenosis is the most common cause of acquired stridor, and usually follows long-term

endotracheal intubation. A snugly fitting endotracheal tube may cause mucosal trauma and inflammation in the subglottis, the narrowest part of the larynx leading to scarring. Patients present with progressive biphasic stridor a few days after extubation. Minor stenosis requires careful observation; severe stenosis requires release of stenosis with CO₂ laser and dilatation, widening with cartilage grafts or excision of stenotic segment, with tracheotomy. Special T-shaped silicone tracheostomy tubes are used for temporary stenting until complete healing. If prolonged intubation is expected, early tracheotomy prevents the complication of post-intubation subglottic stenosis. The use of cuffed tracheostomy tubes should be avoided in children; if a cuffed tube is essential, intermittent deflation is advised.

Another complication of prolonged intubation is **laryngeal granuloma**, typically located in the posterior part of the vocal cord. Small granulomas cause hoarseness while large lesions present with breathing difficulty. They are diagnosed by endoscopy and amenable to endoscopic removal.

Foreign Body Aspiration

Foreign body aspiration should always be considered in children presenting with acute onset stridor and airway obstruction (Fig. 14.11). If a foreign body is not expelled by coughing, it migrates into the lower airway lodging most commonly in the subglottis, the narrowest lumen in the airway leading to breathing difficulty. Objects such as balloons pose the greatest risk of choking to death, followed by round objects such as balls or marbles. Rigid bronchoscopy and removal of foreign body by an experienced surgeon is urgently required. Small foreign

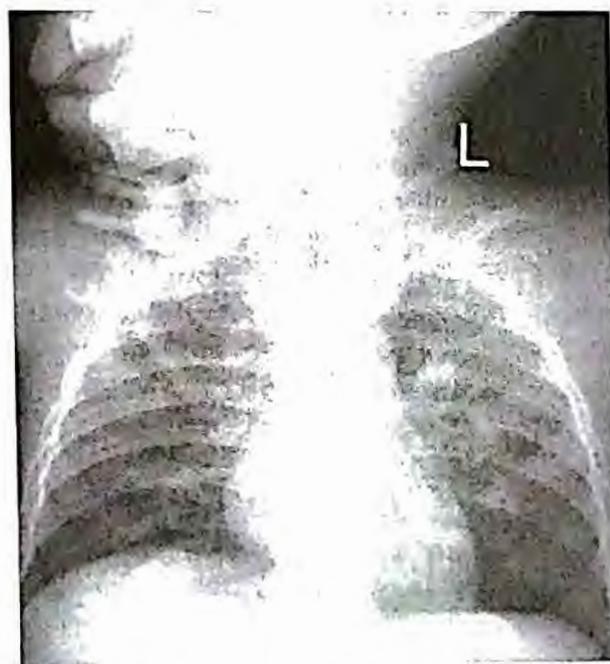


Fig. 14.11: Foreign body, broken part of tracheostomy tube, in the lower trachea and left main bronchus

bodies may lodge in secondary bronchioles and present later with pneumonia. Management comprises of bronchoscopy for foreign body removal, lavage and physiotherapy to clear up secretions and antibiotics. Occasionally, thoracotomy may be required for foreign bodies that cannot be retrieved endoscopically.

Tracheostomy

The requirement of prolonged ventilatory support, neurologic dysfunction causing aspiration, and need for pulmonary toileting are indications for tracheostomy. Caretakers should be explained about the implications of tracheostomy, including the inability of patients to vocalize and the care required. Tracheostomy is performed under general anesthesia with mechanical ventilation provided through an endotracheal tube or laryngeal mask. The trachea is opened at the level of the third or fourth ring by a vertical incision that is kept patent using two non-absorbable sutures placed on either side of the incision. Usually, an uncuffed tracheostomy tube is placed in children unless there is concern of aspiration, in which case a cuffed tube may be used. Care after tracheostomy includes repeated suctioning to maintain patency, change of tube every 5–7 days, chest physiotherapy and peristomal skin care. When tracheostomy is performed in infancy and kept for long, speech and language development may be delayed or impaired.

Hoarseness

Vocal nodules are the chief cause of hoarseness in children. Caused by vocal abuse, these are seen most often in children who scream habitually. The severity of hoarseness fluctuates, worsening with vocal abuse and improving with rest. Endoscopy reveals small, bilateral, opposing nodules at the junction of anterior and middle-thirds of the vocal cord. Speech therapy is advised; surgery is rarely indicated.

Reflux is implicated in occurrence of laryngitis, subglottic stenosis, chronic sinusitis and otitis media with effusion. Diagnosis is established with 24-hour pH monitoring. Patients respond to lifestyle changes and use of proton pump inhibitors; fundoplication is required in severe cases.

Hypothyroid myxedema may occasionally cause vocal fold edema, presenting as hoarseness or stridor.

Laryngotracheal cleft is a rare congenital defect in the posterior part of cricoid cartilage of the larynx. The condition may be associated with Opitz-Frias or Pallister-Hall syndromes. Symptomatic clefts require multilayer

repair, either by endoscopy or using transcervical approach.

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DISEASES OF THE SALIVARY GLANDS

Infections

Bacterial parotid sialoadenitis is frequent in young children and presents with painful unilateral parotid swelling. Purulent material can be expressed intraorally from the parotid duct upon parotid massage. Management involves oral antibiotics, hydration, sialogogues, parotid gland massage and warm compresses.

Mumps: Patients usually present with bilateral painful parotid enlargement and mild fever, and rarely, with acute unilateral hearing loss or vestibular weakness. Therapy comprises adequate hydration and analgesics.

Tuberculosis may affect the parotid or other salivary glands with or without lung involvement. **Sarcoidosis** may present with unilateral or bilateral parotid swelling, along systemic symptoms and peripheral lymphadenopathy. HIV infection commonly involves the parotid glands, presenting as bilateral intraglandular cysts that recur after needle aspiration.

Drooling

Drooling (sialorrhea) is common in infancy but persists beyond 2–3 years in children with neuromuscular disorders and in mouth breathers. Common causes of drooling are dental malocclusion, adenoid hypertrophy, cerebral palsy and lip incompetency. Chronic drooling may lead to skin excoriation, dyselectrolytemia, social isolation, learning difficulties and, in severe cases, aspiration pneumonia. Initial treatment is conservative and includes correcting the posture, orodental rehabilitation, oromotor training and anticholinergic agents like glycopyrrolate. Injection of Botox into the salivary glands provides relief for 3–6 months. Refractory patients, >5 years old, are considered for surgery, including bilateral submandibular gland excision, ductal ligation or rerouting, or resection of parasympathetic fibers.

Disorders of Respiratory System

Sushil K Kabra

DEVELOPMENTAL PHYSIOLOGY

At birth, the newborn has to contend with sudden transition from fetal life to extrauterine existence. During fetal life, the placenta helps in the gas exchange. Therefore, fetal oxygen tension remains constant, independent of the maternal levels of oxygen. Prior to 28–32 weeks, the lungs have an inherent tendency to collapse and are unable to retain any air. The surfactant, a protein in the alveolar lining layer decreases the alveolar surface tension and imparts finite elasticity to the interface. As a result, less pressure is needed to distend the lungs. When the lung is inflated from a small or negligible volume such as in atelectasis or from a situation when the alveoli are filled with liquid as happens during the first breath at birth, lesser force is required to open up the alveoli, if there is low surface tension at the air-liquid interface and if the radius of the terminal units of the lung is adequate. Although surfactant can be detected in the lung exudate from human fetuses as early as 24 weeks, the quantity increases greatly towards the end of term gestation. Its deficiency leads to respiratory distress syndrome.

Gas transport in fetal life: Carbon dioxide tension falls from 35 mm Hg at 10th week of gestation to 28 mm Hg at full term. The difference in oxygen dissociation curves and increase in hemoglobin concentration enable the fetus to carry out effective oxygenation of the tissues. The affinity of hemoglobin for oxygen is increased in the presence of 2,3 diphosphoglycerate (2,3 DPG). However, fetal hemoglobin is relatively insensitive to the effect of 2,3 DPG. The uptake of carbon dioxide also shifts the oxygen dissociation curve to the right; thus adequate oxygen delivery is ensured by the high tissue levels of carbon dioxide.

Onset of respiration: Hypoxia, hypercapnia and increased sensitivity of chemoreceptors are the main factors responsible for initiation of respiration at birth.

Neonatal respiratory function: Before birth, the lungs are filled with fluid that needs to be replaced by air. Some fluid is extruded from the mouth and some is absorbed by the lymphatics. Intrapleural negative pressure required for the first breath is 40 to 100 cm H₂O. This pressure is

higher initially, because of low compliance of the newborn lung (1.5 mL/cm H₂O at birth). The compliance increases in the first few hours to 6 mL/cm H₂O and resistance to air flow decreases. The tidal volume of a 3 kg infant is approximately 16 mL at 28 breaths per minute. Resting lung volume gradually increases in the first few hours to reach a maximum of 80 mL within 24 hours.

Gas exchange in newborn: The normal newborn requires about 7 mL of oxygen/minute/kg, which is almost twice the requirement of an adult based on relative weight. Oxygen uptake is a complex process involving transport across the alveolar capillary membrane (diffusion). The dead space in newborn is about 2 mL/kg with resting tidal volume being 20 mL; 35% of the breath is wasted as compared to 30% in the adults. Persisting fetal channels and the ventilation perfusion problems lead to increase in the right-to-left shunt.

Gas transport: Relative hypoxia in a newborn is corrected in 5 minutes, hypercapnia by 20 minutes and acidosis in 24 hours. The initial acidosis is partly metabolic, due to high blood levels of lactate. The higher hemoglobin concentration and shift to the left of the oxygen dissociation curve allows the newborn to carry higher concentration of oxygen than the adult.

Mechanical Function throughout Childhood

The total lung capacity in a newborn is 150 mL compared to ~5000 mL in adults. With growth of lungs, there is multiplication of alveoli and increase in the size of alveoli and airways. Pores of Kohn or interalveolar communications also develop with increasing age. There is a large increase in compliance and fall in resistance. The reciprocal of resistance, i.e. conductance, rises in proportion to the increase in lung volumes. Increase in minute ventilation reflects the increase in the metabolic rate. Dead space, tidal volume and change in frequency reflect changes in the mechanics of the lungs.

Gas transport: The rise of p_H and pCO₂ together means that the buffer base of the blood also increases. Bicarbonate rises from 19 mEq/L at 2-year to ~24 mEq/L at 16-year of

age. Arterial paO_2 is ~75 mm Hg in the newborn period and around 5-year reaches adult levels of 95 mm Hg.

Suggested Reading

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COMMON RESPIRATORY SYMPTOMS

Cough

After maximal inspiration, air is suddenly released through the partially closed glottis, because of forceful contraction of the expiratory muscles. This produces a bout of cough. The cough reflex is controlled by a center in the medulla. Irritation of the pharynx, larynx, trachea, bronchi and pleura is transmitted by afferent impulses through the vagus or glossopharyngeal nerves. Efferent pathways relay to the larynx and respiratory muscles.

Cough is an important defense mechanism that helps remove infected secretions from the trachea and bronchi. Cough should not be suppressed in young children as retention of secretions may cause atelectasis and pulmonary complications. On the other hand, persistent cough interferes with sleep and feeding. It fatigues the child and may result in vomiting.

Causes of Acute Cough

- Upper respiratory tract infection. Common cold, postnasal discharge due to sinusitis, hypertrophied tonsils and adenoids, pharyngitis, laryngitis and tracheobronchitis
- Nasobronchial allergy and asthma
- Bronchiolitis, pneumonia, and pulmonary abscess; empyema
- Measles
- Whooping cough
- Foreign body in air passages

Causes of Chronic and Recurrent Cough

- *Inflammatory disorders of airway:* Asthma and Loeffler syndrome
- *Infection:* Viral, bacterial, chlamydia, mycoplasma, tuberculosis, parasitic
- Inhalation of environmental irritants such as tobacco smoke, dust

- *Suppurative lung disease:* Bronchiectasis, cystic fibrosis
- Foreign body retained in bronchi
- Congenital malformations, sequestered lobe, bronchomalacia
- Immune deficiency, primary ciliary dyskinesia
- *Anatomic lesions:* Tumors, tracheal stenosis, H-type tracheoesophageal fistula
- Psychogenic, habit cough
- Post-nasal discharge, sinusitis
- Gastroesophageal reflux disease
- Interstitial lung disease

Expectoration

Children have difficulty in expectorating, and hence swallow respiratory secretions. Older children with chronic respiratory problems may bring out expectoration. Common causes of significant expectoration include bronchiectasis, lung abscess, bronchitis, asthma, and tuberculosis. The amount and nature of expectoration may give clue about the etiology. Investigations such as cell count, Gram stain and culture or stain for AFB and culture help in diagnosis and guiding treatment.

Hemoptysis

Hemoptysis is defined as blood-stained expectoration. Causes of hemoptysis may be necrotizing pneumonia, foreign body aspiration, bleeding diathesis, cavitary tuberculosis, idiopathic pulmonary hemosiderosis, mitral stenosis, dilated cardiomyopathy, Goodpasture syndrome and small vessel vasculitis.

Respiratory Sounds

Sounds originating from the respiratory system may be heard with or without a stethoscope (Table 15.1). The intensity and pitch of these sounds vary based on their site of origin within the respiratory tract, the dictum being that the pitch increases and the intensity decreases as one goes lower into the respiratory tract. Snoring is a loud but low-pitched sound because it results from the oropharynx, while wheeze is high pitched and less intense since it originates from the lower tract. Generally, extrathoracic airway obstruction produces inspiratory sounds, intrathoracic major airway produces inspiratory as well as expiratory sounds and distal airway obstruction produces predominantly expiratory sounds.

Table 15.1: Respiratory sounds

Sound	Causes	Character
Snoring	Oropharyngeal obstruction	Inspiratory, low pitched, irregular
Grunting	Partial closure of glottis	Expiratory
Rattling	Secretions in trachea/bronchi	Inspiratory, coarse
Stridor	Obstruction of larynx or trachea	Inspiratory sound; may also have expiratory component
Wheeze	Lower airway obstruction	Continuous high-pitched musical sound; expiratory

Rattling

Rattling is due to excessive secretions in the pharynx or tracheobronchial tree, as in asthma, bronchitis, tracheobronchial stenosis and aspiration of gastrointestinal contents into the tracheobronchial tree may also result in rattling.

Wheezing

Wheezing refers to high-pitched whistling sounds audible without auscultation. Wheezing causes considerable anxiety to the parents. Partial obstruction of the bronchi and bronchioles leading to narrowing produces wheezing. However, sufficient air must flow through the narrowed airway to produce the wheezing sound. Wheezing may be due to causes within the lumen or in walls of the bronchi.

- *Wheeze associated lower respiratory tract infection; viral infection with wheeze:* Wheezing is often due to heightened sensitivity of the respiratory tract, following infections that cause bronchospasm. Attacks of wheezing are preceded by a cold or acute respiratory disease. These are most frequent between 3 and 8 years of age and become less frequent thereafter. These episodes may be relieved by use of bronchodilators.
- *Bronchiolitis*
- *Bronchial asthma*
- *Tropical eosinophilia* is more frequent in adults than in children. It is an unusual form of infection with filariasis, e.g. *Dirofilaria immitis*, *W. bancrofti* and *B. malayi*. Clinical features simulate chronic recurrent asthma. X-ray films show fine infiltrates with snowflake like appearance, which should be distinguished from miliary tuberculosis. Leukocyte count shows eosinophilia. The patients are treated with diethyl carbamazine (10 mg/kg) in 3 divided doses orally for 2 to 3 weeks. Two or three courses may be given.
- *Loeffler syndrome* occurs due to migration of *Ascaris* larvae through the lungs, resulting in transient episodes of wheezing, respiratory distress and eosinophilia.
- *Hypersensitivity pneumonitis.*
- *Inhaled foreign bodies* cause sudden onset unilateral localized wheeze.
- Enlarged mediastinal nodes (tuberculosis or neoplasm), anomalous left pulmonary artery compressing the right main bronchus, cystic fibrosis, pulmonary hemosiderosis and mediastinal cysts constitute rare causes of wheezing.

Stridor

Stridor indicates upper respiratory obstruction and is accompanied by hoarseness, brassy cough, dyspnea, retractions of the chest during inspiration and restlessness. Accessory muscles of respiration are usually being used. Stridor is common in infants and attributed to the (i) small size of the larynx, (ii) loose submucous connective tissue around the glottis, and (iii) rigid cricoid cartilage encircling the subglottic zone.

Acute stridor: Acute upper airway obstruction in the region of glottis may be produced by inflammation and edema, and may be life-threatening. The obstruction may either be supraglottic (epiglottitis) or subglottic (infectious croup) (Table 15.2).

Chronic stridor: Congenital laryngeal stridor is caused by flaccidity (laryngomalacia) or easy collapsibility of the aryepiglottic folds or epiglottis. This condition manifests by the end of the first week or during the second week after birth. The stridor is characteristically intermittent, and is aggravated by crying or feeding. It is modified in sleep or by change of posture. While the loud inspiratory sound frightens the parents, the infant is relatively comfortable. Respiratory distress and chest retractions are absent or minimal, and feeding behavior and activity are generally normal. Breathing difficulty may be significant, if micrognathia and cleft palate are associated. Congenital laryngeal stridor disappears spontaneously by 6–12 months of age. Infants may develop aspiration of feeds and frequent lung infections.

Congenital laryngeal tracheal stenosis or web is characterized by weak cry, hoarse labored breathing and reduced air entry in infants. In subglottic tracheal stenosis, the cry is unaffected and the stridor is both inspiratory and expiratory.

Laryngeal cysts or neoplasm including angioma, papilloma, lymphangioma and retention cysts may cause stridor. Stridor is common in infants with hydrocephalus and Down syndrome.

Bilateral vocal cord paralysis may result from brainstem injury. Unilateral paralysis is due to the involvement of the recurrent laryngeal nerve that is more common on the left side, due to the longer course of the nerve that hooks around the aorta from the front to back.

Extrinsic obstruction: Vascular rings show intermittent stridor that becomes worse when the neck is flexed. Infants

Table 15.2: Distinguishing between stridor due to supraglottic and tracheal obstruction

Clinical features	Supraglottic obstruction	Tracheal obstruction
Stridor	Inspiratory	Usually expiratory
Severity	Usually less serious	More serious
Cry	Muffled	Normal
Dyspnea	Less severe	More marked
Cough	Less marked	Deep barking, brassy

thus prefer to keep the head in a position of hyperextension. *Tumors of the neck* such as mediastinal goiter, lymphangioma and thyroglossal duct cyst rarely cause respiratory obstruction and stridor.

Treatment: The diagnosis of congenital laryngeal stridor is made on direct laryngoscopy. Fluoroscopy after barium swallow is required to rule out extrinsic obstruction. Tumors and cysts require surgical excision. Corticosteroids may hasten recovery in patients with laryngeal edema. Most infants with congenital laryngeal stridor do not require specific treatment. Gavage feeding is done, if respiratory distress is marked.

Dyspnea

Tachypnea means abnormally rapid respiration. Dyspnea refers to labored or difficult breathing, usually accompanied by pain and air hunger. The causes are listed below.

Respiratory System

Newborn: Hyaline membrane disease, hypoplastic lung, diaphragmatic hernia and eventration, meconium aspiration, pulmonary edema, congenital heart disease, septicemia or neurologic depression.

Infants and children: Pneumonia, bronchiolitis, bronchial asthma, aspiration, pneumothorax, pleural effusion, collapse, obstructive emphysema or pulmonary edema.

Cardiovascular System

Myocarditis, pulmonary edema, pericarditis, congestive heart failure.

Miscellaneous

Anemia, Pickwickian syndrome, chest deformities, painful breathing due to fractured rib or pleuritis, acidosis, diabetes and uremia, smoke inhalation, myasthenia gravis.

Epistaxis

Epistaxis or bleeding from the nose is rare in children below the age of 3 years. It may occur due to local or systemic causes. Local causes include: (i) trauma to nose caused by nose picking, (ii) capillary malformations in the Little area, (iii) foreign body, (iv) bleeding polyps, (v) allergic rhinitis and nasal diphtheria. Systemic causes include: (i) systemic hypertension, (ii) blood dyscrasia (coagulation, bleeding disorders), and (iii) pertussis.

Treatment: Pressure on alae nasi for 10 minutes controls bleeding in most cases. In resistant cases, the nasal mucosa is plugged with gauze piece soaked in 1:10,000 solution of adrenaline hydrochloride as a temporary measure. Profuse bleeding is more likely to arise posteriorly, from the sphenopalatine vessels. Firm anterior and posterior packing is done.

Suggested Reading

- Kabra SK. History taking and physical examination. In: *Essential Pediatric Pulmonology*, 3rd edn. Jaypee, New Delhi 2018.

INVESTIGATIONS FOR RESPIRATORY ILLNESSES

Bronchoscopy

Flexible fiberoptic bronchoscopy, done under local anesthesia, is used for diagnosis of structural abnormality of airways, detection of foreign bodies, obtaining bronchoalveolar lavage samples for cell morphology and culture, and performing biopsies. Rigid bronchoscopy requires general anesthesia and is commonly used for removal of foreign bodies or obtaining biopsies.

Pulmonary Function Tests (PFT)

PFT are important tools for monitoring patients with respiratory illness. Since the procedure requires cooperation of the patient, these tests are usually performed above the age of 5–7 years. Commonly measured parameters are forced expiratory volume in first second (FEV1), forced vital capacity (FVC), mid-expiratory flow rate (FEF25-75) and ratio of FEV1/FVC. Normal FEV1/FVC ratio is between 0.8 and 1.0; in obstructive diseases (e.g. asthma), the ratio is reduced. In restrictive lung diseases (interstitial lung disease), the ratio of FEV1/FVC is normal but FVC is reduced below 80% of predicted.

Blood Gas Analysis

Estimation of blood pH and partial pressures of oxygen and carbon dioxide gives an estimate of pulmonary functions. Arterial blood gas analysis is used for monitoring therapy in respiratory failure. Partial pressures of oxygen less than 60 mm Hg and of carbon dioxide more than 50 mm Hg suggest respiratory failure.

Imaging

A standard radiograph and newer tools like computerized tomography (CT) are non-invasive diagnostic methods. X-ray films help in diagnosis of soft tissue and bony abnormalities, diagnosis of acute and chronic pulmonary infections. CT scans are used for visualization of lymph nodes, tumors, bronchiectasis and pleural pathologies.

Sweat Chloride

Estimation of sweat chloride is done using pilocarpine iontophoresis. In normal children, sweat chloride values are <40 mEq/L; level more than 60 mEq/L is seen in cystic fibrosis. Values between 40 and 60 mEq/L are borderline and need to be repeated.

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- Miller A, Enright PL. PFT interpretive strategies: American Thoracic Society/European Respiratory Society 2005 guideline gaps. *Respir Care* 2012; 57:127-33.
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UPPER RESPIRATORY TRACT INFECTIONS

Nasopharyngitis (Common Cold)

Common cold is the most frequent illness in childhood, caused by adenoviruses, influenza, rhinovirus, parainfluenza or respiratory syncytial viruses. These are spread by droplet infection. Predisposing factors include chilling, sudden exposure to cold air, and overcrowding. Rhinitis could also be due to allergy.

Clinical Features

These include fever, thin nasal discharge and irritability. Cervical lymph nodes may enlarge. Nasopharyngeal congestion causes nasal obstruction and respiratory distress. Eustachian tube opening may be blocked leading to serous otitis media and congestion of tympanic membrane. In allergic rhinitis, there is a clear mucoid discharge with sneezing. There is no contact with an infected patient and history of allergy is usually present. Wheezing may occur in a significant proportion of cases.

Narrowing of the airway and pharyngeal irritation causes dry hacking cough. Excessive lacrimation is due to the blocked lacrimal ducts in the nose. Nasal discharge may become purulent, if secondarily infected. The illness usually lasts for 2-3 days but cold may persist up to two weeks.

Complications

Otitis media, laryngitis, sinusitis, bronchiolitis, bronchopneumonia and exacerbation of asthma.

Differential Diagnosis

Nasal foreign body may present with unilateral serosanguineous or purulent discharge from nose.

Snuffles is clear mucoid discharge from the nose in the first few weeks of life. Snuffles of congenital syphilis is rare and causes bilateral serosanguineous discharge commonly excoriating the upper lip and leaving fine scars. Nasal strictures may ulcerate leaving a flat nasal bridge.

Treatment

Relieve nasal congestion: Nose drops of saline may give symptomatic relief. Nasal decongestants (ephedrine, xylometazoline) may cause rebound congestion and should be avoided. Antihistaminics dry up thin secretions and relieve sneezing but should be avoided in the first 6 months of life. Newer non-sedating agents (loratidine, cetirizine) are useful in allergic rhinitis.

Fever is controlled by antipyretics such as paracetamol.

Cough syrups suppress cough and retention of mucoid secretions that predispose to spasmodic cough, wheezing, atelectasis and suppuration. These agents should be avoided in infants and young children.

Antibiotics are of little value in viral infections. These are used, if the secretions become purulent, the fever continues to rise and if the child develops bronchopneumonia.

Nursing care includes protecting from sudden exposure to chills. Feeding should be continued to maintain hydration.

Acute Tonsillopharyngitis (Sore Throat)

Acute inflammation of the pharynx and tonsils is usually caused by viral infections such as adenovirus, influenza, parainfluenza, enterovirus and Epstein-Barr virus. It may also be caused by measles, rubella, *Streptococcus pyogenes* especially group A β -hemolytic streptococci, *Mycoplasma pneumoniae* and *Candida albicans*.

Clinical Features

Fever, malaise, headache, nausea and sore throat are characteristic. It is difficult to distinguish clinical syndromes due to viral or streptococcal infections. Hoarseness, cough and rhinitis are common in viral infection. In these, the onset is gradual and there is less toxemia. In streptococcal infections, cervical lymph nodes are enlarged and illness is more acute with high fever, exudates over tonsillar surface and absence of nasal discharge or conjunctivitis. Young children may not complain of sore throat, but refuse to feed normally.

Complications

The illness may be complicated in the acute stage by otitis media, sinusitis, and peritonsillar and retropharyngeal abscesses. The infection may spread down the tracheobronchial tree and cause tracheobronchitis and pneumonia. Streptococcal sore throat may be followed a few days later by immune-mediated conditions, presenting with acute rheumatic fever and acute glomerulonephritis.

Diagnosis

The possibility of pharyngitis due to group A beta-hemolytic streptococci should be considered in patient presenting with fever, exudates in throat, tender enlarged cervical nodes and absent nasal or conjunctival congestion. Throat culture for group A β -hemolytic streptococci helps in definitive diagnosis. Neutrophil count is often elevated. Rapid diagnostic tests for β -hemolytic streptococci are not frequently available.

Differential Diagnosis

Herpangina is an acute febrile illness caused by group A Coxsackievirus. Patients have dysphagia, sore throat and papulovesicular lesions surrounded by erythema over the tongue, pharynx, anterior tonsillar pillars and soft palate. Pharynx appears congested.

Diphtheria is characterized by moderate grade fever, severe toxemia, sore throat and membrane formation over the fauces or palate. The diagnosis is confirmed by urgent smear examination from throat swab.

Agranulocytosis may present with similar symptoms; blood count shows neutropenia.

Patients with pharyngoconjunctival fever present with fever, conjunctivitis, pharyngitis and cervical lymphadenitis due to infection with adenovirus type III.

Infectious mononucleosis is characterized by lymphadenopathy, morbilliform rash, hepatosplenomegaly and sometimes aseptic meningitis.

Treatment: Paracetamol is administered for fever. Soft food is given because swallowing is painful. Warm saline gargles are prescribed for older children. Younger children are encouraged to sip warm tea.

Antibiotics are not used for viral infections. Infections with β -hemolytic streptococci are treated with penicillin V orally, injections of procaine penicillin or oral erythromycin for 10 days. Parents must be counseled regarding the need to complete 10 days therapy with antibiotics. If compliance is a problem, a single dose of intramuscular benzathine penicillin is advised. Cotrimoxazole and fluoroquinolones, which are otherwise used for a variety of indications, should not be used in these patients.

Recurrent Attacks of Sore Throat

Parents often seek advice for the treatment of recurrent sore throat in their children. A detailed history and physical examination is done. Paranasal sinuses and ears should be examined for infection that if present, should be appropriately treated. Smoky and dusty atmosphere should be avoided. Damp environment and overcrowding predispose children to recurrent upper respiratory tract infections.

Every episode of bacterial pharyngitis should be treated with adequate doses of antibiotics for at least 10 days. A single intramuscular dose of benzathine penicillin is also adequate. Patients with β -lactamase producing bacteria in the pharynx should receive coamoxiclav. Clindamycin is an effective agent to eradicate the carrier state. In patients with recurrent streptococcal sore throat, penicillin prophylaxis for 3–6 months is recommended.

Tonsillectomy does not prevent recurrence of streptococcal infections. The procedure may be recommended in children with multiple episodes of tonsillitis or in case of tonsillar or peritonsillar abscess. It may reduce the incidence of group A beta-hemolytic streptococcal infection.

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LOWER RESPIRATORY TRACT INFECTIONS

Acute lower respiratory tract infections are the leading cause of death in children below 5 years of age. Diseases under this heading include the croup syndromes, bronchitis, bronchiolitis and pneumonia.

Croup

The term croup is used for conditions with a peculiar brassy cough with or without inspiratory stridor, hoarseness or respiratory distress. Conditions associated with this syndrome include acute epiglottitis, laryngitis, laryngotracheobronchitis and spasmodic laryngitis.

Epiglottitis

Supraglottitis including epiglottitis and inflammatory edema of the hypopharynx, is caused chiefly by *Haemophilus influenzae type b*. The illness starts with a minor upper respiratory tract illness, which progresses rapidly within a few hours. The child has high fever and difficulty in swallowing. The child is not able to phonate and often sits up leaning forwards with his neck extended and saliva dribbling from his chin which appears to be thrust forwards. Accessory muscles of respiration are active and there is marked suprasternal and subcostal retractions. As the child becomes fatigued, the stridor diminishes. The diagnosis of epiglottitis is made by a cautious direct laryngoscopy; the epiglottis is angry red and swollen. Injudicious attempt to examine the throat may, at times cause death by sudden reflex spasm of the larynx. In case these procedures are considered essential, the equipment and personnel for respiratory resuscitation should be readily available.

Laryngitis and Laryngotracheobronchitis (Infectious Croup)

These conditions are almost always caused by viral infections, chiefly parainfluenza type 1. Other viruses include respiratory syncytial, parainfluenza types 2 and 3, influenza, adeno and rhinovirus. The onset of illness is gradual with cold for a few days before the child develops brassy cough and an inspiratory stridor. As obstruction increases, the stridor is marked; suprasternal and sternal recessions become manifest. The child becomes restless and anxious with tachypnea due to increasing hypoxemia. Eventually cyanosis appears. As obstruction worsens, breath sounds are inaudible and stridor may apparently decrease.

Spasmodic Croup

It occurs in children between the age of 1 and 3 years. There is at times no preceding coryza. The child wakes up suddenly in the early hours of the morning with

Table 15.3: Assessment of severity of acute laryngotracheobronchitis

	Mild	Moderate	Severe
General appearance	Happy, feeds well, interested in surroundings	Irritable; can be comforted	Restless, agitated or altered sensorium
Stridor	Stridor on coughing, none at rest	Stridor at rest; worsens if agitated	Stridor at rest; worsens on agitation
Respiratory distress	No distress	Tachypnea; chest retractions	Marked tachypnea; chest retractions
Oxygen saturation	>92% in room air	>92% in room air	<92% in room air; may be cyanosed

brassy cough and noisy breathing. The symptoms improve within a few hours, but the illness recurs on subsequent days. The course is benign and patients recover completely. Humidification of the room might benefit.

Differential Diagnosis

Croup syndromes should be distinguished from each other, and from diphtheritic croup and occasionally with measles. Angioneurotic edema, retropharyngeal abscess or aspiration of foreign body may also cause respiratory obstruction.

Management

Patients with epiglottitis need hospitalization. Humidified oxygen is administered by hood; face masks are not well tolerated. As oxygen therapy masks cyanosis, watch is kept for impending respiratory failure. Sedatives should not be used. Unnecessary manipulation (that may induce laryngeal spasm) is avoided. Fluids are administered for adequate hydration by IV route. Third generation cephalosporins (cefotaxime, ceftriaxone 100 mg/kg/day) is recommended for patients with epiglottitis. Endotracheal intubation or tracheostomy may be required, if response to antibiotics is not adequate and obstruction is worsening.

Patients with laryngotracheobronchitis should be assessed for severity of illness based on general appearance, stridor (audible with/without stethoscope), oxygen saturation and respiratory distress (Table 15.3).

Mild cases can be managed on ambulatory basis with symptomatic treatment for fever and encouraging the child to take liquids orally. Parents are explained about the progression of diseases and to bring the child back to hospital in case of worsening of symptoms. Moderately severe patient require hospitalization and treatment with epinephrine (1:1000 dilution 0.1–0.5 mL/kg; maximum 5 mL) administered through nebulizer for immediate relief of symptoms. All patients with severe croup should receive a single dose of dexamethasone (0.3–0.6 mg/kg IM) within the first 24 hours. Inhalation of budesonide, at dose of 1 mg twice a day for 2 days, has also shown satisfactory results.

Severe croup requires urgent hospitalization with oxygen inhalation, therapy with epinephrine and steroids (as above), and occasionally short-term ventilation.

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PNEUMONIA

Pneumonia may be classified anatomically as lobar or lobular pneumonia, bronchopneumonia and interstitial pneumonia. Pathologically, there is a consolidation of alveoli or infiltration of the interstitial tissue with inflammatory cells or both.

Etiology

A viral etiology, chiefly RSV, influenza, parainfluenza or adenovirus is present in ~40% patients. In over two-thirds of patients, a bacterial etiology is identified. Common bacterial agents in the first 2 months of life include gram negative (*Klebsiella*, *E. coli*) and gram-positive organisms (pneumococci, staphylococci). Between 3 months to 3 years, the chief bacterial organisms are pneumococci, *H. influenzae* and staphylococci. After 3 years, common bacterial pathogens include pneumococci and staphylococci. *Chlamydia* and *Mycoplasma* species may cause community-acquired pneumonia in adolescents and children. Gram-negative organisms cause pneumonia in early infancy, severe malnutrition and immunocompromised children. *Pneumocystis jirovecii* and histoplasma may also cause pneumonia in the immunocompromised. The etiology remains unknown in one-third of the cases.

Clinical Features

Risk factors for pneumonia include low birth weight, malnutrition, vitamin A deficiency, lack of breastfeeding, passive smoking, large family size, family history of bronchitis, advanced birth order, crowding, young age and air pollution. Indoor air pollution is a major risk factor for acute lower respiratory tract infection in children in developing countries. Onset of pneumonia may be insidious starting with upper respiratory tract infection or acute with high fever, tachypnea, dyspnea and grunting respiration. There is flaring of alae nasi and retractions of lower chest and intercostal spaces. Signs of consolidation are observed in lobar pneumonia.

Pneumococcal Pneumonia

Respiratory infections due to *S. pneumoniae* are transmitted by droplets and are common in winter months. Overcrowding and reduced host resistance predisposes the children to infection with pneumococci. Bacteria multiply in the alveoli, resulting in an inflammatory exudate. Scattered areas of consolidation occur that coalesce around bronchi and later become lobular or lobar in distribution.

The incubation period is 1 to 3 days. The onset is abrupt with headache, chills, cough and high fever. Cough is initially dry but may be associated with thick rusty sputum. Child may develop chest pain that is occasionally referred to the shoulder or abdomen. Respiration is rapid. In severe cases, there may be grunting, chest indrawing, difficulty in feeding and cyanosis. Percussion note is impaired, air entry is diminished, and crepitations and bronchial breathing is heard over areas of consolidation. Bronchophony and whispering pectoriloquy may be observed. Meningismus may be present in apical pneumonia.

The diagnosis is made on history, examination, X-ray findings of lobar consolidation (Fig. 15.1) and leukocytosis. Bacteriological confirmation is difficult but sputum may be examined by Gram staining and culture. Blood culture may be positive in 5–10% cases. Demonstration of polysaccharide antigen in urine and blood is not specific for pneumonia, since it may be positive in patients with colonization in throat.

Penicillin G 50000 IU/kg/day is given IV or IM in divided doses for 7 days. Therapy with IV cefotaxime, ceftriaxone or coamoxiclav is equally effective.

Staphylococcal Pneumonia

Staphylococcal pneumonia occurs in infancy and childhood. Pneumonia may be primary infection of the parenchyma or secondary to staphylococcal septicemia. It may be a complication of measles, influenza and cystic



Fig. 15.2: X-ray chest showing staphylococcal pneumonia. Note consolidation in both lung fields with pneumatoceles (arrow)

fibrosis or follow staphylococcal pyoderma. Debilitating conditions including malnutrition, diabetes mellitus and macrophage dysfunction also predispose to infection with staphylococci.

In infants, the pneumonic process is diffuse initially, but soon the lesions suppurate resulting in bronchoalveolar destruction. Multiple microabscesses are formed, which erode the bronchial wall and discharge their contents in the bronchi. Air enters the abscess cavity during inspiration; progressive inflation results in formation of pneumatoceles that are pathognomonic of staphylococcal pneumonia (Fig. 15.2). Staphylococcal lung abscesses may erode into the pericardium causing purulent pericarditis. *Empyema below 2 years of age is nearly always staphylococcal in etiology.*

Pulmonary infection may be associated with disseminated disease, with abscesses in joints, bone, muscles, pericardium, liver, mastoid or brain. The diagnosis of staphylococcal pneumonia is suspected in infants with pneumonia with features of systemic staphylococcal infection. Complications of pyopneumothorax and pericarditis are highly suggestive of the diagnosis.

The child is hospitalized. Fever is controlled with antipyretics and hydration is maintained by IV fluids. Oxygen is administered to relieve the dyspnea and cyanosis. Antibiotic therapy should be prompt and carried out with penicillin G, coamoxiclav, cloxacillin or ceftriaxone. If the patient does not respond, vancomycin, teicoplanin or linezolid may be used. Prolonged therapy (2–6 weeks) is desirable.

Complications: Pneumatoceles do not require specific measures. Empyema and pyopneumothorax are treated by intercostal drainage under water seal or low pressure aspiration. Metastatic abscesses require surgical drainage. Significant pleural thickening that might prevent expansion of the underlying lung may require decortication, by open thoracotomy or thoracoscopic surgery.



Fig. 15.1: X-ray chest showing lobar consolidation of right upper lobe

Hemophilus Pneumonia

H. influenzae infections occur between the age of 3 months and 3 years, nearly always associated with bacteremia. Infection begins in the nasopharynx and spreads locally or through blood. Patients present with moderate fever, dyspnea, grunting and retraction of lower intercostal spaces. The presentation may mimic acute bronchiolitis; however, at times the course is subacute and prolonged. Complications include bacteremia, pericarditis, empyema, meningitis and polyarthrititis.

Hemophilus pneumonia is best treated with parenteral ampicillin (100 mg/kg/day) and coamoxiclav. Cefotaxime (100 mg/kg/day) and ceftriaxone (50–75 mg/kg/day) are satisfactory agents for therapy.

Streptococcal Pneumonia

Streptococcal infection by group A beta-hemolytic streptococci may follow measles, varicella, influenza or pertussis. Though uncommon in India, group B streptococcal pneumonia is an important cause of respiratory distress in newborns. Streptococci cause interstitial pneumonia, which may at times be hemorrhagic.

The onset is abrupt with fever, chills, cough, dyspnea, rapid respiration and blood-streaked sputum. Signs of bronchopneumonia are generally less pronounced, as the pathology is usually interstitial. *Thin serosanguineous or purulent empyema is a complication.*

Radiograph shows interstitial pneumonia with segmental involvement, diffuse peribronchial densities or an effusion, which needs to be distinguished from primary atypical pneumonia. Blood counts show neutrophilic leukocytosis. Penicillin G is recommended at doses of 50,000 to 100,000 IU/kg body weight, daily in divided doses for 7–10 days. Alternative antibiotics include second or third generation cephalosporins (cefaclor, cefuroxime, ceftriaxone, cefotaxime).

Primary Atypical Pneumonia

The etiological agent of primary atypical pneumonia is *Mycoplasma pneumoniae*, a small free living organism. Other pathogens include *Chlamydia* and *Legionella* spp. The disease is transmitted by droplet infection, occurring in epidemics chiefly in winter among children in overcrowded living. Disease due to *Mycoplasma* spp. is uncommon below 4 years of age, although subclinical and mild infections are reported.

The incubation period is 12 to 14 days; onset of the illness may be insidious or abrupt. Initial symptoms are malaise, headache, fever, sore throat, myalgia and cough. Cough is dry at first but later associated with mucoid expectoration, which may be blood streaked. Dyspnea is unusual. There are very few physical signs, except mild pharyngeal congestion, cervical lymphadenopathy and a few crepitations. Cold agglutinins are elevated in 30–60% patients; hemolytic anemia is uncommon.

X-ray findings are more extensive than suggested by physical findings. Infiltrates involve one lobe, usually the lower. Poorly defined hazy or fluffy exudates radiate from the hilar regions, occasionally with enlarged hilar lymph nodes and pleural effusion. It is difficult to distinguish *Mycoplasma* from viral or rickettsial pneumonia. Diagnosis is made by detection of IgM antibody by ELISA during the acute stage; IgG antibodies are present after 1 week. *M. pneumoniae* may be recovered from the pharynx and sputum; the diagnosis is confirmed on polymerase chain reaction.

Patients are treated with macrolide antibiotics (erythromycin, azithromycin, clarithromycin) or tetracycline for 7–10 days.

Pneumonia due to Gram-negative Organisms

E. coli, *Klebsiella* and *Pseudomonas* affect small children (<2 months old), children with malnutrition and poor immunity. *Pseudomonas* may colonize airways of patients with cystic fibrosis and causes recurrent pulmonary exacerbations. The onset of illness is gradual and assumes serious proportions. Signs of consolidation are minimal. Constitutional symptoms are more prominent than respiratory distress. Radiograph shows multiple areas of consolidation; those with *E. coli* or *Klebsiella pneumoniae* may have pneumatoceles. Administration of IV cefotaxime or ceftriaxone (75–100 mg/kg/day) with or without an aminoglycoside is recommended for 10 to 14 days. In case of suspected *Pseudomonas* infection, ceftazadime is the drug of choice.

Viral Pneumonia

Respiratory syncytial virus is the chief cause under 6 months of age. At other ages, parainfluenza, influenza and adenoviruses are common, presenting with extensive interstitial pneumonia. Clinical signs of consolidation are absent. Radiological signs consist of perihilar and peribronchial infiltrates.

Aliphatic Hydrocarbon Associated Pneumonia

Kerosene exerts its toxic effects on the lungs and central nervous system. Milk and alcohol promote absorption through the gastrointestinal tract. Since kerosene has low viscosity and low surface tension, it diffuses quickly from the pharynx into the lungs. Features of hydrocarbon pneumonia include cough, dyspnea, high fever, vomiting, drowsiness and coma. Physical signs are minimal. X-ray film of the chest shows ill-defined homogeneous or patchy opacities, and may resemble miliary mottling.

Vomiting is not induced. Gastric lavage is avoided to prevent inadvertent aspiration. The patient is kept on oxygen. Routine antibiotics are not indicated.

Loeffler Syndrome

During their life cycle, larvae of many nematodes (intestinal parasites) enter the portal circulation, and pass through the hepatic vein and inferior vena cava into the heart and lungs. In the lungs, the larvae penetrate the capillaries, enter the alveoli, and block bronchi with mucus and eosinophilic material. Clinical features include cough, low fever and scattered crepitations. There is eosinophilia; radiograph shows pulmonary infiltrates of varying sizes that superficially resemble miliary tuberculosis. Treatment is symptomatic.

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ACUTE RESPIRATORY TRACT INFECTION (ARI) CONTROL PROGRAM

Acute lower respiratory tract infection (LRTI) is the chief cause of mortality in children below 5 years of age. Various studies from developing countries show that the etiological agent in LRTI is bacterial in 50–60% children. Common bacteria causing LRTI in preschool children (*H. influenzae*, *S. pneumoniae*, staphylococci) are sensitive to antibacterial agents like cotrimoxazole and amoxicillin. Judicious use of antibiotics in children suffering from ALRTI may prevent death due to pneumonia. In order to control LRTI deaths at primary health care level, the WHO has recommended criteria for diagnosis of pneumonia applicable for countries where the infant mortality rate is >40/1000 live births.

Criteria for diagnosis of pneumonia include rapid respiration with or without difficulty. Rapid respiration is defined as rate more than 60, 50 or 40/minute in children below 2 months, 2–12 months, and 1–5 years of age, respectively. Difficulty in respiration is defined as lower chest indrawing.

The WHO recommends that in primary care setting, children with cough (between 2 months and 5 years of age) should be examined for rapid respiration and difficulty in breathing, cyanosis or difficulty in feeding (Table 15.4). If the respiratory rate is normal, there is no chest indrawing and is feeding well, the child is assessed to be suffering from upper respiratory tract infection and managed symptomatically. If the child has rapid respiration and chest indrawing, but no hypoxia (normal oxygen saturation), feeding well and does not have danger signs, he may be treated on ambulatory basis with oral amoxicillin at a dose of 40 mg/kg/dose twice daily for 5 days.

If there is severe chest indrawing, evidence of hypoxia or danger signs (lethargy, cyanosis, poor feeding, seizures), the patient is considered to have severe pneumonia. These patients require admission, supportive care and treatment with IV penicillin or ampicillin and gentamicin for at least 5 days. IV ceftriaxone may be used as second-line treatment. In children below 2 months old, the presence of any of the following indicates severe pneumonia: Fever $\geq 38^{\circ}\text{C}$, seizures, abnormally sleepy or difficult to wake, stridor, wheezing, not feeding, tachypnea, chest indrawing, altered sensorium, central cyanosis, grunting, apneic spells or distended abdomen.

Suggested Reading

- Lodha R, Randev S, Kabra SK. Oral antibiotics for community acquired pneumonia with chest indrawing in children aged below five years: A systematic review. *Indian Pediatr* 2016; 53:489–95.
- Revised WHO classification and treatment of pneumonia in children at health facilities: evidence summaries. http://apps.who.int/iris/bitstream/10665/137319/1/9789241507813_eng.pdf

BRONCHIOLITIS

This is one of the most common acute lower respiratory infections in infants, usually occurring in winter or spring. Affected infants are between the ages of 1 and 6 months,

Table 15.4: Children (2 months to 5 years) with cough or difficult breathing: Facilitate treatment decisions

Category	Essential features	Treatment category
Cough or cold	No fast breathing; no indicators of severe pneumonia	Home care; home remedy for cough; paracetamol for fever
Pneumonia with or without lower chest indrawing	Fast breathing: 2–12 months ≥ 50 /minute; 1–5 years ≥ 40 /minute Lower chest indrawing, normal saturation	Home care; oral amoxicillin
Severe pneumonia	Lower chest indrawing; unable to drink or breastfeed, convulsions, lethargy, unconsciousness, severe respiratory distress, central cyanosis	Inpatient care IM, IV benzylpenicillin or ampicillin and gentamicin

but the disease can affect children up to 2 years. Respiratory syncytial virus (RSV) is implicated in most cases. Other causative organisms are parainfluenza, adeno and influenza viruses and rarely *M. pneumoniae*.

Protection against RSV is mediated by antibodies of IgG3 subclass. These antibodies have short half life and do not cross the placenta in substantial amount so as to offer protection to the infant. Since high quantities of secretory IgA antibodies to RSV are present in the colostrum, breastfeeding reduces the risk of an infant being hospitalized with bronchiolitis.

Pathogenesis

Inflammation of the bronchiolar mucosa leads to edema and bronchiolar spasm, thickening, formation of mucus plugs and cellular debris. As airway resistance is inversely related to the fourth power of the radius, even slight narrowing causes marked increase in resistance and reduced airflow. Resistance to airflow is increased both during inspiration and expiration. During expiration, the bronchioles are partially collapsed and, therefore, egress of air from the lungs is severely restricted during this phase. This leads to trapping of the air inside the alveoli causing emphysema. When obstruction is complete, the trapped air is absorbed resulting in atelectasis. Diminished ventilation and diffusion in severe bronchiolitis result in hypoxemia and respiratory acidosis.

Clinical Features and Diagnosis

The disease begins as an upper respiratory infection. After a few days, the child has high fever with rapid breathing and respiratory distress. Those with severe disease show retraction of lower intercostal spaces and suprasternal notch. In severe infection, infants have respiratory distress and are cyanosed. Expiration is prolonged; fine crepitations and rhonchi are auscultated. Breath sounds are faint or inaudible in severe cases. As air is trapped in the lungs, the liver and spleen are pushed down; anteroposterior diameter of the chest is increased and hyperresonance is noted on percussion.

X-ray chest shows hyperinflation and infiltrates (Fig. 15.3). The diaphragm is pushed down and lung fields appear abnormally translucent. The leukocyte count is normal or slightly elevated. A rapid test on nasopharyngeal aspirate can identify the presence of RSV.

Course and Prognosis

Bronchiolitis is generally a self-limited illness, with symptoms subsiding in 3–7 days. Death may occur, due to respiratory failure, in one percent of severely ill patients. The relationship of acute bronchiolitis to bronchial asthma in later life is seen in about one-fourth of cases.

Differential Diagnosis

Bronchial asthma: Bronchial asthma is unusual below the age of 1 year. There is often a family history of asthma.

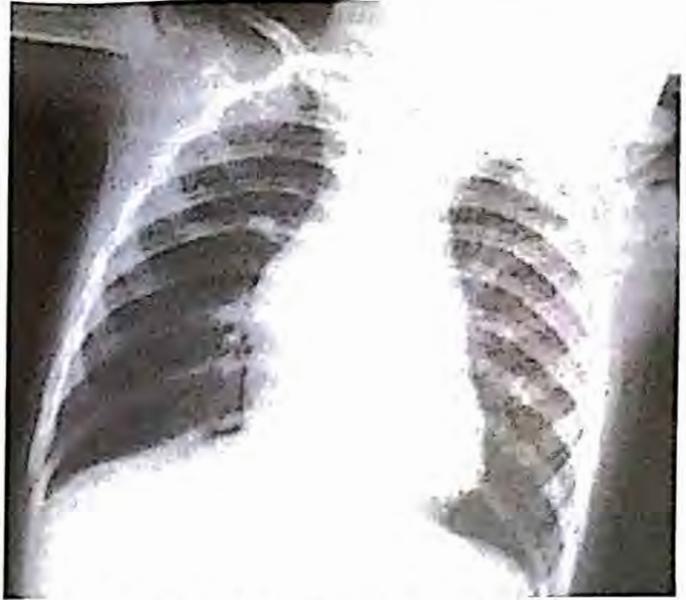


Fig. 15.3: X-ray chest in a 1-year-old with acute bronchiolitis. Note hyperinflation on both sides and a few infiltrates

Several attacks occur in the same patient. Response to bronchodilators is more consistent in children with asthma, compared to bronchiolitis.

Heart failure: Congestive heart failure is suggested in presence of cardiomegaly, tachycardia, enlarged liver, raised JVP, edema and basal crepitations.

Foreign bodies: These are diagnosed by history of aspiration of foreign body, localized wheeze and signs of collapse or localized obstructive emphysema.

Bacterial pneumonia: In bacterial pneumonia, the signs of obstruction are less pronounced, fever is high and adventitious sounds in lungs are prominent.

Treatment

Treatment of bronchiolitis is symptomatic. The child should be nursed in a humid atmosphere preferably in reclining position at 30° to 40° with head and neck elevated. Infants with mild disease can be cared for at home in a humidified atmosphere. If respiratory distress increases or feeding problems appear, the patient should be hospitalized. Moist oxygen inhalation is the mainstay of treatment, administered continuously even in absence of cyanosis. Fluids and electrolyte balance should be maintained. Very sick infants may need a concentration of 60% oxygen given through a hood, to maintain oxygen saturation more than 92%.

Antibiotics have no role. Ribavirin, an antiviral agent, has no role in the treatment of infants who were previously healthy. However, the medication shortens the course of illness in infants with underlying congenital heart disease, chronic lung disease and immunodeficiency. Ribavirin is delivered by a nebulizer 16 hours a day for 3–5 days in such cases.

Bronchodilators, inhaled or systemic steroids and epinephrine have not been found useful in infants with acute bronchiolitis. If a patient shows improvement with bronchodilator or epinephrine, further doses may be given every 4–6 hours. Inhaled hypertonic saline has been shown to be effective in a subgroup of patients. Its routine use is not recommended. Continuous positive airway pressure (CPAP) or assisted ventilation is required to manage respiratory failure. Extracorporeal membrane oxygenation is effective in severe cases.

Suggested Reading

- Osvald CE, Clarke JR. NICE clinical guideline: bronchiolitis in children. Arch Dis Child Educ Pract Ed 2016; 101:46–8.
- Walsh P, Rothenberg SJ. American Academy of Pediatrics 2014 bronchiolitis guidelines: bonfire of the evidence. West J Emerg Med 2015; 16:85–8.

BRONCHIAL ASTHMA

Bronchial asthma is a disease characterized by increased responsiveness of the airways to various stimuli. Widespread narrowing of the airways causes paroxysmal dyspnea, wheezing or cough. The diffuse obstruction to the airflow is reversible in a large majority of cases, either spontaneously or in response to treatment.

Pathophysiology

Diffuse airway obstruction in asthma is caused by (i) edema and inflammation of mucous membrane lining the airways, (ii) excessive secretion of mucus, inflammatory cells and cellular debris, and (iii) spasm of the smooth muscle of bronchi.

Asthma has been classified as atopic (earlier called extrinsic; IgE mediated, triggered by allergens), non-atopic (earlier called intrinsic; non-IgE mediated, triggered by infection), mixed, exercise induced or aspirin induced. Inhalation of an allergen leads to a biphasic response with early and late reactions ultimately causing bronchoconstriction.

Triggers of Asthma

Infections: Viral infections in young children are important triggers of airway narrowing. Viral infections might interfere with the integrity of mucosal surface by opening up tight intraepithelial cell junctions, inducing epithelial shedding. They also result in mucosal edema and mucus secretion.

Exercise: Exercise-induced asthma occurs in genetically susceptible individuals with hyperreactive airways because of evaporative water losses from the respiratory tract. Water loss induces mucosal hyperosmolarity, which stimulates mediator release from mast cells.

Weather: Sudden change of weather may result in: (i) evaporative water losses from lower airways; and

(ii) release of airborne allergens in atmosphere that exacerbate asthma.

Emotions: Stress, through the vagus nerve, may initiate bronchial smooth muscle constriction.

Food: Allergy to food proteins or additives has an insignificant role in pathogenesis of asthma.

Endocrine: Children may get increase in symptoms during puberty.

Clinical Features

The clinical features of asthma vary from recurrent cough to severe wheezing; symptoms occur with change in season and are aggravated by exercise and more in nights. Acute asthma may usually begin with a cold or bouts of spasmodic coughing more so at night. In early phase of the attack, cough is non-productive. The patient is dyspneic, with prolonged expiration and wheezing. With increasing severity, accessory muscles of respiration are used. The child sweats profusely and is apprehensive and restless.

In severe episodes, the child shows air hunger and fatigue. The presence of cyanosis, pulsus paradoxus and cardiac arrhythmias indicates severe illness. The chest is hyperresonant because of air trapping. Occlusion of bronchi by mucus plugs may result in collapse of small segments of the lung. As obstruction becomes severe, the airflow decreases markedly and breath sounds are feeble. Wheezing which was earlier audible may disappear. Thus absence of wheezing in presence of cyanosis and respiratory distress does not suggest clinical improvement. During clinical recovery, airflow increases and wheezing may reappear.

Persistence of hyperinflation of the chest even after subsidence of an acute episode signifies that the apparent relief from bronchospasm will be short lived. In chronic intermittent cases, the chest becomes barrel shaped. Clubbing of fingers, however, is unusual.

Diagnosis

The diagnosis of asthma is clinical in most cases. Recurrent attacks of wheezing or spasmodic cough are highly suggestive of bronchial asthma. Cough, which is associated with asthma generally, worsens after exercise. Sputum is clear and mucoid, but might be yellow due to large number of eosinophils.

Pulmonary function tests (PFT) are important for diagnosis of doubtful cases and monitoring response to therapy. Important parameters on spirometry include PEFr, FEV₁, FVC and FEV₂₅₋₇₅, all being decreased in asthma. FEV₁ is commonly used for documenting the severity of asthma. FEV₂₅₋₇₅ is effort independent and more sensitive indicator of airway obstruction. PEFr is measured with flow meter, while spirometry is required

for others. Abnormalities in PEFR suggestive of asthma include: Diurnal variation of more than 20%, $\leq 80\%$ of predicted, and improvement of $\geq 20\%$ after bronchodilator therapy.

Absolute eosinophil counts might help distinguish allergic from infectious nature of chronic respiratory disease. When eosinophilia is present, the symptoms generally respond to antispasmodic therapy.

Chest X-ray film shows bilateral and symmetric air trapping in case of asthma. Patches of atelectasis due to mucus plugs are not unusual. Main pulmonary artery may be prominent in severe cases due to pulmonary hypertension. Bronchial cuffing may occur due to the presence of edema fluid in perivascular and peribronchial interstitial space. Extensive areas of collapse or consolidation should suggest an alternative diagnosis. Occasionally, the chest radiograph may be normal.

Allergy tests (e.g. skin test, RAST radioallergosorbent allergen specific IgE) have limited usefulness. Blood IgE may be raised in children with atopic asthma, but cannot be used as diagnostic test. The role of skin tests to identify sensitivity to different antigens, and desensitization is limited.

Differential Diagnosis

Bronchiolitis occurs within the first 2 years, usually within the first 6 months of life, usually in winter or spring. Generally, there is a single attack. Repeated attacks indicate viral infection associated wheeze or multi-trigger wheeze or asthma. Hyperinflation of chest with scattered areas of infiltration may be seen in chest X-ray. Asthma may start at any age; more than 3 episodes are usual and wheezing is prominent. Infants with bronchiolitis and atopic dermatitis, high IgE levels or family history of allergy need follow up for later development of asthma.

Congenital malformations with obstruction (vascular rings due to aberrant right subclavian artery or double aortic arch, bronchogenic cysts, tracheomalacia) should be excluded in differential diagnosis.

Aspiration of foreign body may result in localized area of wheeze, hyperresonance and reduced air entry. A history of foreign body aspiration may be forgotten. Most children have frequent infections in the lung.

Hypersensitivity pneumonitis may follow inhalation of organic dust (molds, wood, cotton or fur dust, bird droppings, grain) or exposure to specific agents (epoxy resins, PAS, sulfonamide, nitrofurantoin). Patients have fever, chills, dyspnea, malaise, aches and pain, rales (crackles) and weight loss. X-ray chest shows interstitial pneumonia with prominent bronchial markings. Levels of IgG antibodies to specific antigen are increased. Skin test shows Arthus phenomenon with local hemorrhage, edema and pain within 8 hours. The diagnosis is established on lung biopsy.

Cystic fibrosis presents with recurrent wheezing; patients show clubbing and malabsorption. X-ray chest shows hyperinflation, peribronchial cuffing and pneumonia. The diagnosis is made on sweat testing.

Management of Asthma

Bronchial asthma cannot be cured but can be controlled. Goals of therapy are: (i) maintain near normal pulmonary function; (ii) maintain near normal physical activity; (iii) prevent nighttime cough or wheezing with minimal chronic symptoms; (iv) prevent recurrences; (v) avoid adverse effects of therapy. Effective long-term management of asthma involves three major areas:

- i. Identification and elimination of exacerbating factors
- ii. Pharmacological therapy
- iii. Education of patient and parents about nature of disease and steps to avoid acute exacerbation

Identify and Eliminate Exacerbating Factors

Factors associated with development and precipitation of asthma are passive smoking, associated allergic disorders, inadequate ventilation at home with dampness, cold air, cold food, smoke, dust and pets in the family. Acute viral respiratory infections are one of the chief causes of exacerbation.

Following measures may help in reducing risk of recurrences:

- i. The bedroom should be clean and free from dust. Wet mopping of the floor is encouraged.
- ii. Since heavy tapestry attracts dust, light plain cloth sheets should be used as curtains in the child's bedroom.
- iii. Periodic cleaning of carpets, stuffed furniture, loose clothing and hangings, calendars and books.
- iv. The child's bed should be made of light material and aired regularly.
- v. Caressing of animal pets is discouraged, as the child may be sensitive to their fur.
- vi. It is usually not necessary to restrict the diet, since food allergy is not the cause in most cases.
- vii. Adolescent patients should refrain from smoking.
- viii. Exposure to strong odors such as wet paint, disinfectants and smoke should be minimized.
- ix. The child should avoid attics or basements, especially if unoccupied and closed.

Pharmacotherapy

Pharmacological therapy of bronchial asthma involves agents that relax smooth muscle and dilate airways, and those that decrease inflammation. Medications for long-term treatment of asthma include bronchodilators, steroids, mast cell stabilizers, leukotriene modifiers and theophylline (Table 15.5).

Bronchodilators: Commonly used short-acting bronchodilators are adrenaline, terbutaline and salbutamol, all

Table 15.5: Medication for long-term treatment of asthma

Medication, route	Side effects	Dose	Comments
Salbutamol 100 µg/puff MDI Respirator solution 5 mg/mL Respules 2.5 mg/3 mL Dry powder capsules 200 µg	Tachycardia, tremors, headache, hypokalemia hyperglycemia	1–2 puff 4–6 hours 0.15–0.2 mg/kg/dose nebulization 1 dry powder cap 4–6 hours	Drug of choice for acute exacerbation Prior to exercise to prevent exercise-induced bronchospasm
Terbutaline 250 µg/puff MDI	–do–	1–2 puff 4–6 hours	
Salmeterol 25 µg/puff MDI Dry powder capsules 50 µg (Rotacap)	–do–	1–2 puffs 12–24 hours 1 dry powder cap inhalation 12–24 hours 1–2 puffs 12–24 hrly	Long-term prevention of symptoms; useful for nocturnal symptoms and exercise-induced episodes
Formoterol 12 µg/puff MDI Dry powder capsules 12 µg (Rotacap)	–do–	1–2 dry powder cap 12–24 hours	Not for acute symptoms Use with anti-inflammatory therapy; not as substitute
Theophylline 100, 150, 200, 300 mg tablets (Oral)	Toxicity at >20 mg/kg/day; nausea, headache, tachycardia, drowsiness, seizures	5–15 mg/kg/day 2 divided dose	Drug interactions (anti-tubercular, anticonvulsants, ciprofloxacin) May use in step II when inhalation route not possible
Sodium cromoglycate 5 µg/ puff MDI	Medicinal taste Reflex coughing	1–2 puffs 3 times/day 1–2 puffs 3 times/day	Continuous prophylaxis for control of symptoms
Nedocromil sodium inhalation Ketotifen 1 mg tab, 1 mg/5 mL Oral	Bitter taste, cough Sedation, weight gain	1 mg twice a day	May take 4–6 weeks for clinically evident effect Safe oral agent
Beclomethasone 50, 100, 200, 250 µg/puff Budesonide 50, 100, 200 µg/ puff MDI Respules 0.5, 1 mg/mL Rotacaps 100, 200, 400 µg	Cough, dysphonia, oral thrush; negligible side effects at <400–800 µg/day	Low dose 100–200 µg/day in 2 divided doses Medium dose 400 µg/day in 2 divided doses High dose >800 µg/day in 2 divided doses	Budesonide and fluticasone are completely inactivated during first pass metabolism and have minimal systemic side effects Prolonged high dose therapy may cause systemic side effects
Fluticasone 25,50,125 µg/ puff MDI Dry powder capsules 50, 100, 250 µg Respules 0.5 and 1 mg/mL Ciclesonide 80, 160 µg/puff			Use minimum required dose preferably on alternate days Ciclesonide is not recommended for use <12-year-old
Montelukast 4, 5, 10 mg tabs	Generally well tolerated Churg-Strauss syndrome reported	2–5 years: 4 mg/day 5–12 years: 5 mg/day >12 years: 10 mg/day	Exercise-induced asthma Alternative to long-acting β-agonist

having a quick onset of action. Adrenaline stimulates α and both β receptors, with ensuing cardiac side effects. Terbutaline and salbutamol are specific β_2 agonist and hence, have less cardiac effects. While adrenaline is given subcutaneously, the others can be given by oral, inhalation or parenteral route. Inhalation route is preferred because of rapid onset of action and a few side effects.

Long-acting β_2 agonists are salmeterol and formoterol. The onset of action is delayed by 30–60 minutes but lasts 12–24 hours. Their safety and efficacy has been shown in children above 4 years of age.

Corticosteroids: Corticosteroids, being potent anti-inflammatory agents, are the cornerstone of long-term treatment of asthma. Systemic glucocorticoids, when used early for therapy of exacerbation, reduce emergency visits and hospitalization. Therapy with inhaled corticosteroids

reduces the risk for systemic adverse effects. Commonly used inhaled steroids include beclomethasone, budesonide and fluticasone; budesonide (BDS) and fluticasone are considered superior to beclomethasone (BDP). The chief concern with long-term use of inhaled steroids is their adverse effect on growth with 20% reduction in growth velocity reported in the first year. The growth velocity later recovers and ultimately children attain predicted adult height.

Mast cell stabilizers: Cromolyn sodium reduces bronchial reactivity and symptoms induced by irritants, antigens and exercise. Indications for use of cromolyn include mild to moderate persistent asthma and exercise-induced asthma. The medication should be given for 6–8 weeks before declaring it ineffective. Nedocromil is another agent used for control of mild to moderate asthma. Ketotifen is

Table 15.6: Assessment of symptom control

Feature	Controlled: All of the following	Partially controlled: Any measure present in any week	Uncontrolled
Daytime symptoms	None (twice a week or less)	More than twice per week	Three or more features of partially controlled asthma present in any week
Limitation of activity	None	Any	
Nocturnal symptoms, awakening	None	Any	
Need for reliever or rescue drugs	None (less than twice a week)	More than twice per week	

administered orally; significant clinical improvement is seen after 14 weeks of therapy.

Leukotriene modifiers: Leukotriene inhibitors are useful for treatment of mild to moderate persistent asthma and exercise-induced asthma. These agents act either by decreasing the synthesis of leukotrienes (zileuton) or by antagonizing the receptors (montelukast and zafirlukast). Montelukast and zafirlukast are approved for use in children with asthma; montelukast can be used in children >1 year of age while zafirlukast >12 years.

Theophylline: Theophylline has concentration-dependent effects. While the bronchodilator effect is by inhibition of phosphodiesterase, the agent also has anti-inflammatory and immunomodulatory effects at therapeutic serum concentration. Recent guidelines recommend theophylline as an alternative second-line therapy (combined with glucocorticoids) in moderate persistent asthma in children ≥5 years, as second-line therapy for mild persistent asthma in older children and adults, and adjunctive therapy (for nocturnal symptoms) in moderate or severe persistent asthma.

Immunotherapy: This consists of administering gradually increasing quantities of an allergen extract to a sensitive subject, so as to ameliorate symptoms associated with subsequent exposure to the causative allergen. This form of therapy is considered occasionally in highly selected children who are sensitive to specific allergens, e.g. grass pollen, mites. Immunotherapy is carried out only under specialist supervision.

Pharmacological management includes the following key steps: (i) assessment of symptom control; (ii) assessment of risk of exacerbation; (iii) selection of medication; (iv) selection of appropriate inhalation device; and (v) monitoring.

Assessment of symptom control: Control of disease is graded based on frequency and severity of symptoms, and functional impairment. This is assessed by asking for frequency of symptoms including daytime symptoms, limitation of activity, nocturnal symptoms and need for rescue medications, in past 4 weeks (Table 15.6), and classifying as controlled, partially controlled and uncontrolled.

Table 15.7: Assessment of risk of exacerbation in near future

Uncontrolled asthma symptoms
One or more severe exacerbation requiring hospitalization in previous year
Ever intubated or PICU admissions
Start of the usual 'flare-up' season
Exposure: Tobacco smoke; indoor or outdoor air pollution; indoor allergens
Major psychological or socioeconomic problems for child or family
Poor adherence with controller medication, or incorrect inhaler technique
Co-morbidities: Obesity, rhino-sinusitis, confirmed food allergy

Assessment of risk of exacerbations: Based on history, children are assessed for risk of exacerbations (Table 15.7). Appropriate treatment to children who are at risk of exacerbation may help in prevention of exacerbation.

Selection of medication: After assessment of control of asthma and risk for exacerbation, antiasthma drugs are selected. Treatment of asthma according to the assessment is shown in Table 15.8.

Infrequent episodes with no risk for exacerbation are treated with salbutamol or terbutaline as and when required. The oral route is used, if inhalation is not possible for any reason. Children with infrequent episodes but having risk factor(s) for exacerbation, or children with day time symptoms >2 per week or nighttime symptoms once a month should be treated with low dose inhaled steroids with salbutamol inhalation, as and when required. An alternate strategy is montelukast or sustained release theophylline.

Children with troublesome symptoms on most days or waking once a week or more, need low dose inhalation steroids in 2 divided doses and long-acting β-agonist (formoterol, salmeterol) above 12 years of age, and medium dose steroids below 12 years. Children with severe uncontrolled symptoms need high dose inhalation steroids in divided doses and long-acting β-agonists. Montelukast can be used as add on treatment for better control of symptoms. Persistent symptoms might require the use of low dose prednisolone, preferably on alternate days.

Selection of appropriate inhalation device: Drugs for maintenance treatment can be administered by inhalation

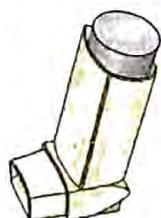
Table 15.8: Initial treatment of asthma

Symptom control	First choice	Other choice
Infrequent symptoms: not uncontrolled or partly controlled and no risk factors	No controller medications Short-acting β -agonists as and when required	—
Asthma (even infrequent symptoms) + any risk factor for exacerbations Symptoms more than twice a month Waking due to asthma more than once a month	Low dose inhaled steroids Short-acting β -agonists as and when required	Montelukast
Troublesome symptoms on most days Waking once a week or more	>12 years: Low dose inhaled steroids + long-acting β -agonists 6–11 years: Medium dose inhaled steroids	Low/medium dose inhaled steroids + leukotriene receptor antagonists Or Sustained release theophylline
Severely uncontrolled symptoms	Medium to high dose inhaled steroids + long-acting β -agonists	Short course oral steroids; low dose oral steroids on alternate days; montelukast

or oral route. The former are more effective, with rapid onset of action and less side effects. Commonly available inhalation devices include: (i) metered dose inhaler (MDI), (ii) MDI with spacer, (iii) MDI with spacer and face mask, (iv) dry powder inhaler, (v) nebulizer.

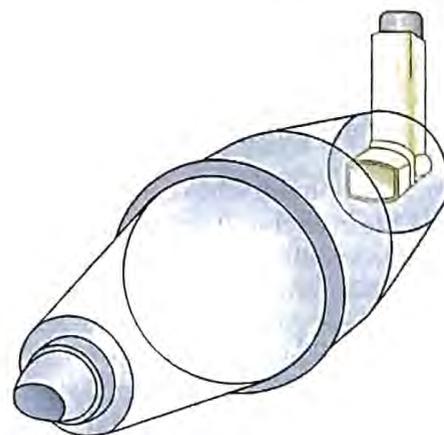
Metered dose inhaler (Fig. 15.4): An MDI is a device, which delivers a fixed amount of medication in aerosol form each time it is activated. It is used for exacerbation and maintenance therapy. It is effective but requires considerable coordination, which might not be possible in young children. After actuation, the drug comes out at a pressure and a significant amount of the drug gets deposited in the oropharynx. MDIs continue to work past the labeled number of doses because of excess propellant.

MDI with spacer (Fig. 15.5): Use of spacer inhalation device with an MDI should be encouraged as it results in a larger proportion of the medication being delivered in the lung, with less impaction in the oropharynx. They also overcome the problems of poor technique and coordination of actuation and inspiration, which occur with MDI alone. Furthermore, use of spacer allows MDI to be used for the young patient. MDI used with spacer has been found to be comparable to nebulizer in delivering salbutamol in acute exacerbation of asthma in children. Spacers have the limitation of being bulky, relatively costly and cannot be used in young infants and toddlers. A homemade spacer (prepared from mineral water bottle) can effectively deliver salbutamol in acute exacerbation.



1. Remove cap and shake inhaler in vertical direction
2. Breathe out gently
3. Put mouthpiece in mouth. At start of inspiration that should be slow and deep, press canister down and continue to inhale deeply
4. Hold breath for 10 seconds or as long as possible then breathe out slowly
5. Wait for a few seconds before repeating steps 2–4.

Fig. 15.4: Metered dose inhaler



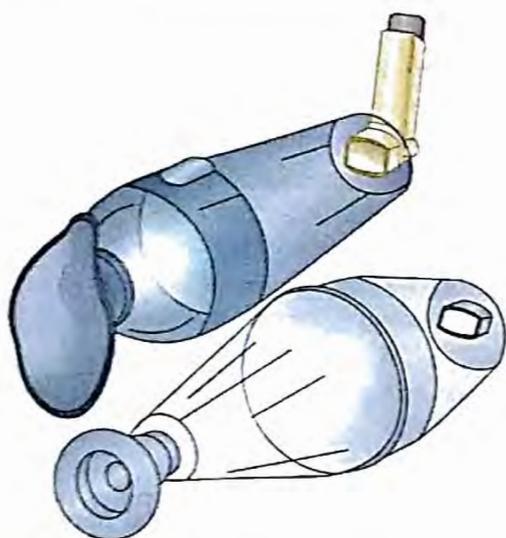
1. Remove cap, shake inhaler and insert into spacer device
2. Place mouth piece of spacer in mouth
3. Start breathing in and out gently and observe movements of valve
4. Once breathing pattern is established press canister and continue to breath 5–10 times (tidal breathing)
5. Remove the device from mouth and wait for 30 seconds before repeating steps 1–4.

Fig. 15.5: Metered dose inhaler with spacer

MDI with spacer and face mask (Fig. 15.6): Attaching a face mask to the spacer facilitates their use in young infants.

Dry powder inhaler (DPI) (Fig. 15.7): These are breath-activated devices (Rotahaler; Diskhaler, Spinhaler, Turbohaler, Acuhaler) that can be used in children above 4–5 years old. They are portable and do not require coordination of actuation with breathing. They are environment friendly, since they do not contain CFC. However, the effect of these inhalers depends on a certain inspiratory flow rate, with risk of reduced effect during acute exacerbations or in children with low pulmonary function.

Nebulizers (Fig. 15.8): Nebulizers with air compressors are bulky and inconvenient to use. With advent of efficient spacer systems, the need for nebulizers has greatly diminished. However, there is role for nebulized β -agonist



1. Attach baby mask to the mouth end of spacer
2. Shake MDI; insert it in the MDI end of spacer device
3. Cover baby's mouth and nose with baby mask
4. Press canister and encourage the child to take tidal breathing with mouth open (if possible) 5–10 times
5. Remove baby mask and wait for 30–60 seconds before repeating steps 1–4.

Fig. 15.6: Metered dose inhaler with spacer and face mask



1. Hold Rotahaler vertically and insert capsule (clear end first) into square hole, make sure that top of the capsule is level with top of hole
2. Hold Rotahaler horizontally, twist barrel in clockwise and anti-clockwise direction, this will split the capsule into two
3. Breathe out gently; put mouth end of Rotahaler in mouth and take deep inspiration
4. Remove Rotahaler from mouth; hold breath for 10 seconds

Fig. 15.7: Rotahaler

in acute severe asthma, especially in young irritable and hypoxic children who do not tolerate MDI with spacer and face mask. At a flow rate of 6–12 L/min, 30–50% of aerosol is in the respirable range of 1–5 mm. Slow, deep inhalations and breath holding improves delivery.

It is necessary to select an appropriate device by which the maintenance medication is administered. Inhalation method should be chosen on individual basis, but a guideline is as follows:



1. Connect output of compressor to nebulizer chamber by the tubing provided with nebulizer
2. Put measured amount of drug in nebulizer chamber; add normal saline to make the total volume 2.5–3 mL
3. Switch on the compressor and look for aerosol coming out from the nebulizer chamber
4. Attach face mask to nebulizer chamber; ensure appropriate fit to cover nose and mouth of the child
5. Encourage child to take tidal breathing with open mouth

Fig. 15.8: Nebulizer

- Children <4-year-old: MDI with spacer with face mask
- Children >4-year-old: MDI with spacer preferred
- Children >12-year-old: MDI used directly. Use of spacer improves drug deposition.

Monitoring and Modification of Treatment

After initiating treatment, patients should be seen every 4–12 weeks. At each visit, history regarding frequency of symptoms, sleep disturbance, physical activity, school absenteeism, visit to a doctor and need for bronchodilators, and PEF is recorded. The inhalation technique and compliance is checked. The patient or parents should be encouraged to maintain a symptom diary. Patient is assessed as controlled, partially controlled or uncontrolled (Table 15.6).

If disease is partially controlled or uncontrolled, the causes, apart from disease severity, could be poor compliance, wrong technique of inhalation, continued use of empty canister, inappropriate doses, associated infections (otitis media, sinusitis, pneumonitis) or continued exposure to allergens. Children with asthma have a higher risk of sinusitis. Bronchial hyper-responsiveness and symptoms of asthma improve with therapy for associated upper respiratory diseases, including allergic rhinitis and sinusitis.

If no cause is found, step up, i.e. increase in dose and frequency of medication is required. Step down, if control is sustained for 3–6 months and follow a stepwise reduction in treatment (Table 15.9).

Exercise-Induced Bronchoconstriction

Children who show bronchoconstriction after exercise may avoid participation in outdoor games. They may be treated with appropriate stepwise management, and

Table 15.9: Stepwise treatment of asthma

	Symptoms	Treatment	
Step 4: Severe persistent	Continuous Limited physical activity	High dose inhaled steroids + Long-acting β_2 agonist	Add montelukast Refer to specialist
Step 3: Moderate persistent	Daily use β_2 agonist Daily attack affects activity	Low dose inhaled steroids + Long-acting β_2 agonist <i>OR</i> Medium dose inhaled steroids	
Step 2: Mild persistent	Low grade symptoms twice a month Nighttime awakening once per month	Low dose inhaled steroids Short-acting β_2 agonist, whenever symptoms	
Step 1: Intermittent	Infrequent Asymptomatic and normal PEFR between attack	Short-acting β_2 agonist, whenever symptoms	

require additional agents like short- and long-acting β -agonists or leukotriene modifiers. Short-acting β -agonists should be taken before going for exercise. Long-acting β -agonists administered in the morning show action throughout the day. Leukotriene modifiers are satisfactory alternative to long-acting β -agonists.

Seasonal Asthma

A proportion of children get symptoms of asthma for a brief period in particular season. They remain asymptomatic for the rest of the year. These children can receive maintenance treatment 2 weeks in advance. Medications are selected according to severity of asthma. After the season is over, patients are reexamined after discontinuing the medications.

Newer Therapies

A number of novel therapies have been examined for clinical use. Monoclonal antibodies against IgE (omalizumab), IL4, IL5 and IL13 may have promise as therapy for patients with refractory illness.

Education of Parents

Education of patients and their parents is an important aspect of management. A description of the etiopathogenesis of asthma in plain language should be made. The spectrum of severity of the illness, likely course and satisfactory outcome is explained. Parents need to be involved in the steps required to minimize exposure to potential environmental triggers. Avoidance of all kinds of smoke at home, including tobacco smoke, wood burning and kerosene stove is emphasized. Parents should be advised regarding minimizing the use of carpets, curtains and other dust attracting articles.

Parents should be asked to maintain a record of daily symptoms such as cough, coryza, wheeze and breathlessness. A record of sleep disturbances, absence from school due to illness and medication required to keep the child symptom-free is advised. These records help in stepping up or down the pharmacotherapy.

The parents, and where possible the patient, should understand how the medications work, proper adminis-

tration, use of spacer and potential harmful effects of drugs. Parents concerned about the use of steroids needs to be reassured that in conventional inhalation dosage, the risk of serious illness outweighs the side effects of medication. Peak flow monitoring done properly by informed parents can help by:

- Detecting early deterioration in lung function
- Managing patients who have difficulty in sensing the change in severity of airway obstruction
- Managing patients whose asthma severity changes very rapidly

Home Treatment of Acute Exacerbation

The parent/patient is instructed regarding recognition and management of acute exacerbation of asthma at home. A written action plan is given. Acute exacerbation is identified by increase in cough, wheeze and breathlessness. PEFR, if measured, may be 15% lower from the baseline. For acute exacerbation, parents should administer short-acting β -agonists by MDI \pm spacer \pm facemask one puff at a time repeated every 30–60 seconds up to a maximum of 10 puffs with monitoring of symptoms. If symptoms are relieved and PEFR is increased at end of inhalation, the child can continue the β -agonists (salbutamol or terbutaline) every 4–6 hours and plan a visit to the physician. If there is no improvement or partial improvement or symptoms of life threatening attack at any time, the child should be transferred to a hospital.

Patients with life-threatening asthma or those failing to show satisfactory response to inhalation therapy at home should receive a single dose of oral prednisolone (1–2 mg/kg) before going to the hospital.

Managing Acute Exacerbation

An increase in symptoms (cough, wheeze, and/or breathlessness) is termed as exacerbation of asthma. The severity of exacerbation is variable and can be classified as mild, moderate, severe based on physical examination, measurement of PEFR/FEV1 and oxygen saturation (Table 15.10).

Table 15.10: Grading of severity of acute asthma

Clinical parameter	Mild	Moderate	Severe
Color	Normal	Normal	Pale
Sensorium	Normal	Anxious	Agitated
Respiratory rate	Increased	Increased	Increased
Dyspnea	Absent	Moderate	Severe
Speech	Can speak sentences	Can speak in phrases	Difficulty in speech
Use of accessory muscles	Nil or minimal	Chest indrawing	Indrawing; nasal flare
Pulsus paradoxus	<10 mm	10-20 mm	>20 mm
Rhonchi	Expiratory and/or inspiratory	Expiratory and/or inspiratory	Expiratory or absent
Peak expiratory flow rate	>80%	60-80%	<60%
Oxygen saturation	>95%	90-95%	<90%

Life-threatening Asthma

Presence of *any* of the following indicates life-threatening asthma: Cyanosis, silent chest, poor respiratory efforts, exhaustion or fatigue, altered sensorium, PEFr <30% of predicted, and oxygen saturation <90%. Such patients should immediately receive oxygen by mask or hood. An injection of terbutaline or adrenaline is given subcutaneously, inhalation of salbutamol or terbutaline and ipratropium is started, an injection of hydrocortisone (5 mg/kg) given and arrangements made to transfer the patient to an intensive care unit (ICU) preferably with an accompanying physician.

If the patient shows improvement, the salbutamol/terbutaline inhalation is continued every 20-30 minutes, hydrocortisone (3-5 mg/kg) is continued every 6-8 hourly till patient starts accepting orally. If patient does not improve or deteriorates a slow IV infusion of magnesium sulfate (50 mg/kg) or a loading dose of theophylline is given. If there is no improvement with this management, the patient is prepared for mechanical ventilation. Patients should also be screened for causes of poor response such as acidosis, pneumothorax, electrolyte imbalance and infection, and treated accordingly.

Mild Acute Asthma

Patients with mild exacerbation have cough, rapid respiration and some wheezing, but no chest indrawing and are able to speak and drink well. PEFr >80% of predicted and oxygen saturation >95% in room air.

The patient should receive β_2 agonists by nebulizer or MDI + spacer with or without face mask. If MDI is used, one puff of the agonist is given every minute for up to 10 puffs. If case of significant improvement, the patient is sent home on inhalation or oral β_2 agonists every 6-8 hours and called back after 1-2 weeks for reassessment and long-term treatment. In case of unsatisfactory response, the patient should be treated as moderate exacerbation.

Acute, Moderate and Severe Asthma

These patients have rapid respiration, chest indrawing, wheezing, pulsus paradoxus, difficulty in speech and

feeding; PEFr and oxygen saturation is decreased and sensorium is normal.

Patients should receive inhalation β_2 agonist as described for treatment of mild asthma. Oxygen inhalation is started and oral prednisolone 1-2 mg/kg administered. The patient is assessed for improvement at the end of 1 hour. In case of improvement, the child is continued on inhaled β_2 agonists every 30 minutes, and the interval gradually increased to 4-6 hourly. Oxygen inhalation is stopped, if patient is able to maintain oxygen saturation >95%. Prednisolone is continued once daily for 5-7 days, and then stopped without tapering. The patient is discharged from hospital when the need for bronchodilators is every 4-6 hours, able to feed and speak well, maintains oxygen saturation >95% in room air and PEFr >75% of predicted. These patients should be educated about the disease, need for regular follow-up and avoidance of triggers. They should be assessed for long-term treatment.

In case of no improvement at the end of 1 hour, inhalation of salbutamol is continued and inhaled ipratropium 250 mg given every 20 minutes. An injection of hydrocortisone 10 mg/kg is given and reassessed at end of 2 hours. If satisfactory response is obtained, the patient is treated like early responders. If case of non-response, IV theophylline bolus is followed by continuous infusion. Such patients respond well to magnesium infusion at a dose of 50 mg/kg (with dextrose over 30 minutes). If no improvement occurs, these patients should be prepared for possible mechanical ventilation.

Indications for transfer to an intensive care unit include worsening hypoxia or hypercapnia, exhaustion, feeble respiration, confusion, drowsiness, coma or respiratory arrest.

Discharge from the hospital: Patients should be on discharge medication for 24 hours prior to discharge. The correct inhaler technique is checked and recorded. If recorded PEFr >75% of predicted of the best and PEFr diurnal variation is less than 20%, treatment should include soluble steroids tablets and inhaled steroids in addition to the bronchodilator. The patient should given

a self-management plan or instructions should be given to the parents.

Recurrent Wheezing in Children below 5-Year-Old

Wheezing is a common clinical symptom and ~50% children have had one episode of wheezing by 6 years. Some patients show episodic wheezing during repeated viral infections. These episodes decrease by 5 years of age, with decline in incidence of viral infections. On the other hand, a few children may have wheezing following viral infection as well as other triggers. Some patients continue to wheeze even after 5 years of age and are treated as asthma.

Young children respond well to bronchodilators. Each episode should thus be treated with inhaled salbutamol and in severe cases a short course of systemic steroids. Children getting frequent episodes of wheezing should receive low dose inhaled corticosteroids for 8–12 weeks. If the response is satisfactory, inhaled steroids are stopped and child is followed for recurrence of symptoms. In case of recurrence, such children are treated as older children with asthma.

Suggested Reading

- Anderson WC 3rd, Gleason MC, Miyazawa N, Szeffler SJ. Approaching current and new drug therapies for pediatric asthma. *Pediatr Clin North Am* 2017; 64:1197–1207.
- Global Strategy for Asthma Management and Prevention (2016 update) http://ginasthma.org/wp-content/uploads/2016/04/GINA-2016-main-report_tracked.pdf
- Pike KC, Levy ML, Moreiras J, Fleming L. Managing problematic severe asthma: beyond the guidelines. *Arch Dis Child* 2017; doi: 10.1136/archdischild-2016; 311–368.

FOREIGN BODY ASPIRATION

Young children between 1 and 4 years of age are prone to aspirate small objects in their air passages. Unless recognized and treated, this results in significant respiratory morbidity, such as recurrent wheezing, cough and pneumonia. Immediate response to foreign body aspiration is a choke, gag, cough or localized wheeze. After the initial episode, symptoms may improve for some time and the whole episode forgotten.

Subsequently, the course of illness depends on the nature of foreign body, its size, extent and site of obstruction. Foreign bodies of organic or vegetable source swell up and cause more symptoms. A partial obstruction may cause ball valve type effect leading to localized hyperinflation. The overlying chest wall may show hyperresonance, diminished vocal resonance and poor air entry. In small children, it may be difficult to elicit hyperresonance. Thus a localized area of poor air entry in a child with chronic respiratory illness should arouse suspicion of a foreign body. Complete obstruction and surrounding inflammation cause distal atelectasis and suppuration of the surrounding parenchyma of the lungs. The elastic recoil of the bronchi is lost and the bronchi show segmental dilatation with eventual development of

bronchiectasis. In children, incidence of right and left bronchial location of foreign body is nearly equal.

Bronchoscopy should be undertaken, if the clinical and radiological picture suggests the diagnosis even when a history of foreign body aspiration is not forthcoming. Foreign bodies are removed through a rigid bronchoscope. Appropriate antibiotics are given for secondary infection.

Suggested Reading

- Foltran F, Ballali S, Passali FM, et al. Foreign bodies in the airways: Meta-analysis of published papers. *Int J Pediatr Otorhinolaryngol* 2012; 76 Suppl 1:S12–9

APPROACH TO CHRONIC COUGH

Chronic cough can be distressing and often a cause for consultation. The diagnosis is possible by analysis of the following: Age of the child; nature of cough and sputum; relationship to time or posture; any wheezing or stridor; effect of season; response to previous therapy; nutrition; signs in the chest; clubbing.

Staccato paroxysms of cough suggest whooping cough or *Chlamydia* infection. Barking or brassy cough with change in the voice indicates laryngotracheal disease. In case of postnasal drip, cough is an attempt to clear the throat and is described as hawking. Cough of psychogenic nature is 'honking' (Table 15.11).

Purulent sputum indicates the presence of suppurative lung disease. Although sputum is mucoid in asthma, yellowish sputum may be present due to eosinophils. Hemoptysis indicates the possibility of bronchiectasis, tuberculosis, mitral stenosis, cystic fibrosis or foreign body in the bronchus. Wheezing is indicative of asthma.

Chronic cough that is more common in certain seasons during the year should arouse suspicion of asthma. Chronic cough occurring only in winters indicates a viral etiology. Malnutrition associated with chronic cough may be found in patients with tuberculosis, bronchiectasis, pertussis, cystic fibrosis, severe chronic asthma or immune deficiency.

Chest X-ray film, examination of the sputum, blood counts and tuberculin test are necessary for diagnosis. Bronchoscopy may be necessary in some cases. CT scan is non-invasive important investigation.

Table 15.11: Diagnosis of chronic cough in relation to age

Age	Cases
Onset in first month	Laryngeal webs, vascular rings or H-type tracheoesophageal fistula, congenital infections
Early infancy	Gastroesophageal reflux
Late infancy	Bronchitis, asthma, cystic fibrosis, whooping cough
Preschool age	Recurrent bronchitis, asthma, foreign body, suppurative lung disease, eosinophilia
At all ages	Asthma, whooping cough, viral bronchitis, tuberculosis, foreign body aspiration

Management

Bronchial asthma should be excluded before evaluating other causes of cough. Cough suppressants are avoided, except if the cough is dry and exhausting or, if it disturbs sleep and prevents adequate nutrition, e.g. in whooping cough. Dextromethorphan is an effective cough suppressant and non-habit forming.

Bronchodilators are useful in the treatment of children with cough due to occult asthma because of retained tracheobronchial secretions. Mucociliary transport of secretions is helped by the beta-adrenergic agonists and the xanthine group of drugs, in asthmatic as well as non-asthmatic children. Physiotherapy, e.g. chest clapping, vibrations and postural drainage are useful in facilitating removal of bronchial secretions.

Suggested Reading

- Chang AB. Pediatric cough: children are not miniature adults. *Lung* 2010; 188 Suppl 1:S33–40.
- De Blasio F, Virchow JC, Polverino M, et al. Cough management: a practical approach. *Cough* 2011; 7: 7.
- Laya BF, Restrepo R, Lee EY. Practical imaging evaluation of foreign bodies in children: An update. *Radiol Clin North Am* 2017; 55: 845–67.

SUPPURATIVE LUNG DISEASE

Lung Abscess

Lung abscess in children is most frequently a complication of bacterial pneumonia especially those due to *S. aureus* and *K. pneumoniae*. It may also develop in sequestration of lung tissue or in association with foreign bodies, bronchial cysts or stenosis. Staphylococcal lung abscesses are often multiple, while others may be solitary. The abscess may rupture into the pleural space leading to pyopneumothorax. The main pathological changes are necrosis and liquefaction with inflammation in the surrounding lung tissue.

The patient has fever, anorexia, lethargy, pallor and cough with foul smelling expectoration. Physical signs may be minimal. Amphoric breath sounds, coarse crepitations and whispering pectoriloquy are characteristic, but often not elicited. The diagnosis is made on plain radiograph, ultrasound or CT chest. Appropriate antibiotics to which the organisms isolated from the sputum or bronchoscopic aspirate are sensitive, are administered for 4 to 6 weeks. Physiotherapy is carried out for effective drainage. Surgical resection of the involved area of lung is indicated, if medical therapy is not effective.

Bronchiectasis

This is a chronic suppurative disease characterized by destruction of bronchial and peribronchial tissues, dilatation of the bronchi and accumulation of infected material in the dependent bronchi.

Most cases follow recurrent episodes of bronchitis, bronchiolitis, post-measles or post-pertussis lung infections, cystic fibrosis and pneumonia in infancy and early childhood. Infections damage the bronchial wall resulting in segmental areas of collapse that exert negative pressure on the damaged bronchi, making them dilate in a cylindrical, fusiform or saccular manner. Aspiration of foreign body, food or mucus plug in the bronchus may occlude the bronchial lumen and similarly result in segmental collapse, with dilatation of bronchi due to negative pressure by collapsed segments. Extrinsic compression by the tuberculous lymph nodes often causes collapse of right middle lobe.

Rare causes include congenital disorders (bronchomalacia, communicating bronchial cyst, sequestered lung), primary ciliary dyskinesia (Kartagener syndrome), cystic fibrosis, immunodeficiency syndromes and Young syndrome (sinusitis, bronchiectasis, azoospermia).

The onset is insidious; general health is poor with recurrent respiratory infections that tend to persist and show a waxing and waning course. The patient complains of loss of appetite, irritability and poor weight gain; clubbing of fingers is usual. The chief symptom is cough with copious mucopurulent expectoration, which is more marked in the morning and in some postures. Younger children may not expectorate, and often swallow the sputum, which is occasionally blood streaked.

Radiograph may show honeycombing, indicating multiple small abscess cavities. Bronchography, the gold standard for diagnosis of bronchiectasis, has been replaced with high resolution CT scan. Bronchoscopy is done, if there is a possibility of surgical intervention. Sputum should be sent for culture, tuberculin reaction to screen for tuberculosis and pilocarpine iontophoresis for estimating sweat chloride.

Management: During exacerbations, bacterial infections should be controlled and airway kept clear of secretions. This is facilitated by effective cough and postural drainage at regular intervals. Assistance by a pulmonary physiotherapist is useful. Surgical resection of the involved area is undertaken only in children with marked symptoms and if the disease is localized. Extrinsic compression of bronchi by mediastinal masses requires surgical intervention. Children with generalized disease may improve significantly clinically with medical treatment alone.

Suggested Reading

- Gupta AK, Lodha R, Kabra SK. Non cystic fibrosis bronchiectasis. *Indian J Pediatr* 2015; 82:938–44.
- Redding GJ, Carter ER. Chronic suppurative lung disease in children: definition and spectrum of disease. *Front Pediatr* 2017;5:30.

EMPHYEMA THORACIS

Empyema thoracis is defined as collection of pus in the pleural cavity, commonly due to a complication of

pneumonia or rupture of subdiaphragmatic or liver abscess in the pleura. The condition is commonly one of the sequelae of staphylococcal pneumonia. It can also occur secondary to pneumonia due to pneumococci, gram-negative bacilli and *Mycoplasma*.

Clinical features include fever with systemic toxicity and breathing difficulty. There is reduced movement of chest with respiration, dull percussion note, decreased air entry and reduced vocal resonance. Occasionally, the empyema might extend outside the pleural cavity into the soft tissue and chest wall, manifesting as a pulsatile swelling, called *empyema necessitans*.

X-ray film of the chest shows shift in the mediastinum with obliteration of costophrenic angle and varying degree of opacification. Pleural tap shows purulent material with leukocytes, high protein and low sugar. Gram stain and culture may show causative agent. Empyema should be differentiated from other causes of pleural effusion, including tubercular and neoplastic.

Treatment consists of administration of antibiotics that are active against *Staphylococcus*, chiefly cloxacillin, vancomycin, teicoplanin and linezolid. The empyema is managed by continuous intercostal drainage through underwater seal. After antibiotics and drainage, if the lung is not expanding or there are loculations in the pleura, CT scan of chest is done for thickened pleura or loculated empyema. Such patients require decortication by thoracotomy or thoracoscopy.

Suggested Reading

- Redden MD, Chin TY, van Driel ML. Surgical versus non-surgical management for pleural empyema. *Cochrane Database Syst Rev* 2017; 3:CD010651.

CYSTIC FIBROSIS

Cystic fibrosis (CF) is the most common life-limiting recessive genetic disorder in Caucasians with an incidence of approximately 1 in 2500 children born in the United Kingdom. It is less common in African Americans (1 in 15000), Asian Americans (1 in 31000), native Americans (1 in 80000) and Indian migrated to UK (1 in 10000 and 12000).

Molecular Genetics

The defect is a mutation in the gene for the CF transmembrane conductance regulator (CFTR), a membrane protein and chloride channel. Failure of chloride conductance by epithelial cells leads to dehydration of secretions that are too viscid and difficult to clear. The defective gene is located on the long arm of chromosome 7. Till now more than 1600 mutations in the gene are recognized; commonest being *delta F508* ($\Delta F508$).

Clinical Manifestations

Clinical features include meconium ileus in neonates, recurrent bronchiolitis in infancy and early childhood,

Table 15.12: Complications of cystic fibrosis

0 to 2 years	%
Meconium ileus	10–15
Obstructive jaundice	
Hypoproteinemia, anemia	
Bleeding diathesis	
Heat prostration, hyponatremia	
Failure to thrive	
Steatorrhea	85
Rectal prolapse	20
Bronchitis, bronchiolitis	
Staphylococcal pneumonia	
2–12 years	%
Malabsorption	85
Recurrent pneumonia	60
Nasal polyposis	6–36
Intussusception	1–5
>13 years	%
Chronic pulmonary disease	70
Clubbing	
Abnormal glucose tolerance; diabetes	20–30; 7
Chronic intestinal obstruction	10–20
Focal biliary cirrhosis	
Portal hypertension	25
Gallstones	4–14
Azoospermia	98

recurrent lower respiratory tract infections, chronic lung disease, bronchiectasis, steatorrhea, and later pancreatitis and azoospermia. Pancreatic insufficiency is present in >85% patients (Table 15.12).

Diagnosis

The diagnosis of CF should be suspected by the presence of typical phenotype or family history and confirmed by the demonstration of high sweat chloride (>60 mEq/L) on at least two occasions and/or by identifying mutations in both copies of *CFTR*. Nasal potential difference measurements can be used as an adjunct to sweat test but is not widely available.

Management

The treatment of cystic fibrosis in children includes respiratory management, nutritional care, anticipation and early diagnosis of liver disease, diabetes and other organ dysfunction.

Respiratory management: The principal components of care used to achieve this include airway clearance techniques, antibiotics and anti-inflammatory agents.

Nutritional management: The aim of nutrition is to achieve normal growth and development, by:

- Increasing caloric intake by encouraging parents to feed the child more frequently. If appetite is poor due

to persistent infection, feeding may be given by nasogastric route or by gastrostomy.

- ii. Supplement fat-soluble vitamins (vitamins A, D, E) in twice the recommended doses. These are given along with food and enzymes.
- iii. Enteric coated tablets or spherules of pancreatic enzymes are given with each feed. Enzymes are started at 1–2000 IU of lipase/kg given in divided doses and increased by noting weight gain, nature of stool and abdominal symptoms.

Suggested Reading

- Castellani C, Duff AJA, Bell SC, et al. ECFS best practice guidelines: the 2018 revision. *J Cyst Fibrosis* 2018; 17:153–178.
- Mandal A, Kabra SK, Lodha R. Cystic fibrosis in India: Present, past and future. *J Pulm Med Respir Res* 2015; 1:002.

ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)

ARDS is defined as pulmonary edema not originating from the heart. Common causes of ARDS include severe pneumonia followed by sepsis. Other predisposing factors include shock, tissue injury, aspiration, toxins, microthrombi, intravascular coagulation, uremia and increased intracranial pressure.

Increased permeability of alveolar capillary membrane leads to aggregation of leukocytes in the pulmonary circulation, followed by release of mediators such as free oxygen radicals and platelet activating factors that injure the vascular epithelium. In the acute stage, there is edema and hyaline membrane formation, followed by fibrosis. Microthrombi formation in vessels contributes to increased pulmonary vascular resistance and right to left shunting.

Clinical features: ARDS can occur at any age. Initially symptoms are less and lungs are clear. Later within



Fig. 15.9: X-ray film of chest showing diffuse opacities bilaterally, compatible with acute respiratory distress syndrome

6–8 hours, the patient becomes breathless followed by refractory hypoxia and hypercapnia. Lung fields show bilateral reticular opacities (Fig. 15.9). Mortality is very high, being 30–50% even in the best centers.

Treatment: Patients should be managed in an intensive care unit with cardiorespiratory monitoring and artificial ventilation. Ventilation is achieved by high PEEP or inverse ratio ventilation. The cause of ARDS should be treated simultaneously.

Suggested Reading

- Heidemann SM, Nair A, Bulut Y, Sapru A. Pathophysiology and management of acute respiratory distress syndrome in children. *Pediatr Clin North Am* 2017; 64:1017–37.

Disorders of Cardiovascular System

R Krishna Kumar • Manu Raj

Diseases of the cardiovascular system are an important cause of childhood morbidity and mortality. The majority of heart diseases presenting in early childhood are congenital, resulting from structural defects during development. Rheumatic heart disease continues to be prevalent in India. Systemic hypertension is increasingly recognized in childhood and predisposes to cardiovascular morbidity. A variety of other cardiovascular conditions may present in childhood. The management of these patients requires an integrated approach with inputs from various specialties.

CONGESTIVE CARDIAC FAILURE

Congestive cardiac failure is the inability of the heart to maintain an output, at rest or during stress, necessary for the metabolic needs of the body (systolic failure) and the inability to receive blood into the ventricular cavities at low pressure during diastole (diastolic failure). Thus, due to systolic failure, it is unable to propel blood into the aorta and in diastolic failure it receives inadequate amount of blood. Diastolic heart failure is recognized by clinical features of heart failure and evidence of increased filling pressures with preserved systolic function and in many instances, cardiac output. An increase in left-sided pressures results in dyspnea from pulmonary congestion. An increase in right-sided pressures results in hepatomegaly and edema. Besides hypertrophied ventricles, diastolic failure occurs in restrictive heart disease and constrictive pericarditis.

Etiopathogenesis

The common causes of diastolic failure are indicated in Table 16.1. While mitral and tricuspid valve stenoses result in elevated atrial pressure, they are not, in the strictest sense diastolic heart failure. The causes of congestive failure can be classified according to age (Table 16.2). Rheumatic fever and rheumatic heart disease is typically encountered beyond 5 years age; its prevalence appears to be declining in selected urban populations. Heart failure from congenital heart disease typically happens within the first 1–2 years of life. Patients with left-to-right shunts

Table 16.1: Heart failure due to diastolic dysfunction

Mitral or tricuspid valve stenosis*
Constrictive pericarditis
Restrictive cardiomyopathy
Acute ventricular volume overload (acute aortic or mitral valve regurgitation)
Myocardial ischemia [#]
Marked ventricular hypertrophy (hypertrophic cardio-myopathy, storage disorders, severe hypertension, severe aortic or pulmonary valve stenosis)
Dilated cardiomyopathy [#]

*Elevated atrial pressures with normal ventricular diastolic pressures

[#]Often have combined systolic and diastolic dysfunction

Table 16.2: Causes of congestive cardiac failure

Infants

Congenital heart disease
Myocarditis and primary myocardial disease
Tachyarrhythmias, bradyarrhythmias
Kawasaki disease with coronary occlusion
Pulmonary hypertension (persistent pulmonary hypertension of the newborn; primary pulmonary hypertension; hypoxia, e.g. upper airway obstruction)
Miscellaneous causes
Anemia
Hypoglycemia
Infections
Hypocalcemia
Neonatal asphyxia (myocardial dysfunction, pulmonary hypertension)

Children

Rheumatic fever, rheumatic heart disease
Congenital heart disease complicated by anemia, infection or endocarditis
Systemic hypertension
Myocarditis, primary myocardial disease
Pulmonary hypertension (primary, secondary)

tend to develop CCF around 6 to 8 weeks of life. Unlike left to right shunts, congenital leakage of the mitral or the tricuspid valve can result in heart failure at an early age. Congenital tricuspid regurgitation (TR) manifests early because the elevated pulmonary artery pressures increases its severity. If the TR is not severe, it may improve with time as pulmonary vascular resistance declines.

The age of occurrence of heart failure may point towards the underlying cause (Table 16.3). Heart failure at an unexpectedly early age should prompt the search for an associated condition such as coarctation.

Arrhythmias are an important cause of congestive cardiac failure in infancy. Heart rates above 180/min tend to precipitate heart failure. If the tachycardia persists for 36 hours, about 20% will develop heart failure and almost 50% will do so in 48 hours. Any long-standing tachyarrhythmia can be associated with ventricular dysfunction that may mimic cardiomyopathy. Typical examples include ectopic atrial tachycardia and permanent junctional re-entrant tachycardia. Severe bradycardia, typically from complete heart block, can also result in heart failure.

With a normal heart, hemoglobin levels of 5 g/dL can result in heart failure. In a diseased heart, failure may be precipitated even with hemoglobin levels of 7–8 g/dL.

Clinical Features

The recognition of cardiac failure in older children is based on the same principles as in adults.

Symptoms

Slow weight gain is related to two factors. The infant takes small feeds because of easy fatigability and there is an excessive loss of calories from increased work of breathing. Uncommonly, there may be an unusual gain in weight due to collection of water, manifesting as facial puffiness or rarely as edema on the feet. The difficulty in feeding may manifest itself as 'poor feeder', a complaint that the baby does not take more than one to two ounces of milk at a time or that he is hungry within a few minutes after taking a small feed. Since hunger persists, the infant is

irritable and crying all the time. Often a mother may state that the baby breathes too fast while feeding or that the baby is more comfortable and breathes better when held against the shoulder—which is the equivalent of orthopnea in older children. Not infrequently, the baby is brought with persistent hoarse crying, wheezing, excessive perspiration and less commonly, because of facial puffiness (Table 16.4).

Signs

Left-sided failure is indicated by tachypnea and tachycardia. Persistent cough, especially on lying down, hoarse cry and wheezing are other evidences of left-sided failure; basal rales in the chest are usually not audible. Right-sided failure is indicated by hepatomegaly and facial puffiness. Examination of the neck veins in small babies is not helpful. Firstly, it is difficult to evaluate the short neck with baby fat and secondly, hemodynamic studies show that right atrial mean pressures stays normal in many infants with congestive failure. Edema on the feet occurs late. Common to both left- and right-sided failure is the presence of cardiac enlargement, third sound gallop and poor peripheral pulses with or without cyanosis (Table 16.5).

Treatment

Management of heart failure is a four-pronged approach for correction of inadequate cardiac output: (i) reducing cardiac work, (ii) augmenting myocardial contractility, (iii) improving cardiac performance, and (iv) correcting the underlying cause. Identifying the cause is important since it has direct bearing on survival.

Reducing Cardiac Work (Fig. 16.1)

The work of the heart is reduced by restricting patient activities, sedatives, treatment of fever, anemia, obesity, and by vasodilators. Mechanical ventilation helps when heart failure is severe by eliminating the work of breathing.

Neonates with heart failure are nursed in an incubator and handled minimally. The baby is kept propped up at an incline of about 30°. The pooling of edema fluid in the

Table 16.3: Time of onset of congestive failure

Age	Lesion
Birth–1 week	Duct-dependent systemic circulation (hypoplastic left heart syndrome, critical aortic stenosis, severe coarctation, arch interruption); total anomalous pulmonary venous return (obstructed), congenital mitral and tricuspid valve regurgitation, neonatal Ebstein anomaly
1–4 weeks	Patent ductus arteriosus (PDA) in preterms, ventricular septal defect (VSD) with coarctation, persistent truncus arteriosus, transposition with large VSD or PDA, severe coarctation, critical aortic stenosis, congenital mitral or tricuspid regurgitation, single ventricle physiology with unrestrictive pulmonary blood flow
1–2 months	Transposition with VSD or PDA, endocardial cushion defects, VSD, PDA, severe coarctation; total anomalous pulmonary venous return, anomalous left coronary artery from pulmonary artery, single ventricle physiology with unrestrictive pulmonary flow
2–6 months	VSD, PDA, endocardial cushion defect; anomalous left coronary artery from the pulmonary artery, coarctation, single ventricle physiology with unrestrictive pulmonary blood flow

Table 16.4: Symptoms of cardiac failure

Poor weight gain
Difficulty in feeding
Breathes too fast; breathes better when held against the shoulder
Persistent cough and wheezing
Irritability, excessive perspiration and restlessness
Pedal edema

Table 16.5: Signs of congestive cardiac failure

Left-sided failure	Failure of either side	Right-sided failure
Tachypnea	Cardiac enlargement	Hepatomegaly
Tachycardia	Gallop rhythm (S3)	Facial edema
Cough	Peripheral cyanosis	Jugular venous engorgement
Wheezing	Small volume pulse	
Rales in chest	Lack of weight gain	Pedal edema

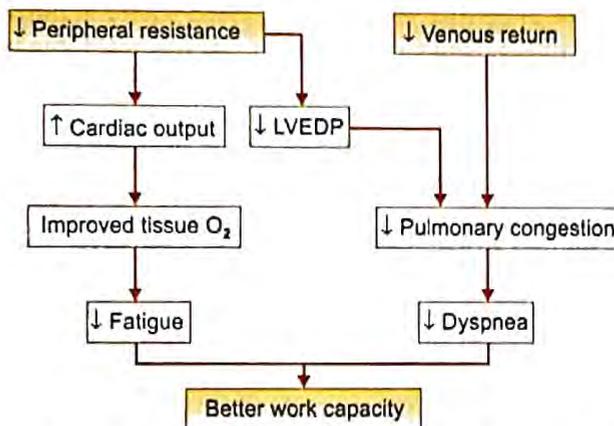


Fig. 16.1: By reducing the systemic vascular resistance and decreasing the venous tone vasodilators provide better work capacity. LVEDP left ventricular end-diastolic pressure

dependent areas reduces the collection of fluid in lungs, thus reducing the work of breathing. At a temperature of 36–37°C, the overall circulatory and metabolic needs are minimal, thus reducing work of heart. Humidified oxygen to maintain a concentration of 40 to 50% improves impaired oxygenation secondary to pulmonary congestion. If the infant or the child is restless or dyspneic, sedation may be appropriate. Opiates (e.g. morphine) or benzodiazepine (midazolam) are useful for sedation in selected circumstances to reduce anxiety and lower the catecholamine secretion, thereby reducing physical activity, respiratory and heart rates.

Fever, anemia and infection increase the work of the heart. In infants and small children, the presence of superadded pulmonary infection is difficult to recognize. Antibiotics are, therefore, sometimes administered empirically. In older children, antibiotics are used, only if evidence of infection is present.

Anemia imposes stress on the heart because of the decreased oxygen carrying capacity of blood. Anemia results in tachycardia and in a hyperkinetic circulatory state. Correction of anemia decreases cardiac work. Typically, packed cell volumes of 10–20 mL/kg are required to correct severe anemia; a single dose of furosemide IV is often given prior to the transfusion. Less common conditions causing stress to the heart are repeated pulmonary emboli, thyrotoxicosis and obesity.

Vasodilators counteract the compensatory mechanisms in heart failure and improve cardiac output (Fig. 16.1). Arteriolar and venous vasoconstriction is mediated through catecholamines. Arteriolar constriction maintains blood pressure by increasing the systemic vascular resistance, which increases the work of heart (Fig. 16.2). Venoconstriction results in decreased venous capacitance and increased venous return, increasing the filling pressures of the ventricles to increase the cardiac output. Since compensatory mechanisms are inappropriately excessive, vasodilators, by reducing the arteriolar and venous vasoconstriction, reduce the work of heart. Nitrates are used as preferential venodilators.

ACE inhibitors (captopril, enalapril) are effective for treating heart failure in infants and children. These agents suppress renin-angiotensin-aldosterone system thereby reducing vasoconstriction and salt and water retention. By suppressing catecholamines, they prevent arrhythmias and other adverse effects on the myocardium. The major side effect of ACE inhibitors is cough, which can be troublesome. Persistent cough may necessitate the use of angiotensin receptor blockers, such as losartan. Initially, it is necessary to monitor the renal function: Urine analysis, blood levels of creatinine and electrolytes once a week for 6 to 8 weeks. These medications may cause first-dose hypotension; the first dose should be one-quarter of the calculated dose.

Although beta-blockers might precipitate CCF, they improve symptoms especially in patients with dilated cardiomyopathy, who continue to have tachycardia. Useful agents include metoprolol and carvedilol. The latter

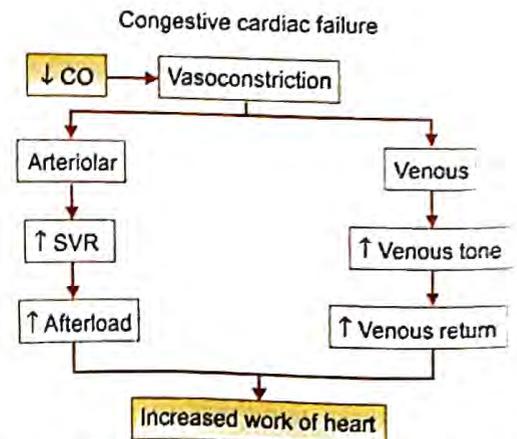


Fig. 16.2: Low cardiac output (CO) results in vasoconstriction. Increasing systemic vascular resistance (SVR) and venous tone leading to increase in the work of heart

is preferred since it has properties of beta-blockers with peripheral vasodilation; treatment is started at low dose and increased depending on tolerability (0.08 to 0.4 mg/kg/day, maximum 1.0 mg/kg/day). Calcium channel blockers adversely affect cardiac contractility and should be avoided unless indicated for systemic hypertension.

In the acute care setting, sodium nitroprusside is used as a vasodilator, since it acts on the venous and arterial systems. Phosphodiesterase inhibitors, such as milrinone and calcium sensitizers (levosimendan), have become popular especially in postoperative period. These agents have powerful vasodilatory and inotropic effects. Specific indications for use of vasodilators include acute mitral or aortic regurgitation, ventricular dysfunction resulting from myocarditis, anomalous coronary artery from pulmonary artery and in the early postoperative setting.

Augmenting Myocardial Contractility

Inotropic agents like digoxin improve cardiac output by augmenting myocardial contractility. It has a rapid onset of action and is eliminated quickly. It is available for oral and parenteral administration. Oral digoxin is available as 0.25 mg tablets and as digoxin elixir (1 mL = 0.05 mg) (Table 16.6). Parenteral digoxin (0.5 mg/2 mL) is available; its dose is 70% of the oral dose. Infants tolerate digitalis well. In a hospitalized patient, full digitalization should be sought to maximize benefit. Children are digitalized within a 24-hour period; $\frac{1}{2}$ of the calculated digitalizing dose is given initially, followed by $\frac{1}{4}$ in 6–8 hours and the final $\frac{1}{4}$ after another 6–8 hours. The maintenance dose is usually one-quarter of the digitalizing dose (Table 16.6). Before the third daily dose, an electrocardiogram is done to rule out digitalis toxicity. Toxicity can be controlled by omitting the next one or two doses. The PR interval is a useful indicator; if it exceeds the initial interval by 50%, digitalis toxicity is present. The upper limit of normal PR interval in infants is 0.14 second.

Digitalis is used with caution in the following situations: (i) premature neonates; (ii) heart failure due to myocarditis; and (iii) very cyanotic patients. Myocardial damage, gross cardiomegaly, hypoxia, acidosis, and

hepatic, renal and pulmonary insufficiency increase the sensitivity of the myocardium to digitalis. Digoxin is beneficial for symptom relief and is advised in patients with mild, moderately severe or severe congestive failure, with or without sinus rhythm. Digoxin can be combined with ACE inhibitors for synergistic effect.

Intravenous Inotropic Agents

These agents belong to three groups: (i) catecholamine inotropes: dopamine, dobutamine and adrenaline, (ii) phosphodiesterase inhibitors: amrinone and milrinone (combine inotropic effects with peripheral vasodilation, inodilators) and (iii) levosimendan, a calcium sensitizer that is used in acute care settings as a potent inodilator with systemic and coronary vasodilatation. Unlike milrinone, it does not increase risk of rhythm disturbances.

If blood pressure is low, dopamine should be used, as an intravenous infusion. At a dose of less than 5 $\mu\text{g}/\text{kg}/\text{min}$, dopamine causes peripheral vasodilation and increases myocardial contractility. Renal blood flow improves, resulting in natriuresis; higher doses result in peripheral vasoconstriction. The dose of dobutamine is 2.5 to 15 $\mu\text{g}/\text{kg}/\text{min}$; the dose should be increased gradually until the desired response is achieved. In patients with dilated cardiomyopathy, dobutamine is used as 24 hours infusion once or twice a week and retains its effectiveness for varying lengths of time. Milrinone is given in infusion 0.3–0.7 $\mu\text{g}/\text{kg}/\text{min}$ following a loading dose of 50 $\mu\text{g}/\text{kg}$. The dose of levosimendan is 6 to 12 $\mu\text{g}/\text{kg}$ loading dose over 10 minutes followed by 0.05 to 0.2 $\mu\text{g}/\text{kg}/\text{min}$ as infusion.

Improving Cardiac Performance by Reducing Venous Return (Preload)

Diuretics reduce the blood volume, decrease venous return and ventricular filling. This tends to reduce the heart size. The larger the heart, the more the wall tension and the poorer is its performance. With reduction in heart size and volume, the myocardial function and the cardiac output improve. Diuretics reduce the total body sodium thereby, reducing blood pressure and peripheral vascular resistance. This helps in increasing the cardiac output and reducing the work of the heart.

Diuretics are the first line of management in congestive failure. The action of oral furosemide starts within 20 min. Furosemide should be used in combination with a potassium sparing diuretic (triamterene, spironolactone, amiloride). The combination prevents potassium and magnesium and reduces the risk of arrhythmias. Furosemide activates the renin–angiotensin–aldosterone axis, which is responsible for vasoconstriction and sodium and water retention. When furosemide is combined with ACE inhibitors, the combination suppresses the axis and is, therefore, synergistic.

Sodium restriction is recommended but difficult to implement in infants and young children. Low sodium diets should be used, only if the heart failure cannot be

Table 16.6: Dosage of digoxin and diuretics

	Digitalizing dose, mg/kg	Maintenance dose $\mu\text{g}/\text{kg}/\text{day}$
Digoxin		
Premature, neonates	0.04	0.01
1 month to one year	0.08	0.02–0.025
1 to 3 years	0.06	0.015–0.02
Above 3 years	0.04	0.017
Diuretics		
Furosemide	1–3 mg/kg per day orally or 1 mg/kg per dose IV	
Spironolactone	1 mg/kg orally every 12 hours	

controlled with digitalis, diuretics and ACE inhibitors. However, it is prudent to advise such patients to avoid salt-rich foods such as chips and pickles. Since heart failure increases calorie requirements, adequate intake is advised.

Correcting the Underlying Cause

The focus of management of CHF has shifted towards identifying and correcting the underlying cause. It is now possible to rapidly identify the cause of CHF in most children with suspected heart disease. Many of these are managed by curative or palliative operations. A diagnosis of idiopathic dilated cardiomyopathy requires exclusion of conditions that are known to cause ventricular dysfunction. The conditions that might be missed are sustained tachyarrhythmias, coarctation of aorta and obstructive aortitis, anomalous origin of the left coronary artery from pulmonary artery and hypocalcemia. It is important to look for subtle evidence of sustained tachyarrhythmias. Anomalous origin of the left coronary artery is treated surgically. The presence of CCF in a child with rheumatic heart disease does not necessarily mean presence of active carditis. In any patient of rheumatic heart disease, if active carditis has been excluded and an adequate trial has been given to medical management, operative treatment should be considered. Uncommon causes of CCF in infants include upper respiratory obstruction, hypoglycemia, neonatal asphyxia and hypocalcemia.

CONGENITAL HEART DISEASE

Congenital heart disease (CHD) encompasses a broad and diverse range of conditions that manifest from prenatal period to late adulthood. In common terms, CHD refers to structural heart defects that are present at birth. Diagnosis requires a systematic approach including history, physical examination, chest X-ray, ECG and echocardiography. Palliative or corrective surgery is feasible for most patients with CHD, if undertaken in a timely fashion.

Epidemiology and Etiology

CHD accounts for nearly one-third of all major congenital anomalies. The prevalence of CHD in infancy is estimated at 6–8 per 1000 live births; 25% are life-threatening and require early intervention. A proportion of patients with CHD have an identifiable genetic basis (Table 16.7). Table 16.8 shows the association of CHD with acquired disorders and teratogens.

Physiology of Congenital Heart Disease

Pressure, Flow and Resistances

The pressures and resistances in the pulmonary and systemic circulations are indicated in Table 16.9. The pulmonary and systemic flows are equal, if there are no abnormal communications between the two sides.

Table 16.7: Inherited syndromes associated with congenital heart disease

Syndrome	Genetic mutation; inheritance	Cardiac lesions	Other features
CATCH 22	Microdeletion in 22q; autosomal dominant	Interrupted aortic arch, TOF, VSD, persistent truncus arteriosus, double outlet right ventricle	Cleft palate, hypocalcemia, thymic hypoplasia, nasal regurgitation, gastroesophageal reflux, learning disability
Williams-Beuren	Microdeletion in <i>elastin</i> (7q11.23); AD	Supravalvar aortic stenosis, pulmonary stenosis, hypertension	Elfin facies, mental retardation, hypersocial personality, short stature, hypercalcemia
Down	Trisomy 21; Robertsonian translocation or mosaicism	AV canal defect, perimembranous VSD, TOF	Characteristic facies, clinodactyly, mental retardation; hypotonia
Turner	45XO or 46/45XO mosaic	Bicuspid aortic valve, coarctation	Short stature, gonadal dysgenesis, lymphedema
Noonan	<i>PTPN11</i> ; AD	Pulmonic stenosis, hypertrophic cardiomyopathy, ASD	Short stature, dysmorphic facies, webbed neck, developmental delay, cryptorchidism
VATER association	Sporadic	VSD, TOF	Vertebral, renal and limb defects, anal atresia, tracheoesophageal fistula
Holt-Oram	<i>TBX5</i> ; AD	Ostium secundum ASD; VSD	Radial ray anomalies
CHARGE association	<i>CHD7</i> ; often <i>de novo</i>	Branch pulmonary artery stenosis, TOF, VSD	Coloboma, growth failure, choanal atresia, genital hypoplasia, ear anomalies
Alagille	<i>JAG1</i> ; most cases are <i>de novo</i>	Pulmonary stenosis, TOF	Dysmorphic facies, cholestatic jaundice, butterfly vertebrae, renal anomalies

AD: Autosomal dominant; AV: Atrioventricular; ASD: Atrial septal defect; TOF: Tetralogy of Fallot; VSD: Ventricular septal defect

Table 16.8: Prenatal exposures that increase risk of congenital heart disease

Gestational diabetes (transposition, atrioventricular septal defects, hypoplastic left heart, cardiomyopathy, PDA)
Febrile illness in first trimester (increased risk)
Rubella (PDA, peripheral pulmonary stenosis, VSD)
Lupus (complete heart block)
Phenylketonuria (VSD, TOF, PDA, single ventricle)
Vitamin deficiency (increased risk of heart disease)
Teratogens (first trimester), e.g. anticonvulsants, NSAIDs, cotrimoxazole, thalidomide, retinoic acid
Exposure to organic solvents, herbicides, pesticides, ionizing radiation

NSAIDs: Nonsteroidal anti-inflammatory drugs; PDA: Patent ductus arteriosus; TOF: Tetralogy of Fallot; VSD: Ventricular septal defect

According to Poiseuille's equation, modified for application to blood flow through vessels,

$$\text{Pressure} = \text{Flow} \times \text{Resistance}$$

The pressure is measured in mm Hg, flow in liters/min and resistance in dynes/sec/cm⁵ or units (80 dynes/sec/cm⁵ = 1 unit). Although this equation is not strictly accurate when applied to flow of blood in pulmonary and systemic circuits, it helps in understanding the hemodynamics.

Systemic pressure = Systemic flow × peripheral vascular resistance

Pulmonary arterial pressure = Pulmonary flow × pulmonary vascular resistance

It is thus obvious that the pressure in a vessel is dependent on the flow through the vessel and the resistance, offered by the vessel to the flow of blood. It is possible to increase the pressure in a vessel either by increasing the flow or by increasing the resistance. Increase in flow through the pulmonary artery means a left-to-right shunt, as occurs in atrial or ventricular septal defect or patent ductus arteriosus. Generally, this increase in flow is not associated with significant increase in pressure as the distensibility characteristics of the pulmonary artery are such that it can accommodate almost three times the normal flow without an increase in pressure. Hence, large left-to-right shunts can take place without an increase in pressure.

Increase in pulmonary vascular resistance means obstructive disease in the pulmonary circuit. The pulmonary vessels develop medial hypertrophy and later intimal changes are added, to further obstruct the flow of blood through the pulmonary circulation. After a certain stage, it is an irreversible process. The increase in resistance to flow in the pulmonary circuit is associated with reduction in flow. The increase in pressure in the pulmonary artery associated with normal resistance is called hyperkinetic pulmonary arterial hypertension whereas when the pressure is increased due to increase in pulmonary vascular resistance, it is called obstructive pulmonary arterial hypertension. Clinically, the two conditions can be distinguished on clinical examination.

Fetal Circulation (Fig. 16.3)

The heart assumes its normal four-chambered shape by the end of 6 weeks of intrauterine life. From then on only minor changes occur and consist mainly in the growth of the heart as a whole with increasing age of the fetus. For the exchange of gases, the fetus is dependent on placental circulation, whereas the neonate is dependent on the lungs. Immediately following birth, the lungs expand with air and the gas exchange function is transferred from the placenta to the lungs; following various circulatory adjustments.

Blood oxygenated in the placenta is returned by way of umbilical veins, which enter the fetus at the umbilicus and join the portal vein (Fig. 16.3). The ductus venosus provides a low resistance bypass between the portal vein and the inferior vena cava. Most of the umbilical venous blood shunts through the ductus venosus to the inferior vena cava. Only a small proportion mixes with the portal venous blood and passes through the liver. Blood from inferior vena cava comprising that from hepatic veins, umbilical veins and that from lower extremities and kidneys enters the right atrium. On reaching the right atrium, the bloodstream is divided into two by the inferior margin of septum secundum—the crista dividens. About one-third of the inferior vena cava blood enters the left atrium, through the foramen ovale, the rest two-thirds mix with the venous return from the superior vena cava to enter the right ventricle.

The blood reaching the left atrium from the right atrium mixes with small amount of blood reaching the left atrium

Table 16.9: Systolic and diastolic pressures and resistance in the pulmonary and systemic circuits

Chamber/vessel	Pressure (mm Hg)	Chamber/vessel	Pressure (mm Hg)
Superior vena cava	0-6	Pulmonary vein	6-10
Right atrium	0-6	Left atrium	6-10
Right ventricle	25/0-6	Left ventricle	80-120/5-10
Pulmonary artery	25/10	Aorta	80-120/60-85
Resistance, dynes/sec/cm⁵			
Pulmonary vascular	80-240	Systemic vascular	800-1600

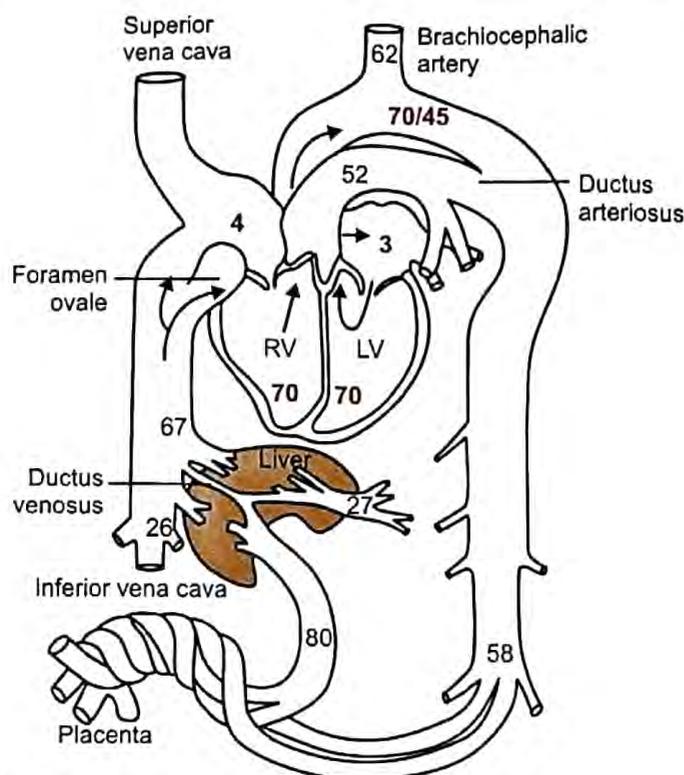


Fig. 16.3: Fetal circulation: Details of the circulation are provided in the text. Saturations of blood (%) in various chambers and vessels are indicated in black font and pressures (mm Hg) are indicated in red font

through the pulmonary veins and passes to the left ventricle. The left ventricle pumps out the blood into the ascending aorta for distribution to the coronaries, head and upper extremities. The superior vena cava stream, comprising blood returning from the head and arms, passes almost directly to the right ventricle. Only minor quantities (1 to 3%) reach the left atrium. The right ventricle pumps out blood into the pulmonary trunk. A small amount of this blood enters the pulmonary circulation, the rest passes through the ductus arteriosus into the descending aorta to mix with the small amount of blood reaching the descending aorta from the aortic arch (derived from the left ventricle).

The main differences between the fetal and postnatal circulation are: (i) presence of placental circulation, which provides gas exchange for the fetus; (ii) absence of gas exchange in the collapsed lungs; this results in very little flow of blood to the lungs and thus little pulmonary venous return to left atrium; (iii) presence of ductus venosus, joining the portal vein with the inferior vena cava, providing a low resistance bypass for umbilical venous blood to reach the inferior vena cava; (iv) widely open foramen ovale to enable oxygenated blood (through umbilical veins) to reach the left atrium and ventricle for distribution to the coronaries and the brain; and lastly (v) wide open ductus arteriosus to allow right ventricular blood to reach the descending aorta, since lungs are non-functioning.

Circulatory Adjustments at Birth—Transitional Circulation

Circulatory adjustments continue to occur for a variable period after birth. Loss of low resistance placental circulation following clamping of the umbilical cord, after birth, results in a sudden increase in systemic vascular resistance. This tends to increase the aortic blood pressure and the left ventricular systolic pressure. The left ventricular diastolic pressure also tends to rise and increases the left atrial pressure. The loss of placental circulation results in a sudden reduction of flow through the ductus venosus that closes off. The loss of placental flow results in a decrease in the volume of blood returning to the right atrium. The right atrial pressure decreases. The left atrial pressure becomes higher than the right atrial pressure and the septum primum, which acts as a valve of the fossa ovalis, approximates with the septum secundum to close off the foramen ovale. Functional closure of the foramen ovale occurs relatively quickly. Over a period of months to years, the septum primum and septum secundum become adherent resulting in anatomical closure of the foramen ovale.

Sudden expansion of lungs with the first few breaths causes a fall in pulmonary vascular resistance and an increased flow into the pulmonary trunk and arteries. The pulmonary artery pressure falls due to lowering of pulmonary vascular resistance. The pressure relations between the aorta and pulmonary trunk are reversed so that the flow through the ductus arteriosus is reversed. Instead of blood flowing from the pulmonary artery to aorta, the direction of flow through the ductus, is from the aorta to pulmonary trunk. The increased oxygen saturation following birth causes the ductus arteriosus to constrict and close. Some functional patency and flow can be demonstrated through the ductus arteriosus for a few days after birth. The ductus arteriosus closes anatomically within 10 to 21 days.

These changes result in the establishment of the postnatal circulation. Over the next several weeks, the pulmonary vascular resistance continues to decline with a decline in the pulmonary artery and right ventricular pressures. The adult relationship of pressures and resistances in the pulmonary and systemic circulations is established by the end of approximately two to three weeks (Fig. 16.4).

Hemodynamic Classification of Congenital Heart Disease

CHD has been broadly classified as cyanotic and acyanotic heart disease (Table 16.10). While broad classifications work for most situations, there are patients who cannot be classified into common physiologic categories. Additionally, there are often specific issues, such as valve regurgitation, that determine the clinical manifestations. The following physiological concepts are important to understand common congenital malformations:

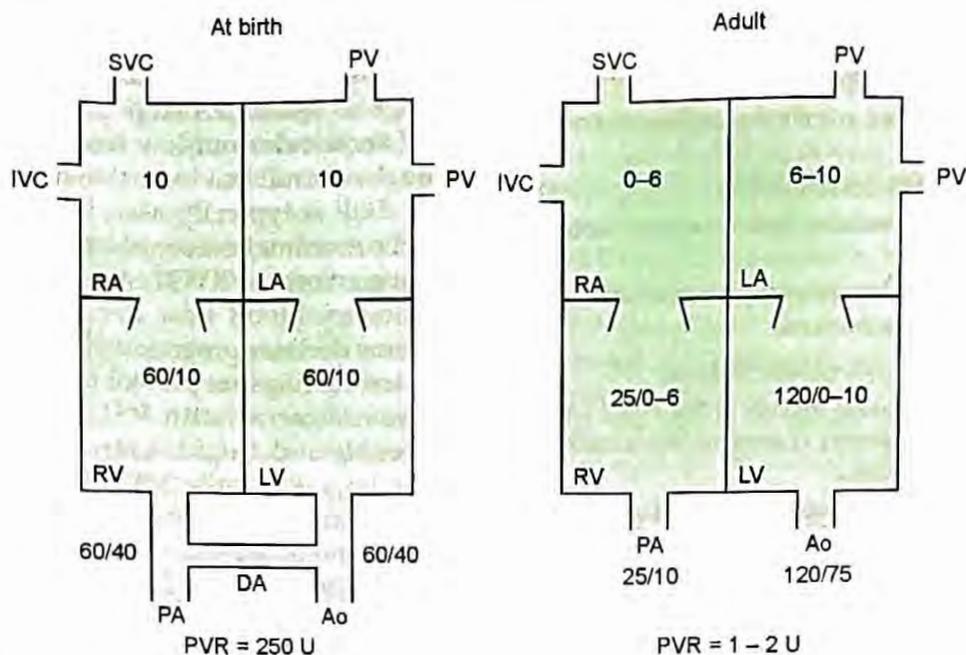


Fig. 16.4: Pressure and resistance in the right- and left-sided chambers and vessels at birth compared to adults. Ao aorta; DA ductus arteriosus; IVC inferior vena cava; LA left atrium; LV left ventricle; PA pulmonary artery; PV pulmonary vein; PVR peripheral vascular resistance; RA right atrium; RV right ventricle; SVC superior vena cava

- i. Pretricuspid versus post-tricuspid shunts
- ii. VSD-PS physiology
- iii. Single ventricle physiology
- iv. Duct-dependent lesions
- v. Unfavorable streaming and parallel circulation

Pretricuspid versus Post-tricuspid Shunts

Cyanotic heart disease with left-to-right shunts is traditionally classified as pretricuspid and post-tricuspid shunts. There are important differences in physiology that impact clinical manifestations and natural history. Left-to-right shunts at or proximal to the level of the atria are known as pretricuspid shunts. They include atrial septal defects and partial anomalous pulmonary venous connection. The left-to-right shunt and the consequent excessive pulmonary blood flow is dictated by relative stiffness of the two ventricles. Since the right ventricle is relatively stiff (non-compliant) at birth and during early infancy, the shunt is small. Over the years, the pulmonary vasculature becomes capacious and right ventricle progressively enlarges to accommodate the excessive pulmonary blood flow. This explains why atrial septal defects (ASD) seldom manifest with symptoms of pulmonary over-circulation during infancy and childhood. The clinical signs are also easily explained by the physiology of pretricuspid shunts. The diastolic flow murmur of ASD is across the much larger tricuspid valve and is, therefore, relatively subtle or even inaudible. The excessive blood in the right ventricle is ejected into the pulmonary artery resulting in an ejection systolic murmur. The second heart sound splits widely and is fixed because

of the prolonged right ventricular ejection time and prolonged "hang-out" interval resulting from increased capacitance of the pulmonary circulation. Pulmonary arterial hypertension (PAH) is typically absent or, at most, mild. The presence of moderate or severe PAH in ASD is worrisome and suggests the onset of irreversible changes in the pulmonary vasculature.

Post-tricuspid shunts are different in that there is direct transmission of pressure from the systemic to the pulmonary circuit at the ventricular level (VSD) or great arteries (PDA and aortopulmonary window). The shunted blood passes through the lungs and finally leads to a diastolic volume overload of the left ventricle. The hemodynamic consequences are dictated by the size of the defect. For patients with large post-tricuspid shunts, symptoms begin in early infancy, typically after regression of elevated pulmonary vascular resistance in the newborn period.

The excessive pulmonary blood flow returns to left atrium and flows through the mitral valve resulting in apical diastolic flow murmur that is a consistent marker of large post-tricuspid shunts. The left atrium and ventricle are dilated as a result of this extra volume. Elevated pulmonary artery pressure is an inevitable consequence of large post-tricuspid shunts, and is labeled hyperkinetic PAH. This needs to be distinguished from elevated pulmonary vascular resistance that results from long-standing exposure to increased pulmonary blood flow. Correction of large post-tricuspid shunts results in rapid and dramatic reduction in elevated pulmonary artery pressures.

Table 16.10: Broad physiologic categories of congenital heart disease**Acyanotic heart disease: Left-to-right shunts**

Pretricuspid: Partial anomalous pulmonary venous drainage, atrial septal defect

Ventricular: Ventricular septal defects (VSD)

Great artery: Aortopulmonary window, patent ductus; ruptured sinus of Valsalva

Both pre- and post-tricuspid: Atrioventricular septal defect, left ventricle to right atrial communications

Acyanotic heart disease: Obstructive lesions

Inflow: Cor-triatriatum, obstructive lesions of the mitral valve

Right ventricle: Infundibular stenosis, pulmonary valve stenosis, branch pulmonary artery stenosis

Left ventricle: Subaortic membrane, valvar aortic stenosis, supra-valvar aortic stenosis, coarctation of aorta

Miscellaneous: Coronary artery abnormalities, congenital mitral and tricuspid valve regurgitation

Cyanotic heart disease*Reduced pulmonary blood flow*

Intact interventricular septum: Pulmonary atresia with intact ventricular septum, critical pulmonic stenosis with right-to-left shunt at atrial level, Ebstein anomaly; isolated right ventricular hypoplasia

Unrestrictive ventricular communication: All conditions listed under VSD with pulmonic stenosis

Increased pulmonary blood flow

Pretricuspid: Total anomalous pulmonary venous communication, common atrium

Post-tricuspid: All single ventricle physiology lesions without pulmonic stenosis, persistent truncus arteriosus, transposition of great vessels

Pulmonary hypertension

Pulmonary vascular obstructive disease (Eisenmenger physiology)

Miscellaneous

Pulmonary arteriovenous malformation, anomalous drainage of systemic veins to LA

VSD-PS Physiology (Fallot Physiology)

This situation is characterized by a large communication at the ventricular level together with varying degrees of obstruction to pulmonary blood flow. Typically, this is in the form of subvalvar (infundibular), valvar, annular (small annulus) and occasionally supra-valvar stenosis. The free communication between the two ventricles results in equalization of pressures. Severity of PS dictates the volume of blood flowing through pulmonary arteries and, therefore, amount of oxygenated blood returning via pulmonary veins. Severe PS results in right-to-left shunt across the VSD with varying degrees of hypoxia and, consequently, cyanosis. Cyanosis is directly proportionate to the severity of PS. Because the right ventricle is readily decompressed by the large VSD, heart failure is unusual.

The best example of VSD-PS physiology is tetralogy of Fallot (TOF). In its least severe form, TOF is often not associated with cyanosis (pink TOF). Here PS is significant enough to result in a large pressure gradient across the right ventricular outflow tract (RVOT), but not severe enough to result in a reduction in pulmonary blood flow. Pink TOF is typically associated with a loud ejection systolic murmur because of a reasonable volume of blood flowing across the RVOT. As the severity of PS increases, pulmonary blood flow declines and the intensity of murmur declines progressively. Identical symptoms and physical findings are present in (i) complete transposition of great arteries with VSD and pulmonic stenosis, (ii) double outlet right ventricle with pulmonic stenosis and a large subaortic VSD, (iii) tricuspid atresia with diminished pulmonary blood flow, (iv) single ventricle with pulmonic stenosis, and (v) corrected transposition of great arteries with VSD and pulmonic stenosis.

Single Ventricle Physiology

This refers to a group of conditions where there is complete mixing of pulmonary and systemic venous returns. In addition to single ventricle (double inlet ventricle), a variety of conditions come under the category of single ventricular physiology. Atresia of one of the AV valves, severe hypoplasia of one of the ventricles, severe straddling of one of the AV valves over a large VSD are all examples of situations where there is mixing of pulmonary and systemic venous returns. The clinical manifestations are dictated by whether or not there is PS. In absence of PS, there is excessive pulmonary flow especially in infants because of the relatively lower pulmonary vascular resistance. The proportion of oxygenated blood from pulmonary veins that mixes with the systemic venous return is high. Cyanosis is minimal and measured oxygen saturation may be 90% or more. However, preserved oxygenation is at the cost of heart failure and permanent elevation of pulmonary vascular resistance (pulmonary vascular obstructive disease). If the child survives infancy, pulmonary vascular resistance progressively increases with increasing cyanosis.

Single ventricle and its variants can be associated with varying degrees of PS. The features are similar to VSD-PS physiology except for relatively severe hypoxia because of free mixing of systemic and pulmonary venous return. Palliative operations are the only option for most conditions. The definitive procedure is the Fontan operation that allows separation of systemic venous return from pulmonary venous return thereby, eliminating cyanosis.

Duct-Dependent Lesions

An infant or a newborn with CHD that is dependent on the patency of the ductus arteriosus for survival can be termed as having a duct-dependent lesion. These are newborns where the systemic blood supply is critically

dependent on an open PDA (duct-dependent systemic circulation, DDSC) or pulmonary blood flow is duct dependent (duct-dependent pulmonary circulation, DDPC). Closure of the PDA in DDSC results in systemic hypoperfusion (often mistaken as neonatal sepsis), as in hypoplastic left heart syndrome, where the entire systemic circulation is supported by the right ventricle through the PDA, and interrupted aortic arch where the descending aortic flow is entirely through the PDA. Severe coarctation and critical aortic stenosis are also examples of DDSC. Closure of PDA in DDPC results in severe hypoxia and cyanosis in neonates; examples include all forms of pulmonary atresia (irrespective of underlying heart defect) where the PDA is the predominant source of pulmonary blood flow. Patients with pulmonary atresia, where pulmonary blood supply is from major aortopulmonary collaterals, may survive even after the PDA closes. Critical PS can present as duct-dependent pulmonary blood flow. Newborns with severe Ebstein anomaly can also present as DDPC (physiologic pulmonary atresia) even though the pulmonary valve is anatomically normal, because of inability of the right ventricle to function effectively.

Neonates with duct-dependent physiology require prostaglandin E1 (PGE1) for survival. Early recognition of a duct-dependent situation allows early initiation of PGE1 and stabilization until definitive procedure is accomplished.

Unfavorable Streaming and Parallel Circulation

Unfavorable streaming refers to a situation where oxygen rich pulmonary blood flow is directed towards the pulmonary valve and poorly oxygenated blood towards the aortic valve. The best example of unfavorable streaming the parallel circulation in transposition of great arteries (TGA) with intact ventricular septum. Here survival depends on the presence of a communication (ideally at atrial level) that allows mixing of pulmonary and systemic venous return. The presence of a VSD may improve the situation in TGA but significant cyanosis is usually present unless the pulmonary blood flow is torrential.

Clinical Features

While it is often easy to recognize the presence of CHD in older children, manifestations of heart disease can often be subtle in newborns and young infants. Conditions that do not primarily involve the cardiovascular system can result in clinical manifestations that overlap with those resulting from CHD in the newborn. Nonetheless, careful clinical evaluation is often rewarding and allows identification of CHD in most infants and many newborns.

Cyanosis

Parents seldom report cyanosis unless it is relatively severe (saturation <80%). It is often easier for them to notice episodic cyanosis (when the child cries or exerts).

Difficult Feeding and Poor Growth

The parent may report that the child has difficulty feeding. This is usually a feature of an infant with congestive heart failure and may include slow feeding, small volumes consumed during each feed, tiring easily following feeds and requirement of periods of rest during feeds. Excessive sweating involving forehead or occiput is commonly associated. Not infrequently, no history of feeding difficulty may be obtained, but examination of growth charts reveals that the growth is not appropriate for age. A recent decline in growth rate (falling off the growth curve) or weight that is inappropriate for age (<5th centile) may result from a large left-to-right shunt. Characteristically, growth retardation affects weight more than height.

Difficult Breathing

Tachypnea (respiratory rate >60/min in infants <2 months; >50/min in older infants; >40/min after 1 year) is a manifestation of heart failure in newborns. For infants, subcostal or intercostal retractions together with flaring of nostrils are frequently associated with tachypnea.

Frequent Respiratory Infections

The association of respiratory infections that are frequent, severe and difficult to treat with large left-to-right shunts is frequent but not a specific feature.

Specific Syndromes

The presence of chromosomal anomalies or other syndromes that are associated with CHD should alert the clinician to the presence of specific cardiac defects. Trisomy 21 is the commonest anomaly associated with heart disease; others include trisomy 13 and 18, Turner and Noonan syndromes, and velocardiofacial and DiGeorge syndromes (Table 16.7).

Nadas Criteria

The assessment for presence of heart disease can be done using the Nadas criteria. Presence of one major or two minor criteria is essential for indicating the presence of heart disease (Table 16.11).

Major criteria

Systolic murmur grade III or more in intensity: A pansystolic murmur is always abnormal no matter what is its intensity.

Table 16.11: Nadas' criteria for clinical diagnosis of congenital heart disease

<i>Major</i>	<i>Minor</i>
Systolic murmur grade III or more	Systolic murmur grade I or II Abnormal second sound
Diastolic murmur	Abnormal electrocardiogram
Cyanosis	Abnormal X-ray
Congestive cardiac failure	Abnormal blood pressure

There are only three lesions that produce a pansystolic murmur: VSD, mitral regurgitation and tricuspid regurgitation. An ejection systolic murmur may be due to an organic cause or it may be functional. An ejection systolic murmur associated with a thrill is an organic murmur. Grade III ejection systolic murmur of a functional type may be heard in anemia or high fever especially in small children.

A number of children around the age of 5 years may have a soft, short ejection systolic murmur. If it is accompanied with a normal second sound, then it is unlikely to be significant. Before labeling a murmur as innocent, it is necessary to reassess after an interval. Typically, innocent murmurs are often detected during a febrile illness and often disappear. It may be necessary to obtain an ECG and an echocardiogram to rule out heart disease and allay parental anxiety.

Diastolic murmur: A diastolic murmur almost always indicates the presence of organic heart disease.

Central cyanosis: Central cyanosis suggests that either unoxygenated blood is entering the systemic circulation through a right-to-left shunt or blood passing through the lungs is not getting fully oxygenated. Oxygen saturation of the arterial blood is less than normal (normal being around 98%). If blood is not getting oxygenated in the lungs, it is called pulmonary venous desaturation and indicates severe lung disease. Cyanosis due to a right-to-left shunt indicates presence of heart disease. Central cyanosis is present in fingers, toes and mucous membranes (mouth, tongue). It results in polycythemia and clubbing.

Peripheral cyanosis does not imply the presence of heart disease. Peripheral cyanosis results due to increased oxygen extraction from the blood by the tissues, and is seen in fingers and toes but not in mucous membranes. The arterial oxygen saturation is normal. Presence of central cyanosis indicates CHD if lung disease has been excluded. However, cyanosis that is obvious clinically usually results from significant desaturation (typically <85%). Poor lighting, anemia and dark skin may mask cyanosis. The routine use of pulse oximeters allows detection of mild hypoxia. Saturations <95% while breathing room air are abnormal.

Congestive cardiac failure: Presence of congestive cardiac failure indicates heart disease except in neonates and infants, where it might occur due to extracardiac causes, including anemia hypocalcemia and hypoglycemia.

Minor criteria

Systolic murmur less than grade III: However, soft, less than grade III, murmurs by themselves do not exclude heart disease.

Abnormal second sound: Abnormalities of the second sound always indicate presence of heart disease. It has been included as a minor criterion only because auscultation is an individual and subjective finding.

Abnormal electrocardiogram: Electrocardiogram is used to determine the mean QRS axis, right or left atrial hypertrophy and right or left ventricular hypertrophy. Criteria for ventricular hypertrophy, based only on voltage criteria are not diagnostic for the presence of heart disease, since these may be affected by changes in blood viscosity, electrolyte imbalance, position of electrodes and thickness of the chest wall.

Abnormal X-ray: The reason for abnormal X-ray as a minor criterion is twofold. In infants and smaller children, the heart size varies with expiration and inspiration. If there is cardiomegaly on an inspiratory film, it suggests heart disease. The second reason is that enlarged thymus in children up to 2-year-old might mimic cardiomegaly. Fluoroscopy is helpful in separating the shadow of the thymus from the heart.

Abnormal blood pressure: It is difficult to obtain accurate blood pressure in smaller children. It is important to use appropriate sized cuffs while measuring blood pressure.

Diagnostic Implications of the Second Heart Sound

Of the various heart sounds and murmurs, the most important is the assessment of the second heart sound (Fig. 16.5). The normal second heart sound can be described in three parts:

- i. It has two components: Aortic closure sound (A2) and pulmonary closure sound (P2).

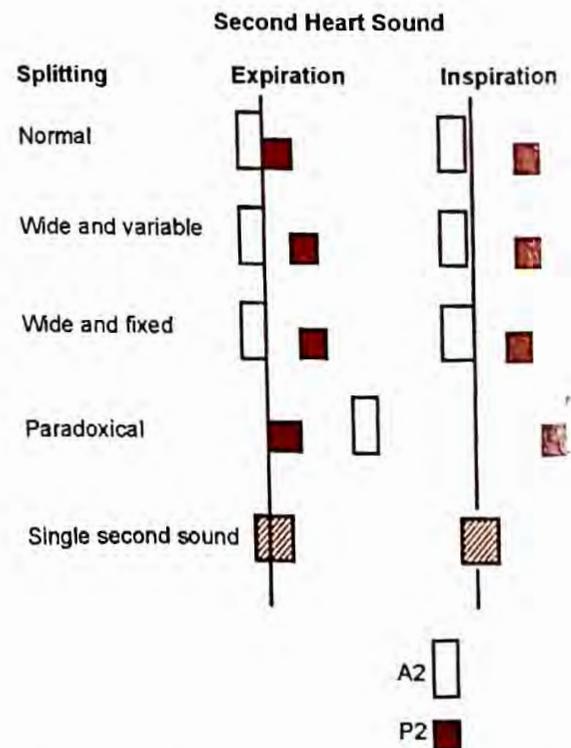


Fig. 16.5: Second sound (S2): The relationship of aortic (A2) and pulmonic component (P2) in inspiration and expiration. Single S2 means that it may be either A2 or P2 or a combination of both

- ii. During quiet breathing, both the components are superimposed on each other during expiration, thus only a single second sound is heard. During inspiration, the aortic component comes early whereas the pulmonary component is delayed, resulting in a split in which the A2 precedes the P2.
- iii. The aortic component is louder than the pulmonary component, except in young infants.

When we say that the second sound is normal, it is in context of the above three aspects. Abnormalities of the second sound might occur in each of these aspects.

Abnormalities of aortic component: The A2 may be accentuated or diminished in intensity. It can also occur early or late in timing. The A2 is accentuated in systemic hypertension from any cause and in AR; diminished or may be absent when the aortic valve is immobile because of fibrosis or calcification; or if absent, in aortic valve atresia. The A2 is delayed when the left ventricular ejection is prolonged as in aortic valvar or subvalvar stenosis, patent ductus arteriosus with a large left to right shunt, AR, left bundle branch block and left ventricular failure. The A2 occurs early in VSD, mitral regurgitation and constrictive pericarditis.

Abnormalities of pulmonic component: The P2 may be accentuated or diminished in intensity or delayed in timing. Although it may occur early in tricuspid regurgitation, it is not recognized since tricuspid regurgitation as an isolated lesion (without pulmonary arterial hypertension) is rare. Accentuated P2 is present in pulmonary arterial hypertension from any cause. The P2 is diminished in intensity in pulmonic stenosis. It is absent when the pulmonary valve is absent as in pulmonary valvar atresia. The P2 is delayed in pulmonic stenosis, atrial septal defect, right bundle branch block, total anomalous pulmonary venous connection and type A WPW syndrome.

Abnormalities in splitting of the second sound (S2): The normal S2 is single (or closely split, <0.03 sec) in expiration and split in inspiration with the louder A2 preceding P2. Wide splitting of the second sound is defined as splitting during expiration due to an early A2 or late P2 or the A2-P2 interval of 0.03 sec or more during expiration. If the interval increases during inspiration, it is called wide variable splitting, but if it is the same in expiration and inspiration it is defined as widely split and fixed S2. Wide and variable splitting of S2 is seen in pulmonic stenosis, mitral regurgitation and VSD. In pulmonic stenosis, it is due to a delay in P2 whereas in mitral regurgitation and VSD, it is due to an early A2. Wide and fixed splitting of the S2 occurs in atrial septal defect, right bundle branch block and total anomalous pulmonary venous connection and is due to a delay in P2.

The delay in A2 results in closely split, single or paradoxically split S2. In paradoxically split S2, the split

is wide in expiration but narrows during inspiration (Fig. 16.5). A single second sound means that it is either A2 or P2 or a combination. The decision whether it is aortic or pulmonic or a combination, depends not on the location or intensity of the single second sound, but on the clinical profile. In tetralogy of Fallot, only a single S2 is heard and it is the A2 since the pulmonic component is delayed and so soft that it is inaudible. In VSD with pulmonary arterial hypertension and right-to-left shunt (Eisenmenger complex), single S2 represents a combination of A2 and P2. While based on auscultation alone, it might be difficult to differentiate between tetralogy of Fallot and Eisenmenger complex, the history and chest X-ray can distinguish these conditions.

Imaging Studies

Echocardiography: Echocardiography has revolutionized the diagnosis of CHD and its diagnostic yield makes this investigation cost-effective (Fig. 16.6). This is particularly true for infants and newborns where excellent images are readily obtained. Transesophageal echocardiography can supplement transthoracic studies in older children.

Cardiac magnetic resonance imaging: Cardiac MRI is important for evaluation of CHD, especially in older patients and for postoperative evaluation. MRI also defines extracardiac structures such as branch pulmonary arteries, pulmonary veins and aortopulmonary collaterals. Useful physiologic data (blood flow calculations at a number of locations; estimate of ventricular function) is obtained. Limitations include lack of expertise for interpretation and need for general anesthesia to enable breath-holding.

Computed tomography: CT overcomes some of the limitations of MRI because it has a much lower image acquisition time. However, exposure to ionizing radiation is a concern.

Diagnostic cardiac catheterization: The role of diagnostic cardiac catheterization for patients with CHD has declined with the availability of high quality echocardiography, MRI and CT. Since cardiac catheterization is an invasive procedure, its performance requires planning so that the information desired may be obtained with minimum risk to the patient. Diagnostic cardiac catheterization should be advised, if non-invasive investigations do not provide information that is required for surgery.

Definitive and Palliative Treatment

To ensure the best possible results of management of CHD, it is necessary to have a team of qualified individuals who are part of a comprehensive pediatric heart program.

Surgery

Surgery is still the best option for definitive treatment or palliation of most CHD. Surgeries for CHD are broadly

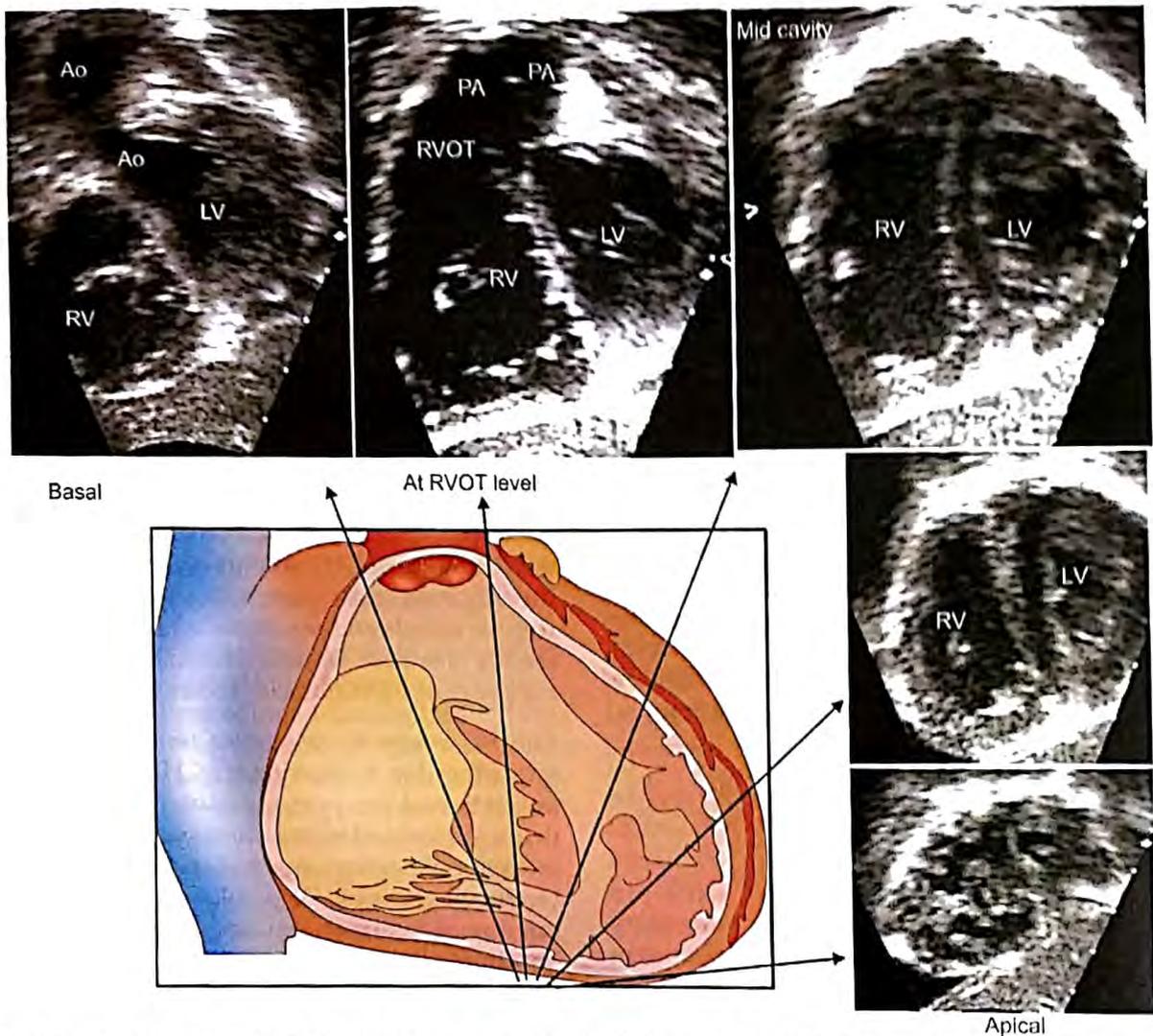


Fig. 16.6: Two-dimensional echocardiography. An illustrative example of how the ventricular septum can be sectioned at different levels to screen for ventricular septal defects. The lines with arrows represent levels at which cross-sectional images are obtained. The still frames of the respective echocardiograms are shown in relation to each of the level at which a section is obtained. Ao aorta; LV left ventricle; PA pulmonary artery; RV right ventricle; RVOT right ventricular outflow tract

classified as open heart (requiring use of cardiopulmonary bypass—CPB) and closed heart (not requiring CPB). Most corrective operations and many palliative operations fall under the former category. These procedures are generally a more significant and expensive undertaking because of the use of the CPB circuit. The morbidity of open heart operations is proportionate to the duration of exposure to CPB and the cross-clamp time (the period of time when heart beating is deliberately brought to a standstill through the use of cardioplegia).

Corrective operations: Corrective surgery is possible for atrial and ventricular septal defects, with no significant long-term concerns. If the repair of TOF does not result in pulmonary valve incompetence, long-term concerns are minimal. Certain operations require careful follow-up because long-term concerns are substantial, especially after 10–20 years follow-up. These include the Senning operations (atrial switch) for transposition where the right

ventricle continues to support the systemic circulation, TOF repair where the pulmonary valve is rendered incompetent through a transannular patch and operations that require the placement of a right ventricle to pulmonary artery conduit. Corrective surgeries associated with excellent long-term survival include the arterial switch operation, repair of total anomalous pulmonary venous connection and coarctation.

Surgery for single ventricle physiology: This category includes all anatomic examples of single ventricle. In addition, this includes situations when one atrioventricular valve is atretic or one of the ventricles is hypoplastic. The surgical management of single ventricle physiology is performed in stages. The first stage involves early pulmonary arterial band (usually under the age of 3 months) for patients who have increased pulmonary blood flow and the modified Blalock-Taussig shunt for those who have reduced pulmonary blood flow with

cyanosis. The second operation is the bidirectional Glenn shunt. The superior vena cava is anastomosed to the right pulmonary artery. This operation allows effective palliation until the age of 4–6 years, sometimes longer. The Fontan operation is finally required for elimination of cyanosis. All the systemic venous return is routed to the pulmonary artery. There are important long-term issues in a substantial proportion of survivors.

Catheter Interventions

Catheter interventions are possible in many patients. Many defects such as secundum ASD, PDA and selected muscular VSD can be closed in the catheterization laboratory. Additionally, balloon valvotomy is now the first line of treatment for stenosis of the pulmonary and aortic valves (Table 16.12). These interventions are far less traumatic than surgery, accomplished with ease and allow rapid recovery.

Complications of Congenital Heart Disease

Pulmonary arterial hypertension (PAH): Lesions that have the greatest likelihood of developing PAH include cyanotic heart disease with increased pulmonary blood flow. Here irreversible changes in pulmonary vasculature develop rapidly, often during infancy. It is important to correct or appropriately palliate these lesions early (within the first

few months of life). Large acyanotic post-tricuspid shunts are also prone to early development of PAH and should be ideally corrected early, preferably within the first year. In pretricuspid shunts, PAH develops slowly and unpredictably. While most patients with ASD will have mild or no PAH throughout their lives, a small proportion develops accelerated changes in pulmonary vasculature. Features associated with early development of PAH are: Large size of the defect; presence of pulmonary venous hypertension; airway obstruction; syndromic association, (e.g. trisomy 21); prolonged duration of increased pulmonary blood flow; and residence at high altitude.

Infective endocarditis or endarteritis (IE): Endocarditis can complicate CHD, especially in patients with significant turbulence created by high-pressure gradients, e.g. restrictive VSD and PDA, tetralogy of Fallot and left ventricular outflow obstruction. Some surgical operations (Blalock-Taussig shunt) are also associated with increased risk of IE or endarteritis. Lesions with little or no turbulent flows, such as ASD, do not show an increased risk. The importance of good dental hygiene cannot be over-emphasized.

Impaired growth and nutrition: This is affected in all forms of CHD and is striking in large left-to-right shunts.

Table 16.12: Congenital heart defects amenable to catheter-based interventions

Lesion	Procedure	Comments
Atrial septal defect	Device closure	Amenable to device closure, if the defect is in the fossa ovalis and has sufficient margins
Patent ductus arteriosus (PDA)	Coil or device closure	Majority can be closed by catheter interventions, except large PDA in infants
Muscular ventricular septal defect (VSD)	Device closure	Device closure is an option for older infants (>8 kg)
Membranous VSD	Device closure	Controversial; carries a small risk of heart block
Pulmonary valve stenosis valvotomy	Balloon pulmonary	Treatment of choice for most forms except dysplastic valves in Noonan syndrome
Aortic valve stenosis	Balloon aortic valvotomy	Initial treatment of choice at all ages; however, dilated aortic valves eventually need surgery
Branch pulmonary artery stenosis	Balloon dilation with stenting	Stenting preferred to surgery
Coarctation of aorta	Balloon dilation with or without stenting	Neonates: Surgery preferred due to high risk of recurrence Older infants: Balloon dilatation satisfactory Children >10 years: Dilatation with stenting is curative
Coronary artery fistula	Coil or device closure	Treatment of choice
Pulmonary arteriovenous malformations	Coil or device closure	Treatment of choice when discrete; surgery preferred for diffuse malformations
Duct-dependent pulmonary circulation	Stenting of the PDA	Offered, in selected cases, as an alternative to Blalock-Taussig shunt
Pulmonary atresia with intact ventricular septum	Valve perforation followed by balloon dilation	Preferred procedure in some centers
Ruptured sinus of Valsalva aneurysm	Device closure	Preferred option in selected cases
Transposition of great arteries	Balloon atrial septostomy	For palliation before definitive surgery

Patients with CHD show high prevalence of malnutrition, which improves after correction of the underlying condition.

Myocardial dysfunction: Chronic volume overload results in ventricular enlargement and ventricular dysfunction that is reversed after correction. A proportion of patients with severe hypoxia may develop severe dysfunction involving both ventricles. Heart failure is mostly the result of hemodynamic consequences of increased pulmonary blood flow, mitral or tricuspid valve regurgitation and severe myocardial hypertrophy. Systolic dysfunction is a relatively less common cause.

Neurologic consequences and development delay: Chronic hypoxia, *in utero* hypoxia and hypoperfusion and open-heart surgery contribute substantially to morbidity. Brain abscess is uniquely associated with cyanotic heart disease (typically beyond the age of 2 years).

Erythrocytosis: Older children with cyanotic CHD are prone to complications from chronically elevated red cell turnover. These include symptoms of hyperviscosity, gout, renal failure and gallstones.

Rhythm disorders and sudden death: Chronic enlargement of heart chambers predispose to tachyarrhythmia. Chronic right atrial enlargement (ASD, Ebstein syndrome, severe tricuspid regurgitation) predisposes to atrial flutter. Chronic right ventricular enlargement predisposes to ventricular tachycardia and may precipitate sudden cardiac arrest. This is a significant long-term concern after TOF repair where the pulmonary valve is rendered incompetent. Left ventricular hypertrophy and dysfunction is also associated with high risk of ventricular tachycardia.

Cyanotic spells: Patients with the VSD-PS physiology are prone to cyanotic spells. Cyanotic spells occur due to acute decrease in pulmonary blood flow, increased right-to-left shunt and systemic desaturation due to (i) infundibular spasm secondary to increase in circulating catecholamines, during feeding or crying; or (ii) activation of mechanoreceptors in right ventricle (due to decrease in systemic venous return) or in left ventricle (due to reduced pulmonary blood flow). These changes result in peripheral vasodilatation and fall in systemic vascular resistance, producing increased right-to-left shunt and systemic desaturation.

A cyanotic spell is an emergency, which requires prompt recognition and intervention to prevent disabling cerebrovascular insults or death. The spell needs to be taken seriously also because it indicates the need for early operation. It is commonly seen below 2 years (peaks between 2 and 6 months). The onset is spontaneous and unpredictable and occurs more often in early morning, although it can occur at anytime in the day. The infant cries incessantly, and is irritable and inconsolable.

Tachypnea is prominent feature without significant subcostal recession. Cyanosis deepens as the spell progresses. Later gasping respiration and apnea ensues, which leads to limpness and ultimately anoxic seizures. Spells can last from minutes to hours. Auscultation reveals softening or disappearance of pulmonary ejection murmur. The management is summarized in Table 16.13.

Natural History

Some CHD have a tendency towards spontaneous closure and this influences the timing of intervention. Defects known to close spontaneously are atrial and ventricular septal defects, and patent ductus arteriosus. Variables influencing the likelihood of spontaneous closure include: Age at evaluation (lower likelihood of closure with increasing age), size of the defect (smaller defects more

Table 16.13: Management of hypercyanotic spells

Immediate steps

- Check airway; deliver oxygen by face mask or nasal cannula
- Knee chest position
- Sedate with morphine (0.2 mg/kg SC or ketamine 3–5 mg/kg dose IM)
- Sodium bicarbonate at 1–2 mL/kg (diluted 1:1 or in 10 mL/kg N/5 in 5% dextrose)
- Correct hypovolemia (10 mL/kg of dextrose normal saline)
- Transfuse packed red cell, if anemic (hemoglobin <12 g/dL)
- Metoprolol at 0.1 mg/kg IV slowly over 5 min; repeat every 5 min; for maximum 3 doses; may be followed by infusion at 1–2 µg/kg/min
- Monitor saturation, heart rates and blood pressure; keep heart rate below 100/minute

Persistent desaturation and no significant improvement

Consider vasopressor infusion: Methoxamine 0.1–0.2 mg/kg/dose IV or 0.1–0.4 mg/kg/dose IM, or phenylephrine 5 µg/kg as IV bolus and 1–4 µg/kg/min as infusion

If spells persist: Paralyze the patient, electively intubate and ventilate; plan for palliative or corrective surgery

Seizures are managed with diazepam at 0.2 mg/kg IV or midazolam at 0.1–0.2 mg/kg/dose IV

Following a spell

- Conduct a careful neurological examination; CNS imaging, if focal deficits are present
- Initiate therapy with beta-blocker at the maximally tolerated dose (propranolol 0.5–1.5 mg/kg q 6–8 hr); helps improve resting saturation and decreases frequency of spells
- Ensure detailed echocardiography for disease morphology
- Plan early corrective or palliative surgery
- Administer iron in therapeutic (if anemic) or prophylactic dose

Prevention

- Counsel parents regarding the possibility of recurrence of spells and precipitating factors (dehydration, fever, pain)
- Encourage early surgical repair

Table 16.14: Spontaneous closure of heart defects

Variable	Likelihood of spontaneous closure
Age at evaluation	More likely in younger patients; most ASD and VSD that finally close or become very small do so by the age of 3 years; PDA either close in the first 2–4 weeks or not at all, particularly in preterm infants
Size of the defect	Larger defects are unlikely to close spontaneously, such as ASD >8 mm and large unrestrictive VSD
Location of the defect	Fossa ovalis ASD tend to close spontaneously; ostium primum and sinus venosus defects do not close; muscular VSD have high likelihood of spontaneous closure; perimembranous VSD can also close spontaneously; outlet (subpulmonic) VSD may close by prolapse of the aortic valve, resulting in aortic regurgitation; inlet VSD and malaligned VSD (as in tetralogy of Fallot) do not close spontaneously

ASD atrial septal defect; PDA patent ductus arteriosus; VSD ventricular septal defect

likely to close) and location of defects (fossa ovalis ASD and perimembranous and muscular VSDs often close) (Table 16.14).

Without correction, many children especially those with cyanotic CHD, will not survive beyond early childhood. The outcomes are improved by correction through surgery and, in some situations, through catheter interventions. Despite curative surgery, some patients have important long-term sequelae. For example, patients with tetralogy of Fallot who have undergone "curative" repair might show progressive right ventricular dilation with increased risk of late heart failure and sudden cardiac death. There are concerns after the arterial switch operation (aortic root dilation, silent coronary occlusion), AV canal repair (AV valve regurgitation) and coarctation (residual hypertension, aortic aneurysm). Operations that involve placement of conduits (pulmonary atresia, Rastelli operations) require replacement upon growth of the child. Conditions associated with satisfactory long-term survival include small left-to-right shunts and bicuspid aortic valves. Survival is satisfactory for many patients with atrial septal defect, coarctation of aorta, pink TOF, mild Ebstein anomaly and some forms of corrected transposition of great arteries.

Prevention of CHD

Most CHD do not have an identifiable etiology and there is no effective strategy for their prevention. Education of public on the risks associated with consanguinity, drugs and teratogens in the first trimester of pregnancy and widespread immunization against rubella have limited role in preventing CHD. Fetal echocardiography is an important modality for early diagnosis of CHD. Conditions that involve major chamber discrepancy (such as hypoplastic left heart syndrome), single ventricle and common AV canal can be identified by routine four chamber view screening as early as 14–16 weeks gestation. With some refinement, additional conditions such as tetralogy of Fallot, large VSD, transposition of great vessels and persistent truncus arteriosus can be detected. Once a serious CHD is identified, it is vital to counsel the families about postnatal manifestations, natural history, surgical options and their long-term outlook. Before 20 weeks of gestation, medical termination of pregnancy is an option.

Detection of serious defects through fetal echocardiography enables delivery at a center with a pediatric heart program. While echocardiography is recommended for future pregnancies after diagnosis of serious CHD in a child, this has low yield because only 2–8% CHD recur, with the highest risk for obstructive lesions of the left heart.

ACYANOTIC CONGENITAL HEART DEFECTS

Atrial Septal Defect

Atrial septal defect (ASD) as an isolated anomaly accounts for 5–10% of all CHD. Based on anatomy, ASD is classified as follows (Fig. 16.7):

Fossa ovalis ASD: They are located in the central portion of atrial septum, in the position of foramen ovale. These defects are amenable to closure in the catheterization laboratory.

Sinus venosus ASD: These are located at junction of superior vena cava and right atrium. These defects do not have a superior margin because the superior vena cava straddles the defect. These defects are associated with anomalous drainage of one or more right pulmonary veins.

Ostium primum ASD: These defects are created by failure of septum primum, and are in lower part of the atrial

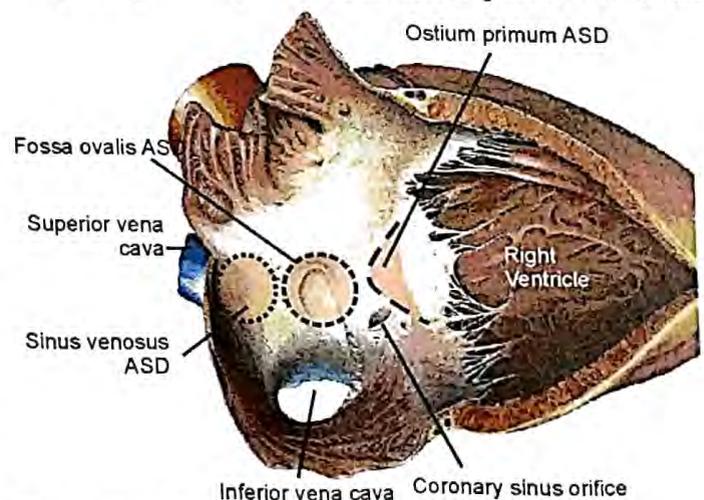


Fig. 16.7: Right-sided cardiac chambers showing the three commonest types of atrial septal defects (ASD)

septum; inferior margin of ASD is formed by the atrioventricular valve.

Coronary sinus ASD: An unroofed coronary sinus is a rare communication between the coronary sinus and the left atrium, which produces features similar to other types of ASD.

Physiology and Findings

The physiology of ASD is that of a pretricuspid shunt. The enlarged right ventricle results in a parasternal impulse. The ejection systolic murmur originates from the pulmonary valve because of the increased blood flow. An increased flow through the tricuspid valve may result in a soft delayed diastolic rumble at the lower left sternal border. The overload of the right ventricle due to an increase in venous return prolongs the time required for its emptying resulting in delayed P2. This delay also results from the prolonged 'hang-out' interval because of very low resistance in the pulmonary circulation. Additionally, since the two atria are linked via the large ASD, inspiration does not produce any net pressure change between them, and respiration-related fluctuations in systemic venous return to the right side of the heart are abolished; thereby the fixed S2 (Fig. 16.8).

The electrocardiogram of ostium secundum ASD is characterized by right axis deviation and right ventricular hypertrophy. The characteristic configuration of the lead V1 is rsR' seen in almost 90% patients (Fig. 16.9). Presence of left axis deviation beyond -30° suggests ostium primum ASD (Fig. 16.10). The chest X-ray (Fig. 16.11) shows mild to moderate cardiomegaly, right atrial and right

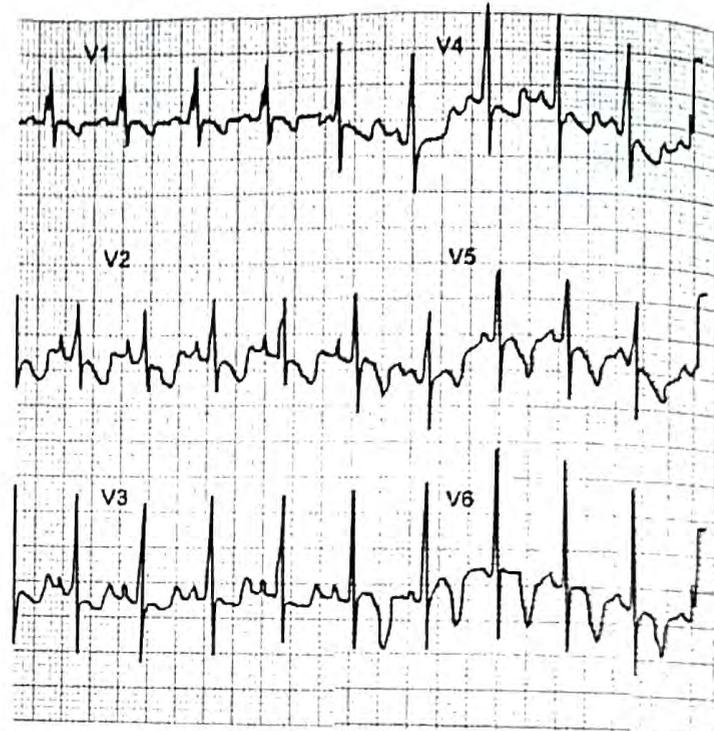


Fig. 16.9: Electrocardiogram of atrial septal defect of the secundum type showing rsR' pattern in lead V1

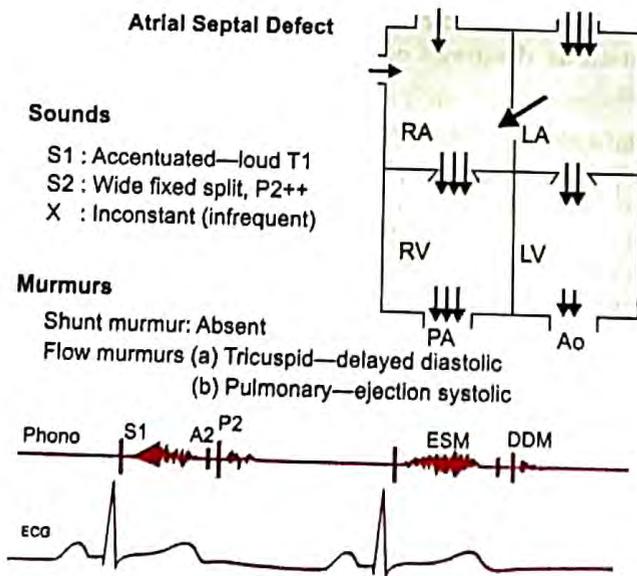


Fig. 16.8: Summary of auscultatory findings in the atrial septal defect, Ao aorta; A2 aortic component of the second sound; ESM ejection systolic murmur; LA left atrium; LV left ventricle; PA pulmonary artery; P2 pulmonic component of the second sound; RA right atrium; RV right ventricle; S1 first sound; S2 second sound; X click

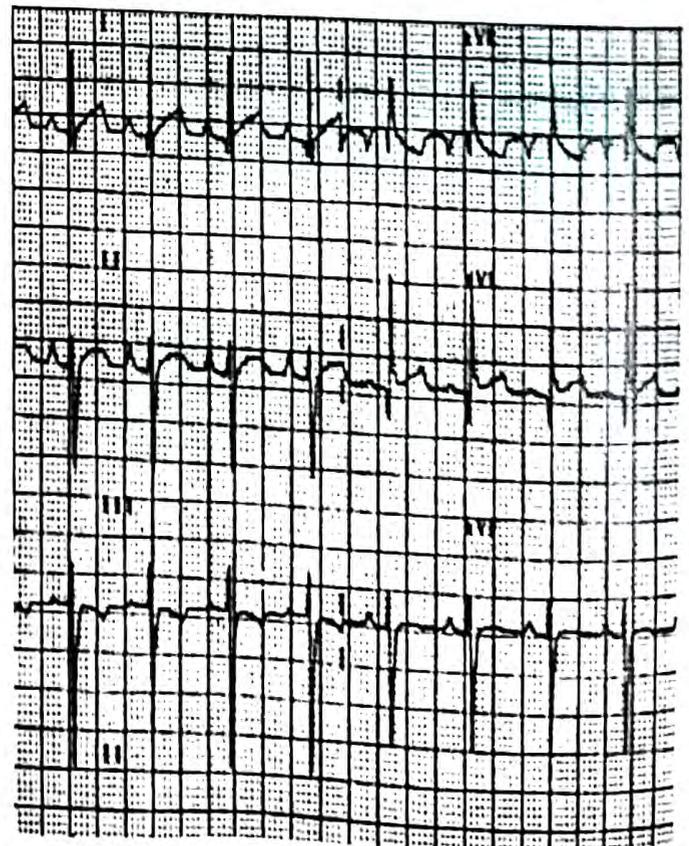


Fig. 16.10: Electrocardiogram of atrial septal defect of the primum type associated with endocardial cushion defect. The mean QRS axis is -60°

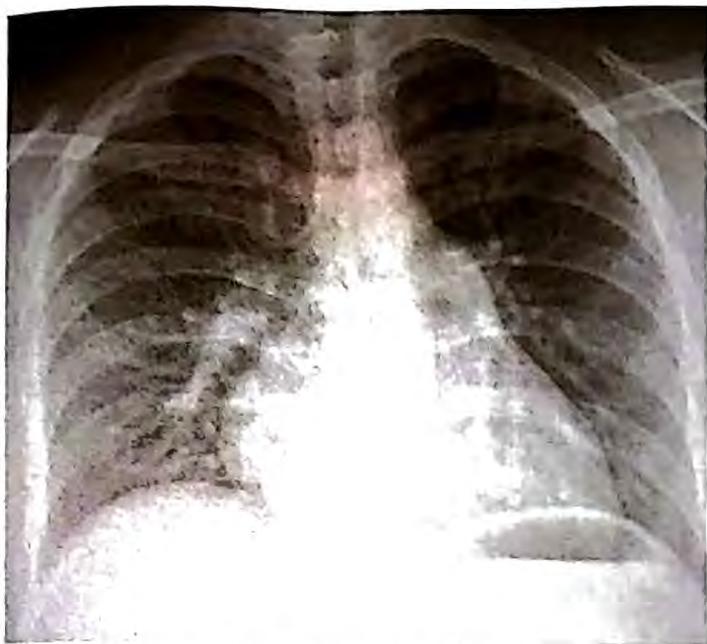


Fig. 16.11: Chest X-ray of an 18-year-old patient with large atrial septal defect. Note the dilated right atrium, prominent main pulmonary artery and increased pulmonary blood flow

ventricular enlargement, prominent main pulmonary artery segment, a relatively small aortic shadow and plethoric lung fields. The left atrium does not enlarge in size in atrial septal defect, unless associated with other anomalies like mitral regurgitation. Echocardiogram shows increased size of the right ventricle with paradoxical ventricular septal motion. 2D echo in subcostal view often best identifies the defect. The echocardiogram allows decision regarding suitability of catheter closure, based on measurements of the defect and the adequacy of margins (Fig. 16.12).

Assessment of the Severity

The size of the left-to-right shunt is directly proportional to the intensity of the murmurs and heart size. The larger the shunt, the more the cardiomegaly and the louder the pulmonary and tricuspid murmurs.

Natural History and Complications

Heart failure is exceptional in infancy. A small proportion of patients might develop pulmonary hypertension by the second or third decade. Closure of ASD is recommended to prevent complications of atrial arrhythmias and heart failure in late adulthood.

Treatment

Most fossa ovalis defects with good margins can be closed percutaneously in the catheterization laboratory with occlusive devices. Others require surgical closure. Closure is recommended before school entry to prevent late complications. Small defects (<8 mm) can be observed. Spontaneous closure is well recognized in small defects that are diagnosed in infancy or early childhood.



Fig. 16.12: Echocardiogram of ASD. Subxiphoid short axis view of the atrial septum shows deficient posterior-inferior rim (arrow). LA left atrium; RA right atrium; SVC superior vena cava

Ventricular Septal Defect (VSD)

This is the most common congenital cardiac lesion identified at birth accounting for one-quarter of all CHD. VSD is a communication between the two ventricles; 90% are located in the membranous part of the ventricular septum with variable extension into the muscular septum. Others are located in the muscular septum and can be multiple (Fig. 16.13).

Hemodynamics

VSD results in shunting of oxygenated blood from the left to the right ventricle. The left ventricle starts contracting before the right ventricle. The flow of blood from the left-to-right ventricle starts early in systole. When the defect is restrictive, a high pressure gradient is maintained between the two ventricles throughout the systole. The murmur starts early, masking the first sound and continues throughout the systole with almost the same intensity appearing as a pansystolic murmur on auscultation and palpable as a thrill. Toward the end of systole, the declining left ventricular pressure becomes lower than the aortic pressure. This results in closure of the aortic valve and occurrence of A2. At this time, however, the left ventricular pressure is still higher than the right ventricular pressure and the left-to-right shunt continues. The pansystolic murmur, therefore, ends beyond A2 completely masking it (Fig. 16.14).

The left-to-right ventricular shunt occurs during systole at a time when the right ventricle is also contracting and

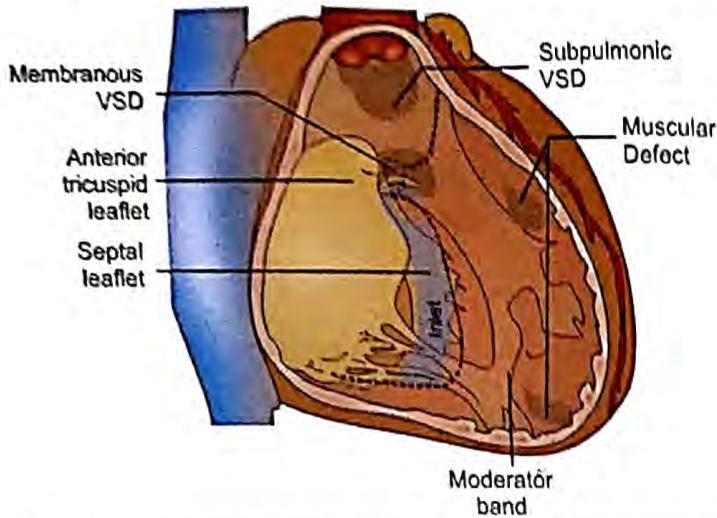


Fig. 16.13: Diagrammatic representation of the common locations of ventricular septal defects (VSD). Membranous septum is the commonest location. Subpulmonic VSDs, located in the outlet septum, have a high risk of aortic valve prolapse. Muscular VSDs can occur anywhere in the muscular part of septum

On the bedside, however, the ejection systolic murmur cannot be separated from the pansystolic murmur.

The large volume of blood passing through the lungs is recognized in the chest X-ray as pulmonary plethora. The increased volume of blood finally reaches the left atrium and may result in left atrial enlargement. Passing through a normal mitral valve, the large volume of blood results in a delayed diastolic murmur at the apex. The intensity and duration of the delayed diastolic murmur at the apex is directly related to the size of the shunt. The large flow across the normal mitral valve also results in accentuated first sound, not appreciable on the bedside as it is drowned by the pansystolic murmur. Since the left ventricle has two outlets, the aortic valve allowing forward flow and the VSD resulting in a backward leak, it empties relatively early. This results in an early A2. Since the ejection into the right ventricle and pulmonary artery is increased because of the left-to-right shunt the P2 is delayed. Therefore, the second sound is widely split but varies with respiration in patients with VSD and a large left-to-right shunt. There is also an increase in the intensity of the P2.

Clinical Features

Patients with VSD can become symptomatic around 6 to 10 weeks of age with congestive cardiac failure. Premature babies with a VSD can become symptomatic even earlier. Palpitation, dyspnea on exertion and frequent chest infection are the main symptoms in older children. The precordium is hyperkinetic with a systolic thrill at the left sternal border. The heart size is moderately enlarged with a left ventricular type of apex. The first and the second sounds are masked by a pansystolic murmur at the left sternal border. The second sound can, however, be made out at the second left interspace or higher. It is widely split and variable with accentuated P2. A third sound may be audible at the apex. A loud pansystolic murmur is present at the left sternal border. The maximum intensity of the murmur may be in the third, fourth or the fifth left interspace. It is well heard at the second left interspace but not conducted beyond the apex. A delayed diastolic murmur, starting with the third sound is audible at the apex (Fig. 16.16).

The electrocardiogram in VSD is variable. Initially, all patients with VSD have right ventricular hypertrophy. Because of the delay in the fall of pulmonary vascular resistance due to the presence of VSD, the regression of pulmonary arterial hypertension is delayed and right ventricular hypertrophy regresses more slowly. In small- or medium-sized VSD, the electrocardiogram becomes normal. In patients with VSD and a large left-to-right shunt, without pulmonary arterial hypertension, the electrocardiogram shows left ventricular hypertrophy by the time they are 6–12 months old. There are, however, no ST and T changes suggestive of left ventricular strain pattern. Patients of VSD who have either pulmonary

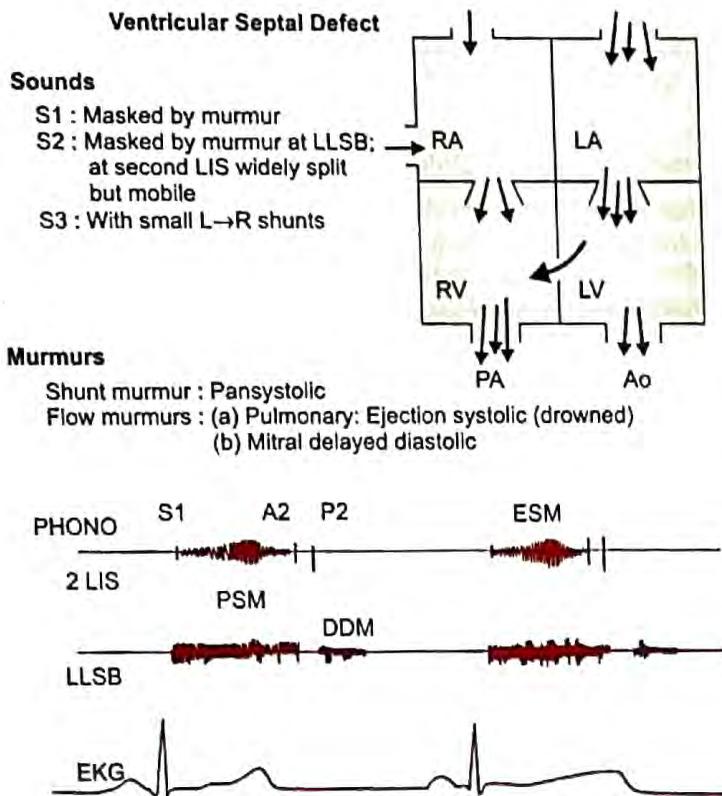


Fig. 16.14: Summary of auscultatory findings in ventricular septal defect. 2 LIS second left interspace; LLSB lower left sternal border; PSM pansystolic murmur; DDM delayed diastolic murmur; ESM ejection systolic murmur.

its volume is decreasing. The left-to-right shunt, therefore, streams to the pulmonary artery more or less directly. This flow of blood across the normal pulmonary valve results in an ejection systolic murmur at the pulmonary valve.

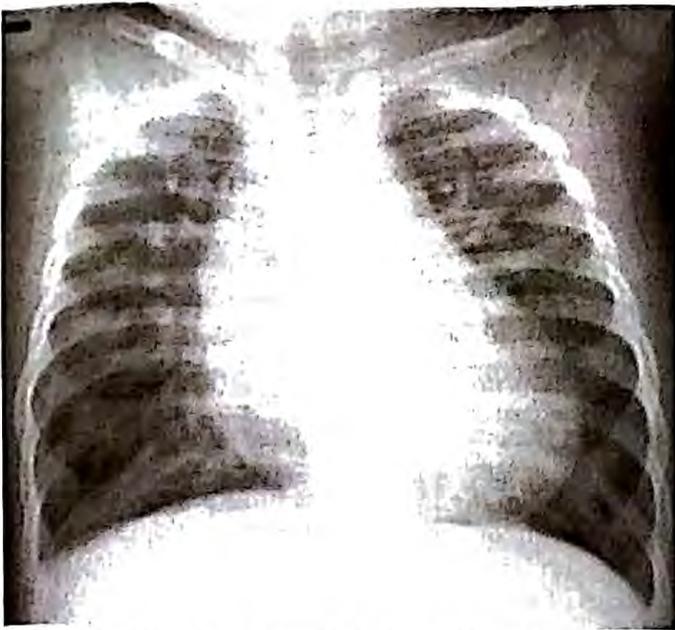


Fig. 16.15: Chest X-ray in ventricular septal defect. Note the cardiac enlargement mainly involving the left ventricle together with increased lung vasculature as suggested by the size and increased number of end-on vessels in the lung fields

stenosis or pulmonary arterial hypertension may show right as well as left ventricular hypertrophy or pure right ventricular hypertrophy. The mean QRS axis in the frontal plane generally lies between $+30^\circ$ and $+90^\circ$.

The cardiac silhouette on chest X-ray is left ventricular type with the heart size determined by the size of the left-to-right shunt (Fig. 16.15). The pulmonary vasculature is increased; aorta appears normal or smaller than normal in size. There may be left atrial enlargement in patients with large left-to-right shunts. Patients of VSD with a small shunt either because the ventricular defect is small or because of the associated pulmonic stenosis or pulmonary arterial hypertension have a normal-sized heart. Echo-

cardiogram shows increased left atrial and ventricular size as well as exaggerated mitral valve motion. 2D echo can identify the number, site and size of defect almost all cases (Fig. 16.16), presence or absence of pulmonic stenosis or pulmonary hypertension and associated defects.

Assessment of Severity

If the VSD is small, the left-to-right shunt murmur continues to be pansystolic but since the shunt is small, the second sound is normally split and the intensity of P2 is normal. There is also absence of the delayed diastolic mitral murmur. If the VSD is very small, it acts as a stenotic area resulting in an ejection systolic murmur. This is a relatively common cause of systolic murmurs in young infants that disappear because of the spontaneous closure. If the VSD is large, it results in transmission of left ventricular systolic pressure to the right ventricle. The right ventricular pressure increases and the difference in the systolic pressure between the two ventricles reduces. The systolic left-to-right shunt murmur becomes shorter and softer, and on the bedside is heard as an ejection systolic murmur.

Patients of VSD may have either hyperkinetic or obstructive pulmonary arterial hypertension. The P2 is accentuated in both. In the former, there is large left-to-right shunt whereas the latter is associated with a small left-to-right shunt. In hyperkinetic pulmonary arterial hypertension, the cardiac impulse is hyperkinetic with a pansystolic murmur and thrill, wide and variably split S2 with accentuated P2 and a mitral delayed diastolic murmur. Obstructive pulmonary arterial hypertension is associated with a forcible parasternal impulse, the thrill is absent or faint, the systolic murmur is ejection type, the S2 is split in inspiration (closely split) with accentuated P2 and there is no mitral murmur. Thus, on the basis of the assessment of physical findings, it is possible to separate very small, small, medium-sized and large VSD.

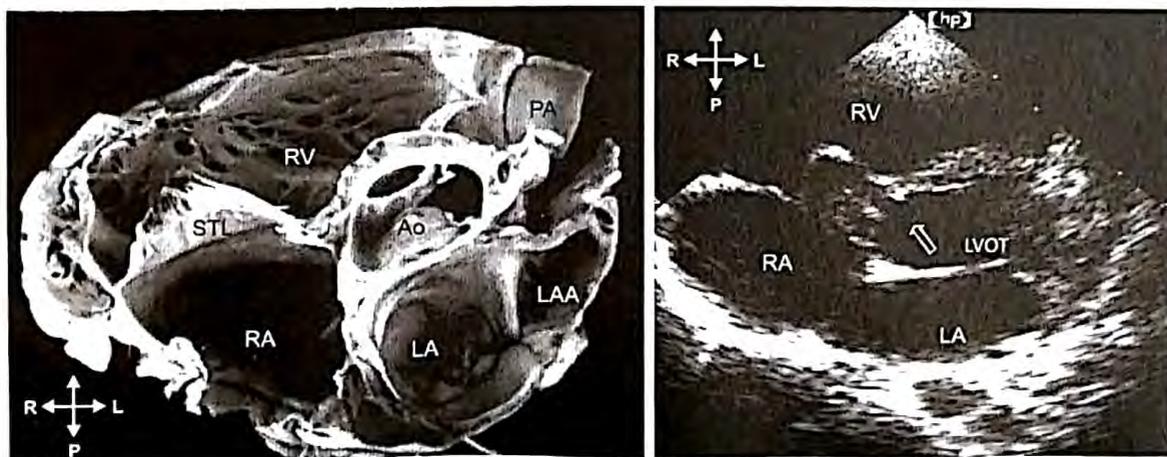


Fig. 16.16: Echocardiogram (right frame) with anatomic correlates (left) in membranous ventricular septal defects. This view is a parasternal short axis view. Arrow points to the VSD that is partly closed by aneurysm of septal leaflet of the tricuspid valve. Ao aortic root; LA left atrium; LVOT left ventricular outflow tract; RA right atrium, RV right ventricle; LAA left atrial appendage; STL septal tricuspid leaflet; PA pulmonary artery

It is also possible to decide whether there is associated pulmonic stenosis or pulmonary arterial hypertension of the hyperkinetic or obstructive variety.

Echocardiography allows further refinement of clinical evaluation. Left atrial and left ventricular enlargement is consistent with a large shunt. The size of the defect can be measured; Doppler echo estimates the gradient between the left and right ventricles, helping in the assessment of right ventricular and pulmonary artery pressure. Flow direction across the defect is indicative of the pulmonary vascular resistance. A predominantly left to right flow is often indicative of operable status.

Course and Complications

Patients with VSD have a very variable course. A patient with a small VSD usually remains asymptomatic throughout life. They may develop congestive cardiac failure in infancy, which is potentially life-threatening. It is estimated that almost 70% of all ventricular defects become smaller in size. A smaller proportion will disappear entirely. In almost 90% of patients who have spontaneous closure of the defect, it occurs by the age of three years, though it may occur as late as 25 years or more. Muscular VSD have the highest likelihood of spontaneous closure. Perimembranous VSD close with the help of the septal leaflet of the tricuspid valve and subpulmonic VSDs often become smaller as the aortic valve prolapses through it. However, this is not a desirable consequence and is often an indication for surgical closure.

Patients with an uncomplicated VSD may: (i) pulmonic stenosis due to hypertrophy of the right ventricular infundibulum, (ii) pulmonary arterial hypertension or rarely, (iii) aortic regurgitation due to prolapse of the right coronary or the non-coronary cusp of the aortic valve. Development of pulmonary arterial hypertension is a dreaded complication in obstructive type of pulmonary arterial hypertension, the patient becomes inoperable.

VSD is the commonest congenital lesion complicated by infective endocarditis. The incidence of infective endocarditis has been estimated as 2/100 patients in a follow-up of 10 years, that is 1/500 patient years. The incidence of infective endocarditis is small enough that it is not an indication for operation in small defects. However, it is important to emphasize good oral-dental hygiene in all patients with VSD.

Treatment

Medical management consists of control of congestive cardiac failure, treatment of chest infections and prevention and treatment of anemia and infective endocarditis. The patients should be followed carefully to assess the development of pulmonic stenosis, pulmonary arterial hypertension or aortic regurgitation.

Surgical treatment is indicated if: (i) congestive cardiac failure occurs in infancy; (ii) the left-to-right shunt is large

(pulmonary flow more than twice the systemic flow); and (iii) if there is associated pulmonic stenosis, pulmonary arterial hypertension or aortic regurgitation. Surgical treatment is not indicated in patients with a small VSD (exception subpulmonic VSD with aortic valve prolapse) and in those who have severe pulmonary arterial hypertension and significant right-to-left shunt.

Operative treatment consists of closure of VSD with the use of a patch. The operation is performed through the right atrium. The operation can be done as early as a few months after birth, if congestive failure cannot be controlled with medical management. With evidence of pulmonary hypertension, the operation should be performed as early as possible. Modern centers prefer to close VSD surgically in young infants. It is unwise to make the sick infants wait for a certain weight threshold because most infants with large VSD do not gain weight satisfactorily. Episodes of respiratory infections require hospitalization and are particularly difficult to manage. For sick infants with pneumonia who require mechanical ventilation, surgery is considered after initial control of the infection. Major complications of surgery, including complete heart block or bifascicular block and residual VSD are rare.

Catheter closure of VSD is best suited for muscular defects in relatively older children (>8–10 kg). Perimembranous defects can also be closed in the catheterization laboratory. However, the risk of complete heart block with the membranous VSD closure is real and can occur late after implantation.

Patent Ductus Arteriosus

Patent ductus arteriosus (PDA) is a communication between the pulmonary artery and the aorta. The aortic attachment of the ductus arteriosus is just distal to the left subclavian artery. The ductus arteriosus closes functionally and anatomically soon after birth; its persistence is called PDA.

Hemodynamics and Clinical Features

PDA results in a left-to-right shunt from the aorta to the pulmonary artery. The flow occurs both during systole and diastole as a pressure gradient is present throughout the cardiac cycle between the two great arteries, if the pulmonary artery pressure is normal. The flow of blood results in a murmur that starts in systole, after the first sound, and reaches a peak at the second sound. The murmur then diminishes in intensity and is audible during only a part of the diastole. Thus, it is a continuous murmur.

PDA results in a systolic as well as diastolic overloading of the pulmonary artery. The increased flow after passing through the lungs reaches the left atrium. To accommodate the flow, the left atrium enlarges in size. The increased volume of blood reaching the left atrium enters the left ventricle in diastole, across a normal mitral valve. The passage of this increased flow across the mitral valve

results in an accentuated first sound as well as a mitral delayed diastolic murmur. The large volume of blood in the left ventricle causes a prolongation of the left ventricular systole and an increase in the size of the left ventricle to accommodate the extra volume. The prolonged left ventricular systole results in delayed closure of the aortic valve and a late A2. With large left-to-right shunts, the S2 may be paradoxically split.

The large left ventricular volume ejected into the aorta results in dilatation of the ascending aorta. A dilated ascending aorta results in an aortic ejection click, and precedes the start of the continuous murmur. The large volume of blood from the left ventricle passing through a normal aortic valve results in an aortic ejection systolic murmur, however, on the bedside it is drowned by the loud continuous murmur and is usually not made out as a separate murmur.

Patients with PDA may become symptomatic in early life and develop congestive cardiac failure around 6–10 weeks of age. Older children give history of effort intolerance, palpitation and frequent chest infections. The flow from the aorta to the pulmonary artery is a leak from the systemic flow. This results in a wide pulse pressure and many of the signs of wide pulse pressure seen in aortic regurgitation are present in patients who have a PDA. On the bedside, presence of prominent carotid pulsations in a patient with features of a left-to-right shunt suggests the presence of PDA. The cardiac impulse is hyperkinetic with a left ventricular type of apex. A systolic or a continuous thrill may be palpable at the second left intercostal space. The first sound is accentuated and the second narrowly or paradoxically split with large left-to-right shunts. With small shunts, the second sound is normally split. The P2 is louder than normal. It is difficult to evaluate the S2 in patients with PDA, since the maximum intensity of the continuous murmur occurs at S2. The continuous murmur indicates presence of both a systolic as well as a diastolic difference in pressure between the aorta and pulmonary artery, thus excluding significant pulmonary arterial hypertension. The murmur starts after the first sound and reaches the peak at the second sound. The murmur then diminishes in intensity and is audible only during a part of the diastole. The peak at the second sound differentiates the PDA murmur from other causes of a continuous murmur. Additionally, the systolic portion of the murmur is very grating and rough. It appears to be broken into multiple systolic sounds—the multiple clicks. The murmur is best heard at the second left interspace and is also well heard below the left clavicle where it maintains its continuous character. There is a third sound at the apex, followed by a delayed diastolic murmur in large shunts (Fig. 16.17).

The electrocardiogram shows normal axis with left ventricular dominance or hypertrophy. Deep Q waves in left chest leads with tall T waves are characteristic of volume overloading of left ventricle. The roentgenogram

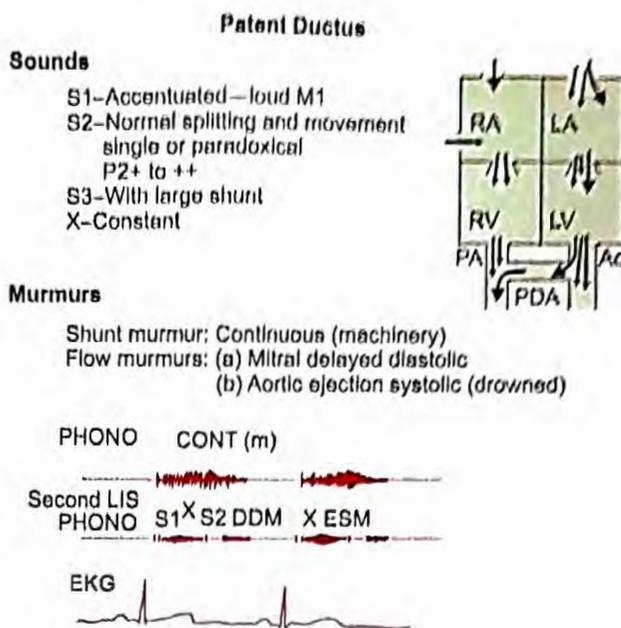


Fig. 16.17: Summary of auscultatory findings in patent ductus arteriosus (PDA) CONT continuous; DDM delayed diastolic murmur; ESM ejection systolic murmur; M1 mitral component of first sound

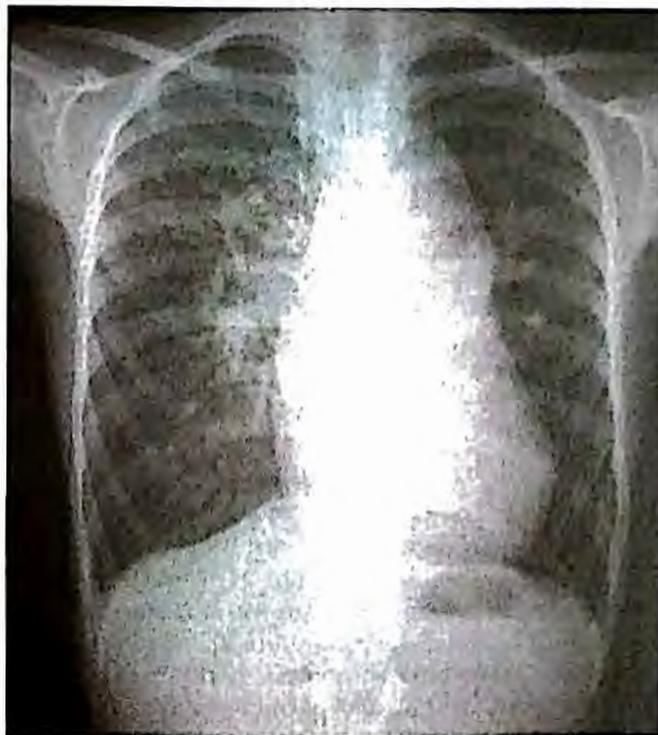


Fig. 16.18: Chest X-ray in an adolescent with a large patent ductus arteriosus. Note the enlargement of the aorta with a prominent aortic knuckle, large main pulmonary artery-left pulmonary artery and increased vascularity. There is no X-ray evidence of cardiac enlargement

(Fig. 16.18) exhibits cardiac enlargement with a left ventricular silhouette; cardiac size depends on the size of the left-to-right shunt. There may be left atrial

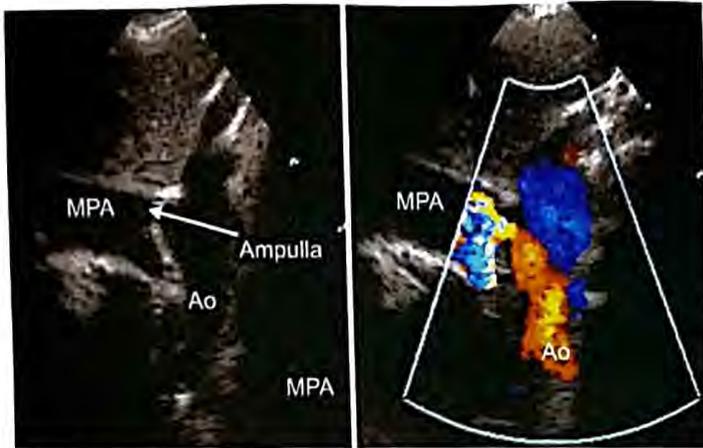


Fig. 16.19: Echocardiography in patent ductus arteriosus (PDA). The frame on the left is a cross-sectional two-dimensional view of the PDA and the frame on the right is a color flow image. The red flow represents flow reversal in the descending thoracic aorta as a result of a left-to-right shunt across the PDA. Ao aorta; MPA main pulmonary artery

enlargement. The ascending aorta and the aortic knuckle are prominent; pulmonary vasculature is plethoric. 2D echocardiogram confirms the diagnosis and measures size of PDA and identifies its hemodynamic consequences. It is possible to obtain a semiquantitative assessment of shunt size and assess pulmonary artery pressure (Fig. 16.19).

Assessment of Severity

The evaluation of the size of the left-to-right shunt depends on a number of features: (i) the larger the heart size the larger the left-to-right shunt; (ii) absence of the third sound and delayed apical diastolic murmur indicates a small left-to-right shunt. Presence of the third sound indicates a moderate left-to-right shunt whereas an audible delayed diastolic murmur suggests a large left-to-right shunt; (iii) the wider the pulse pressure the larger the shunt.

Course and Complications

Neonates and infants have pulmonary hypertension at birth. The regression of pulmonary hypertension occurs slowly in the presence of PDA. The PDA murmur, therefore, is an ejection systolic murmur to start with (like in VSD) and assumes the continuous character only some weeks or months later. Congestive cardiac failure may occur within the first six weeks of life; cardiac failure can be controlled medically in uncomplicated patients. Patients with PDA develop pulmonary arterial hypertension earlier than VSD.

PDA may be associated with hyperkinetic or obstructive pulmonary arterial hypertension, as in VSD. In both situations, the murmur tends to lose the diastolic component and P2 is accentuated. The hyperkinetic pulmonary hypertension is associated with cardiomegaly and mitral delayed diastolic murmur, whereas the

obstructive variety is accompanied with a normal heart size and absence of the diastolic murmur. With severe pulmonary arterial hypertension and a right-to-left shunt through a PDA, the normal splitting of S2 is maintained but the murmur disappears and patients show differential cyanosis.

Differential Diagnosis

The combination of a pansystolic murmur of a VSD with an early diastolic murmur of AR, which are superimposed on each other, may simulate a continuous murmur over the precordium. Differential diagnosis of a continuous murmur includes: (i) coronary arteriovenous fistula; (ii) ruptured sinus of Valsalva fistulae into the right side; (iii) aortopulmonary window; (iv) systemic arteriovenous fistula over the chest; (v) aortopulmonary collateral murmurs; (vi) pulmonary arteriovenous fistula; (vii) peripheral pulmonic stenosis; (viii) venous hum including that associated with total anomalous pulmonary venous connection; and (ix) small ASD associated with mitral stenosis (Lutembacher syndrome).

Treatment

A large PDA is better tolerated by term newborns when compared to premature newborns. Premature newborns with hemodynamically significant PDA that results in heart failure, respiratory distress or necrotizing enterocolitis require prompt management. Indomethacin or ibuprofen is likely to be effective before the age of 2 weeks in preterm newborns and is unlikely to be useful in term babies. The dose of indomethacin is 0.2 mg/kg/dose orally every 12–24 hours for three doses (second and third doses are 0.1 mg/kg/dose for <48-hr-old and 0.25 mg/kg/dose for >7-day-old). Newborns not responding to these agents require surgical ligation. The PDA in term infants may close spontaneously as late as one month after birth and it is worth waiting, if the duct is large unless the heart failure is refractory.

Large PDA may result in congestive cardiac failure in infancy. Echocardiography allows confirmation of the diagnosis and estimation of hemodynamic severity. Catheter-based treatment (occlusive devices or coils) is now realistic in most patients with PDA (Fig. 16.20). They are technically challenging in small infants especially those <5 kg and should be performed in centers with experience. Indications for surgery for PDA include small infants with large ducts, preterm infants, and ducts that are larger than size of available devices.

Patients who have a PDA with pulmonary arterial hypertension are considered inoperable, if a right-to-left shunt has appeared. Since the right-to-left shunt through the PDA flows down the descending aorta, cyanosis is present in toes but not in fingers. This is called differential cyanosis and is characteristic of PDA with pulmonary arterial hypertension and right-to-left shunt.

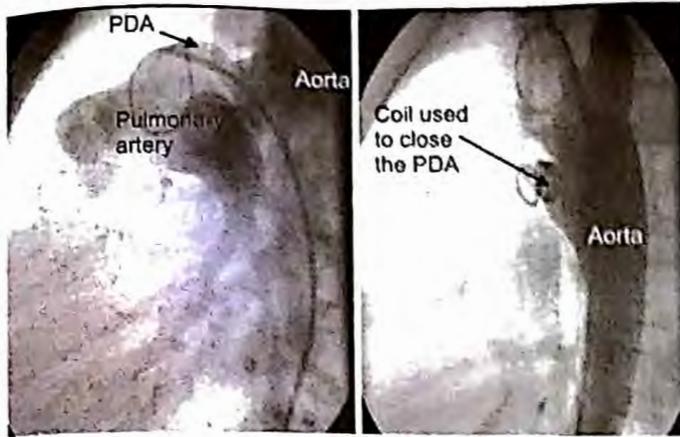


Fig. 16.20: Angiograms (aortogram) obtained before and after coil occlusion of a moderately large patent ductus arteriosus (PDA) showing complete occlusion

CYANOTIC HEART DISEASE

Tetralogy of Fallot

Among cyanotic CHD, tetralogy of Fallot (TOF) has a relatively favorable natural history that allows survival beyond infancy in about 75% of cases. As a result, it is the most common cyanotic CHD encountered beyond the age of 1 year, constituting almost 75% of all patients. The physiology is that of VSD with pulmonic stenosis, as described above. Anatomically, it is characterized by the classic tetrad of severe right ventricle outflow obstruction, large VSD, aorta that overrides the VSD and right ventricular hypertrophy. Multiple anatomical variations exist, which influence treatment (Table 16.15).

Hemodynamics

Physiologically, the pulmonic stenosis causes concentric right ventricular hypertrophy without cardiac enlargement and an increase in right ventricular pressure (Fig. 16.21). When the right ventricular pressure is as high as the left ventricular or the aortic pressure, a right-to-left shunt appears to decompress the right ventricle. Once the right and left ventricular pressures have become identical, increasing severity of pulmonic stenosis reduces the flow of blood into the pulmonary artery and increases the right-to-left shunt. As the systolic pressures between the two ventricles are identical, there is little or no left-to-right shunt and the VSD is silent. The right-to-left shunt is also silent since it occurs at insignificant difference in pressure between the right ventricle and the aorta. The flow from the right ventricle into the pulmonary artery occurs across the pulmonic stenosis producing an ejection systolic murmur. The more severe the pulmonic stenosis, the less the flow into the pulmonary artery and the bigger the right-to-left shunt. Thus, the severity of cyanosis is directly proportional to the severity of pulmonic stenosis, but the intensity of the systolic murmur is inversely related to the severity of pulmonic stenosis.

The VSD of TOF is always large enough to allow free exit to the right-to-left shunt. Since the right ventricle is effectively decompressed by VSD, congestive failure seldom occurs. Exceptions to this rule are (i) anemia; (ii) infective endocarditis; (iii) systemic hypertension; (iv) right ventricular dysfunction from long-standing severe hypoxia, and (v) aortic or tricuspid valve regurgitation.

Table 16.15: Anatomic variations in tetralogy of Fallot

Structure	Common variation	Implications
Right ventricular outflow tract	Degree of stenosis at various levels: infundibulum, valve, pulmonary annulus, main pulmonary artery stenosis	Severe stenosis manifests early; annular narrowing requires correction with transannular patch with significant late sequelae; predominant valvar stenosis may allow palliation with balloon valvotomy in selected cases
Branch pulmonary arteries (PA)	Stenosis of left pulmonary artery (LPA), absence of either branch PA, hypoplastic	Small branch PA may not allow surgical correction at early age; absent branch PA require placement of PA conduit
Pulmonary valve	Absent pulmonary valve with aneurysmal branch PA	Severe airway compression; manifestations chiefly respiratory
Ventricular septal defect (VSD)	VSD extended to inlet or outlet septum; restrictive VSD with severe right ventricular hypertrophy; additional muscular VSD	Surgical approach needs to be tailored
Coronary arteries	Origin of left anterior descending artery from right coronary artery	Abnormal vessel comes in way of corrective surgery
Atrial communication	Atrial septal defects, patent foramen ovale	Patent foramen ovale often helpful in early post-operative period; enables recovery
Aortopulmonary collaterals	Large major aortopulmonary collaterals	Collaterals need to be defined and closed, if their supply overlaps with the native pulmonary artery supply

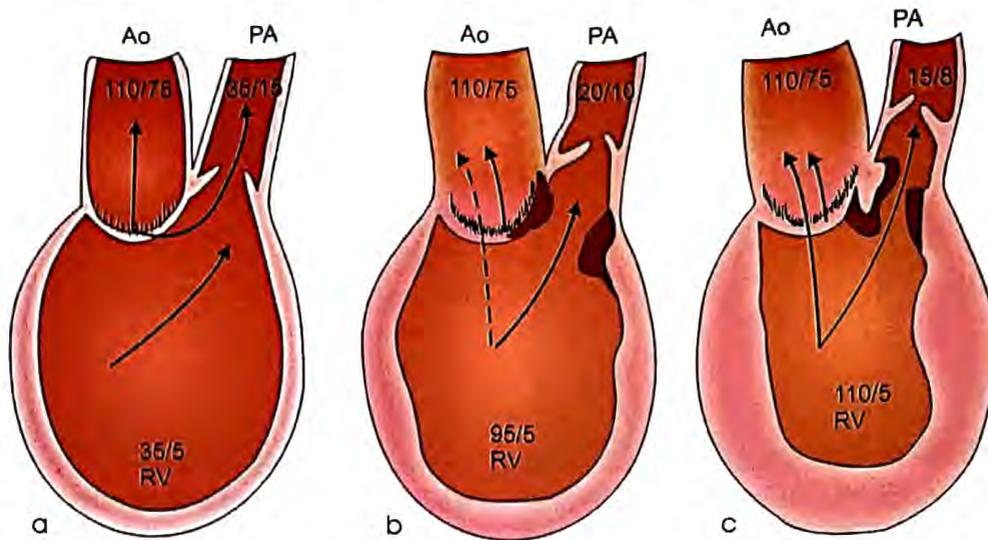


Fig. 16.21: Diagrammatic portrayal: (a) Ventricular septal defect, (b) ventricular septal defect with moderate pulmonic stenosis, and (c) Fallot's tetralogy. (a) In the absence of pulmonic stenosis, the right ventricular (RV) and the pulmonary artery (PA) pressures are normal or slightly elevated. Since the left ventricular (LV) pressure is higher, there is a systolic flow of blood from the LV into the PA through the RV. (b) If a VSD is associated with moderate pulmonic stenosis, the RV systolic pressure increases and there is RV hypertrophy. The left-to-right shunt decreases and the VSD murmur becomes softer. The pulmonic stenosis murmur, however, is loud. (c). In Fallot's tetralogy, the RV and LV pressures are identical. There is no left-to-right shunt and as such the VSD is silent. The flow from RV to PA decreases, decreasing the intensity of pulmonic stenosis murmur. A right-to-left shunt occurs from RV to aorta (Ao) at identical pressures. As such the right-to-left shunt is silent.

The right ventricular outflow obstruction results in a delay in the P2. Since the pulmonary artery pressure is reduced, the P2 is also reduced in intensity. The late and soft P2 is generally inaudible in TOF. The S2 is, therefore, single and the audible sound is A2. Since the aorta is somewhat anteriorly displaced, the audible single A2 is quite loud. The ascending aorta in TOF is large and may result in an aortic ejection click. On auscultation, the diastolic interval is completely clear in TOF as there is no third or fourth sound or a diastolic murmur. Concentric right ventricular hypertrophy reduces distensibility of the right ventricle during diastole. The right atrial contraction at the end of diastole causes relatively large 'a' waves. However, these waves not too tall unless right ventricular dysfunction is present.

Clinical Features

Patients with TOF may become symptomatic at any time after birth. Neonates as well as infants may develop anoxic spells (paroxysmal attacks of dyspnea). Cyanosis may be present from birth or make its appearance some years after birth. The commonest symptoms are dyspnea on exertion and exercise intolerance. The patients assume a sitting posture (squatting) as soon as they get dyspneic. Although squatting is not specific for TOF, it is the commonest congenital lesion in which squatting is noted. Anoxic spells occur predominantly after waking up or following exertion. The child starts crying, becomes dyspneic, bluer than before and may lose consciousness. Convulsions may occur. The frequency varies from once in a few days to numerous attacks every day.

Physical examination discloses cyanosis, clubbing, slightly prominent 'a' waves in the jugular venous pulse, normal-sized heart with a mild parasternal impulse, normal first sound, single second sound and an ejection systolic murmur which ends before the audible single second sound (Fig. 16.22). The electrocardiogram in TOF shows right axis deviation with right ventricular hypertrophy. T waves are usually inverted in right precordial leads; *P pulmonale* may be present, but is uncommon. V1 may show pure R waves but transition to R/S complex occurs at V2. Chest X-ray shows a normal-sized heart with upturned apex suggestive of right ventricular hypertrophy. The absence of main pulmonary artery segment gives it the shape described as

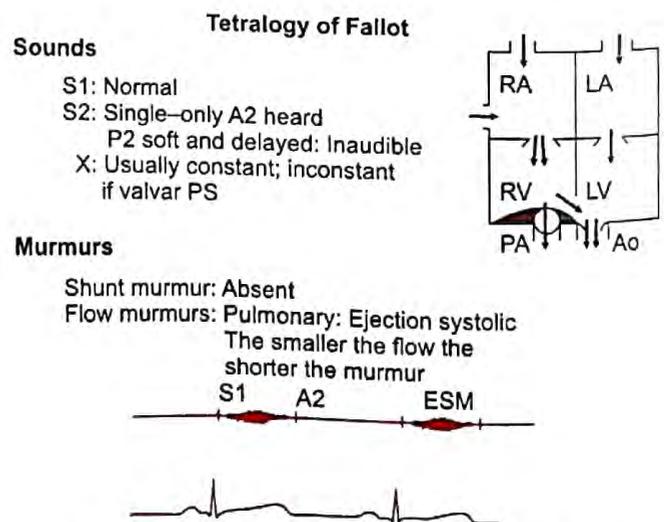


Fig. 16.22: Summary of auscultatory findings in tetralogy of Fallot. X systolic click. PS pulmonic stenosis

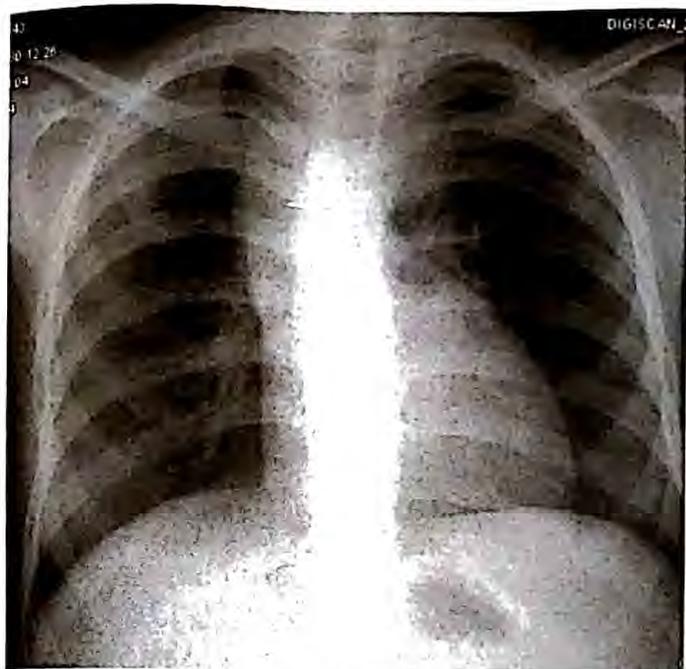


Fig. 16.23: Chest X-ray in tetralogy of Fallot with right aortic arch. The key findings are reduced lung vasculature as suggested by the dark lung fields, normal heart size, concavity in the region of the main pulmonary artery (pulmonary bay). This X-ray also shows a right aortic arch. The arrow indicates the indentation of the right arch on the right side of the trachea.

Coeur en Sabot. The aorta is enlarged and right aortic arch is present in 30% cases. The right aortic arch in a postero-anterior roentgenogram is recognized by its concave impression on the right side of trachea. The pulmonary fields are oligemic (Fig. 16.23).

The murmur shortens and the cyanosis increases with increasing severity of the right ventricular outflow tract obstruction. Paroxysmal attacks of dyspnea can be present with mild as well as severe TOF. However, effort intolerance is directly related to the severity.

Diagnosis

The diagnosis of TOF is confirmed by echocardiography; cardiac catheterization is seldom necessary. Additional specific information required for surgical decision is also obtained through echocardiography. Cardiac catheterization or CT/MRI may be required in older children with limited echo windows and in selected specific circumstances (associated aortopulmonary collaterals, uncertainties in coronary artery anatomy).

Course and Complications

The pulmonic stenosis becomes progressively severe with age, and dyspnea and increasing exercise intolerance limit patient activities. Each attack of anoxic spell is potentially fatal. Anemia, by decreasing the oxygen-carrying capacity of blood, reduces the exercise tolerance still further. It can result in cardiac enlargement and congestive cardiac failure. Patients are prone to infective endocarditis.

Neurological complications occur frequently. Anoxic infarction in the central nervous system may occur during an anoxic spell and result in hemiplegia. Anemia increases the propensity towards strokes by reducing red blood cell deformability. Paradoxical embolism to central nervous system and venous thrombosis due to sluggish circulation from polycythemia can also result in hemiplegia. Brain abscess is not an infrequent complication, and should be suspected, if patients show irritability, headache, convulsions, vomiting with or without fever and neurological deficit. The fundus needs expert evaluation since polycythemia results in congested retina and recognition of papilledema is difficult.

Treatment

The medical management of TOF is limited to prevention and management of complications and correction of anemia. Oral beta-blockers help prevent cyanotic spells. Maximally tolerated doses of propranolol ranging from 0.5–1.5 mg/kg/dose should be administered. Iron supplementation is recommended for all infants and young children with TOF. The management of anoxic spells is indicated in Table 16.13.

Definitive surgery for TOF involves closure of VSD and relief of the right ventricular outflow tract obstruction. The relief of the obstruction might involve placement of a transannular patch across the pulmonary valve resulting in severe pulmonary regurgitation. There is growing emphasis on retaining the pulmonary valve during initial repair to prevent pulmonary regurgitation and its major late consequences (RV dilation, arrhythmia, heart failure and sudden death). However, this is not possible, if the pulmonary annulus is small.

Although definitive operation is feasible in young infants, some centers opt for palliative options initially. This is typically done through the Blalock-Taussig shunt, which consists of subclavian artery-pulmonary artery anastomosis using a Goretex graft. Alternatives include balloon dilation of the pulmonary valve or stenting of the patent arterial duct (if present). A number of long-term concerns have emerged in survivors of TOF repair 2–3 decades after the operation. These include heart failure and risk of ventricular tachyarrhythmias as a result of right ventricular dilation that results from chronic pulmonary regurgitation, as well as the scar on the right ventricle, if ventriculotomy has been done during operation.

Tricuspid Atresia

Congenital absence of the tricuspid valve is called tricuspid atresia (Fig. 16.24). The right ventricle is hypoplastic. The inflow portion is absent. The hemodynamics is described above; see single ventricle physiology.

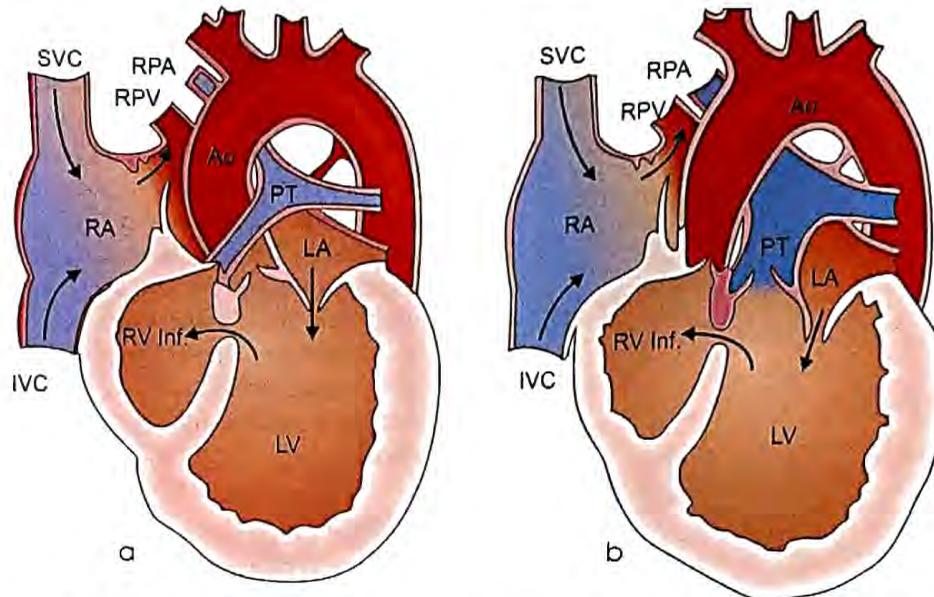


Fig. 16.24: Tricuspid atresia: (a) Normally related great arteries. Systemic venous blood reaching the RA through the superior (SVC) and inferior vena cava (IVC) reaches the LA through an atrial defect (or patent foramen ovale). There is complete mixing of the systemic and pulmonary venous blood in the LA. The LV is large. Aorta (Ao) arises from the LV. A muscular ventricular septal defect is the only route through which blood can reach the hypoplastic right ventricle (RV Inf.). The pulmonary trunk (PT) arises from the right ventricle. (b) Transposed great arteries with tricuspid atresia. The PT is arising from the LV whereas the Ao is arising from RV. LA left atrium; RA right atrium; RPA and LPA right and left pulmonary artery; RV Inf. right ventricular infundibulum; RV and LV right and left ventricle; SVC and IVC superior and inferior vena cava; RPV and LPV right and left pulmonary veins

Clinical Features

Clinical presentation depends on the state of pulmonary flow that may be diminished or increased. Patients who have diminished pulmonary blood flow constitute 90% and symptoms and physical signs are more or less identical to TOF. Features suggesting tricuspid atresia are (i) left ventricular type of apical impulse; (ii) large a waves in jugular venous pulse; (iii) enlarged liver with presystolic pulsations (a waves); and (iv) electrocardiogram characterized by left axis deviation and left ventricular hypertrophy. The mean QRS axis is around -45° . Patients with tricuspid atresia and increased pulmonary blood flow cannot be diagnosed accurately clinically.

Course

Patients with tricuspid atresia follow a course similar to TOF. They are cyanosed at birth. Anoxic spells and squatting may be present; patients are relatively sicker than TOF.

Treatment

Tricuspid atresia is categorized as single ventricle physiology and management is on similar lines.

downwards to a variable extent. The result is an attachment to the posterior wall of the right ventricle. In addition, the leaflets are malformed and fused resulting in obstruction to flow of blood into the right ventricle. The portion of the right ventricle above the leaflet attachment thins out and is called atrialized right ventricle. The right ventricular contraction is also abnormal.

Hemodynamics

The tricuspid valve anomaly results in obstruction to forward flow of blood as well as regurgitation of blood from the right ventricle into the right atrium. In addition, there is a large part of the right ventricle that is atrialized as a result of downward displacement of the tricuspid valve attachment. This atrialized right ventricle contracts with the rest of the ventricle and does not allow effective forward flow into the pulmonary circulation. The right atrium progressively dilates, to accommodate the extra volume. The foramen ovale may be patent or there is an ASD allowing a right-to-left shunt to occur, resulting in cyanosis. The greater the tricuspid valve displacement, the more the cyanosis.

Clinical Features and Diagnosis

Patients present with history of cyanosis, effort intolerance and fatigue. They may also give history suggestive of paroxysmal attacks of tachycardia. Cyanosis varies from slight to severe; clubbing is often present. The jugular venous pulse may show a dominant V wave but there is usually no venous engorgement because of a capacious

Ebstein Anomaly

An unusual and rare cyanotic congenital heart disease with diminished pulmonary blood flow results from an abnormality of the tricuspid valve. The posterior as well as the septal leaflet of the tricuspid valve is displaced

right atrium. The precordium is quiet with a left ventricular apical impulse. A systolic thrill may be palpable at the left sternal border. The first sound is split, however, the tricuspid component often cannot be made out, resulting in a single, normally audible first sound. The abnormal tricuspid valve may produce a mid-systolic click. The second sound is widely split, but variable with a soft pulmonic component. A right ventricular third sound and/or a right atrial fourth sound may be audible. Thus, triple or quadruple sounds are usually heard. The systolic murmur may be a mid-systolic ejection murmur or a loud pansystolic murmur. There is also a short tricuspid delayed diastolic murmur. The combination of sounds clicks and murmurs result in a characteristic auscultatory cadence.

The electrocardiogram shows prominent P waves and right bundle branch block. The R wave in V1 does not exceed 7 mm; lead V6 shows relatively tall R and broad S wave. Wolff-Parkinson-White type of conduction abnormality may be seen (Fig. 16.25). X-ray shows cardiac enlargement due to right atrial and right ventricular enlargement; main pulmonary artery segment is prominent and the aortic knuckle is small (Fig. 16.26); pulmonary vasculature is diminished. 2-D echo is diagnostic as it outlines the displaced tricuspid valve (Fig. 16.27).

Treatment

Surgical treatment consists in obliterating the atrialized portion of the right ventricle and repairing the tricuspid valve. The 'cone repair of tricuspid' valve, which involves mobilization of the displaced tricuspid annulus and repositioning the valve at the level of the normal annulus, is increasingly used.

Transposition of Great Vessels

Transposition of great vessels (TGA) is defined as aorta arising from the right ventricle and pulmonary artery from the left ventricle. In TGA, the aorta generally lies anterior and to the right of the pulmonary artery. For this reason,

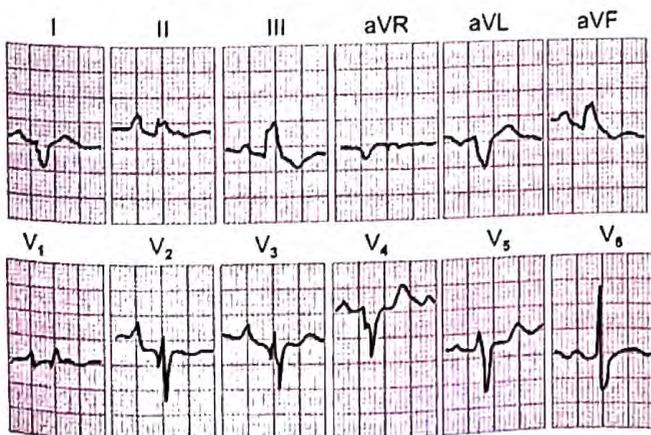


Fig. 16.25: Electrocardiogram typical of Ebstein anomaly. Right bundle branch block with 'R' of less than 7 mm is present

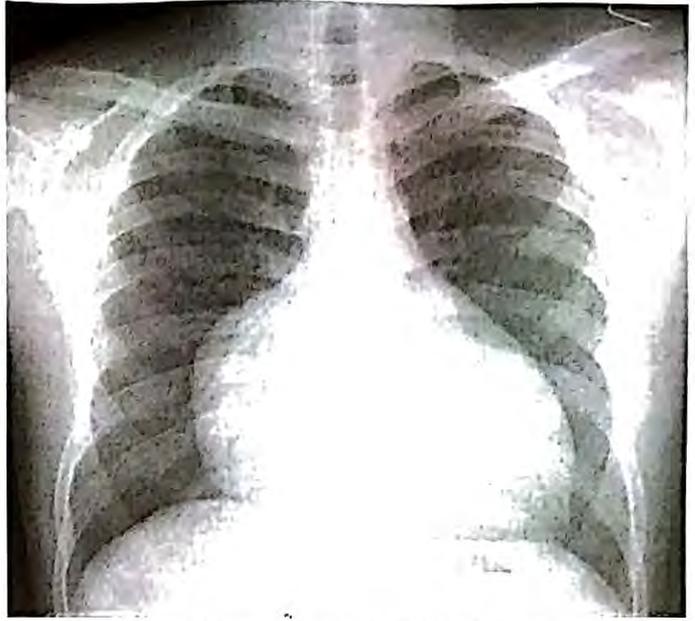


Fig. 16.26: Chest X-ray in Ebstein anomaly. There is considerable enlargement of the right atrium. The lung vascularity is reduced

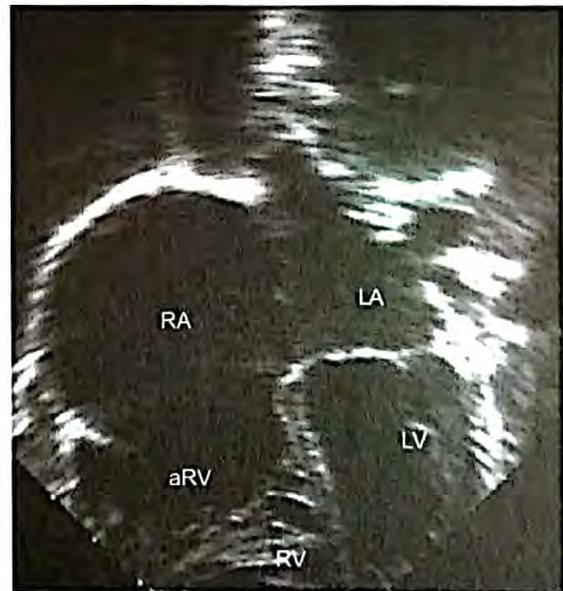


Fig. 16.27: Apical four-chamber view from a patient with Ebstein anomaly. Note the downward displacement of the septal leaflet of the tricuspid valve. aRV atrialized right ventricle; LA left atrium; LV left ventricle; RA right atrium; RV right ventricle

this is also referred to as D-TGA. Since the systemic and pulmonary circulations are separate, survival depends on the presence of atrial, ventricular or aortopulmonary communications. TGA is classified into (i) with intact ventricular septum, and (ii) with VSD. The latter group is further subdivided into cases with and without pulmonic stenosis. Patients with complete TGA, VSD and pulmonic stenosis are included in tetralogy physiology.

In patients with TGA, the oxygenated pulmonary venous blood recirculates in the lungs whereas the systemic venous blood recirculates in the systemic

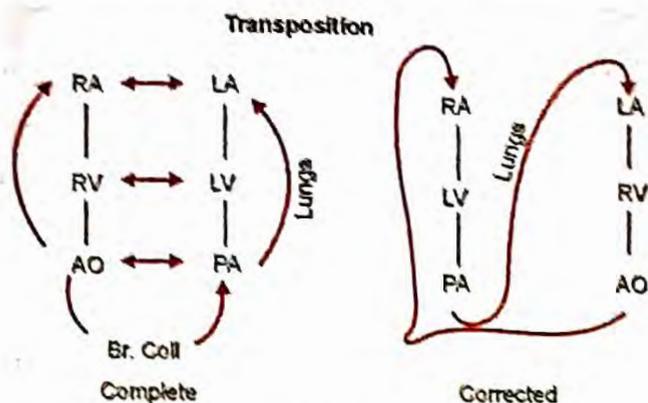


Fig. 16.28: The route of blood flow in complete TGA results in two separate circulations and survival depends on mixing. The mixing can occur at the atrial, ventricular or great vessel level. Bronchial collaterals (Br. Coll.) also increase pulmonary blood flow. In corrected TGA, the route of blood flow is normal. Hemodynamics depend on associated anomalies

circulation. The pulmonary artery saturation is thus always higher than the aortic saturation. Survival depends on the mixing between the two circulations. In patients with intact ventricular septum, the best mixing site is the atrial communication, generally through the patent foramen ovale (Fig. 16.28). Neonates become symptomatic due to severe hypoxemia and systemic acidosis soon after birth.

The presence of a VSD of adequate size results in good mixing. As the fetal pulmonary vasculature regresses, the pulmonary blood flow increases and results in congestive failure around 4–10 weeks of age. The failing left ventricle and the large pulmonary blood flow increase the left atrial pressure leading to pulmonary venous hypertension. The mixing with a large VSD can be so good that at times cyanosis can be missed. The presence of a large VSD equalizes pressures in the two ventricles as well as the great arteries. The pulmonary artery also carries a large flow. Patients with TGA and a large VSD develop pulmonary vascular obstructive disease (Eisenmenger physiology) early in life.

Clinical Features

Patients of complete TGA with intact ventricular septum are cyanosed at birth. Since the interatrial communication results in poor mixing, the neonates present with rapid breathing and congestive failure within the first week of life. Examination shows severe cyanosis, congestive failure, normal first sound, single second sound and an insignificant grade I–II ejection systolic murmur. The electrocardiogram shows right axis deviation and right ventricular hypertrophy. Thoracic roentgenogram shows cardiomegaly with a narrow base and plethoric lung fields. The cardiac silhouette can have an 'egg on side' appearance and the right upper lung fields appear more plethoric than other areas. The thymic shadow is often absent (Fig. 16.29).

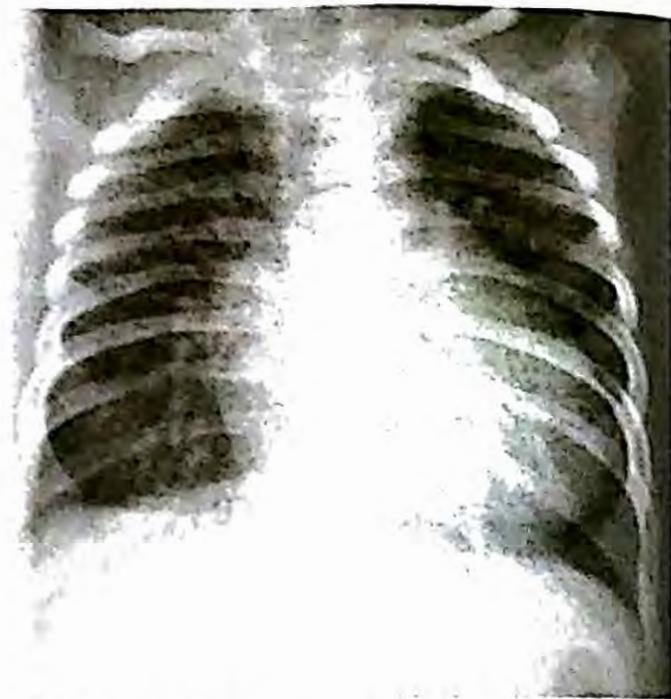


Fig. 16.29: Egg on side appearance in transposition. This characteristic appearance is seen only in about one-third cases and results from a narrow pedicle of the heart because of malposition of great vessels

Patients of TGA with VSD have increased pulmonary blood flow; mixing at the ventricular level determines the severity of cyanosis. They develop congestive failure around 4–10 weeks of age. Physical findings consist of cyanosis, cardiomegaly, congestive failure, normal first sound, single or normally split second sound and grade II–IV ejection systolic murmur. Apical third sound gallop or a mid-diastolic rumble may be present. Electrocardiogram shows right axis deviation with biventricular, right ventricular or left ventricular hypertrophy. Chest X-ray shows cardiomegaly, plethoric lung fields and features of pulmonary venous hypertension.

Treatment

Prostaglandin E1 can help reduce cyanosis by keeping the PDA open. Interim palliation is accomplished through balloon atrial septostomy (Fig. 16.30). This procedure can be done in a catheterization laboratory or in the ICU under echocardiographic guidance. Septostomy is successful only up to the age of 6–12 weeks and gives temporary relief by providing better mixing and reducing left atrial pressure.

The arterial switch operation is the treatment of choice for TGA. In this operation, the pulmonary artery and aorta are transected. The distal aorta is anastomosed to the proximal pulmonary stump (neo-aortic root) and the pulmonary artery to the proximal aortic stump (neo-pulmonary artery). The coronary arteries are moved along to the neo-aortic root along with a cuff of aortic tissue to allow suturing without compromise of coronary blood

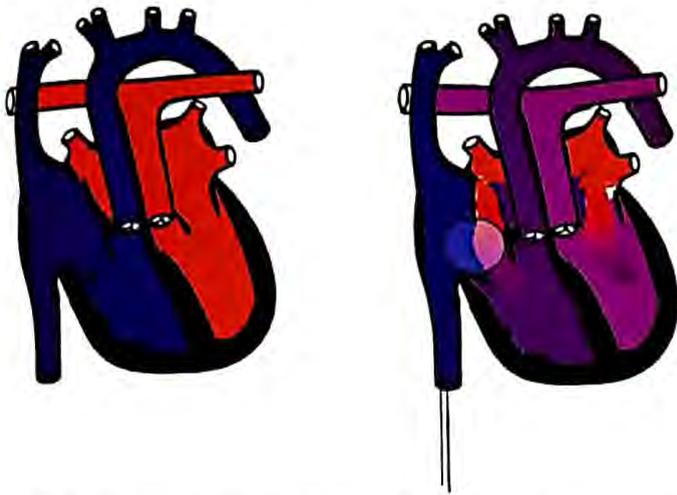


Fig. 16.30: Balloon atrial septostomy; this cartoon shows how a balloon atrial septostomy works. The figure on the left shows the physiology of transposition. The parallel circulation with poor intercirculatory mixing results in very low saturation in the aorta. Balloon atrial septostomy (right) creates an opening in the atrial septum and allows better intercirculatory mixing with improved saturation that is often life saving

flow. Infants with TGA and intact septum should ideally undergo this procedure within the first 2–4 weeks of life. As pulmonary vascular resistance falls after birth, the left ventricle regresses rapidly. In 1–2 months, the left ventricle has the ability to adjust to the elevated systemic vascular resistance after the arterial switch through hyperplasia of the available muscle. After this, it is difficult for the left ventricle to adapt to an arterial switch. Later in infancy, the atrial switch operation (Senning operation) is the only option for TGA with intact ventricular septum. This is not an ideal long-term option because the right ventricle remains as the systemic ventricle for life. Over time, right ventricle dysfunction, severe tricuspid regurgitation and atrial rhythm disturbances may occur.

In presence of a sizable PDA or VSD, there is no fear of early regression of left ventricle because the pulmonary artery pressures are high. Nevertheless, the window of time for operation of TGA-VSD and TGA-PDA is also limited. This is because there is accelerated development of pulmonary vascular obstructive disease in these patients. Surgical correction involves the arterial switch operation with closure of VSD or PDA within 3 months of age. Beyond this age, there is increasing risk of irreversible changes in the pulmonary vasculature. Many centers are able to perform arterial switch operations with operative mortality of <5%. Twenty-year survival is >90%. Concerns after surgery include aortic root dilation and aortic regurgitation, right ventricular outflow tract obstruction and coronary artery occlusion.

Corrected TGA

In corrected TGA, the right atrium is connected to the left ventricle and vice-versa. The left ventricle gives rise to

the pulmonary artery and right ventricle to the aorta. The aorta lies anterior and to the left of the pulmonary artery (hence the term L-TGA). The ascending aorta forms the left upper border of the cardiac silhouette. Since the route of blood flow is normal, it is the associated anomalies (present in more than 98% cases) that determine the clinical features. Common anomalies include (i) VSD with or without pulmonic stenosis; (ii) left-sided Ebstein anomaly of the tricuspid valve (simulates mitral regurgitation); and (iii) atrioventricular conduction abnormalities, including atrioventricular block, each in approximately 65%. The most useful clue for the diagnosis of corrected TGA is related to inversion of the ventricles. The precordial leads V4R, V1, and V2 show a Q wave that is absent in the left precordial leads. Chest X-ray shows a smooth left upper border corresponding to the ascending aorta. The diagnosis depends on echocardiographic identification of ventricular inversion as well as the additional anomalies. Management depends on the type of associated anomalies.

Total Anomalous Pulmonary Venous Connection (TAPVC)

Here, all the pulmonary veins instead of joining the left atrium are connected anomalously to result in the total pulmonary venous blood reaching the right atrium. The anatomical classification of TAPVC is into supracardiac, cardiac, infracardiac and mixed varieties. In supracardiac TAPVC, the pulmonary veins join together to form a common pulmonary vein that may drain into the left innominate vein or the right superior vena cava. In the cardiac TAPVC, the veins join the coronary sinus or enter the right atrium directly. In the infracardiac variety, the common pulmonary vein drains into the portal vein.

Hemodynamics

TAPVC results in the pulmonary venous blood reaching the right atrium, which also receives the systemic venous blood. This results in almost complete mixing of the two venous returns. The blood flow to the left atrium is the right-to-left shunt through a patent foramen ovale or atrial septal defect. The oxygen saturation of the blood in the pulmonary artery is often identical to that in the aorta because of mixing of the blood in the right atrium. Physiologically, TAPVC can be divided into (i) patients with pulmonary venous obstruction, and (ii) patients without pulmonary venous obstruction. Pulmonary venous obstruction results in pulmonary arterial hypertension as well as restriction to pulmonary blood flow. In the absence of pulmonary venous obstruction, pulmonary blood flow is large and results in early onset cardiac failure. TAPVC of the infracardiac type is always obstructive whereas cardiac and supracardiac types may or may not have pulmonary venous obstruction.

Clinical Features and Diagnosis

Non-obstructive TAPVC is commoner than the obstructive type. Patients present with cyanosis and congestive failure

as the fetal pulmonary vasculature regresses. The onset of congestive failure is around 4–10 weeks of age. Occasionally, with large pulmonary blood flow, the cyanosis is minimal or clinically not recognizable. The patients are irritable and have failure, to thrive. Besides features of congestive failure the patients have cardiomegaly, hyperkinetic precordium, normal or accentuated first sound, widely split and fixed second sound with accentuated pulmonic component, a grade two to four pulmonary ejection systolic murmur and a tricuspid flow murmur. The physical findings are identical to ASD. A continuous venous hum may be audible at the upper left or right sternal border or in the suprasternal notch.

Patients with obstructive type of TAPVC present with marked cyanosis and congestive failure typically within the first 1–2 weeks of life. Physical findings consist of a normal-sized heart with parasternal heave, normal first sound, accentuated pulmonic component of S2 and insignificant murmurs. Tricuspid regurgitation can occur and results in cardiomegaly. These infants are severely compromised and need admission in an intensive care unit and emergency corrective surgery.

The electrocardiogram in TAPVC with or without pulmonary venous obstruction shows right axis deviation and right ventricular hypertrophy. Chest roentgenogram shows cardiomegaly with plethoric lung fields in non-obstructive TAPVC. The characteristic pattern of the "snowman" or figure of '8' configuration in the supracardiac TAPVC draining to left innominate vein is seen only after the age of 2 years (Fig. 16.31). The characteristic X-ray of the obstructive TAPVC consists of a normal-sized heart with severe pulmonary venous

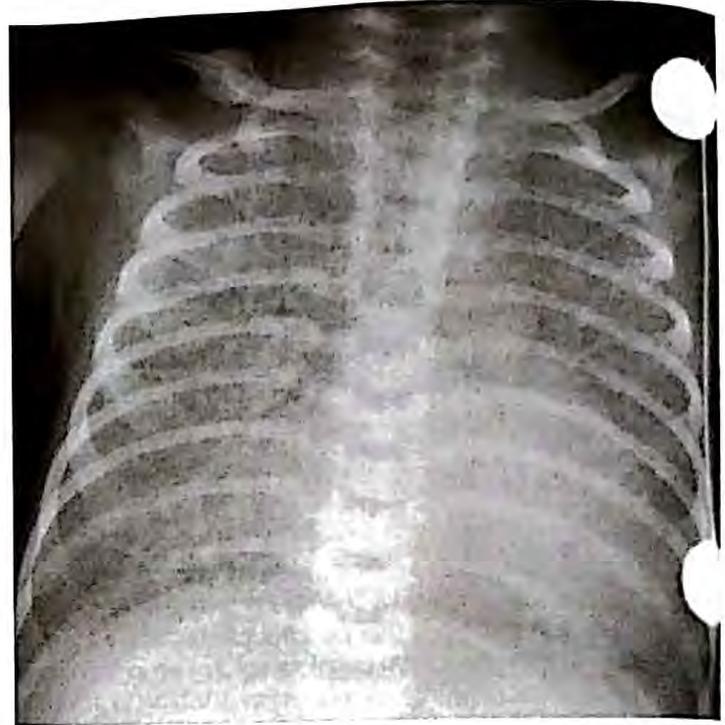


Fig. 16.32: Chest X-ray from a newborn with obstructed infracardiac total anomalous pulmonary venous connection. Note the characteristic ground glass appearance

hypertension resulting in "ground glass" appearance of the lungs very much like that of hyaline membrane disease (Fig. 16.32). Echocardiogram allows confirmation of the diagnosis, definition of the individual pulmonary veins and assessment of the site of obstruction. In addition, the pulmonary artery pressure can be quantified. In most situations, echo alone is adequate for surgical planning.

The diagnosis of the obstructive TAPVC is made in a neonate with cyanosis and normal-sized heart with ground glass lung fields. The diagnosis of non-obstructive TAPVC is suspected, if the auscultatory features of ASD are associated with either cyanosis or congestive failure in the first 2–3 months of life.

Management

Surgery is indicated as early as possible since 80% of infants die within the first 3 months of life, if not operated. Obstructed TAPVC needs surgery at short notice. The results of surgery for TAPVC are good in most centers but newborns and infants with obstructed TAPVC sometimes need a long time to recover after surgery. These patients may develop pulmonary hypertensive crisis in the postoperative period.

Additional Conditions with Cyanosis and High Pulmonary Flow

Apart from transposition of great vessels and total anomalous pulmonary venous connection, single ventricle without obstruction to pulmonary blood flow, persistent truncus arteriosus, tricuspid atresia with absence of obstruction to pulmonary blood flow and double outlet



Fig. 16.31: Chest X-ray in unobstructed supracardiac total anomalous pulmonary venous connection to the innominate vein via the left vertical vein in an 8-year-old child. This is the characteristic figure of '8' sign or the snowman's sign

right ventricle without pulmonic stenosis present with cyanosis and increased pulmonary blood flow. Patients present with congestive failure in the neonatal period and are characterized by cyanosis, cardiomegaly and failure to thrive. Almost 80% die within 3 months of life due to congestive cardiac failure or pulmonary infection. Those who survive develop pulmonary arterial hypertension. Echocardiography is necessary to arrive at the specific diagnosis. Since the mortality of unoperated patients is high and patients develop Eisenmenger syndrome early in life, it is necessary that patients presenting with cyanosis and increased pulmonary blood flow be referred to specialized centers as early as possible.

Cyanotic Heart Disease with Pulmonary Arterial Hypertension

Patients with Eisenmenger syndrome have severe pulmonary arterial hypertension resulting in right-to-left shunt at the atrial, ventricular or pulmonary arterial level. Eisenmenger complex consists of pulmonary arterial hypertension with a VSD providing the right-to-left shunt.

Hemodynamics

The pulmonary arterial hypertension is due to pulmonary vascular obstructive disease. If a communication is present at the pulmonary arterial level or the ventricular level, the right ventricular pressure cannot go beyond the systemic pressure. The right-to-left shunt decompresses the right ventricle. The right ventricle has only concentric hypertrophy without significant increase in the size. In patients who have a PDA or VSD, there is only a mild parasternal impulse without significant heave. In patients who do not have a VSD or PDA, the right ventricle besides hypertrophy also dilates. The right-to-left shunt at the atrial level is an indication of right ventricular failure to accommodate this volume and push into the pulmonary artery. Patients of Eisenmenger syndrome with communication at the atrial level only exhibit a parasternal heave and cardiac enlargement.

A right-to-left shunt at the atrial level or the ventricular level reaches the ascending aorta and is thus distributed to the whole systemic circulation. This results in equal cyanosis of fingers and toes. A right-to-left shunt through a PDA is directed downwards into the descending aorta, which results in differential cyanosis affecting lower limbs, with pink upper limbs.

Clinical Features

Patients present with history of cyanosis, fatigue, effort intolerance and dyspnea. There may also be history of repeated chest infections in childhood. On physical examination, they have cyanosis and clubbing. Differential cyanosis separates patients who have a PDA from those who have a VSD or atrial septal defect. The features indicative of pulmonary arterial hypertension consist of parasternal impulse and palpable second sound. The

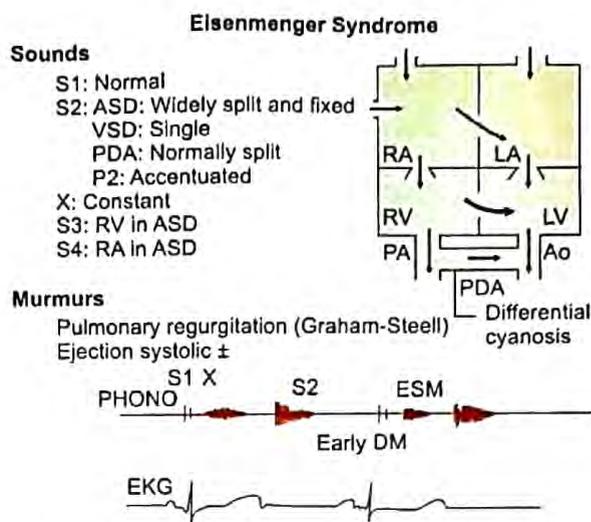


Fig. 16.33: Summary of auscultatory findings in Eisenmenger syndrome

pulmonary component of the second sound is accentuated and louder than the aortic component. The splitting of the second sound remains wide and fixed in atrial septal defect. Due to superimposition of A2 and P2, the second sound is single in patients who have a VSD. Patients who have a PDA continue to have a normally split second sound. A constant pulmonary ejection click, unlike in patients of valvar pulmonic stenosis, is well heard both during inspiration and expiration at the second left interspace. A functional pulmonary regurgitation murmur can be present along the left sternal border. Patients with atrial septal defect, in whom Eisenmenger physiology is uncommon, can develop tricuspid regurgitation (Fig. 16.33).

Electrocardiogram reveals right axis deviation and right ventricular hypertrophy, P pulmonale may be present. The chest radiograph is characteristic, showing prominent pulmonary artery segment, large right and left main pulmonary arteries and their branches, and oligemic peripheral lung fields (Fig. 16.34).

Treatment

Ideally, pulmonary vascular obstructive disease should be prevented. This means early diagnosis and correction of all CHD associated with increased pulmonary blood flow. Patients with cyanosis and increased pulmonary blood flow develop Eisenmenger physiology very early and need to be operated by 2–3 months of age. Medications are available for the management of pulmonary hypertension.

OBSTRUCTIVE LESIONS

Aortic Stenosis

Pathologically, the site of obstruction may be at valve level, above the valve (supravalvar) or below the valve (subvalvar). At the valve level, aortic stenosis (AS) results



Fig. 16.34: Chest X-ray in Eisenmenger syndrome following ventricular septal defect. The proximal right pulmonary artery is enlarged. There is a relative paucity of vasculature in the periphery with a sudden tapering of caliber of the right pulmonary artery (pruning)

from either unicuspid or a bicuspid aortic valve. Rarely the aortic valve annulus may itself be small. Supravalvar aortic stenosis results from obstruction in root of aorta, above the aortic valve, as in Williams syndrome. Subvalvar aortic stenosis may be discrete (membranous), fibromuscular or muscular (hypertrophic obstructive cardiomyopathy).

Hemodynamics

Valvar obstruction is overcome by raising the systolic pressure of the left ventricle. This is brought about by concentric hypertrophy of the left ventricle. Because of a powerful, muscular left ventricle, the emptying of the left ventricle is complete but the duration of the systole is prolonged. The prolongation of left ventricular ejection time causes delayed closure of the aortic valve resulting in delayed A2. Flow across the obstruction results in the aortic ejection systolic murmur that is typically diamond shaped, starting after the first sound and ending before the aortic component of the second sound with a mid-systolic peak. The systolic murmur is always palpable as a thrill at the second right interspace, suprasternal notch and the carotid vessels. The powerful left ventricle can maintain a normal forward cardiac output. The prolonged ejection results in a characteristic pulse that is best described as slowly rising to a peak that is sustained and then has a slow down slope. The peak is low so that the pulse is of low amplitude and prolonged duration.

Concentric hypertrophy of the left ventricle results in decreased distensibility of the left ventricle in diastole-reduced compliance. In severe AS with marked left

ventricular hypertrophy, the left ventricular diastolic pressure also rises. With increase in left ventricular diastolic pressure, the left atrial pressure must increase to be able to fill the left ventricle during diastole. Hence, with severe AS accompanied with marked left ventricular hypertrophy, a forceful left atrial contraction results in a palpable as well as audible fourth sound (S4). When the left ventricle starts failing in AS, besides hypertrophy dilatation also appears and causes increase in heart size and an audible third sound (S3). In valvar AS, there is post-stenotic dilatation of ascending aorta, seen on posteroanterior chest radiograph. In supravalvar and subvalvar AS, this is absent. In valvar stenosis, the first sound is followed by an aortic ejection click that precedes the starts of the murmur; the click is heard at the apex, and along left sternal border.

Clinical Features

Patients with mild to moderate AS are asymptomatic. With severe stenosis, the initial symptom is generally dyspnea on exertion. The patients may also give history of angina on effort and syncope. Presence of any one of these three symptoms suggests severe AS. The blood pressure is normal with mild disease; the width of pulse pressure relates inversely with severity of AS resulting in low amplitude prolonged duration pulse. Cardiac size remains normal unless left ventricular failure is present. The apical impulse is forcible or heaving. In severe AS, the fourth sound may be palpable. If left ventricular failure is present, the S3 may be palpable. A systolic thrill is palpable at the second right interspace, suprasternal notch and the carotid arteries. S1 is normal and followed by an ejection click in valvar aortic stenosis. The aortic component of the second sound (A2) is delayed but not diminished in intensity in AS. The delay results in closely split, single or paradoxically split second sound according to the severity of obstruction. With severe AS, S4 is audible, while in patients with left ventricular failure, S3 is palpable and audible. The ejection systolic murmur starting after the ejection click reaches a peak in mid-systole (Fig. 16.35). With increasing severity, the peak gets delayed so that the maximum intensity of the murmur is closer to the end rather than being midsystolic. With immobile valves, due to fibrosis or calcification, the systolic click as well as A2 diminish in intensity and may become inaudible (Fig. 16.36).

Subvalvar AS is distinguished by absence of ejection click and post-stenotic dilatation of the ascending aorta on X-ray. An aortic regurgitation murmur may be audible. The maximum intensity of the systolic murmur and thrill is in the 3rd or 4th left interspace. Supravalvar AS (Williams syndrome) is associated with elfin facies, mental retardation, dental abnormalities, strabismus and peripheral pulmonic stenosis. Since the obstruction is above the aortic valve, the pressure in the segment of aorta before the obstruction is elevated and results in loud A2. The jet through the supravalvar narrowing may be

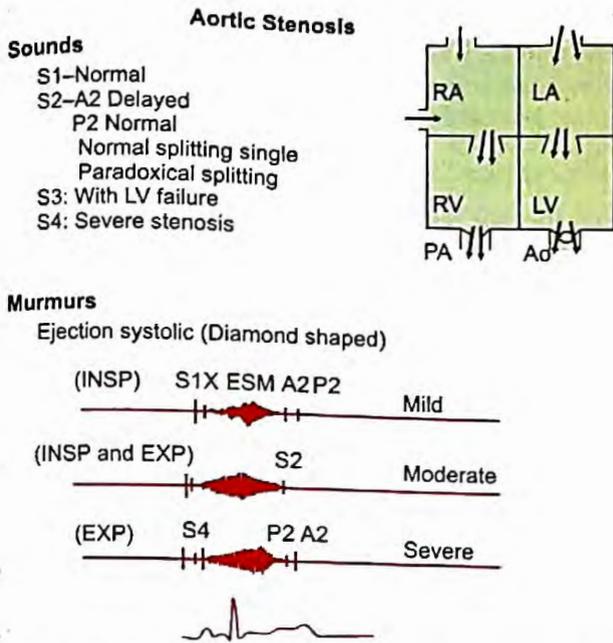


Fig. 16.35: Summary of auscultatory findings in aortic stenosis. S4 fourth sound; X aortic click

directed toward the innominate artery resulting in higher systolic pressure in the right arm compared to left.

The electrocardiogram reveals left ventricular hypertrophy. Presence of ST and T wave changes suggest severe disease (Fig. 16.37). However, a normal electrocardiogram does not exclude severe AS. Chest X-ray

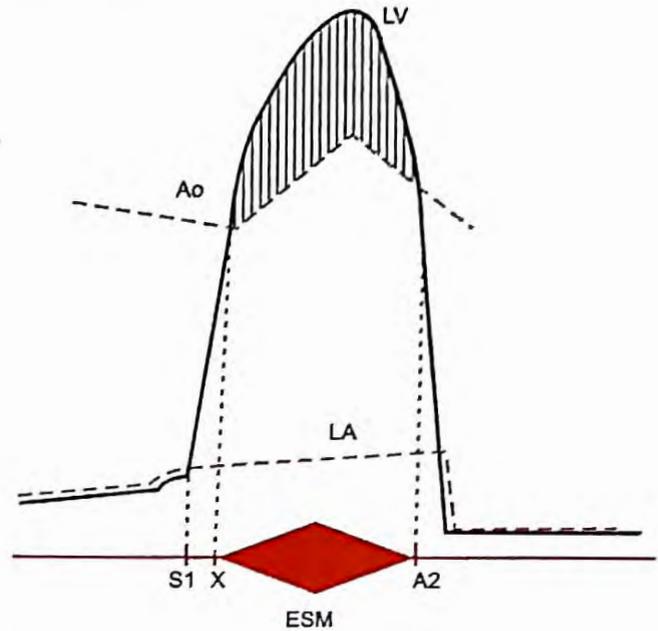


Fig. 16.36: Aortic stenosis: Diagrammatic portrayal of the hemodynamic basis for aortic stenosis murmur. The first sound (S1) occurs as the left ventricular (LV) pressure increases above left atrial (LA) pressure. This is followed by the ejection click (X) occurring after the aortic valve opens. The shape of the gradient between LV and aorta (Ao) corresponds to the shape of the aortic ejection systolic murmur (ESM). The murmur ends before the aortic components of the second sound (A2)

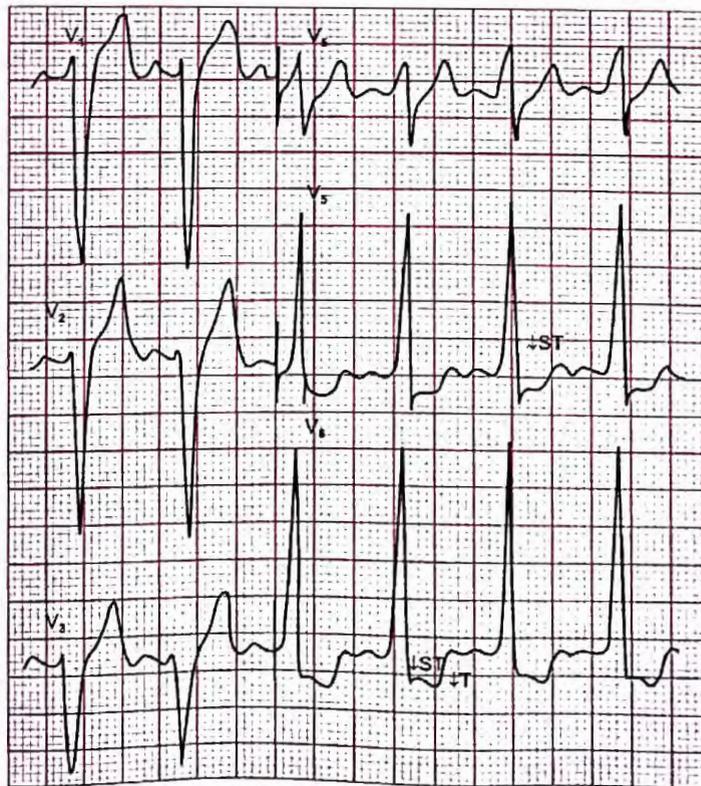


Fig. 16.37: Electrocardiogram from a patient with severe aortic stenosis showing prominent left ventricular voltages together with ST segment depression and T wave inversion in lateral leads (strain pattern)

shows a normal-sized heart with dilated ascending aorta in valvar AS. In supra- and subvalvar stenoses, the thoracic roentgenogram may be normal. Presence of cardiac enlargement indicates severe AS. Echocardiogram can identify the site of stenosis, and assess the gradient across the obstruction accurately.

Assessment of Severity

The severity of AS is determined, based on the following

- i. Symptomatic patients have severe AS; lack of symptoms does not exclude severe disease.
- ii. Narrower the pulse pressure, the more severe the AS.
- iii. Systolic thrill at second right interspace suggests at least moderately severe AS.
- iv. The later the peak of the ejection systolic murmur, the more severe the narrowing.
- v. Delay in A2 correlates well with severity. With mild AS, the S2 is normally split; with moderate AS, it is closely split; with severe or critical AS, it is single or paradoxically split.
- vi. Presence of S4 is indirect evidence for severe AS.
- vii. Presence of S3 indicates severe AS and congestive cardiac failure.
- viii. ST and T changes in the electrocardiogram suggest severe stenosis.
- ix. Cardiac enlargement on chest radiograph indicates severe AS with left ventricular failure.
- x. Doppler can quantitate the gradient across the aortic valve accurately. Two-dimensional echo reveals concentric left ventricular hypertrophy; ventricular dysfunction is associated with heart failure.

Treatment

Patients with AS should be followed closely, with 6–12 monthly electrocardiogram. Symptoms should be carefully evaluated. Doppler echo can be used to quantitate the gradient at each visit and ventricular function is monitored. Severe AS is risk for sudden death. Patients should be discouraged from outdoor games, athletics, competitive sports and strenuous exercises, if AS is significant (gradient of >50 mm Hg).

Balloon aortic valvuloplasty is the procedure of choice for valvar AS. A balloon introduced through the femoral artery can be placed at the aortic valve and inflated to tear the valve along the commissure. It is indicated, if the gradient is above 75 mm Hg. Supra- and subvalvar AS do not respond to balloon dilation; the procedure should also be avoided in patients with significant aortic regurgitation. Surgical options include aortic valve repair and replacement with a prosthetic valve.

Coarctation of the Aorta

Coarctation of the aorta is located at the junction of the arch with the descending aorta. It is a sharp indentation involving the anterior, lateral and posterior wall of the

aorta; the medial wall is spared. It may be distal or proximal to the ductus or ligamentum arteriosus and also the left subclavian artery. A bicuspid aortic valve is a common association.

Hemodynamics

In fetal life, the right ventricular output passes into the descending aorta through the ductus arteriosus. The left ventricular output empties into the innominate, left carotid and left subclavian arteries and little output reaches the descending aorta. The portion of the aorta distal to the left subclavian and before the portion where the ductus arteriosus joins is called the isthmus. At birth, the isthmus is the narrowest part of the aorta. Following closure of the ductus arteriosus, the descending aorta must receive its total supply from the left ventricle via the ascending aorta. Neonates with severe coarctation, therefore, become symptomatic immediately as the duct starts to close. However, a significant proportion present late.

The exact cause of systemic hypertension is not known; aortic obstruction is partly responsible. The narrow pulse pressure in the descending aorta distal to coarctation is implicated in the renal mechanism for causation of hypertension. The obstruction stimulates growth of collateral vessels between the proximal and distal segments. The intercostal vessels also participate in decompressing the hypertensive upper segment. They enlarge and become palpable at the lower borders of the ribs. Palpable collaterals are also felt at the medial and inferior angle of scapula. Because of the decompression of upper segment by collaterals, the resting blood pressure in upper extremities may be normal, but rises on exercise.

Clinical Features

Coarctation has a continuum of severity and the age at presentation is linked to severity. Newborns with severe coarctation present as soon as the duct starts to close. Infants with coarctation present with left ventricular dysfunction and heart failure. It is important to examine femoral pulses in newborns and infants with heart failure. Later in life, coarctation is often not associated with symptoms.

The only symptoms in uncomplicated coarctation may be intermittent claudication, pain and weakness of legs and dyspnea on running. Examination shows delayed and weak femorals and strong brachial arteries. The heart size remains normal with a forcible or heaving left ventricular apex. A systolic thrill may be palpable in the suprasternal notch. There are prominent arterial pulsations in the suprasternal notch and the carotid vessels. The first sound is accentuated and sometimes followed by a constant ejection click. The second sound is normally split with a loud aortic component. A variable intensity ejection systolic murmur is heard with the point of maximum intensity over the back in the interscapular area. The murmur starts late in systole after a considerable gap from

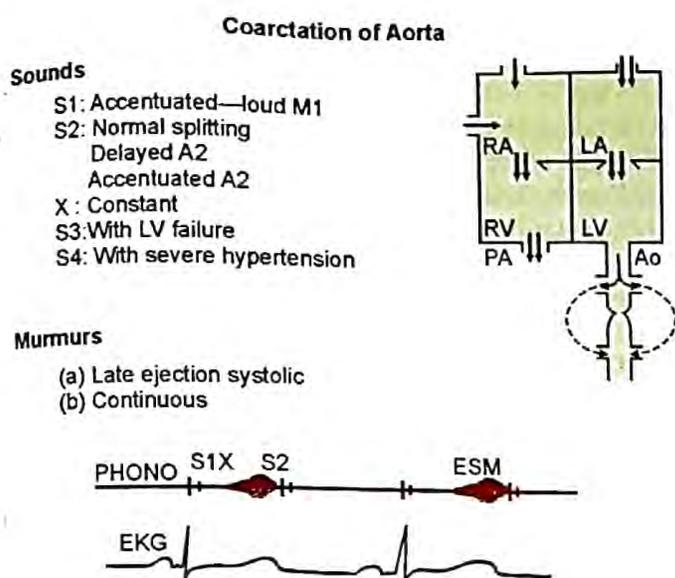


Fig. 16.38: Summary of auscultatory findings in coarctation of the aorta. S3 third heart sound, S4 fourth heart sound

the first sound and click. It may appear to go through the second sound suggesting a continuous murmur. This is because of delay in the transmission of pulse from the heart to the site of coarctation. Continuous murmurs may be audible over collaterals in the chest wall but are uncommon. An aortic ejection systolic murmur and/or a regurgitation murmur may be present because of the commonly associated bicuspid aortic valve (Fig. 16.38).

The electrocardiogram shows left ventricular hypertrophy. ST and T wave changes before the age of 15 years suggest additional aortic stenosis or endocardial fibroelastosis. Chest X-ray shows a normal sized heart with prominent ascending aorta and the aortic knuckle. In an overpenetrated film, the site of coarctation can be localized as the proximal and post-stenotic distal segments are dilated. The characteristic notching of the lower borders of ribs is seen beyond the age of 10 years. Using suprasternal approach coarctation can be seen on echocardiogram and the gradient estimated. Further, the descending aortic flow pattern is altered from phasic systolic flow to continuous low amplitude, systolic-diastolic flow.

Course and Complications

Coarctation may result in congestive failure in infancy. If congestive failure does not occur in infancy, it is unlikely to occur throughout the pediatric age group. The complications of coarctation include rupture of berry intracranial aneurysm and dissection of aorta. These complications are rare in children. Infective endarteritis may occur in the wall of aorta distal to coarctation or there could be endocarditis involving the bicuspid aortic valve.

Treatment

Relief of coarctation is recommended as soon as diagnosis is made. In newborns and infants, prompt surgery is

preferred. In older children, adolescents and adults, balloon dilation with or without stenting is advised. The recurrence rate of balloon dilation in newborns is over 90% and this procedure should only be done as interim palliation in the face of heart failure and severe ventricular dysfunction. Prostaglandin E1 is used to maintain ductal patency prior to surgery in first few weeks of life.

It is likely that coarctation is not a localized disease at the junction of arch and descending aorta and there is generalized weakness of the arterial media. Resection of coarctation does not guarantee freedom from complications like dissection of aorta. Systemic hypertension can persist following operation and re-coarctation can occur, requiring repeat balloon angioplasty.

Pulmonic Stenosis (Pure Pulmonic Stenosis; Pulmonic Stenosis with Intact Ventricular Septum)

Pulmonic stenosis (PS) is usually valvar or subvalvar (infundibular PS). Uncommonly pulmonic stenosis may be supravalvar or in the main right or left branches or peripheral branches.

Hemodynamics and Clinical Features

Flow across the narrow pulmonary valve results in a pulmonary ejection systolic murmur and a thrill in the left second interspace. The heart shows concentric right ventricular hypertrophy. The pulmonary artery beyond the obstruction shows poststenotic dilatation visible on the thoracic roentgenogram as a dilated pulmonary arterial segment. Because of the obstruction, the right ventricular systole is prolonged resulting in delayed closure of P2, and wide and variably split second sound. In valvar PS, a pulmonary ejection click is audible, soon after S1 and just before the onset of murmur, during expiration but disappears or becomes softer during inspiration. With increasing severity of stenosis, the duration and intensity of the murmur increase and the peak gets delayed; the click disappears and P2 becomes softer. With moderate PS, the murmur ends just short of the aortic component of the second sound. The concentric right ventricular hypertrophy results in maintaining a normal heart size, but reduces its distensibility. In severe PS with marked right ventricular hypertrophy, the ventricular diastolic pressure also increases. The right atrial pressure increases to be able to fill the right ventricle and results in a fourth heart sound (S4) as well as prominent 'a' waves in the JVP (Fig. 16.39).

Patients with mild to moderate PS are asymptomatic; with severe stenosis, dyspnea on effort appears. If foramen ovale is patent, a right to left shunt at the atrial level may occur in severe PS and result in cyanosis. Palpitation, easy fatigability and rarely chest pain may occur. Features of Noonan syndrome should be looked for. The cardiac size is normal and the hypertrophied right ventricle results in left parasternal heave. If the right ventricle fails, a right ventricular third sound may be audible. Rarely with right ventricular failure, tricuspid

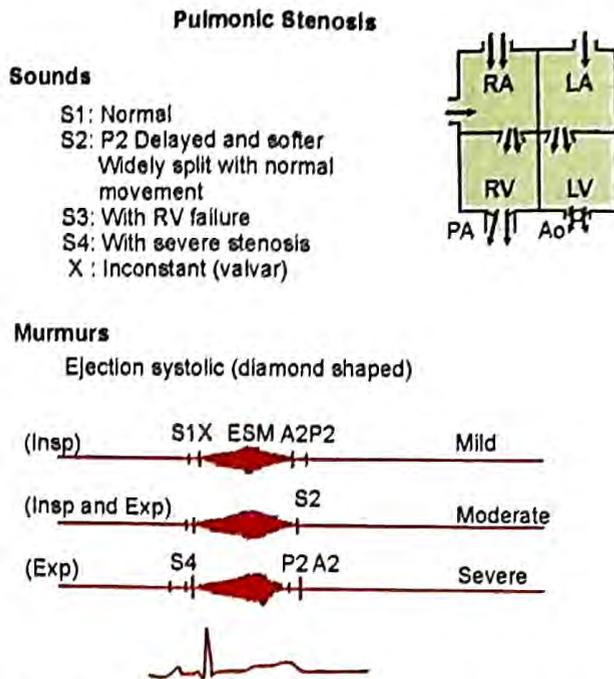


Fig. 16.39: Summary of auscultatory findings in pulmonic stenosis

regurgitation may appear. Since the right atrium offers less resistance to flow of blood than obstruction at the pulmonary valve, the flow through the pulmonary valve diminishes reducing the intensity as well as the duration of ejection systolic murmur.

The electrocardiogram shows right axis deviation and right ventricular hypertrophy, suggested by pure R waves or qR complex in V4R and V1 leads. P pulmonale suggests severe PS. Chest X-ray shows a normal-sized heart with normal pulmonary vasculature in mild, moderate as well as severe PS. Pulmonary oligemia occurs, if the patients develop a right-to-left shunt at the atrial level in severe or critical PS. The main pulmonary artery exhibits post-stenotic dilatation. Echocardiography can identify the site and severity of obstruction and helps in planning catheter intervention.

Treatment

Valvar PS generally does not increase in severity with time unless it is severe or diagnosed in the newborn period. Patients with mild PS (gradient of 50 mm Hg or less) need annual review. Balloon pulmonary valvuloplasty is the treatment of choice for isolated valvar PS. The procedure is sometimes technically challenging in newborn with critical PS. Surgical treatment is indicated only if balloon valvotomy is unsuccessful, as in patients with dysplastic valves or small pulmonary valve annulus.

Suggested Reading

- Allen HD, Shaddy RE, Driscoll DJ, Feltes TF, Moss Adams' Heart disease in infants, children and adolescents, 8th Edition, Kluwer/Lippincott William and Wilkins, Philadelphia, USA, 2012.

RHEUMATIC FEVER

Rheumatic fever is an immunological disorder initiated by group A beta hemolytic streptococci. Antibodies produced against selected streptococcal cell wall proteins and sugars react with the connective tissues of the body as well as the heart and result in rheumatic fever. There is a strong relationship with streptococcal infection and it is possible to prevent the illness by prompt treatment of streptococcal infections with penicillin.

Epidemiology

Rheumatic heart disease (RHD) constitutes from 5 to 50% of the cardiac patients in Indian hospitals.

Age and sex: The incidence of rheumatic fever following streptococcal throat infection is 0.3% in the general population and 1 to 3% in presence of epidemics of streptococcal pharyngitis. The illness commonly affects those between 5 and 15 years of age; first episodes are rare before 3 years or after 30 years age. Although the sexes are nearly equally affected, mitral valve disease and chorea is more common in girls whereas aortic valve involvement is often seen in boys.

Predisposing factors: Poor socioeconomic conditions, unhygienic living conditions and overcrowding predispose to streptococcal infections.

Etiopathogenesis

The etiology of rheumatic fever is unknown. A strong association with beta hemolytic streptococci of group A is indicated by a number of observations:

- History of preceding sore throat is available in 50% patients; more than 85% show elevated levels of anti-streptococcal antibody titer.
- Epidemics of streptococcal infection are followed by higher incidence of rheumatic fever.
- The seasonal variation of rheumatic fever and streptococcal infection is identical.
- In patients with established RHD, streptococcal infection is followed by recurrence of acute rheumatic fever.
- Penicillin prophylaxis for streptococcal infection prevents recurrences of rheumatic fever in those patients who have had it earlier.

Streptococci have never been isolated from rheumatic lesions in joints, heart or the bloodstream. Rheumatic fever appears to be the result of the host's unusual response at both the cellular and humoral level to *Streptococcus* (Fig. 16.40). Following streptococcal sore throat, there is a latent period of 10 days to several weeks before the onset of rheumatic fever. Streptococcal cell wall proteins as well as carbohydrates may induce production of antibodies that are capable of reacting with human connective tissue, resulting in rheumatic fever.

Only heart valves are permanently damaged during an episode of rheumatic fever. All other affected tissues

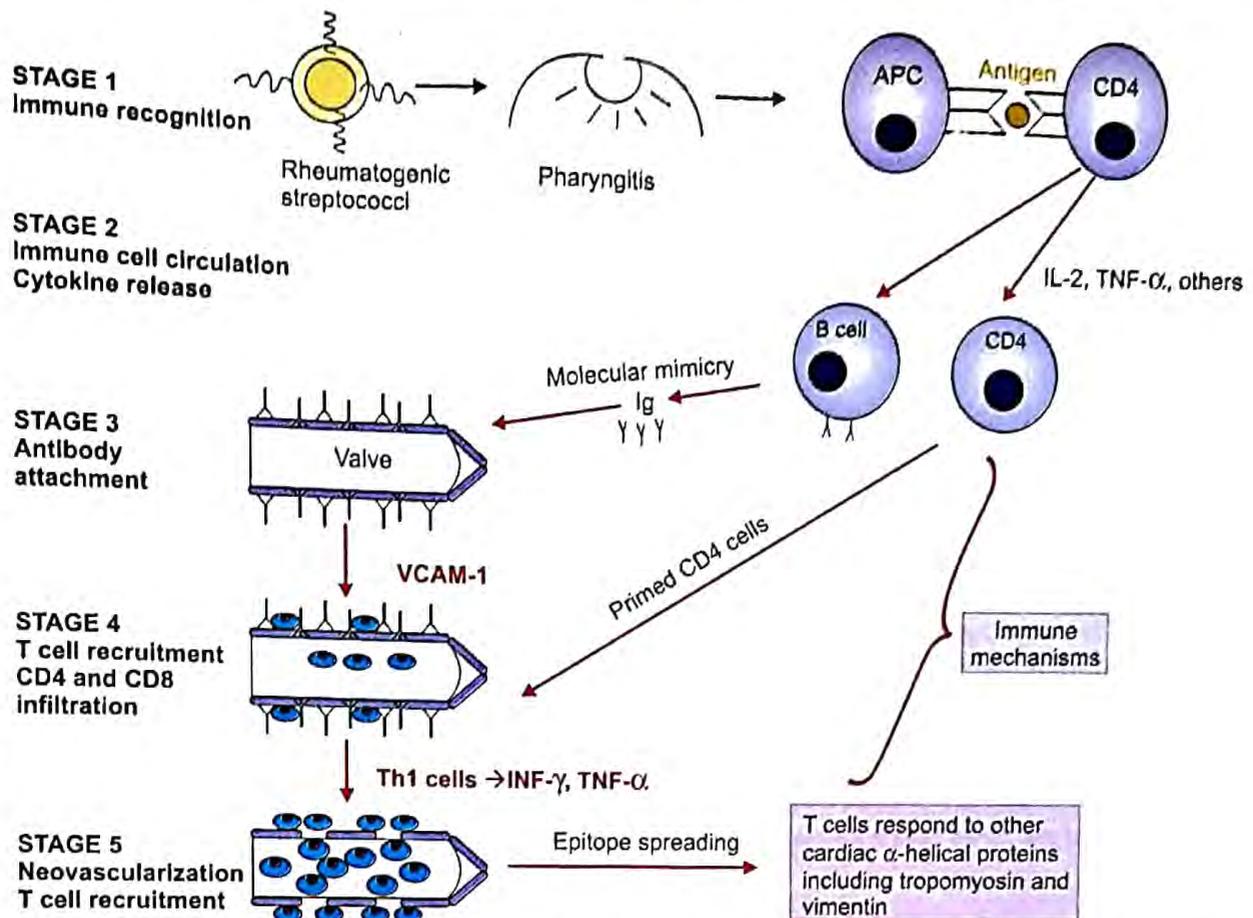


Fig. 16.40: Pathogenesis of rheumatic fever. It is proposed that the endothelium suffers initial damage due to a humoral immune response, the damage resulting in vascular cell adhesion molecule 1 (VCAM-1) being expressed on the endothelium. This is followed by activation of cellular immune response. As a result CD4+, CD8+ T lymphocytes and macrophages get attached to the valvar endothelium and migrate to the connective tissue core. This sets up an inflammatory response. The inflammation is accompanied by neovascularization of the valve substance. IFN- γ Interferon gamma, TNF- α tumor necrosis factor alpha, Th1 T helper cells 1

typically heal without residua: Pericarditis, chorea and arthritis resolve completely without constriction, long-term neurologic consequences or joint disability, respectively.

Clinical Features

Clinical features of rheumatic fever consists of streptococcal pharyngitis with fever followed 10 days to a few weeks later by recurrence of fever and the manifestations of acute rheumatic fever. The history of sore throat is available in less than 50% of the patients. Guidelines for the clinical diagnosis of acute rheumatic fever, originally suggested by T. Duckett Jones, have been revised by the American Heart Association. These guidelines are different for low-risk populations (RHD prevalence of $<1/1000$) versus moderate or high-risk populations. The guidelines consist of major, minor and essential criteria (Table 16.16). Two major or one major and two minor criteria are required in the presence of essential criteria to diagnose the first episode of acute rheumatic fever. For recurrences, three minor criteria are sufficient. These guidelines are meant to help a physician in making a diagnosis of rheumatic fever; physicians should use their judgment in making a diagnosis even in the absence of these criteria.

Major Criteria

Carditis: This is an early manifestation of rheumatic fever. Studies utilizing echocardiography indicates that carditis occurs in almost 90% patients. In 60–70%, it is clinically obvious whereas in the remaining, the diagnosis is based on echocardiographic findings labeled as subclinical carditis. Rheumatic carditis is designated as a pancarditis involving the pericardium, myocardium and endocardium, although studies indicate limited myocardial component. Almost 80% of those patients who develop carditis do so within the first two weeks of onset of rheumatic fever.

Pericarditis results in precordial pain that may be quite severe. On auscultation, a friction rub is present. Clinical pericarditis is seen in approximately 15% of those who have carditis. The electrocardiogram may show ST and T changes consistent with pericarditis. As a rule, the rheumatic pericarditis is associated with only small effusions and does not result either in tamponade or constrictive pericarditis. A patient of rheumatic pericarditis always has additional mitral or mitral and aortic regurgitation murmurs.

Other features of carditis are (i) cardiac enlargement, (ii) soft first sound, (iii) protodiastolic (S3) gallop, (iv) congestive heart failure, and (v) Carey Coombs' murmur.

Table 16.16: Revised Jones criteria for acute rheumatic fever (2015)
American Heart Association and World Heart Federation

For all populations

Initial episode of acute rheumatic fever: Two major or one major + two minor criteria
 Recurrent episodes of acute rheumatic fever: Two major, one major + two minor, or three minor
 Essential criteria: Previous evidence of group A beta hemolytic streptococcal infection

Low-Risk Populations

Incidence <2/100,000 in school-going children;
 rheumatic heart disease prevalence <1/1000

Major criteria

Carditis: Clinical or subclinical
 Arthritis: Polyarthritis only
 Chorea
 Erythema marginatum
 Subcutaneous nodules

Minor criteria

Polyarthralgia
 Fever (>38.5°C)
 ESR ≥60 mm in the first hour; CRP ≥3.0 mg/dL
 Prolonged PR interval, after accounting for age variability
 (unless carditis is a major criterion)

Moderate, High-Risk Populations

Major criteria

Carditis: Clinical or subclinical
 Arthritis: Polyarthritis, monoarthritis
 Polyarthralgia
 Chorea
 Erythema marginatum
 Subcutaneous nodules

Minor criteria

Monoarthralgia
 Fever (>38.0°C)
 ESR ≥30 mm in the first hour; CRP ≥3.0 mg/dL
 Prolonged PR interval, after accounting for age variability
 (unless carditis is a major criterion)

Gewitz MH, et al. Revision of the Jones criteria for the diagnosis of acute rheumatic fever in the era of doppler echocardiography. *Circulation* 2015;131:1806–18

This is a soft delayed diastolic mitral murmur heard transiently during the course of acute rheumatic fever possibly as a result of flow across the inflamed and thickened mitral valve.

Endocarditis is represented by a pansystolic murmur of mitral regurgitation with or without an associated aortic regurgitation murmur. Pathologically mitral valve is involved in all cases of rheumatic fever with carditis. Clinically, however, 5–8% patients may present as pure aortic regurgitation. Thus almost 95% patients will have mitral regurgitation murmur, a quarter of them also have an aortic regurgitation murmur and only 5% present as pure aortic regurgitation. Tricuspid valvulitis resulting in tricuspid regurgitation occurs in 10–30% of cases. Isolated tricuspid valvulitis as a manifestation of rheumatic endocarditis does not occur. Clinical evidence of pulmonary valve involvement in acute rheumatic fever is never seen. The acute hemodynamic overload resulting from acute mitral regurgitation and/or aortic regurgitation leads to left ventricular failure and is the main reason for the morbidity and mortality of rheumatic fever and RHD.

Subclinical carditis: Carditis may occasionally be clinically silent and only identified by echocardiography that shows mitral regurgitation.

Arthritis: Rheumatic arthritis is a polyarthritis involving large joints that include knees, ankles and elbows. Uncommonly smaller joints may also be involved. It is a migratory polyarthritis with the affected joints showing redness, warmth, swelling, pain and limitation of

movement. It is an early manifestation and occurs in 70–75% of cases according to western literature. However, the figures from India indicate that arthritis is seen in 30 to 50% of patients. The pain and swelling appear rather quickly, last 3 to 7 days and subside spontaneously to appear in some other joint. There is no residual damage to the joint. Arthritis tends to be commoner in older patients.

Subcutaneous nodules: Subcutaneous nodules appear on bony prominences like elbows, shins, occiput and spine. They vary in size from pinhead to an almond. They are non-tender. Subcutaneous nodules are a late manifestation and appear around 6 weeks after the onset of rheumatic fever though they have been described as early as 3 weeks from the onset. They occur in about 3 to 20% of cases of rheumatic fever in India. Patients who have subcutaneous nodules almost always have carditis. They last from a few days to weeks but have been known to last for almost a year.

Chorea: Sydenham's chorea is also a late manifestation occurring about three months after the onset of acute rheumatic fever. Generally, by the time a patient manifests chorea, the signs of inflammation usually subside. Chorea consists of semi-purposeful, jerky movements resulting in deranged speech, muscular incoordination, awkward gait and weakness. The affected child is emotionally disturbed and drops things she or he is carrying. It is three to four times more common in females as compared to males. Untreated, it has a self-limiting course of two to six weeks.

Erythema marginatum: It is an early manifestation, predominantly seen over the trunk. It starts as a red spot with a pale center, increasing in size to coalesce with adjacent spots to form a serpiginous outline; the rash is non-itching. Recognition of skin manifestations may be difficult in dark-skinned patients.

Minor Criteria

Clinical criteria

Fever: Rheumatic fever is almost always associated with fever. The temperature rarely goes above 39.5°C.

Arthralgia: Arthralgia is a subjective pain whereas arthritis means subjective symptoms and objective signs of inflammation. While arthritis is a major manifestation, arthralgia is a minor manifestation. Figures from India indicate that arthritis and arthralgia together occur in about 90% of the patients

Previous rheumatic fever or rheumatic heart disease: This criterion applies only for recurrent episodes of rheumatic fever.

Laboratory manifestations

Acute phase reactants: The leukocyte count usually lies between 10000 to 15000/cu mm. The sedimentation rate is elevated during acute rheumatic fever and remains so for 4 to 10 weeks in almost 80% patients. In a small proportion of patients, it may remain elevated even beyond 12 weeks. Although congestive cardiac failure tends to bring the sedimentation rate down towards normal, it is unlikely that patients of acute rheumatic fever with congestive failure will have a normal sedimentation rate. C-reactive protein is elevated in all patients of acute rheumatic fever, and subsides rapidly if the patient is treated with corticosteroids. While absence of raised C-reactive protein is against the diagnosis of rheumatic fever, its presence is non-specific.

Prolonged PR interval: Prolonged PR interval can get prolonged in many infections, nor is diagnostic of carditis. Higher grades of block like second degree atrioventricular block especially Wenckebach type may be seen. Complete atrioventricular block is extremely rare.

Essential Criteria

These include evidence of recent streptococcal infection. Elevated levels of antistreptolysin O (ASO) indicate previous streptococcal infection and not rheumatic fever. Although generally the higher the level the more likely one can conclude a recent infection, lower levels do not exclude a recent streptococcal infection. A basal ASO titer of 50 U/dL that goes up to 250 U/dL is indicative of recent streptococcal infection. Rising titer of ASO is a strong evidence for recent infection.

Positive throat culture for streptococci, at diagnosis of rheumatic fever, is uncommon. A positive culture also

cannot be equated with diagnosis, since this may happen with asymptomatic carriers.

Echocardiography: The recent revision of Jones criteria now includes echocardiographic findings for the diagnosis of rheumatic carditis. Features suggestive of rheumatic carditis include annular dilatation, elongation of the chordae to the anterior leaflet of the mitral valve causing a prolapse and lack of coaptation of the two leaflets resulting in mitral regurgitation. There is focal nodular thickening of the tips of the mitral leaflets; they however do not show the independent chaotic movement seen with infective endocarditis. Occasionally, the tip of the mitral valve leaflet is flail because of chordal rupture resulting in severe mitral regurgitation. The left atrial and ventricular size is increased. Involvement of aortic valve is recognized as aortic regurgitation.

Echocardiography has improved recognition of carditis, which at times is not possible on auscultation. This has led to the recognition of subclinical carditis, characterized by no clinical but echocardiographic findings of mitral regurgitation. While the course of patients with subclinical carditis is not clear, most patients are advised long-term penicillin prophylaxis.

Treatment

Management is symptomatic combined with suppressive therapy.

Bed rest: Bed rest is generally recommended for acute rheumatic fever. Prolonged bed rest (>2–3 weeks) is seldom necessary unless there is clinically apparent carditis with heart failure.

Penicillin: After obtaining throat cultures, the patient should receive penicillin. A single injection of benzathine penicillin is given when the diagnosis of rheumatic fever is made. Penicillin V (250 mg four times a day for 10 days) is an alternative; erythromycin (250 mg four times a day for 10 days) is given to those with penicillin allergy.

Suppressive Therapy

Aspirin or corticosteroids are given as suppressive therapy. Since untreated rheumatic fever subsides in 12 weeks in 80% of the patients, either of the two suppressive agents is given for 12 weeks. Steroids are a more potent suppressive agent as compared to aspirin. However, there is no proof that the use of steroids results in less cardiac damage as compared to aspirin. A number of observations indicate that steroids act faster and are superior at least in the initial phases. Pericardial friction rub tends to disappear within three to five days after starting the steroids. Subcutaneous nodules also resolve faster with use of steroids. Patients who have carditis with congestive cardiac failure have a higher mortality if aspirin is used compared to steroids. In selecting the medication, the following guidelines are followed:

- *Carditis with congestive cardiac failure*: Corticosteroids
- *Carditis without congestive cardiac failure*: Either corticosteroids or aspirin; former preferred
- *No evidence of carditis*: Aspirin

The total duration of therapy is 12 weeks. Aspirin is given at a dose of 90–120 mg/kg/day (in 4 divided doses) for 10 weeks, and then tapered in the next two weeks. Alternatively, prednisolone (2 mg/kg daily; maximum dose 60 mg) is given for three weeks and then tapered gradually in next 9 weeks. The management of congestive cardiac failure is based on principles discussed above.

Surgical replacement of the mitral and/or aortic valve is sometimes indicated, if the patient is deteriorating despite aggressive decongestive measures. Acute hemodynamic overload due to mitral or aortic regurgitation is the main cause of mortality due to rheumatic fever.

Management of chorea: The patient as well as the parents are reassured and told about the self-limiting course of the disease. The signs and symptoms of chorea do not respond well to anti-inflammatory agents or steroids. Supportive measures such as rest in a quiet room and medications such as haloperidol, diazepam and carbamazepine are effective.

Prevention of Rheumatic Fever

Primary prevention requires identification of streptococcal sore throat and its prompt treatment with penicillin. For primary prevention, it is necessary to educate the community regarding the consequences of streptococcal pharyngitis. Logistically, this may be difficult since it requires (i) prompt identification of sore throat, (ii) rapid confirmation of a streptococcal etiology and (iii) availability of penicillin. Recent data indicates that rheumatic fever may follow episodes of asymptomatic streptococcal pharyngitis. Primary prevention can only be possible by using an antistreptococcal vaccine, which is not available.

Secondary prevention consists in giving long-acting benzathine penicillin. The dose is 1.2 million units once every 3 weeks or 0.6 million units every alternate week. The injection is painful and often administered on weekends to avoid school absence. While the responsibility of continuing penicillin prophylaxis is on parents, the physician should explain the seriousness of the problem and need for prolonged treatment (Table 16.17).

Patient without proven carditis should receive prophylaxis for 5 years after the last episode, or until they are 18-yr-old (whichever is longer). Patient with carditis (mild mitral regurgitation or healed carditis) should receive prophylaxis for 10 years after the last episode, or at least until they are 25-year-old (whichever is longer). Patients with established RHD or following valve surgery or balloon valvotomy should receive lifelong prophylaxis. Some cardiologists recommend discontinuation of prophylaxis after the age of 40 years, since the likelihood of recurrence beyond this age is minimal.

Table 16.17: Secondary prophylaxis following an episode of rheumatic fever

Antibiotic	Mode of administration, dose
Benzathine penicillin	Single intramuscular injection every 3 to 4 weeks*, 1200 000 units for patients ≥ 30 kg; and 600 000 units for < 30 kg
Penicillin V	250 mg orally twice daily
Erythromycin (for penicillin allergy)	250 mg orally twice daily

*In high prevalence regions, 3 wk injections are recommended for prophylaxis, in patients > 30 kg and every 2 weeks in patients < 30 kg

RHEUMATIC HEART DISEASE

The sequelae of rheumatic fever consist of mitral, aortic and tricuspid valve disease. Mitral valve involvement manifests predominantly as mitral regurgitation (MR) and much less commonly as mitral stenosis (MS). Aortic valve and tricuspid valve involvement presents as aortic (AR) and tricuspid regurgitation (TR), respectively. Rheumatic aortic stenosis (AS) is very rare in childhood or adolescence.

Mitral Regurgitation

Mitral regurgitation (MR) is the chief manifestation (80–85%) of acute and previous rheumatic carditis.

Hemodynamics

Mitral regurgitation results in a systolic leak of blood to the left atrium. The regurgitant blood reaches the left atrium during ventricular systole at almost systolic pressure. However, during diastole it can pass freely across the mitral valve. Thus, although the left atrial pressure increases during systole, it drops during diastole. The mean left atrial pressure, therefore, stays normal or is only slightly increased. There is only a minimal increase in pulmonary venous pressure and no pulmonary congestion. The increased volume of blood handled by the left atrium and left ventricle results in an increase in the size of both these chambers. Mitral regurgitation provides two exits for the left ventricular blood—forward flow through the aortic valve into the systemic circulation and backward leak into the left atrium. The forward output becomes insufficient during exertion. This decrease in the systemic output results in fatigue, the commonest symptom of significant MR. Absence of pulmonary congestion prevents occurrence of dyspnea unless the MR is severe or the left ventricular myocardium is failing. With failing left ventricle, the left ventricular diastolic pressure increases, the left atrial and pulmonary venous pressure increase and pulmonary congestion appears. There is an increase in pulmonary arterial pressure and features of pulmonary arterial hypertension appear. Thus presence of features of pulmonary arterial hypertension in a patient having pure MR suggests (i) severe MR or (ii) failing left ventricular myocardium.

MR developing during acute rheumatic fever is of sudden onset, and results in hemodynamic overload over the left ventricle. The features of left ventricular failure can occur even with relatively moderate leaks. The size of the left atrium also plays a significant role in MR. With acute MR, the left atrial size is normal and the increased volume reaching the left atrium increases the left atrial and the pulmonary venous pressure, resulting in pulmonary congestion and features of left ventricular failure. With long-standing MR, the left atrium increases in size to accommodate the regurgitant volume without increasing the left atrial pressure and features of left ventricular failure are absent. Another important adjustment consists of decrease in the systemic vascular resistance to help increase the forward flow. The maximum ejection of blood into the aorta takes place during early systole. The combination of these two factors results in an increased systolic and decreased diastolic pressure, resulting in a small water hammer pulse.

Clinical Features

The resting pulse rate is increased to maintain an adequate cardiac output. Features of left ventricular failure are absent and appear late unless the MR is acute, severe or left ventricular myocardium is failing. The heart size is dependent on the severity of MR as well as the status of the left ventricular myocardium. The cardiac apex is displaced downward and outward with forcible apex and hyperkinetic precordium. Less than 10% of patients have a systolic thrill because of posterior direction of the regurgitant stream. The first sound may be soft as it is masked by the systolic murmur. The second sound is normally split with mild MR. With moderate or severe MR, the second sound is widely and variably split. The wide split is due to an early aortic component of the second sound. With failing left ventricle, the wide splitting disappears. Except with very mild MR, a third sound is audible at the apex and indicates increased early rapid filling of the left ventricle. With severe MR, a delayed diastolic mitral murmur starting with the third sound is audible. The delayed diastolic murmur is secondary to a large flow across the mitral valve during diastole. Not infrequently this delayed diastolic murmur may be palpable as a short diastolic thrill. In pure MR, the delayed diastolic murmur always ends somewhere in mid-diastole and there is no late diastolic (presystolic) accentuation. The diagnostic sign is the pansystolic murmur, best heard at the apex and widely radiating to the axilla and back as well as to the left sternal border (Fig. 16.41).

The electrocardiogram shows sinus tachycardia. Signs of left ventricular hypertrophy may be present with long-standing and severe MR. Thoracic roentgenogram shows cardiac enlargement secondary to left ventricular enlargement, the size depending on the severity of MR.

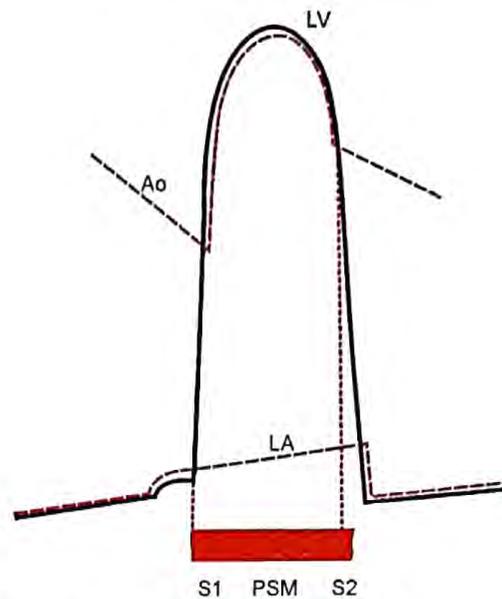


Fig. 16.41: The characteristic pansystolic murmur. As the left ventricular (LV) pressure exceeds the left atrial pressure (LA), the first sound (S1) occurs. However, the murmur of mitral regurgitation will also start at the same time masking the S1. Since the maximum difference in the LV and LA pressure is quickly reached and maintained throughout systole, the murmur maintains the same intensity throughout systole appearing pansystolic. Finally as the LV pressure drops below the aortic (Ao) pressure, A2 occurs. The LV pressure is higher than LA pressure at this time and the murmur goes beyond, A2 thus masking both the S1 and A2. PSM pansystolic murmur

Left atrial enlargement is inferred from the elevation of left bronchus. In the absence of left ventricular failure, there is absence of prominence of pulmonary veins or features of pulmonary congestion. Echocardiogram shows enlarged left atrium and ventricle. The specific findings of mitral valve disease can be seen by two-dimensional and three-dimensional echocardiography. Color Doppler can quantify MR non-invasively (Fig. 16.42).

Differential Diagnosis

Other causes of MR in childhood include: (i) atrial septal defect of the primum variety; (ii) coarctation of the aorta with MR (congenital); (iii) left ventricular fibroelastosis; (iv) congenital corrected transposition of great arteries; (v) papillary muscle dysfunction in dilatation of left ventricle from any cause; (vi) atrial septal defect of the secundum type with floppy mitral valve; (vii) Marfan and Hurler syndrome, and (viii) anomalous origin of left coronary artery from pulmonary artery.

Treatment

Mild to moderate MR is well tolerated for long periods. However, its severity increases with time. Medical management consists of the use of digitalis and diuretics besides penicillin prophylaxis for prevention of

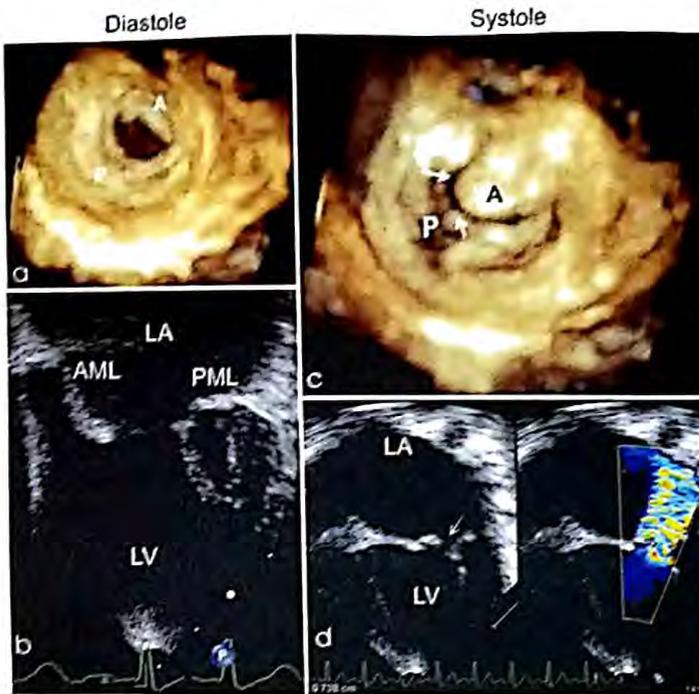


Fig. 16.42: 10-year-old with rheumatic mitral valve disease with mitral stenosis and regurgitation. Three-dimensional echocardiograms are shown in the upper panel and equivalent two-dimensional frames obtained from apical four-chamber views are in the lower panel: (a) The diastolic frame shows the mitral valve from its left atrial aspect. Note that the leaflet substance is seen in diastole; (b) Equivalent diastolic frame on 2D shows several features rheumatic affliction. The anterior mitral leaflet (AML) is thickened. The tip of the AML is oriented horizontally and does not point downwards suggesting restriction of mobility of diastolic motion. The posterior mitral leaflet (PML) is also thickened and mobility is restricted to a greater degree. The chordae tendinae beneath the PML are visibly thickened; (c) During systole, the PML stays in a relatively fixed position. The free edge of the AML moves to a position above the optimal zone of coaptation between the two leaflets. The resultant regurgitation orifice is shown by white arrows in both the 3D and 2D frames. (d) The resultant color Doppler jet of mitral regurgitation is directed posteriorly and laterally

recurrences. The role of systemic vasodilators, most commonly ACE inhibitors and calcium channel blockers, to reduce afterload in isolated MR and aortic regurgitation is controversial. An important additional consideration in RHD is the presence of varying degrees of mitral stenosis that accompanies MR.

There are no clear guidelines for the timing of mitral valve surgery (particularly replacement) in children. Persistent symptoms, in spite of maximally tolerated medications, warrant consideration of surgery especially in the presence of pulmonary artery hypertension. For an asymptomatic child, evidence of even the slightest ventricular dysfunction merits consideration for surgery. The commonest surgical approach is prosthetic valve replacement because rheumatic mitral valves are difficult to repair. Patients with a prosthetic mitral valve need to receive anticoagulants on the long term.

Rheumatic Mitral Stenosis (MS)

Rheumatic MS is less common than MR in children. Juvenile MS (<18 years) is typically seen in regions with high prevalence of RHD.

Hemodynamics (Fig. 16.43)

MS results in obstruction to flow of blood across the mitral valve during left ventricular diastole. The left atrium compensates for this obstruction by increasing its pressure. This increase in pressure results in hypertrophy of the left atrial wall, and prevents decrease in the blood flow across the mitral valve. The increased left atrial pressure is transmitted to pulmonary veins and results in pulmonary capillary engorgement and pulmonary congestion, which produces dyspnea, the commonest symptom of MS. The pulmonary arterial pressure increases to maintain forward flow from the pulmonary artery to the left side of the heart. In the absence of tricuspid regurgitation the right ventricular hypertrophy is concentric without an increase in the size of right ventricular chamber. The heart size is usually normal.

With mild or moderate MS, the forward flow through the mitral valve remains normal. With severe obstruction, the forward flow is diminished with reduced cardiac output resulting in a small volume pulse and cold extremities.

Clinical Features

Boys are twice as commonly affected as girls in the age group up to 12 years. Juvenile rheumatic MS has been described in children as young as 5 years and is now largely limited to high RHD prevalent regions. Patients with MS give history of shortness of breath on exertion or even at rest depending on the severity. Other important

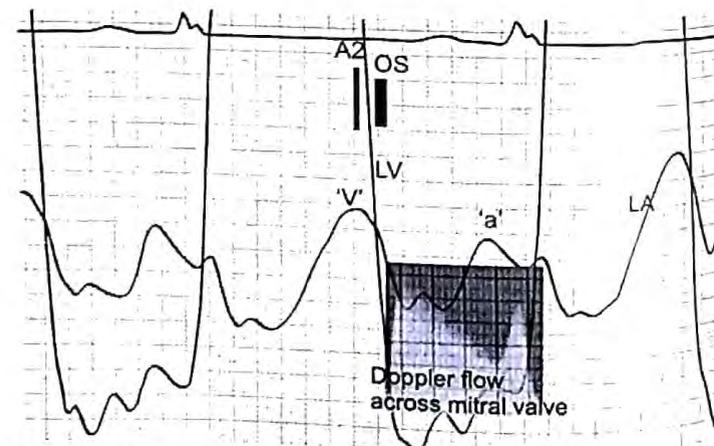


Fig. 16.43: Hemodynamics of mitral valve stenosis: A cardiac catheterization tracing with simultaneous recording of left atrial (LA) with 'a' and 'v' waves and left ventricular (LV) waveforms is shown. A continuous wave Doppler record is superimposed during diastole; note the two peaks in flow acceleration—the second peak coincides with presystolic accentuation. The flow patterns reflect the pressure gradients across the mitral valve in diastole. A2 aortic component of second heart sound; OS opening snap

symptoms consist of cough, hemoptysis, paroxysmal nocturnal dyspnea, attacks of acute pulmonary edema and atypical angina. The pulse volume is small. Depending on the severity, there may or may not be signs of right-sided congestion, in the form of engorged neck veins and enlarged tender liver. The liver may have systolic pulsations if there is associated tricuspid regurgitation; the jugular venous pulse shows prominent 'a' waves. If tricuspid regurgitation is present, the jugular veins show dominant 'V' waves. With moderate or severe MS, signs of pulmonary congestion with rales are present.

Examination reveals a normal sized heart with a tapping apex beat, parasternal impulse and an apical diastolic thrill. The second sound may be palpable at the second left interspace. On auscultation the first sound is accentuated, the second sound normally split with a loud pulmonary component. An opening snap of the mitral valve is best audible just medial to the apex. The delayed diastolic mitral murmur starts immediately following the opening snap, diminishes somewhat in intensity during mid diastole and accentuates again at the end of diastole. The late diastolic accentuation is always present in the presence of MS. Absence of late diastolic accentuation of murmur is against the diagnosis of dominant MS.

The electrocardiogram shows right axis deviation with right ventricular hypertrophy. In addition, there is evidence for P mitrale. Thoracic roentgenogram shows a normal-sized heart with features of pulmonary venous and arterial hypertension, and left atrial enlargement. Echocardiogram shows decreased EF slope, paradoxical posterior leaflet motion, left atrial enlargement and pulmonary hypertension. 2D echo can identify the narrowed mitral opening. Doppler echo provides information on transmitral gradient.

Assessment of severity: The minimum criteria for the diagnosis of MS are accentuated first sound, the mitral opening snap and delayed diastolic murmur with late diastolic accentuation. The closer the opening snap to the second sound, the more severe the mitral obstruction. The intensity or duration of the diastolic murmur does not correlate with the severity since mild as well as severe MS may result in very soft murmurs. The duration of the murmur depends on the heart rate. Severe pulmonary arterial hypertension can occur only with severe mitral obstruction. Echocardiogram combined with Doppler gradient gives more precise assessment of severity. Atrial fibrillation is rare in children.

Differential Diagnosis

A few conditions can be considered in the differential diagnosis in children. Isolated congenital MS is very rare. The opening snap is less commonly heard in congenital MS. Cor triatriatum, obstruction of individual pulmonary veins and left atrial myxoma should be considered in the differential diagnosis.

Treatment

The management of MS is essentially catheter based or surgical. Beta blockers or digoxin work equally well by reducing resting and exercise heart rates thereby improving diastolic filling. Diuretics help by reducing pulmonary venous congestion. Balloon mitral valvotomy (BMV) or percutaneous trans-septal mitral commissurotomy has replaced closed or open commissurotomy for MS in children. Improvement in mitral valve area following these procedures largely results from splitting of the fused commissures. The subvalvar abnormalities of MS remain after valvotomy, so the mitral valve area does not normalize.

Long-term follow-up after valvotomy is mandatory because of significant risk of restenosis with time. Restenosis is typically associated with significant residual MS following balloon mitral valvotomy. A repeat procedure is an option for restenosis and helps postpone mitral valve surgery. Closed mitral valvotomy (CMV) is an inexpensive and equally effective surgical alternative to BMV.

Aortic Regurgitation (AR)

Aortic valve involvement in RHD results in AR. Clinically pure AR, without associated mitral valve disease, is rare and occurs in 5 to 8% patients. Pathologically, pure rheumatic aortic valve disease is almost unknown.

Hemodynamics

AR is a backward leak from the aorta into the left ventricle during diastole. This increases the volume of blood reaching the left ventricle. The left ventricle increases in size to accommodate the extra volume. The size of the left ventricle is thus related to the degree of aortic leak. Because of the backward flow of blood the forward flow is impaired. This is compensated by peripheral vasodilatation as well as increased ejection from the left ventricle during early part of the systole. However, significant AR results in low forward output. Signs of wide pulse pressure in the form of exaggerated arterial and arteriolar pulsations are present unless the AR is mild. Slowing of heart rate increases the diastolic period and increases the regurgitant volume of blood. With good left ventricular myocardial function, even moderate AR is tolerated well for long periods. If left ventricular myocardium is failing, the left ventricular diastolic pressure goes up and results in an increase in left atrial pressure and pulmonary congestion.

Clinical Features

Aortic valve disease is more common in boys compared to girls. The main symptom is palpitation, related to the large stroke volume. With mild to moderate AR, the forward flow can be raised effectively on exercise. Thus fatigue is not an early symptom. The pulse pressure is wide, with a water hammer (collapsing) pulse. The wider

the pulse pressure, the more severe the aortic leak. The diastolic blood pressure may be recorded as zero with severe AR. Prominent carotid pulsations (Corrigan sign), visible arterial pulsations over extremity vessels (dancing peripheral arteries) and visible pulsations of the abdominal aorta are present. Nodding of head may be present with each systole (de Musset sign) in severe AR. Arteriolar pulsations may be seen over the nail bed, uvula, lips, ear lobes and in the eye grounds. There is also exaggeration of the systolic pressure difference between the brachial and femoral arteries (Hill sign). Normally, the difference between the pressures in brachial artery and femoral artery is less than 20 mm Hg, the femoral systolic pressure being higher. Systolic pressure difference between 20 to 40 mm Hg suggests mild AR, 40 to 60 mm Hg moderate AR, and more than 60 mm Hg severe AR. Stethoscope over the brachial or the femoral artery shows pistol shot sounds in severe AR. A systolic murmur may be heard, if pressure is applied to partially occlude the artery proximal to the chest piece, and diastolic murmur if pressure is applied distally; the combination of systolic and diastolic murmurs is the Duroziez sign.

The apex is displaced downward and outward and is forcible or heaving. A diastolic thrill is unusual. The first sound is soft and the aortic component of the second sound may be audible or may be masked by the regurgitant diastolic murmur. The murmur of AR is a high-pitched, decrescendo diastolic murmur starting with the aortic component of the second sound. The intensity and the length of the murmur do not correlate with the severity of AR. The murmur is heard along the left sternal border and may radiate to the apex. With large aortic leaks there is also an ejection systolic murmur at the second right interspace, conducted to the neck and not infrequently associated with a systolic thrill. The systolic murmur is the result of a large stroke volume, passing across rough valves. It does not indicate aortic stenosis, if the pulse pressure is wide and the carotid upstroke is brisk.

The electrocardiogram shows increase in left ventricular voltages with deep S waves in V1 and tall R waves in V6. There are also deep Q waves in left chest leads accompanied with tall T waves, the diastolic overloading pattern of the left ventricle. Thoracic roentgenogram shows cardiac enlargement of the left ventricular type and dilated ascending aorta. Echocardiogram identifies enlarged left ventricle, dilated aorta and flutter of anterior mitral leaflet. Doppler echo can quantify the severity of AR.

Differential Diagnosis

The differential diagnosis of rheumatic AR includes two sets of conditions: (i) conditions associated with a wide pulse pressure like patent ductus arteriosus, arteriovenous fistulae, ventricular septal defect with AR, ruptured sinus of Valsalva, anemia and thyrotoxicosis, (ii) conditions associated with a non-rheumatic regurgitant diastolic murmur like pulmonary regurgitation, AR with ventri-

cular septal defect, ruptured sinus of Valsalva and congenital aortic valve disease. As a rule congenital aortic valve disease is either a leaking bicuspid aortic valve or aortic stenosis. Pure congenital AR is extremely rare. Other conditions that may result in AR include Marfan syndrome, Hurler syndrome and Takayasu aortoarteritis.

Management

Mild to moderate AR is well tolerated for years. There is role for therapy with calcium channel blockers. Significant AR, if associated with either chest pain or left ventricular failure, should be treated surgically. Surgical treatment consists of aortic valve replacement either by homograft or prosthetic valve; valve repair is not feasible for rheumatic AR. Better surgical results are obtained before onset of significant ventricular dysfunction.

Patients planned for valve replacement should be screened for: (i) rheumatic activity; (ii) ability of the patient and the family to monitor lifelong anticoagulation. Aortic valve replacement has fewer long-term complications when compared to mitral valve replacement.

Tricuspid Regurgitation (TR)

Features indicative of TR are seen in 20 to 50% patients of RHD in children. It is often difficult to determine whether TR is organic (due to involvement of the tricuspid valve by the rheumatic process) or functional (due to pulmonary hypertension).

Hemodynamics and Clinical Features

TR results in a systolic backflow of blood from the right ventricle to the right atrium. The systolic leak thus results in a systolic murmur and volume load of the right atrium as well as the right ventricle. As a rule, almost all patients who have TR also have features of pulmonary arterial hypertension. The systolic backflow under pressure results in a prominent systolic wave, the V wave, in the jugular venous pulse as well as the liver. Both the systolic as well as the diastolic murmurs at the tricuspid valve become louder during inspiration. In patients of rheumatic heart disease, the TR may be associated either with MS or with MR. If the TR is associated with MS, it may be either organic or functional due to pulmonary arterial hypertension. If, on the other hand, the TR is associated with dominant or pure MR it is likely organic.

There are no specific symptoms of TR. It is possible that with onset of TR, the dyspnea may be relieved to some extent in patients of MS. The patients may give history of pain in right hypochondrium due to a congested liver and of fatigue due to a decrease in systemic output. In addition to features of TR, there are signs of pulmonary arterial hypertension and those of mitral valve disease. In association with MS, severe TR may result in marked dilatation of the right ventricle and the whole of the anterior surface, including the apex may be formed by

the right ventricle. In such patients, the apex beat is not only displaced outward but also downward. This should not be mistaken for left ventricular enlargement. In these cases, the pansystolic murmur of TR may be heard from the lower left sternal border to the apex. Since the left ventricle is displaced backwards, the MS murmur may be audible only in the axilla or may not be made out at all. It is not uncommon for these patients to be diagnosed as those of MR. Besides clinical signs of TR, the electrocardiogram is helpful in diagnosis. Patients of TR of this severity almost always show severe right ventricular hypertrophy in the electrocardiogram.

Management

Decongestive measures help reduce the severity of TR. Further management depends on the associated mitral valve lesion. TR may resolve following mitral valvotomy. In patients undergoing surgery for the MR, the tricuspid valve can be inspected and tricuspid annuloplasty or repair performed, if needed.

Clinical Problems in Patients with Rheumatic Heart Disease

Two major problems that clinicians face in patients of RHD are discussed below.

Active or Inactive Rheumatic Fever

A lot of judgment or personal bias is involved in this decision. The diagnosis of activity rests on the Jones criteria. Presence of cardiac involvement cannot be used as a major criterion since carditis may be the result of a previous attack of rheumatic fever. However, presence of a pericardial friction rub is evidence of active carditis. If the patient has documented cardiac findings, then the appearance of a new murmur or a significant increase in a pre-existing murmur suggests active rheumatic fever. History of arthralgia or arthritis within a period of less than 12 weeks is suggestive of active rheumatic fever, especially if associated with high sedimentation rate and ASO titers. Despite congestive cardiac failure, it is unusual for the sedimentation rate to be normal in a patient of active rheumatic fever. Patients with rheumatic activity show elevated ASO titers, although there are problems in interpretation of borderline values.

In a Febrile Patient, Is it Active Rheumatic Fever or Infective Endocarditis?

At times separation of rheumatic activity from infective endocarditis can be difficult. The arguments used above for separating active from inactive rheumatic fever can be used for diagnosis of active rheumatic fever. A detailed description of endocarditis follows.

Suggested Reading

- Gewitz MH, Baltimore RS, Tani LY, et al. Revision of the Jones criteria for the diagnosis of acute rheumatic fever in the era of

Doppler echocardiography: a scientific statement from the American Heart Association. *Circulation*. 2015;131:1306-13.

- Bland EF, Jones TD. Rheumatic fever and rheumatic heart disease. A twenty year report on 1000 patients followed since childhood. *Circulation* 1951; 42:836.
- Narula J, Virmani R, Reddy KS, Tandon R. Rheumatic fever. *Amer Registry Path AFIP*. Washington DC, 1999.
- Rheumatic fever and rheumatic heart disease. Report of a WHO expert consultation. World Health Organization, Geneva, 2004 (Technical Report Series No. 923).

INFECTIVE ENDOCARDITIS

Infection of the endocardial lining of the heart is called infective endocarditis, and may involve the endocardium of the valves, the mural endocardium or the endothelium of blood vessels (infective endarteritis). The commonest site of infection is a diseased valve from where the infection can spread along the endothelium.

Etiopathogenesis

Infective endocarditis (IE) predominantly occurs in a diseased heart. The commonest substrate is a damaged endothelium or endocardium resulting from contact with a high velocity jet together with the presence of a significant bacteremia. Endocarditis can occur following a surgical shunt as in Blalock-Taussig shunt. Other congenital lesions, associated with endocarditis are VSD, PDA, tetralogy of Fallot, aortic stenosis and mitral regurgitation. Examples of conditions seldom associated with IE include atrial septal defect and isolated pulmonary valve stenosis.

Infective endocarditis occurs over the mitral or aortic valves in patients with rheumatic heart disease. Patients with prosthetic valves or those who have had a recent cardiac operation are also especially prone to endocarditis. Infections anywhere in body like boils or furuncles, tooth abscess, ear infection, urinary tract infection or osteomyelitis may result in endocarditis. Although interventions like dental procedures, genitourinary procedures or bronchoscopy can be followed by IE, it is uncommon to be able to identify the predisposing event. Perhaps the most important preventable cause of endocarditis is poor dental hygiene. Parenteral drug abuse is a frequent cause of right-sided endocarditis involving the normal tricuspid or the pulmonary valve. Occasionally, it can result in mitral and/or aortic valve disease as well.

The pathogenesis of endocarditis depends on the invasiveness and virulence of the infective organisms. The infection generally starts at a jet lesion, where the high-pressure jet strikes the endocardium or the endothelium. The right ventricular mural endocardium or the tricuspid valve in VSD, aortic endothelium in AS or coarctation of the aorta, ventricular surface of the aortic valve in AR are the usual sites. Endocarditis results in immune-mediated vasculitis and thrombocytopenia.

Bacteremia resulting from an infection such as a boil, furuncle, otitis media or initiated by an intervention such

as cardiac or urinary catheterization or dental extraction is necessary for initiation of endocarditis. Bacteremia may also result from simple events such as brushing teeth. Bacteria that are deposited on the endocardium are covered by fibrin and platelets forming vegetations. Almost any species of bacteria and some species of fungi can cause endocarditis. *Streptococcus viridians*, *S. aureus*, enterococci, *P. aeruginosa* and some gram-negative bacilli are responsible for most episodes. Fungal endocarditis typically results in the setting of chronic hospitalization with indwelling central venous catheters.

Diagnosis

Any fever in a patient with known heart disease raises the question of endocarditis. The minimum criteria for the diagnosis of endocarditis consist of unexplained fever of 7 to 10 days duration in a patient with known heart disease. If this is associated with other clinical manifestations of endocarditis, the diagnosis is more likely.

Endocarditis is subdivided into acute and subacute types, depending on whether the patient presented with a chronic illness or as septicemia. Endocarditis is also identified by the infective organism, for example, viridans endocarditis, staphylococcal endocarditis and enterococcal endocarditis. *S. viridans* results in the subacute form of illness while *S. aureus* and other pyogenic organisms cause a fulminant (acute) and rapidly progressive illness. Identification of the organism is necessary, as it helps determine the choice of antibiotics.

Clinical Features

Infective endocarditis is uncommon below the age of two years. The clinical features may be grouped into those (i) indicating the presence of an infection; (ii) indicating involvement of the cardiovascular system; and (iii) indicating the presence of an immunological reaction to infection. The features indicating the presence of infection consist of fever, chills, rigors, night sweats, general malaise, and weakness, loss of appetite, weight loss and amenorrhea in females. Loss of appetite is a very persistent and important symptom. Arthralgia and diffuse myalgia can occur, however, arthritis does not occur except in acute endocarditis as part of septicemia when it is likely to be monoarticular.

Features indicative of the involvement of the cardiovascular system may be absent in the initial stages. Appearances of left or right heart failure, development of a new murmur or change in a pre-existing murmur, presence of embolic episodes to various parts of the body (stroke from central nervous system embolism, hematuria from renal infarct, left flank pain from splenic infarct, gastrointestinal hemorrhage from mesenteric embolism) indicate involvement of the cardiovascular system. As damage to the valve tissue occurs, regurgitant lesions appear. These regurgitant lesions, aortic, mitral or tricuspid, progress rapidly causing hemodynamic changes that result in congestive failure.

Features of immunological response presenting as vasculitis consist of arthralgia, myalgia, clubbing, splenomegaly and microscopic hematuria. Splinter hemorrhages are hemorrhagic spots under the nails, though suggestive, are not specific for endocarditis as they can result from minor injuries. Petechiae over the skin or mucous membranes and conjunctiva are seen in about 50% patients. Petechiae in the retina are called Roth spots. Osler nodes are tender erythematous nodules over the pulp of fingertips, but are relatively rare. Janeway lesions are non-tender erythematous patches on the palms and soles. Clubbing and splenomegaly tend to appear 3 weeks after the onset of endocarditis.

In the acute form, the symptoms appear early and progress rapidly with hectic fever, chills and rigors. Perforation of valve cusps may result in appearance of acute regurgitant lesions like acute tricuspid, aortic or mitral regurgitation. With inadequate treatment, the course is downhill and death within 6 weeks from the onset. Metastatic lesions causing abscesses in the central nervous system, spleen, mesentery, bones and joints are common. Metastatic abscesses are rare in subacute endocarditis.

Patients with endocarditis of the right side, such as tricuspid or the pulmonary valve, throw emboli to the lungs, which present as repeated episodes of pneumonitis or septic infarcts resulting in lung abscesses. It is common in patients with indwelling central catheters, intravenous drug abuse and VSD. Some patients remain afebrile for several days and yet have large vegetations and elevated acute phase reactants.

Postoperative Endocarditis

Postoperative endocarditis is classified as early (<12 months) and late. Early endocarditis is usually due to pyogenic organisms such as *Staphylococcus*, *Pseudomonas* or gram-negative bacilli introduced at the time of operation. These patients have high fever with chills and rigors and features of septicemia. Late endocarditis is more like native valve endocarditis and the commonest organisms are *S. viridans* and gram-negative bacilli; these patients have a subacute course. Cardiac operations are an important predisposing factor for gram negative endocarditis. Prosthetic valve endocarditis may also be early or late and behaves as above.

Fungal Endocarditis

With extensive use of broad-spectrum antibiotics, yeast and fungal infections occur more frequently than before especially following cardiac operations and in intensive care settings. *Candida* is the commonest fungus; others include *Histoplasma*, *Blastomyces*, *Aspergillus*, *Cryptococcus* and *Mucor*. The organism is cultured from the peripheral blood. Predisposing factors for fungal endocarditis include intravenous drug abuse, indwelling catheters, intensive antibiotic therapy, prolonged steroid administration, radiation, immunosuppressive therapy and prosthetic

valves. Incidence of embolism is high since the fungal vegetations tend to be very large. Despite intensive therapy, mortality is high.

Laboratory Diagnosis

Blood culture is essential for diagnosis. A positive blood culture in a patient with underlying heart disease, suspected to have endocarditis is confirmatory. Three sets of cultures, each containing adequate volumes of blood, taken every half-hour are appropriate and detect 95% cases. The commonest cause for negative cultures is prior antibiotic therapy or unsatisfactory culture technique. Infection with unusual organisms, anaerobic organisms and fungi require special mediums and incubation for 2–3 weeks. Arterial sampling does not offer any advantage over venous samples. Other investigations, which provide supportive evidence for the diagnosis, include: (i) normocytic normochromic anemia, (ii) moderately elevated total leukocyte count, (iii) reduced platelets, (iv) elevated sedimentation rate and C-reactive protein, and (v) microscopic hematuria and albuminuria.

Echocardiography

Echocardiography is a valuable diagnostic tool, especially in patients with culture negative endocarditis. Complications like ruptured chordae, perforated cusps and flail cusps can be identified. Vegetations more than 2 mm can be identified on echocardiography, but its sensitivity is dependent on the site of involvement. For aortic and mitral valves, the sensitivity is more than 90%, while for tricuspid and pulmonary valves, it is 70%. The presence of vegetations has high negative as well as positive predictive value for confirming the diagnosis of infective endocarditis. Transesophageal echocardiography is useful for diagnosing prosthetic valve endocarditis and valve ring abscess.

Complications

Damage to valve cusps or perforation and rupture of chordae tendinae might result in acute regurgitant lesions and hemodynamic deterioration. Migration of vegetations may result in embolic neurological deficit, renal infarcts with hematuria, mesenteric infarct and melena, and loss

of fingers or toes due to obstruction of blood supply. Damage to the vasa vasorum of blood vessels due to vasculitis may result in the formation of mycotic aneurysms that can rupture and result in massive bleeding. The kidneys suffer from embolic infarct with hematuria and focal or diffuse membranoproliferative glomerulonephritis resulting in albuminuria and microscopic hematuria. The findings of IgG, IgM and complement deposits on the glomerular basement membrane indicate that it is an immune complex nephritis. Renal insufficiency tends to appear beyond three weeks of the onset of endocarditis and is progressive until the endocarditis is cured; hematuria can persist for 3–6 months. Even advanced renal insufficiency tends to regress and renal function returns to normal after the endocarditis has been cured.

Treatment

The principles of management consist of: (i) identification of organism and its antibiotic sensitivity; and (ii) prompt, appropriate and prolonged antimicrobial treatment to cure and prevent relapse. If the blood culture is positive, the choice of antibiotics is dictated by the antibiotic sensitivity. If the culture is negative, empirical therapy covering a wide range of organisms is necessary. If the culture is positive, the culture plate should not be discarded. After starting the antibiotic treatment, patient's serum diluted to 1:8 parts or more should be used to determine if it inhibits the growth of the organism in subculture, to indicate the efficacy of treatment. Common organisms causing endocarditis, antibiotic of choice and duration of treatment is shown in Table 16.18. Over the last 2–3 decades are, the threshold for surgery for treatment of endocarditis is lowered considerably. Surgery is indicated, if response to antibiotics is suboptimal, in presence of large vegetation, damage to valve apparatus with severe or refractory heart failure and for fungal endocarditis.

Fungal endocarditis: Fungal endocarditis is resistant to therapy. Therefore, after 2 to 3 weeks of appropriate treatment (amphotericin B), the patient should be operated to remove the fungal mass. The antifungal agents should be continued postoperatively for a minimum of 6 weeks. Relapse following apparently successful treatment can occur even up to 2 years.

Table 16.18: Choice of antibiotics and duration of treatment for infective endocarditis

Organism	Option I	Option II	Duration, weeks
<i>Streptococcus viridans</i>	Penicillin, aminoglycoside	Ceftriaxone, aminoglycoside	4
Group A streptococci	Penicillin, aminoglycoside	Ceftriaxone, aminoglycoside	4
<i>Streptococcus faecalis</i>	Ampicillin, aminoglycoside	Vancomycin, aminoglycoside	4–6
<i>Staphylococcus aureus</i>	Cloxacillin/cefazolin, aminoglycoside	Vancomycin, aminoglycoside	6
<i>Escherichia coli</i>	Ceftriaxone, aminoglycoside	Ampicillin, aminoglycoside	6
<i>Pseudomonas</i> spp.	Ticarcillin, aminoglycoside	Meropenem, aminoglycoside	6
Culture negative	Ampicillin, aminoglycoside	Ampicillin, aminoglycoside	6

The choice of antibiotics should ideally be guided by culture results and organism sensitivity

Culture negative endocarditis: Patients with culture negative endocarditis need to be treated empirically. The choice of treatment is dictated by circumstances anticipating the most likely organism. If the patient seeks help late and has significant renal insufficiency, the medication dose might need to be modified.

Prophylaxis

There have been major changes in the recommendations for prevention of endocarditis. Patients with congenital heart defects such as ventricular septal defect, bicuspid aortic valve and valvar pulmonary stenosis do not routinely require prophylaxis. According to the guidelines of the American Heart Association, since the absolute lifetime risk of endocarditis is small, prophylaxis is only recommended for patients with conditions associated with increased risk of adverse outcome from endocarditis (Table 16.19). The focus of prophylaxis has shifted from prophylactic antibiotics for a dental procedure to the prevention of dental caries, which reduces the incidence of bacteremia from daily activities and is, therefore, more important. These guidelines need validation in developing countries where oral hygiene is unsatisfactory and regular dental health screening is not instituted in the majority.

Antibiotic recommendations for those who need prophylaxis are as follows:

Dental Treatment

- i. Penicillin V 2 g given orally on an empty stomach 1 hour before dental treatment, followed by 0.5 g every 6 hours for 3 days, or
- ii. Crystalline penicillin G 1,000,000 U mixed with 600,000 U of procaine penicillin 30–60 min before dental treatment, followed by oral penicillin as above, or
- iii. Single dose of amoxicillin 50 mg/kg orally 1 hour before the procedure
- iv. Patients with prosthetic heart valves: Injectable penicillin with streptomycin or gentamicin IM 1 hour before the procedure.

Genitourinary and Gastrointestinal Procedures

- i. Amoxicillin 25 mg/kg by mouth 1 hour before, with gentamicin 2 mg/kg IM 30 min before procedure; both

Table 16.19: Conditions where antibiotic prophylaxis is definitely recommended

Prosthetic cardiac valve; prosthetic material used for valve repair
 Past history of infective endocarditis
 Uncorrected cyanotic heart disease, palliative shunts and conduits
 During first 6 months following complete surgical repair of congenital heart disease
 Repaired congenital heart disease with residual defects at or adjacent to the site of repair
 Cardiac transplantation recipients with cardiac valvulopathy

are repeated at least for 2 more doses after the procedure

- ii. Gastrointestinal surgery: Add metronidazole
- Infective endocarditis is a life-threatening disease with significant mortality and morbidity. Treating physicians should advise patients and parents regarding prevention of endocarditis. The maintenance of good oral hygiene is encouraged. Careful attention to prophylaxis, when indicated, is useful.

Suggested Reading

- Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis. Guidelines from American Heart Association. *Circulation* 2007;116(15):1736–54.

MYOCARDIAL DISEASES

Myocarditis

Myocarditis is chiefly caused by ECHO, Coxsackie B, rubella, herpes and influenza viruses. Diphtheritic myocarditis is occasionally noted in South Asia. The presentation may be abrupt, with cardiovascular collapse, or insidious development of heart failure. Arrhythmias and conduction disturbances may be present. Examination shows cardiac enlargement, tachycardia, muffled heart sounds and features of congestive cardiac failure. The electrocardiogram shows low voltages, and nonspecific ST-T changes. Chest X-ray reveals cardiac enlargement with pulmonary venous congestion.

Treatment includes management of congestive failure. Digoxin should be used cautiously, preferably in half to three-quarters the standard dose. Steroids are of uncertain value and should be avoided during acute viremia. ACE inhibitors are a useful adjunct to therapy. The utility of IV immunoglobulins is not proven. Severe heart failure may require admission in an intensive care unit and mechanical ventilation. A variable proportion of children with myocarditis recover completely.

Cardiomyopathies

The term cardiomyopathy is an intrinsic disease of the myocardium which is not associated with a structural deformity of the heart. It is considered primary cardiomyopathy when the etiology is unknown, and secondary, if the myocardial disease is attributed to a systemic disease. Myocardial diseases are classified clinically as (i) dilated, (ii) restrictive, and (iii) hypertrophic cardiomyopathy.

A significant proportion of patients have correctible causes of left ventricular dysfunction that mimics dilated cardiomyopathy (Table 16.20).

Dilated Cardiomyopathy

Dilated cardiomyopathy (DCM) is the commonest form of myocardial disease. The onset of cardiac failure may be acute or insidious. Cardiomegaly and S3 gallop are present. Murmur of MR and uncommonly, that of

Table 16.20: Correctable causes of left ventricular dysfunction in children

Condition	Clues to diagnosis
Congenital cardiovascular diseases	
Anomalous left coronary artery from pulmonary artery	ECG changes of myocardial infarction in I, aVL, V4-6; 2D, Doppler echocardiography
Severe coarctation of aorta	Weak femoral pulses; echocardiography
Critical aortic stenosis	Auscultation; echocardiography
Acquired cardiovascular diseases	
Takayasu arteritis	Asymmetric pulses, bruit, Doppler, scintigraphy, angiography
Tachyarrhythmia	Disproportionate tachycardia
Ectopic atrial tachycardia	ECG
Permanent junctional re-entrant tachycardia	Esophageal electrophysiology
Chronic atrial flutter	
Severe hypertension	Blood pressure; fundus examination
Metabolic and nutritional causes	
Hypocalcemia	Setting (newborns; severe hypoparathyroidism); Chvostek, Trousseau signs; prolonged QTc on ECG
Infantile beri-beri	Prominent edema, diarrhea and vomiting; documented thiamine deficiency in mother (if breastfed)
Carnitine deficiency	Hypoglycemia, congestive heart failure; coma; ventricular hypertrophy; high ammonia, low carnitine
Hypophosphatemia	Poorly controlled diabetes; following hyperalimentation, nutritional recovery syndrome; recovery from severe burns; hyperparathyroidism; vitamin D deficiency; hypomagnesemia, Fanconi syndrome; malabsorption
Selenium deficiency	Keshan disease (endemic in parts of China); chronic parenteral nutrition, AIDS

tricuspid regurgitation, may be present. The patients are prone to embolic phenomena. The electrocardiogram shows non-specific ST and T changes with or without left ventricular hypertrophy, conduction disturbances, arrhythmias or pseudo-infarction pattern. Chest X-ray shows cardiomegaly with pulmonary venous hypertension. Echocardiogram confirms dilated ventricular cavity without hypertrophy of the left ventricle or the septum; left ventricular contractility is reduced.

Treatment consists of decongestive therapy with vasodilators, especially ACE inhibitors. Beta-blockers control the heart rate and reduce catecholamine-induced vasoconstriction. Carvedilol, a beta-blocker with peripheral vasodilator effect, is useful in management of CCF, especially in patients with disproportionate tachycardia. The starting dose is 0.1 mg/kg/day once daily, which is gradually increased to 0.5 mg/kg/day.

Gradual improvement occurs in a significant proportion. The prognosis for individual patients cannot be predicted and treatment should continue for prolonged periods. Despite aggressive therapy, about one-third of children with cardiomyopathy continue to deteriorate and eventually become refractory. Intermittent (weekly or bi-weekly) dobutamine or levosimendan infusions are useful in some patients. It is important to be aware of a number of correctable conditions that can mimic cardiomyopathy (Table 16.24). Clues to these conditions are obtained on clinical and laboratory findings, or ECG (Fig. 16.44).

Anomalous Left Coronary Artery from Pulmonary Artery (ALCAPA)

ALCAPA should be considered in a patient with heart failure with or without a murmur suggesting MR and a pattern on electrocardiogram that suggests anterolateral myocardial infarction (Fig. 16.45). Echocardiography shows a large right coronary artery and absence of the origin of left coronary artery from the aorta. The left coronary artery is seen to arise from the pulmonary artery and shows flow in the reverse direction in the left anterior descending artery and the left circumflex artery. This flow reversal results from collateral flow into the left coronary system from the right coronary artery. Angiography is rarely necessary for the diagnosis. The treatment is surgical and requires mobilization and translocating the origin from pulmonary artery to aorta.

Restrictive Cardiomyopathy (RCM)

It is relatively uncommon in children. Restriction to ventricular filling is usually associated with either endomyocardial fibrosis or endocardial fibroelastosis with a normal or smaller than normal left ventricle. Endomyocardial fibrosis was previously endemic in Kerala, but is now rare. There is dense fibrosis in the apical and inflow regions of the left and right ventricles. Papillary muscles and chordae may be tethered by the connective tissue, resulting in severe mitral or tricuspid regurgitation.

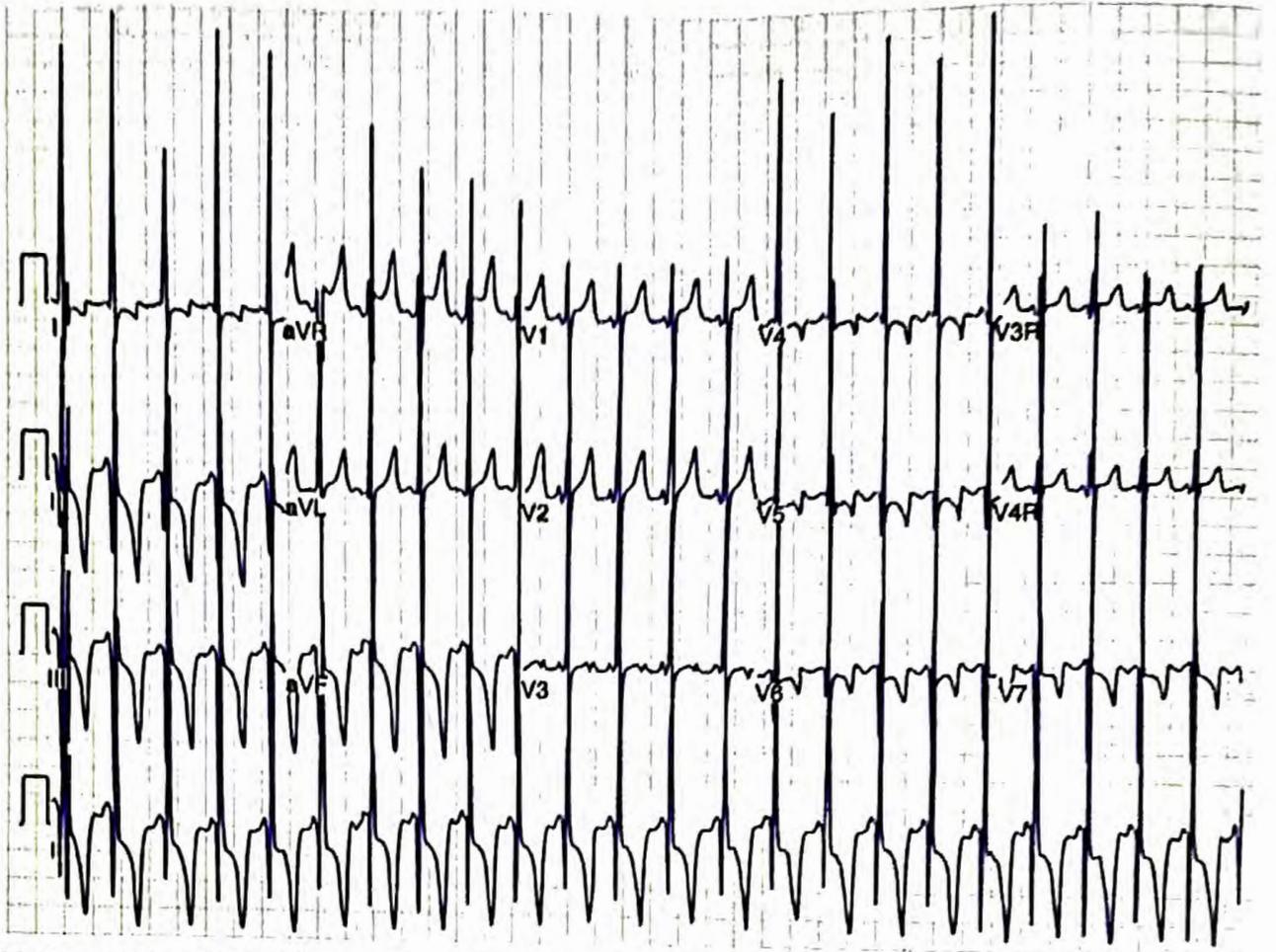


Fig. 16.44: Pompe disease with biventricular hypertrophy. Note the characteristically tall QRS voltages, and T wave inversion

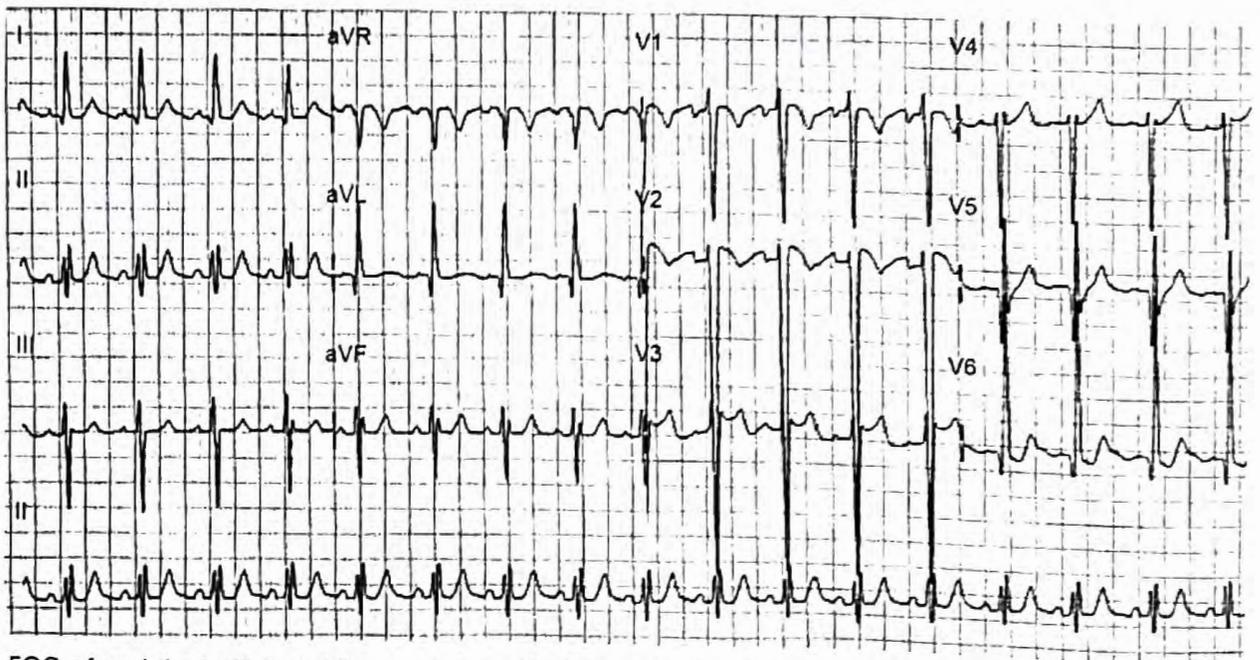


Fig. 16.45: ECG of an infant with heart failure and ventricular dysfunction. The leads I, aVL and V6 show q waves and subtle ST segment elevation suggesting myocardial infarction. The echocardiographic diagnosis of anomalous left coronary artery from pulmonary artery was confirmed at surgery.

16 Patients with predominant left-sided involvement have symptoms of dyspnea, orthopnea, hemoptysis and embolic phenomena. On examination, there is cardiomegaly with or without findings of MR. With predominant right-sided

involvement, patients present with fatigue, pedal edema and ascites. There is cardiomegaly with prominent cardiac pulsations; S3 gallop and TR murmur may be present. Treatment consists of decongestive therapy.

Restrictive cardiomyopathy of other varieties is characterized by features of left- and right-sided failure with a normal-sized heart. Clinically, or even following cardiac catheterization, it may be difficult to distinguish from constrictive pericarditis. Children with restrictive cardiomyopathy show left-sided involvement and disproportionate pulmonary hypertension. Echocardiogram helps exclude constrictive pericarditis. Treatment is supportive with diuretics; prognosis is poor without transplantation.

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy may occur (a) without outflow obstruction, or (b) with outflow obstruction. Obstructive cardiomyopathy is also known as idiopathic hypertrophic subaortic stenosis (IHSS) or asymmetrical septal hypertrophy (ASH) or hypertrophic obstructive cardiomyopathy (HOCM).

HOCM is uncommon in children. Pathologically, there is asymmetrical hypertrophy of the ventricular septum. The free walls of the left and right ventricles are hypertrophied to a lesser extent. The ventricular septum bulges into the left ventricle, and the anterior mitral valve leaflet causes obstruction in the left ventricular outflow during systole. Uncommonly, there is right ventricular outflow obstruction as well.

Patients present with exertional dyspnea, anginal pain, palpitation and syncope; sudden death can occur. The pulse has a sharp upstroke with a bisferiens character. The apex beat is forcible or heaving. An ejection systolic murmur of varying intensity is heard at left sternal edge. A pansystolic murmur or MR and a fourth sound may be heard at the apex. The ejection systolic murmur increases in intensity with maneuvers which increase the myocardial contractility or decrease the volume of the left ventricle. The murmur decreases in intensity with procedures that increase left ventricular volume or decrease the myocardial contractility. Thus, sudden squatting tends to decrease the intensity of the murmur whereas standing upright from sitting position by decreasing the venous return tends to decrease the left ventricular size and increases the intensity of the ejection systolic murmur. The electrocardiogram shows left ventricular hypertrophy, with or without ischemic changes. Echocardiogram shows disproportionate hypertrophy of the ventricular septum, systolic anterior motion of the anterior leaflet of the mitral valve and mid-systolic closure of the aortic valve.

Hypertrophic cardiomyopathy may have an autosomal dominant pattern of inheritance with variable but penetrance. Mutations in beta-myosin, troponin T and alpha-tropomyosin genes are believed to be responsible. Magnetic resonance imaging may help identify myocardial fibrosis and patients at risk of sudden cardiac death. Noonan syndrome is associated with hypertrophic cardiomyopathy.

Patients with hypertrophic obstructive cardiomyopathy should have a 24-hr Holter to document the presence of arrhythmias. These patients should avoid strenuous games and exercise. Digitalis and other inotropic drugs, diuretics and nitrates are contraindicated. Beta-blockers decrease myocardial contractility and thus reduce the obstruction.

PERICARDIAL DISEASES

Inflammatory diseases of the pericardium may present as acute dry pericarditis, pericarditis with effusion or chronic constrictive pericarditis (Table 16.21).

Acute Pericarditis

Acute pericardial inflammation causes precordial pain, which may be dull, sharp or stabbing in character. Occasionally, the pain may be felt over the neck and shoulder and may worsen on lying down. The child is dyspneic and has cough. The pattern of fever and toxemia depends on the etiology. The diagnostic physical sign is the pericardial friction rub, which is a rough scratchy sound, with three components, a systolic, diastolic and a presystolic scratch. It can be heard anywhere over the precordium, is unrelated to the respiratory cycle and increases on pressing the chest piece of stethoscope over the precordium. The electrocardiogram shows generalized ST elevation in the initial stages. Later the ST segment is isoelectric and T waves are inverted. Still later, the ST segment may be depressed.

If effusion develops, the cardiac silhouette increases in size. The heart sounds become muffled and evidence of peripheral congestion in the form of raised jugular venous pressure, hepatomegaly and edema may develop. The pericardial friction rub may persist or disappear. If fluid accumulates rapidly, there is marked interference with cardiac filling resulting in features of cardiac tamponade such as: (i) rising jugular venous pressure; (ii) paradoxical inspiratory filling of the neck veins; (iii) increasing heart rate; (iv) falling pulse pressure; and (v) appearance of pulsus paradoxus. The electrocardiogram shows non-specific ST and T changes with low voltage tracings. Chest X-ray shows cardiomegaly with smooth outline and blunting of the cardiohepatic angle. Echocardiogram

Table 16.21: Etiology of pericardial diseases

<i>Acute</i>	<i>Chronic</i>
Bacterial	Constrictive pericarditis
Viral	Tuberculous
Tuberculous	Idiopathic
Rheumatic fever	Post-pyogenic
Collagen disorders	Post-traumatic
Uremic	
Postoperative	
Idiopathic	

shows an echo-free space behind the posterior left ventricular wall. Evidence of right atrial or right ventricular diastolic collapse indicates a hemodynamically significant effusion. Pericardiocentesis is done to determine the etiology and relieve cardiac tamponade, if present. Treatment will depend on the etiology. Surgical drainage is indicated, if pyopericardium is suspected.

Chronic Constrictive Pericarditis

Constrictive pericarditis is not uncommon in our country, following tuberculous infection and less commonly, following pyogenic pericarditis. Fibrous thickening of both layers of the pericardium encases the heart and restricts filling of both the ventricles equally; calcification is rare in childhood. The myocardium is not involved initially, but the fibrous process may infiltrate the myocardium. Dyspnea, fatigue and progressive enlargement of the abdomen are common.

Jugular venous pressure is always elevated with equally prominent 'a' and 'v' waves and a prominent 'y' descent. Inspiratory filling of neck veins (Kussmaul sign) is seen in about one-half. Liver is enlarged and pulsatile; ascites with unilateral or bilateral pleural effusion is common. Splenomegaly may also be present. Pulse is fast and of low volume and pulsus paradoxus may be present. The precordium is quiet with a normal-sized heart. First and second sounds are normal. An early third heart sound (pericardial knock) is commonly heard. The EKG shows low voltage in 75% patients and non-specific ST-T changes in all cases. Normal electrocardiogram is against the diagnosis of constrictive pericarditis. Occasionally, there is right axis deviation or right ventricular hypertrophy pattern.

The chest X-ray shows normal-sized heart with ragged or shaggy borders and prominent superior vena cava merging with the right atrial margin. The lungs may show pleural effusion and plate atelectasis. Hemodynamic studies reveal elevation of right atrial mean pressure, right ventricular end-diastolic pressure, pulmonary artery diastolic pressure and the pulmonary artery wedge pressures, which are identical. The right ventricular end-diastolic pressure is more than one-third of the systolic pressure. The cardiac index may be normal or reduced, but the stroke volume is low. In some cases, therapy with digitalis may improve the hemodynamics indicating presence of myocardial dysfunction.

Surgical decortication of the pericardium results in normalization of the hemodynamic abnormalities in most cases. Some cases of long-standing constrictive pericarditis with myocardial dysfunction may improve slowly or have residual myocardial dysfunction. A full course of antitubercular treatment often follows pericardiectomy if the cause is not clear.

SYSTEMIC HYPERTENSION

Essential (primary) hypertension, the most common form of hypertension in adults, is increasingly recognized in

children and adolescents. Systemic hypertension is rare in infants and young children, but when present usually due to an underlying disease (secondary hypertension). The prevalence of essential hypertension increases with age. Approximately 3–4% of children and adolescents have hypertension and 10% have elevated blood pressure.

Etiology

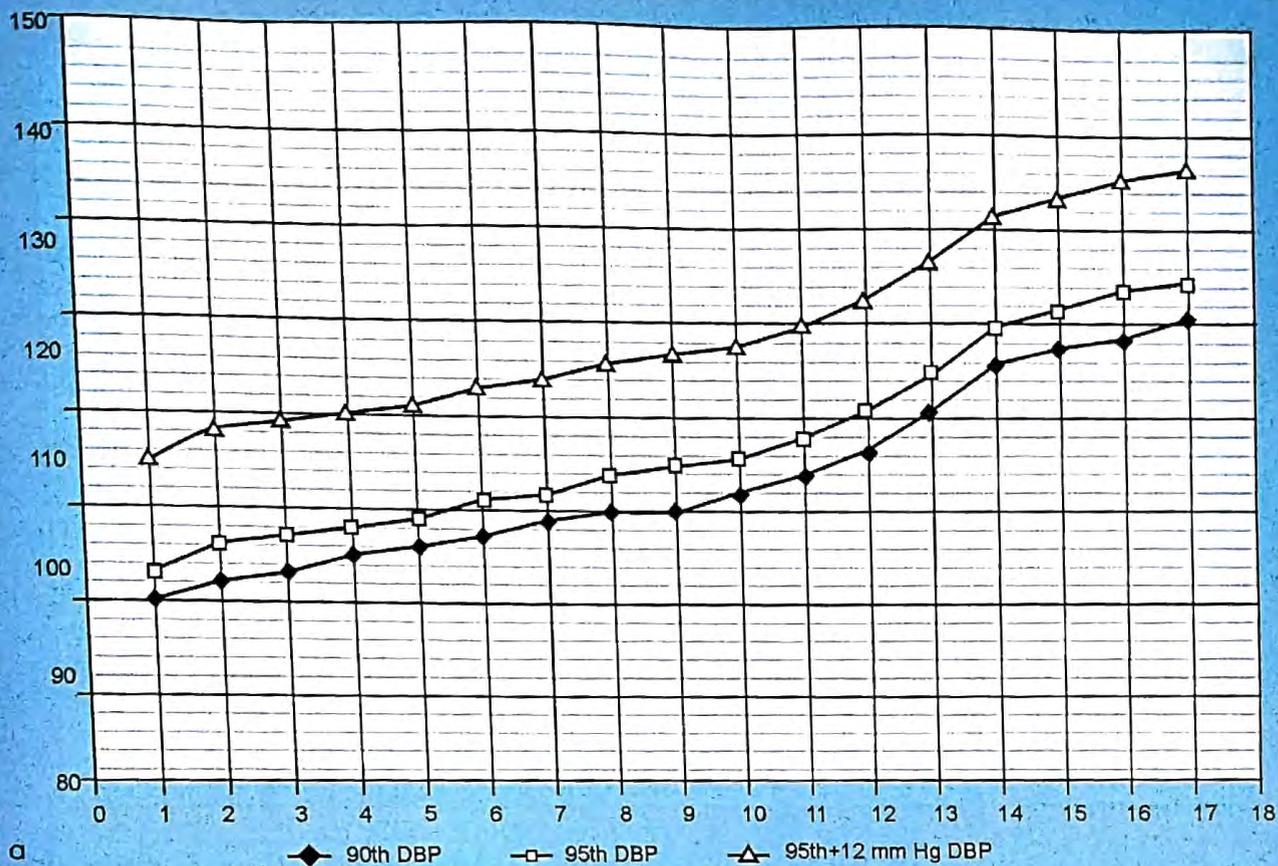
The etiology of essential hypertension is multifactorial. Obesity, insulin resistance, activation of sympathetic nervous system, disorders in sodium homeostasis and renin-angiotensin system, vascular smooth muscle structure and reactivity, uric acid levels, genetic factors and fetal programming have been implicated. There is often a history of hypertension in the parents.

Approximately 90% of secondary hypertension in children are due to renal or renovascular abnormalities. The major renal causes are chronic glomerulonephritis, reflux or obstructive nephropathy, polycystic or dysplastic renal diseases and renovascular hypertension. Coarctation of the aorta and Takayasu arteritis are leading vascular causes. Hyperthyroidism, hyperparathyroidism, congenital adrenal hyperplasia, Cushing syndrome, primary aldosteronism, pheochromocytoma and neuroblastoma are uncommon.

Transient or intermittent hypertension may be caused by postinfectious glomerulonephritis, rapidly progressive (crescentic) glomerulonephritis, Henoch-Schönlein purpura, hemolytic uremic syndrome, acute tubular necrosis, and renal trauma. Raised intracranial pressure, Guillain-Barré syndrome, burns, Stevens-Johnson syndrome, porphyria, poliomyelitis, encephalitis, drugs (e.g. sympathomimetic agents, steroids, cyclosporine), heavy metal poisoning (e.g. lead, mercury) and vitamin D intoxication may result in acute elevation of blood pressure.

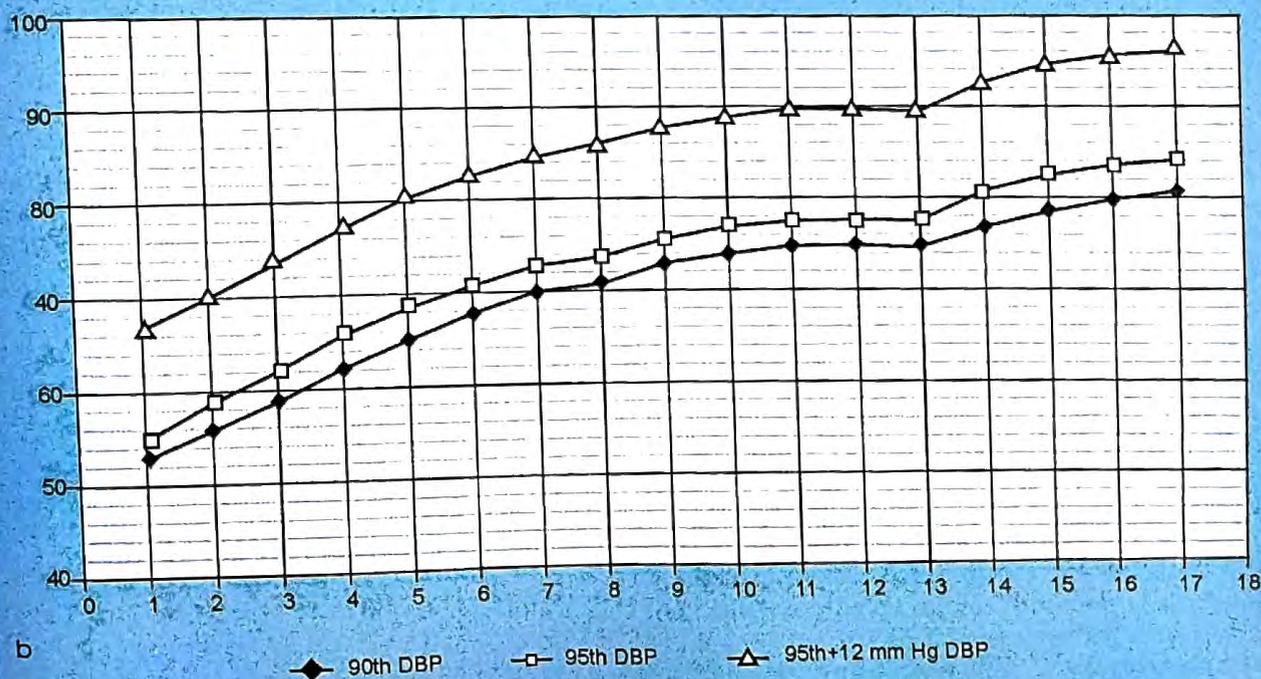
Definition and Staging

The American Academy of Pediatrics (AAP) clinical practice guidelines for screening and management of high blood pressure in children and adolescents (2017) provide revised normative data on distribution of blood pressure in normal weight children. Hypertension is defined as average systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) that is 95th percentile for age, sex and height on three different occasions. Elevated blood pressure is defined as SBP or DBP that are 90th percentile but <95th percentile. Adolescents with blood pressure between 120/80 and 129/<80 mm Hg are also considered as having elevated blood pressure while hypertension is defined by blood pressure >130/80 mm Hg in this age group. Children with blood pressure between the 95th percentile and 95th plus 12 mm Hg are classified as stage I hypertension and children with blood pressure above 95th plus 12 mm Hg have stage II hypertension. Figures 16.46 and 16.47 indicate blood pressure cut off for stage I and stage II hypertension in girls and boys with



a

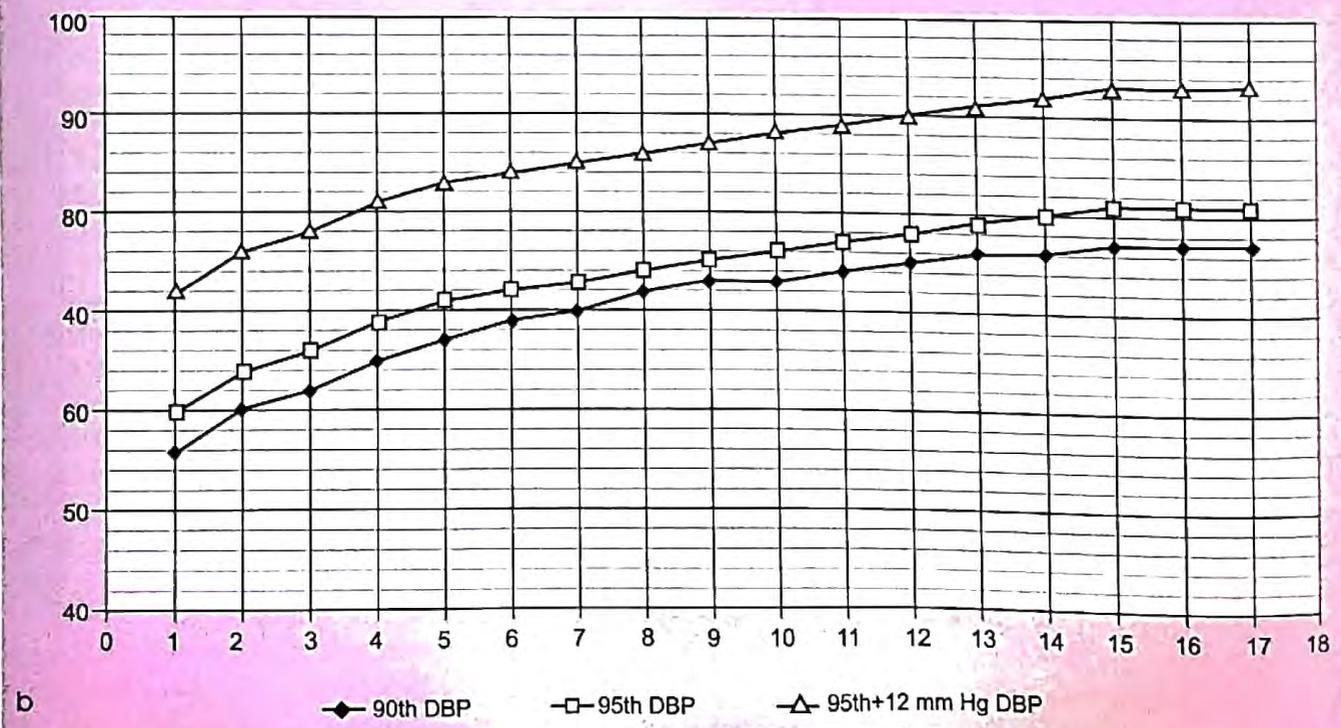
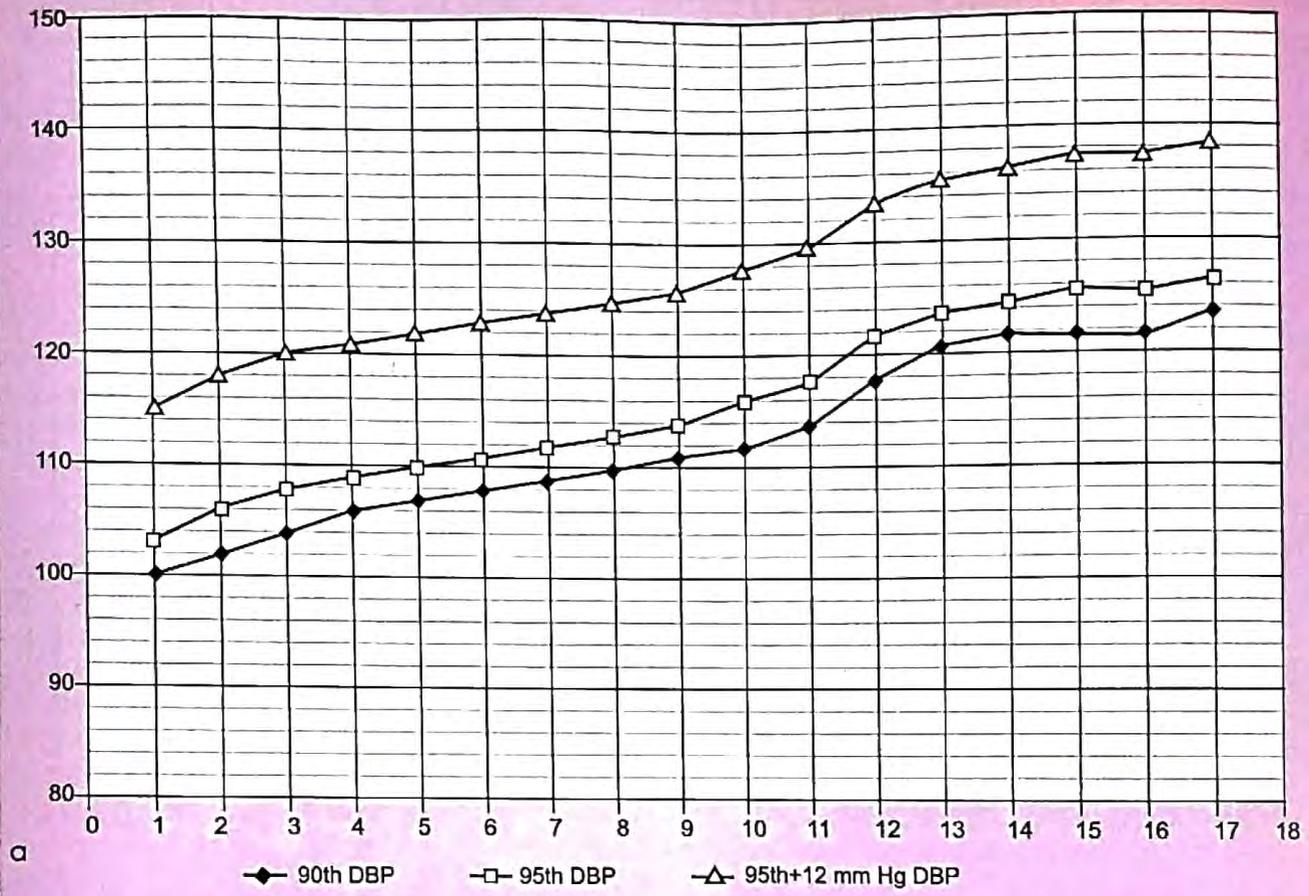
◆ 90th DBP □ 95th DBP △ 95th+12 mm Hg DBP



b

◆ 90th DBP □ 95th DBP △ 95th+12 mm Hg DBP

Fig. 16.46: Blood pressure levels for boys at 50th percentile for height. Chart depicting 90th (closed diamonds), 95th (open squares) and 95th + 12 mm Hg (open triangles) percentile values for (a) systolic and (b) diastolic blood pressures, representing cut values for the diagnosis of elevated blood pressure and stage I and stage II hypertension, respectively, in boys (Based on off values for the diagnosis of elevated blood pressure and management of high blood pressure in children and adolescents, 2017)



16

Fig. 16.47: Blood pressure levels for girls at 50th percentile for height. Chart depicting 90th (closed diamonds), 95th (open squares) and 95th + 12 mm Hg (open triangles) percentile values for (a) systolic and (b) diastolic blood pressures, representing cut off values for the diagnosis of elevated blood pressure and stage I and stage II hypertension, respectively in girls (Based on American Academy of Pediatrics clinical practice guidelines for screening and management of high blood pressure in children and adolescents, 2017)

Table 16.22: Screening blood pressure cut-offs useful for screening for hypertension in children

Age		1	2	3	4	5	6	7	8	9	10	11	12	>13
Girls	SPB	98	101	102	103	104	105	106	107	108	109	111	114	120
	DBP	54	58	60	62	64	67	68	69	71	72	74	75	80
Boys	SBP	98	100	101	102	103	105	106	107	107	108	110	113	120
	DBP	52	55	58	60	63	66	68	69	70	72	74	75	80

stature at median for age. Simplified tables, which can be used in office practice, to define patients who need evaluation are available (Table 16.22). Blood pressure cut-offs identifying children in the outpatient who need further evaluation are provided in Table 16.22.

Measurement of Blood Pressure

Blood pressure can be measured by auscultation, palpation, oscillometry and Doppler ultrasound. While oscillometric devices are readily available and easy to use, they are susceptible to artifacts and require calibration. Hence, the auscultatory method preferred for confirming the diagnosis of hypertension. Blood pressure should be measured after a period of adequate rest (3–5 min), twice on each occasion in the right arm in seated position. The stethoscope is placed over the brachial artery pulse, below the bottom edge of the cuff. An appropriate selection of cuffs is necessary (Table 16.23). Cuffs should have a bladder width of approximately 40% of the arm circumference midway between the olecranon and acromion. The bladder should cover at least two-thirds of the upper arm length and 80–100% of its circumference.

The cuff is inflated rapidly to occlude the brachial artery (at least 20–30 mm Hg above expected SBP). The cuff is deflated slowly at the rate of 2–3 mm Hg per second while auscultating at the cubital fossa. Systolic pressure is indicated by the appearance of Korotkoff sounds (phase I) and diastolic pressure by its disappearance (phase V).

Ambulatory blood pressure monitoring (ABPM) is a procedure where the child wears a device that records blood pressure at regular intervals (usually every 20–30 min), through a 24-hr period while the child performs regular

activities, including sleep. ABPM is more accurate in making a diagnosis of hypertension, and its parameters correlate more strongly with end organ damage, than casual blood pressure. ABPM is recommended in children with high risk of hypertension (chronic kidney disease, diabetes mellitus, obstructive sleep apnea, preterm children and children with obesity), where clinic blood pressure might be normal but ambulatory blood pressure is high (masked hypertension) or vice-versa (white coat hypertension).

Clinical Features

Hypertension in children is usually asymptomatic unless blood pressures are high or sustained. Symptoms are common with secondary hypertension. Headache, dizziness, irritability, epistaxis, anorexia, visual changes and seizures occur with significant elevations of blood pressure. Marked increase in blood pressure may result in cardiac failure, pulmonary edema and renal dysfunction. Hypertensive encephalopathy presents with vomiting, ataxia, stupor and seizures. Hypertensive crisis may present with decreased vision, symptoms of encephalopathy, cranial nerve palsies, cardiac failure and rapid worsening of renal function. Eye examination shows papilledema or retinal hemorrhages. Subclinical target organ injury may occur in asymptomatic children and include left ventricular hypertrophy, increased carotid intima media thickness, retinopathy and microalbuminuria. Children with chronic renal disease present with polyuria, polydipsia, pallor, weight loss and growth retardation.

Evaluation

Children with confirmed hypertension need evaluation to identify potential causes, identify comorbidities and extent of target organ damage. Patients require a detailed history and physical examination. The history should include sleep and treatment history, smoking and alcohol intake, drug abuse and family history (early cardiovascular diseases, hypertension, diabetes, dyslipidemia or renal diseases). The birth history and growth patterns are elicited. Examination should focus on identification of pallor, edema, syndromic facies, ambiguous or virilized genitalia, rickets, goiter, and skin changes (café au lait spots, neurofibromas, rash, striae). Examination of eyes is done for proptosis, extraocular muscle palsies and fundal changes. Detailed examination is done for asymmetry of peripheral pulses, upper and lower limb

Table 16.23: Recommended dimensions for blood pressure cuff bladders

Age group	Width (cm)	Length (cm)	Maximum arm circumference (cm)
Newborn	4	8	10
Infant	6	12	15
Child	9	18	22
Small adult	10	24	26
Adult	13	30	34
Large adult	16	38	44
Thigh	20	42	52

Maximum arm circumference is calculated such that the largest arm would still allow bladder to encircle arm by at least 80% (Adapted from Fourth Task Force report)

blood pressures, cardiomegaly, heart rate, cardiac rhythm abnormalities, murmurs and pulmonary edema. Abdominal examination may show hepatomegaly, abdominal mass or epigastric or renal bruit.

Laboratory evaluation includes estimation of blood levels of creatinine and electrolytes and urinalysis. Renal ultrasound may identify a mass, scars, congenital anomalies or disparate renal size. The evaluation of comorbidities requires fasting lipid profile and glucose levels to identify dyslipidemias, metabolic syndrome and diabetes mellitus. Children with history of sleep-disordered breathing may benefit from polysomnography. An echocardiogram is used to identify left ventricular hypertrophy and screen for coarctation of aorta. Children with suspected renovascular hypertension are investigated by Doppler studies or angiography. Investigations like plasma renin and aldosterone, plasma/urine steroid levels and plasma/urine catecholamines are rarely required.

Treatment

The treatment of hypertension in children and adolescents has two components, therapeutic lifestyle interventions and pharmacotherapy. Weight reduction, increased physical activity and dietary interventions are the major therapeutic lifestyle interventions. Weight reduction in overweight children results in significant reduction of blood pressure, and decreases other cardiovascular risk factors like dyslipidemia and insulin resistance. Current physical activity recommendations for children include 30 to 60 minutes per day at least 3 to 5 days per week or more of moderate intensity aerobic exercise plus limitation of sedentary activity to less than 2 hours per day. Children with hypertension may benefit from a dietary approach to stop hypertension (DASH) diet which incorporates increased intake of fresh fruits and vegetables, fiber, non-fat dairy and whole grain as well as a reduction in sugar and salt consumption. The recommendation for adequate sodium intake is 1.2 g/day for children 4 to 8 years old and 1.5 g/day for older children.

Children with symptomatic essential hypertension, hypertension associated with chronic kidney disease, diabetes-associated hypertension, evidence of target-organ damage (left ventricular hypertrophy), or failed non-pharmacologic interventions require pharmacologic therapy. Agents approved for management of hypertension include angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), beta blockers, calcium channel blockers and diuretics (Table 16.24). ACE inhibitors, calcium-channel blockers and thiazide diuretics should be used as first-line drugs in children. ACE inhibitors or ARB are preferred in patients with diabetes or chronic kidney disease, however, these agents should be used carefully in girls of childbearing age due to risk of injury to the developing fetus.

The goal of therapy for children and adolescents with hypertension is to reduce blood pressure below 90th percentile and <130/80 mm Hg in adolescent, except in presence of chronic kidney disease, where or target organ damage, when the goal is to reduce blood pressure to less than 50 to 75th percentile. Pharmacotherapy is done in a stepped-care approach and usually starts with a low dose of a single agent (step 1). If blood pressure control is not achieved, the dose is titrated 4–6 weeks until blood pressure goals are achieved or the maximum dosage for the drug is reached (step 2). If adequate blood pressure control is not achieved with a single agent, a second agent with a complementary mechanism of action should be added and dose titrated until adequate control or dosage limit is reached (step 3). If adequate blood pressure control is not achieved with a two-drug regime, a third agent from a different drug class should be added (step 4).

In the case of hypertensive emergencies, the safest way is to lower blood pressure up to ~95th percentile by using a medication that is administered by continuous intravenous infusion in an intensive care unit. In general, the pressure should be reduced by up to 25% over the first 8 hours (10% in the first hour), followed by remainder planned reduction over next 12–24 hours. Too rapid a reduction in blood pressure may lead to cerebral ischemia. Drug choices include labetalol, nicardipine and sodium nitroprusside. Nicardipine is preferred in children due to its efficacy and safety, but is not easily available (Table 16.25). Many patients in hypertensive crisis are volume depleted because of a combination of decreased oral intake and pressure natriuresis. Volume repletion in such conditions will help restore tissue perfusion and prevent a precipitous fall in blood pressure that may occur with intravenous antihypertensive therapy.

Prevention

Prevention of high blood pressure in children can be achieved by preventing childhood obesity. Regular physical activity, consumption of fruits and vegetables, moderate salt intake and limited consumption of processed food items and animal fats, and reducing sedentary activities will aid in lowering the prevalence of high blood pressure in children.

Suggested Reading

- National High Blood Pressure Education Program Working Group on High Blood pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation and treatment of high blood pressure in children and adolescents. *Pediatrics*. 2004;114(2 Suppl 4th Report): 555–76.
- Raj M, Sundaram KR, Paul M, Deepa AS, Kumar RK. Obesity in children - time trends and relationship with hypertension, *Natl Med J India*, 2007;20:288–93.

PULMONARY ARTERIAL HYPERTENSION

Pulmonary arterial hypertension (PAH) is defined as resting mean pulmonary arterial pressure greater than

Table 16.24: Dosage of common antihypertensive medications for outpatient management

Agents	Dose; frequency	Comments
ACE Inhibitors, angiotensin receptor blockers		
Captopril	0.3–6 mg/kg/day; tid	Use cautiously if GFR <30 mL/min/1.73 m ² ; avoid in renal artery stenosis Use smaller doses in neonates Monitor serum potassium, creatinine regularly Hyperkalemia, impaired renal functions; anemia, neutropenia, dry cough infrequent
Enalapril	0.1–0.6 mg/kg/day; qd or bid	
Lisinopril	0.06–0.6 mg/kg/day; qd	
Ramipril	6 mg/m ² ; qd	
Irbesartan	4–5 mg/kg/day	
Losartan	0.7–1.4 mg/kg/day; qd	
Calcium channel blockers		
Amlodipine	0.05–0.5 mg/kg/day; qd-bid	Extended release nifedipine must be swallowed whole Side effects: Headache, flushing, dizziness, tachycardia; lower extremity edema, erythema
Nifedipine (extended release)	0.25–3 mg/kg/day; qd-bid release)	
Isradipine	0.15–0.8 mg/kg/day; tid	
Beta-blockers		
Atenolol	0.5–2 mg/kg/day; qd or bid	Decrease dose by 50% at GFR <50 mL/min/1.73 m ² ; give on alternate days at GFR <10 mL/min/1.73 m ² ; sleep disturbances with propranolol, metoprolol; hyperlipidemia; avoid in asthma, heart failure; blunt symptoms of hypoglycemia
Metoprolol	1–6 mg/kg/day; bid	
Labetalol	10–40 mg/kg/day; bid or tid	
Alpha agonists		
Clonidine	5–25 µg/kg/day; tid or qid	Abrupt cessation may cause rebound hypertension; sedation May cause 'first dose' hypotension, syncope
Prazosin	0.05–0.5 mg/kg/day; bid or tid	
Vasodilators		
Hydralazine	1–8 mg/kg/day; qid	Hypertension refractory to other drugs; Side effects: Headache, palpitation, fluid retention, congestive heart failure; pericardial effusions and hypertrichosis with minoxidil
Minoxidil	0.1–1 mg/kg/day; qd or bid	
Diuretics		
Furosemide	0.5–6 mg/kg/day; qd or bid	Monitor electrolytes, fluid status periodically Thiazides: Dyslipidemia, hyperglycemia, hyperuricemia, hypokalemia, hypomagnesemia
Spirolactone*	1–3 mg/kg/day; qd or bid	
Metolazone	0.2–0.4 mg/kg/day; qd	Loop diuretics: Metabolic alkalosis, hypokalemia, hypercalciuria *Use cautiously with ACEI, angiotensin receptor blockers
Hydrochlorothiazide	1–3 mg/kg/day; qd	
Amiloride*	0.4–0.6 mg/kg/day; qd	

qd: Once daily; bid: Twice daily; tid: Thrice daily; qid: Four times qd

Table 16.25: Antihypertensive agents for management of severe hypertension

Medication	Onset	Duration of effect	Route	Dose	Side effects
Sodium nitroprusside	30 sec	<10 min	IV infusion	0.5–8 µg/kg/min (made in 5% dextrose)	Nausea, vomiting, headache, tachycardia, cyanide toxicity (dizziness, confusion, seizures, jaw stiffness and lactic acidosis)
Labetalol	5–10 min	3–6 hr	IV infusion IV bolus	0.25–3 mg/kg/hr 0.2–1 mg/kg/dose q 5–10 min (max 40 mg)	Orthostatic hypotension, bradycardia, pallor, abdominal pain, diarrhea
Nicardipine	1–10 min	3 hr	IV infusion IV bolus	0.5–4 µg/kg/min (max 5 mg/hr) 30 µg/kg (max 2 mg/dose) q 15 min	Flushing, reflex tachycardia, phlebitis, nausea, increased intracranial pressure, headache
Nitroglycerine	2–5 min	5–10 min	IV infusion	1–3 µg/kg/min	Methemoglobinemia, headache, tachycardia
Phentolamine	10 min	30–60 min	IV bolus	0.1–0.2 mg/kg (max 5 mg) q 2–4 hr if required	Reflex tachycardia, abdominal pain
Nifedipine	10–30 min	1–4 hr	Oral	0.2–0.5 mg/kg (max 10 mg) q 4 to 6 hr	Excessive hypotension, peripheral edema
Clonidine	15–30 min	2–4 hr	Oral	0.05–0.1 mg/dose, may repeat q hr; max 0.8 mg total dose	Somnolence, dry mouth

25 mm Hg, or mean pulmonary artery pressure following exercise that exceeds 30 mm Hg. PAH occurs in an idiopathic form or in association with other etiologies. The condition is a critical determinant of morbidity and mortality in diverse pediatric cardiac, lung, hematologic, and other diseases.

Etiology

PAH may be associated with a number of congenital heart diseases. Idiopathic PAH is rare in children. In a small proportion, mutations in the bone morphogenetic protein receptor type 2 (BMPR2) gene, the activin receptor-like kinase type 1 (ACVRL1), or endoglin are identified. Other causes of pulmonary hypertension in children include respiratory disease, upper airway obstruction, connective tissue disease and advanced liver disease (hepatopulmonary syndrome).

Persistent Pulmonary Hypertension of the Newborn (PPHN)

At birth, pulmonary vascular resistance is high and it falls rapidly through the first week of life. By 6 to 8 weeks, pulmonary vascular resistance usually has reached a normal adult level of 1 to 3 Wood units. These changes are accompanied by dilation of the smaller and then the larger muscular pulmonary arteries and development of new arteries and arterioles. PPHN develops when pulmonary vascular resistance remains elevated after birth, resulting in right-to-left shunting of blood through fetal circulatory pathways. Common underlying conditions include congenital diaphragmatic hernia, meconium aspiration syndrome and perinatal asphyxia. These newborns require mechanical ventilation; those with underlying lung disease benefit from high-frequency oscillatory ventilation or extracorporeal membrane oxygenation (ECMO). Pulmonary vasodilators, such as inhaled nitric oxide, improve the outcome and reduce the need for ECMO. Sildenafil is increasingly used as an alternative to inhaled NO.

Clinical Manifestations

The clinical features of PAH are related to the degree of pulmonary hypertension, right ventricular function and status of the right ventricle. Most common symptom is exertional breathlessness due to the inability of the right ventricle to raise cardiac output with exercise. Other symptoms are hemoptysis, atypical chest pain, congestive heart failure, dizziness or syncope and arrhythmias. Cyanosis and its complications are seen in Eisenmenger patients but not otherwise unless there is a patent foramen ovale. A comprehensive evaluation is advised before a diagnosis of idiopathic PAH is made. It is essential to rule out cardiac (congenital heart disease), respiratory, upper airway obstruction (Down syndrome, adenoids), neurogenic causes (sleep apnea) and liver disease (porto-pulmonary hypertension).

Management

Supplemental low-flow oxygen alleviates arterial hypoxemia in patients with chronic pulmonary disease. Patients with Eisenmenger syndrome or idiopathic PAH do not exhibit resting alveolar hypoxia and do not require oxygen unless significantly hypoxic. Children with severe right ventricular failure and resting hypoxemia may require continuous oxygen therapy.

Diuretics are useful in patients with symptomatic right heart failure. The right ventricle is highly preload dependent, and care should be taken to avoid excessive diuresis since this can lead to a fall in cardiac output and compromise other pharmacologic measures, such as vasodilators. Patients are at higher risk of thromboembolic events due to sluggish pulmonary circulation and dilated right-sided cardiac chambers. Anticoagulants may have a role in select cases when the risk for thromboembolism outweighs the likelihood of hemoptysis.

The goal of vasodilator therapy is to reduce pulmonary artery pressure and increase cardiac output without causing systemic hypotension. Sildenafil and tadalafil are oral phosphodiesterase inhibitors that prevent the breakdown of cGMP and potentiate pulmonary vasodilation with endogenous nitric oxide. Symptomatic patients with PAH, PPHN and postoperative PAH benefit with sildenafil. Oral endothelin-receptor antagonists, such as bosentan and ambrisentan, which are selective pulmonary vasodilators are promising for therapy of PAH. Prostacyclin analogs need to be administered IV or SC as a continuous infusion or through frequent inhalations, and are not available in India. Combined heart lung transplantation, or lung transplantation alone has been performed successfully in patients with PAH.

Prognosis

Prognosis is dictated by the underlying etiology and the right ventricular function. An overall 80% 5-years survival has been reported in patients with Eisenmenger syndrome compared with a 2–3-year mean survival after the diagnosis of idiopathic PAH.

Suggested Reading

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RHYTHM DISORDERS

The recognition of cardiac arrhythmias (Table 16.26) in children is challenging and requires a high index of suspicion. It is important to arrive at a precise diagnosis since the treatment is dictated by the specific arrhythmia.

In some situations, it may be possible to affect a complete cure.

Clinical Features

Irregular heart rate: The commonest cause of an irregular heart rate is physiological sinus arrhythmia. This can be recognized by an increase in heart rate with inspiration and decrease with expiration. Sinus arrhythmia is usual following a febrile illness and by drugs that increase vagal tone (such as digoxin). It is readily abolished by exercise. Irregularities of rhythm are commonly seen in premature infants especially bradycardia associated with periodic apnea. Common causes of heart rate irregularity in children include atrial and ventricular premature beats and conduction disturbances (Table 16.27).

Inappropriate heart rate: A heart rate that is inappropriately fast or slow for the clinical condition or physiological state should arouse the suspicion of an underlying arrhythmia. Inappropriately slow heart rate in a child with fatigue, giddiness or syncope should arouse the suspicion of complete heart block. Inappropriately fast rates suggest tachyarrhythmias such as SVT.

Unexplained heart failure: Incessant arrhythmias such as ectopic atrial tachycardia (EAT), permanent junctional re-entrant tachycardia (PJRT) and some forms of ventricular tachycardia can present as heart failure. At the time of initial evaluation, the heart rates may not be inappropriate for the degree of heart failure. Diagnosis may be missed and requires a high index of suspicion. These conditions should be considered in the differential diagnosis of

Table 16.26: Clinical features in arrhythmias

Irregular heart beat
Heart rate that is inappropriate for the clinical condition
Unexplained heart failure
Syncope, palpitations, chest discomfort
Underlying cardiac anomaly known to be associated with rhythm disorders
Family history of sudden cardiac events

Table 16.27: Causes of irregular heart beat

Sinus arrhythmia
Other common and usually benign causes
Supraventricular (atrial and junctional) premature beats
Ventricular premature beats
Transient conduction disturbances (Wenckebach type), atrioventricular and sinoatrial blocks
Transient bradycardia in a premature infant
Uncommon but potentially serious causes
Mobitz type II heart block
Ectopic atrial tachycardia; multifocal atrial tachycardia
Polymorphic ventricular tachycardia and Torsades
Atrial fibrillation, with or without WPW syndrome
Atrial flutter with variable conduction

childhood dilated cardiomyopathy, especially if the heart rate is relatively fixed.

Underlying conditions: A number of congenital and acquired heart diseases and certain systemic conditions are known to be associated with cardiac arrhythmias (Table 16.28). Ventricular and supraventricular arrhythmias can follow cardiac surgery for correction of CHD. Operations resulting in scar formation in the right ventricle, such as repair of tetralogy of Fallot, are known to be associated with ventricular tachycardia. The Fontan operation for single ventricle physiology or the Senning or Mustard procedure for transposition is known to result in a particularly high incidence of re-entrant atrial arrhythmias. Organophosphate exposure, tricyclic anti-depressant overdose, digoxin toxicity, antiarrhythmic drug treatment and substance abuse can be associated with a variety of arrhythmias.

Syncope: The commonest cause of syncope in children is mediated via the autonomic nervous system, known as the neurocardiogenic syncope or vasovagal syncope. A fraction of syncopal episodes result from cardiac arrhythmias. Life-threatening ventricular tachycardia (VT), as associated with long QT syndrome characteristically results in syncope. It is important to differentiate them from vasovagal episodes. Vasovagal syncope occurs in specific situations like prolonged standing in a hot environment, sight of blood, painful stimulus, emotional stress or following a recent illness. Syncopes secondary to arrhythmia are sudden, unpredictable, paroxysmal and usually have no predisposing cause or premonition. Duration of syncope depends upon the duration of

Table 16.28: Arrhythmias suggestive of specific congenital heart disease

Sick sinus syndrome
Sinus venosus, atrioventricular canal defect, Holt Oram syndrome with atrial septal defect (ASD)
Narrow QRS tachycardias
Ebstein anomaly; corrected transposition with Ebstein anomaly
Atrioventricular canal defect, ASD, pulmonic stenosis, total anomalous pulmonary venous connection, tricuspid atresia
Atrial fibrillation and flutter
Congenital mitral stenosis, total anomalous pulmonary venous connection, coronary AV fistula
WPW and pre-excitation syndromes
Ebstein anomaly; corrected transposition with Ebstein anomaly
Wide QRS tachycardias
Anomalous left coronary artery from pulmonary artery, coronary AV fistula, arrhythmogenic right ventricle, atrioventricular conduction defects, corrected transposition of great arteries; Ebstein anomaly
Postoperative patients
Supraventricular, ventricular arrhythmias

arrhythmia. Some forms of long QT syndromes and catecholaminergic tachycardia are precipitated by exercise. Ventricular tachycardia secondary to Brugada syndrome may be precipitated during febrile illness. Syncope during exertion is potentially serious and may suggest specific arrhythmic substrates such as catecholaminergic ventricular tachycardia and long QT syndrome.

Palpitations and chest discomfort: Older children may complain of episodic palpitations. Not infrequently, they have a sensation of chest discomfort or pain during tachyarrhythmia.

Basic Electrophysiology Concepts

Arrhythmia that originates at or above the bundle of His has narrow QRS morphology; that below this level (Purkinje fibers, ventricular muscles) have wide QRS morphology. Majority of tachycardia in children are regular. Common irregular tachycardias are ectopic atrial tachycardia, multifocal atrial tachycardia, atrial flutter with varying conduction, atrial fibrillation (rare in children) and ventricular fibrillation. During a regular narrow QRS tachycardia, if a P wave is identified and has normal morphology, axis and 1:1 P and QRS relation, it suggests sinus tachycardia. Absence of any of the three suggests supraventricular tachyarrhythmia.

Re-entrant vs automatic tachyarrhythmias: Tachyarrhythmia is generally considered to result from one of the three mechanisms: Re-entry, increased automaticity and triggered activity. In children, the first two mechanisms account for most important arrhythmias. Clinical and EKG features together with response to certain medications and maneuvers help distinguish re-entrant tachyarrhythmia from those due to increased automaticity. Re-entrant arrhythmias characteristically have a relatively sudden onset and termination. Successful termination with DC cardioversion or overdrive pacing (pacing at rates faster than the arrhythmia rate) strongly suggests a re-entrant mechanism. Automatic arrhythmias characteristically have a relatively slow onset. Gradual acceleration (warm-up) to the peak rates may be demonstrable at onset and gradual deceleration (cool down) at termination is seen.

Diagnostic Workup of Suspected Arrhythmia

Attempts should be made to answer all the questions listed in Table 16.29. This will allow the specific treatment strategy to be initiated. A 12-lead EKG should be obtained and cardiac rhythm monitoring should be initiated as quickly as possible.

Management of Hemodynamic Instability

Extreme hemodynamic instability is relatively rare in childhood arrhythmias, particularly in absence of structural heart disease. Hemodynamic instability necessitates emergency treatment. Most unstable tachyarrhythmias are broad QRS. Unstable narrow QRS tachycardias are quite uncommon, especially in the absence of structural heart disease. Low energy (0.5–2 J/kg) synchronized DC cardioversion should be performed. If and when possible, cardioversion should always be preceded by administration of a short-acting benzodiazepine such as midazolam (0.1–0.2 mg/kg/dose). Emergency treatment options for bradyarrhythmia are shown in Table 16.30.

Diagnosis and Management of Tachyarrhythmia

A combined strategy that simultaneously addresses both diagnosis and treatment is appropriate. This is determined by the QRS duration on the initial EKG and presence or absence of hemodynamic instability. Based on the QRS duration, arrhythmias can be classified as narrow and wide. This is a useful practical classification and serves as an excellent guide to initial treatment. Age specific normal values for QRS duration are given in Table 16.31. As a preliminary step, sinus tachycardia should be excluded. Rates as high as 240/min are occasionally recorded during sinus tachycardia. There is always an underlying cause for sinus tachycardia and this is usually apparent during

Table 16.29: Initial assessment of arrhythmia

Can the clinical condition result from a cardiac arrhythmia?
Is there hemodynamic instability?
Is the arrhythmia incessant or episodic?
Is this a re-entrant arrhythmia or does it involve an automatic focus?
Where is the arrhythmic focus or circuit located?
Is there an underlying structural heart disease?

Table 16.30: Emergency treatment for bradyarrhythmias

Modality	Indication	Dose
Atropine	Severe sinus bradycardia, AV block with narrow QRS (supraventricular) escape	0.02 mg/kg IV bolus
Isoproterenol	Lack of response to atropine, AV block with wide QRS (ventricular) escape	0.1–2 µg/kg/min IV infusion
Transcutaneous pacing	Severe symptomatic bradycardia, asystole (not suitable for infants, young children)	Twice the capture threshold
Transvenous pacing	Alternative to transcutaneous pacing for infants and young children	Twice the capture threshold

Table 16.31: Normal QRS duration at various age groups

Age group	QRS duration in seconds
0–6 months	0.03–0.07 (0.05)
1–5 years	0.04–0.08 (0.06)
10–15 years	0.04–0.09 (0.07)
>15 years	0.06–0.09 (0.08)

Values represent range (mean)

Table 16.32: Causes of narrow QRS tachycardia

Site	Re-entrant arrhythmias	Automatic arrhythmias
Sinus node Atrium	Sinus node re-entry	Sinus tachycardia
	Intra-atrial re-entrant arrhythmias following cardiac surgery (Fontan, Senning operations)	Ectopic atrial tachycardia Multifocal atrial tachycardia
AV node	Atrial flutter Atrial fibrillation	Junctional ectopic tachycardia
	AV node re-entry	
Accessory pathway	Atrioventricular re-entry involving concealed or manifest (WPW) pathway Permanent junctional re-entrant tachycardia	

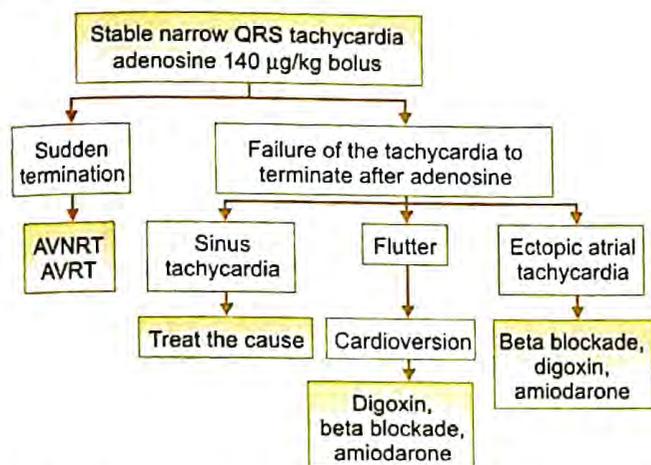


Fig. 16.48: Management algorithm for stable narrow QRS tachycardia. AVNRT atrioventricular nodal re-entrant tachycardia; AVRT atrioventricular re-entrant tachycardia

the initial evaluation. Fever, circulatory failure, extreme dehydration, accidental ingestion of drugs and toxic substances are common examples. Figure 16.48 depicts a useful treatment algorithm.

Narrow QRS tachycardia: Most narrow QRS tachycardias (Table 16.32) are reasonably well tolerated and allow a

preliminary diagnostic workup (Table 16.33). If a patient is seen during an episode of tachyarrhythmia, all attempts should be made to obtain quality data before terminating the arrhythmia. Information that should be specifically sought includes the P wave morphology and P-QRS relationship. P waves that appear normal during the tachyarrhythmia suggest sinus tachycardia. Ectopic atrial tachycardia is suggested by abnormal P wave morphology. Inverted P waves may be seen when atria are activated in a retrograde fashion as in the case of re-entrant tachyarrhythmia involving accessory pathways (AV re-entrant tachycardia) (Fig. 16.49). Often P waves are not clearly seen on baseline EKG but are unmasked by adenosine. Evidence of 2:1 AV conduction as suggested

Table 16.33: Differential diagnosis of narrow QRS tachycardia

Arrhythmia	P waves	P-QRS relationship	Response to adenosine
Sinus tachycardia	Normal	1:1	Transient slowing; AV block
Sinus node-entry	Normal	Usually 1:1	No effect or transient AV block
Ectopic atrial tachycardia	Abnormal and different from baseline	Usually 1:1	No effect or transient AV block
Atrial flutter	Saw tooth appearance rates exceed 240/min	2:1 or 1:1	Transient AV block may unmask flutter waves; rarely arrhythmia terminates
Postoperative intra-atrial re-entry*	Slow atrial flutter, P waves different from baseline	Variable, often 1:1	Transient AV block may unmask flutter waves; rarely arrhythmia terminates
Multifocal atrial tachycardia	Multiform	Usually 1:1	No effect or transient AV block
Junctional ectopic tachycardia	Normal (AV dissociation) or inverted (1:1 retrograde conduction)	Complete AV dissociation is diagnostic	No effect on rate; transient retrograde VA conduction block unmasks AV dissociation
AV nodal tachycardia	Usually not visible (masked by RS complexes)	1:1	Sudden termination is characteristic
AV re-entrant tachycardia	Inverted (retrograde VA conduction)	1:1	Sudden termination
Junctional re-entrant tachycardia	Inverted (long VA conduction time)	1:1	No effect or transient termination

*Postoperative intra-atrial re-entry may follow surgery that results in atrial scarring, e.g. Fontan operation, Senning operation

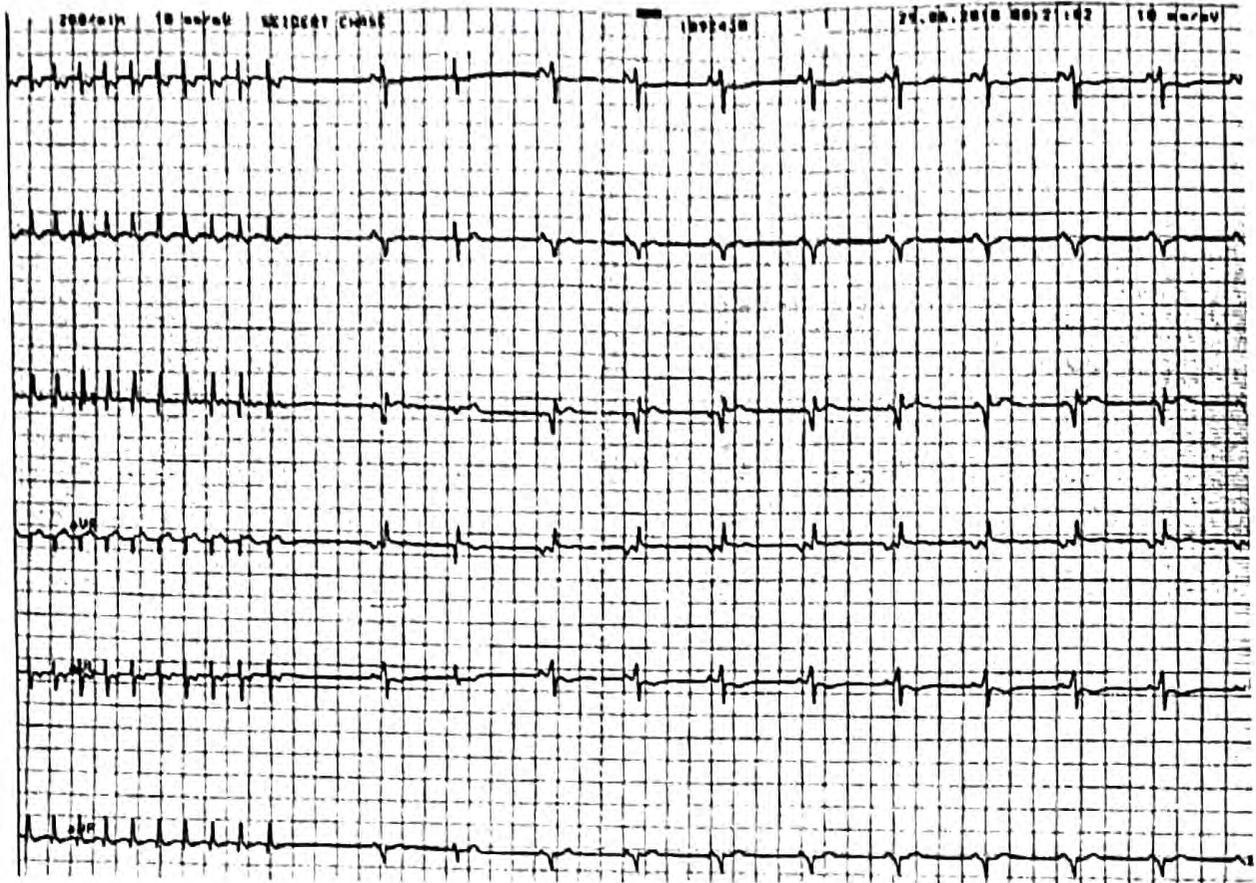


Fig. 16.49: Six-lead ECG. Adenosine was administered to a child with regular narrow QRS supraventricular tachycardia. Note the tachycardia terminates with a P wave. Note delta waves with short PR interval that is prominently seen in lead I

by a 2:1 P-QRS ratio during a narrow QRS tachycardia indicates atrial flutter (Fig. 16.50). Evidence of complete AV dissociation (no consistent P-QRS relationship) indicates junctional ectopic tachycardia.

Adenosine administration acts by producing a marked slowing of AV node conduction (Table 16.33). The effect of adenosine lasts for a few seconds. Side effects are short-lived and include flushing, chest pain and dyspnea. Adenosine needs to be administered rapidly followed by rapid push of normal saline as a bolus. The recommended dose is 50–300 $\mu\text{g}/\text{kg}$. Most re-entrant tachycardias, where AV node is a part of the circuit (AV node re-entrant tachycardia, AV re-entrant tachycardia), will be terminated by adenosine. Atrial flutter is seldom terminated by adenosine. The transient AV block that results from adenosine administration can unmask flutter waves on the EKG thereby confirming the diagnosis (Fig. 16.51). Similarly transient slowing of AV conduction can unmask ectopic atrial tachycardia. If adenosine is not available, vagal maneuvers can be attempted. For infants and young children, an ice filled plastic bag placed on the face is the most effective vagal maneuver. Older children can be encouraged to perform the Valsalva maneuver or carotid sinus massage can be attempted. Eyeball pressure is contraindicated in infants.

Wide QRS tachycardia: Wide QRS complex tachycardias usually result from foci or circuits in the ventricles. Some supraventricular tachycardias can also result in a wide QRS configuration. The overall approach is quite similar to narrow QRS tachycardias, with identification of P waves, defining P-QRS relationship and determining the QRS axis configuration (Fig. 16.52).

Demonstrable AV dissociation (inconsistent P-QRS relation) suggests ventricular tachycardia (VT). In most situations, however, it is not easy to distinguish VT from SVT. If the patient is stable, administration of adenosine will terminate or unmask SVT. If there is no response, treatment for VT should be initiated. In stable patients, it is better to initiate pharmacologic treatment of VT before considering cardioversion since the response to initial treatment can help decide long-term therapy. Lignocaine is the initial choice; procainamide is an effective alternative; others include amiodarone, sotalol, mexiletine and flecainide.

Unstable wide QRS tachycardia: Wide QRS tachycardia with hemodynamic instability is a medical emergency. Synchronized cardioversion (0.5–2 J/kg) should be performed immediately. For pulseless patients, CPR should be initiated. Subsequent treatment should follow standard guidelines recommended for pulseless patients with VT (Fig. 16.53).

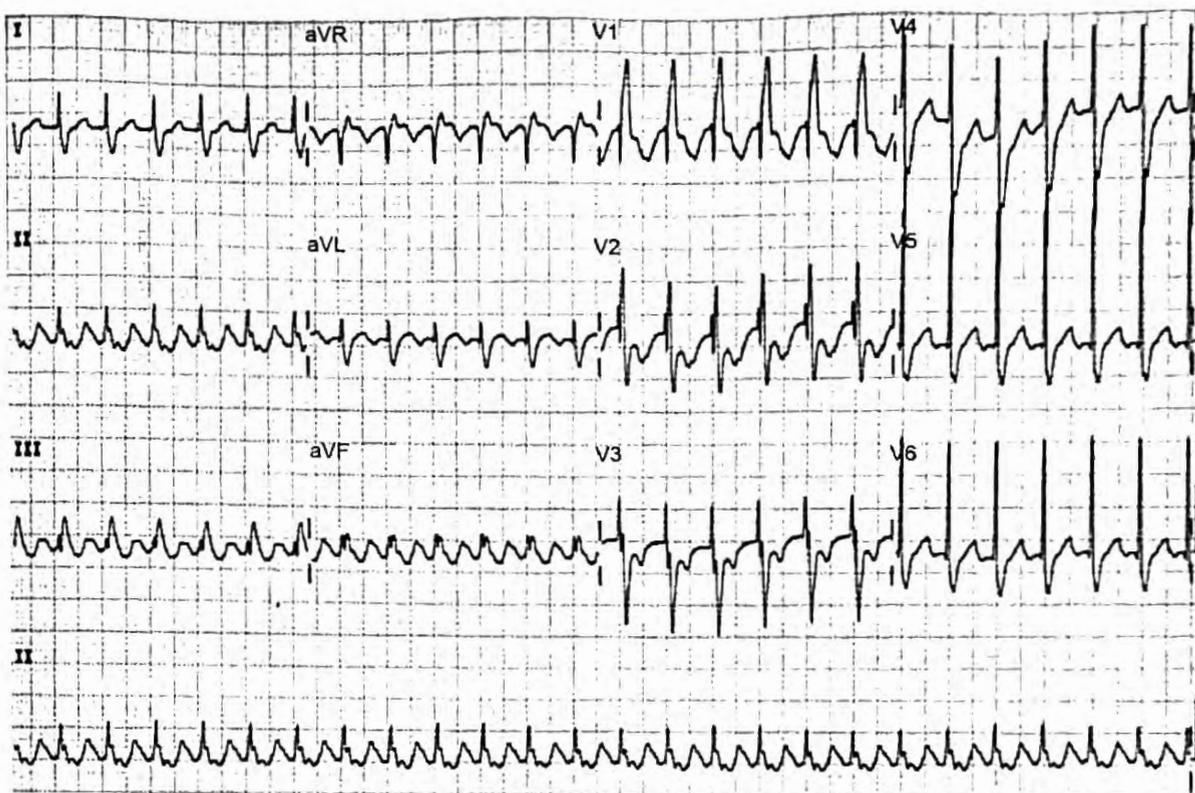


Fig. 16.50: Atrial flutter: Regular narrow QRS tachycardia at a heart rate of 150/min. Heart rate was fixed at 150/min for several hours that was suggestive of underlying arrhythmia. P waves were abnormally broad and tall

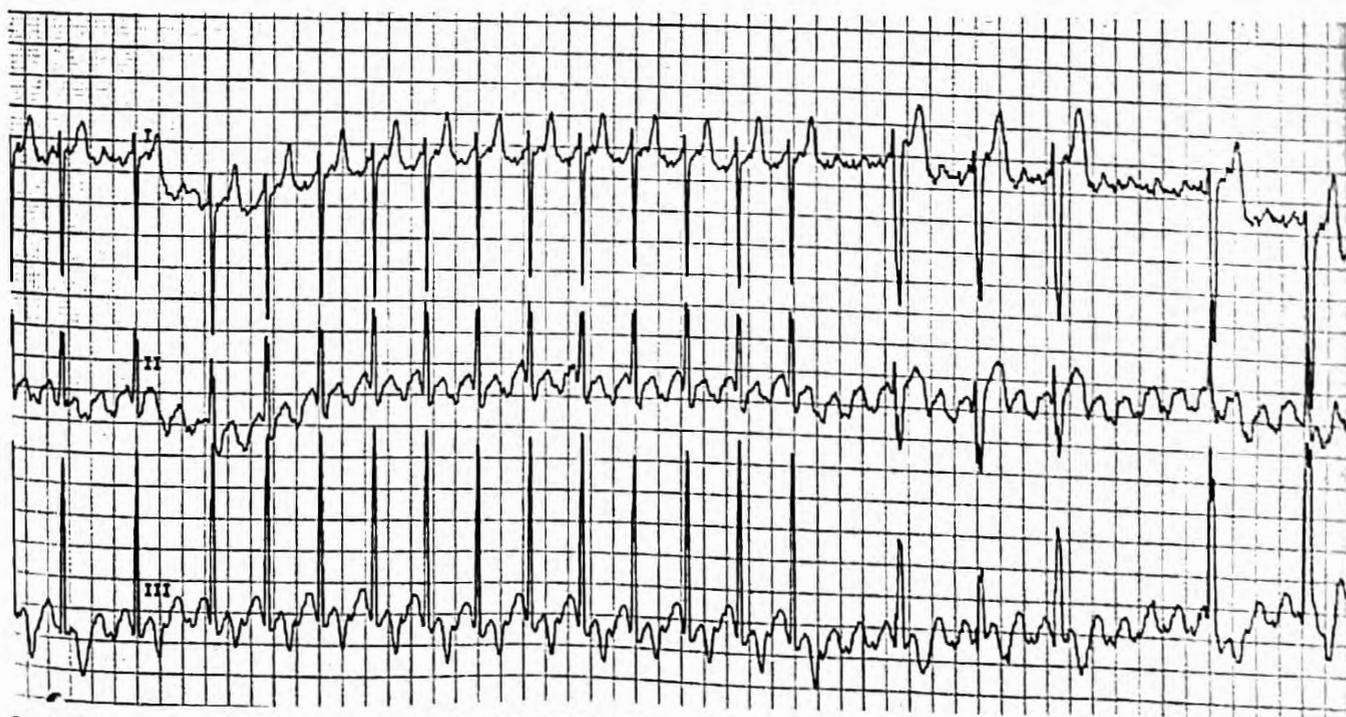


Fig. 16.51: Response to adenosine administration to a child with atrial flutter. Note the unmasking of flutter waves that are prominently seen in lead II and III. P rate was 300/min. Before administration of adenosine, there was 2:1 AV conduction. The blocked P waves were hidden within the QRS complexes. After administration of adenosine, AV block increased and AV conduction block increased to 4:1 unmasking the flutter waves

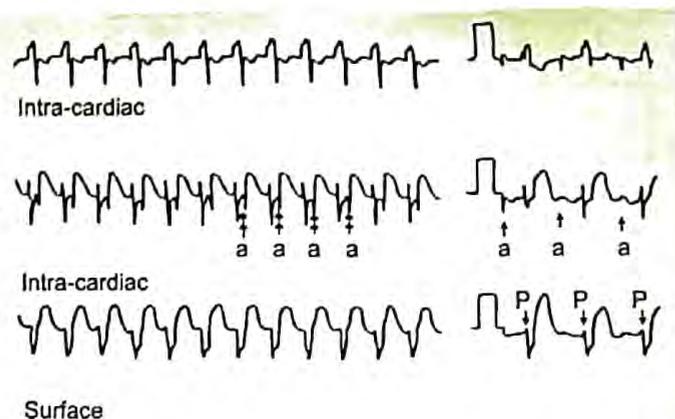


Fig. 16.52: Wide QRS tachycardia resulting from a re-entrant circuit involving an accessory pathway in a patient with right bundle branch block. Surface ECG, can be mistaken for ventricular tachycardia. ECG of the top two rows has been obtained directly from the atrium using postoperative atrial wires as electrodes. The bottom strip is the surface ECG from a monitoring lead. Conversion to sinus rhythm after adenosine is seen in the last four complexes on the right. a atrial contraction, P p wave

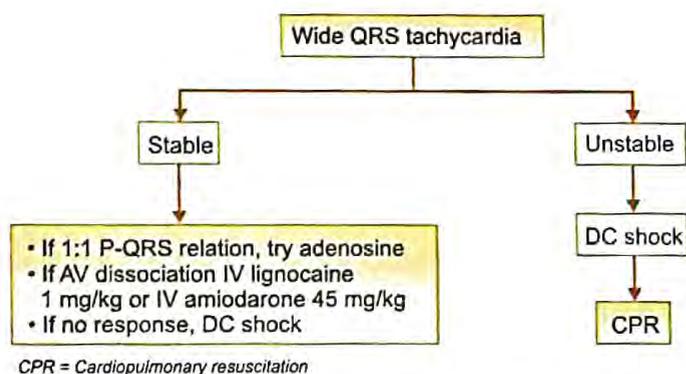


Fig. 16.53: Management of wide QRS tachycardia

Irregular wide QRS tachycardia: Sustained and irregular wide QRS tachycardia is uncommon and usually suggests a diagnosis of Wolf-Parkinson-White (WPW) syndrome with atrial fibrillation. In presence of hemodynamic instability, synchronized cardioversion (1–2 J/kg) is indicated. If the patient is stable, procainamide infusion may be tried.

Once the arrhythmia has been managed, recurrences need to be prevented. Most childhood arrhythmias warrant evaluation by a pediatric cardiologist for follow-up care and to plan definitive treatment. An echocardiogram, Holter test (24 hours ambulatory EKG recording) and esophageal electrophysiologic study is often required. Invasive intracardiac electrophysiologic study is combined with radiofrequency (RF) ablation. Most accessory pathways are now treated by radiofrequency ablation, especially in older children (>4-year-old). For younger children, RF ablation is reserved for refractory situations.

PREVENTING ADULT CARDIOVASCULAR DISEASE

Major risk factors for cardiovascular disease in adulthood are cigarette smoking, physical inactivity, obesity, hypertension, diabetes mellitus and dyslipidemia. Some of these risk factors begin in childhood and are amenable to modification, contributing to primary prevention of cardiovascular disease.

Obesity: Obesity influences major cardiovascular risk factors such as dyslipidemia, hypertension, glucose intolerance and inflammation. Emerging cardiovascular risk factors like carotid intima media thickness as well as carotid elasticity has also shown strong association with childhood obesity. Childhood obesity is managed by a combination of increased physical activity and dietary interventions.

Hypertension: Primary or essential hypertension is the most common form of hypertension in older children and adolescents. Childhood obesity is associated with hypertension in children, which often tracks into adulthood.

Dyslipidemia: Screening for dyslipidemia is recommended for children whose parents and/or grandparents required coronary artery bypass-surgery or balloon angioplasty before 55 years, those with family history of myocardial infarction, angina pectoris, peripheral or cerebrovascular disease, or sudden death before 55 years, and those whose parents have dyslipidemia. Youth with dyslipidemia are treated with a diet low in total and saturated fats and cholesterol. The intake of complex carbohydrates is increased, whereas that of simple sugars is decreased. Drug therapy is used in patients with significantly elevated LDL-cholesterol.

Diabetes mellitus: Diabetes mellitus is associated with cardiovascular complications, which develop early in childhood and adolescence. Endothelial dysfunction seen in both types of diabetes is recognized to aggravate cardiovascular risk in later life. Optimal daily and long-term glycemic control, maintenance of blood pressure and lipid levels in the normal values for age, regular exercise, healthy diet and avoidance of smoking are necessary.

Tobacco consumption: Mechanisms by which smoking exerts its detrimental effects on cardiovascular system include endothelial dysfunction, increased oxidative stress, increased arterial stiffness, alterations in lipoprotein metabolism and induction of prothrombotic state. School-based campaigns to prevent smoking and chewing tobacco are appropriate tools to contain this public health concern. Parents should be role models to children by avoiding or quitting smoking and chewing tobacco.

Early atherosclerotic disease has been documented in certain conditions in children. The risk category, group of diseases in each category and the prevention oriented treatment targets are shown Table 16.34.

Table 16.34: Pediatric diseases with high cardiovascular risk in adulthood

Category	Diseases	Prevention oriented targets
Tier I (high risk)	Homozygous familial hypercholesterolemia (FH); diabetes mellitus type 1; chronic kidney disease; post-heart transplantation; Kawasaki disease with current coronary aneurysms	Maintain body mass index (BMI) <85th centile; blood pressure <90th centile; and LDL cholesterol (LDL-C) <100 mg/dL
Tier II (moderate risk)	Heterozygous FH; Kawasaki disease with regressed coronary aneurysms, diabetes mellitus type 2; chronic inflammatory disease	Maintain BMI <90th centile; blood pressure <95th centile; and LDL cholesterol <130 mg/dL
Tier III (at risk)	Post-cancer-treatment survivors; congenital heart disease; Kawasaki disease without detected coronary involvement	Maintain BMI ≤95th centile; blood pressure ≤95th centile plus 5 mm Hg; and LDL-C ≤160 mg/dL

All tiers require maintaining fasting blood sugar <100 mg/dL and glycosylated hemoglobin (HbA1c) <7%.

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Disorders of Kidney and Urinary Tract

Arvind Bagga • Aditi Sinha • RN Srivastava

RENAL ANATOMY AND PHYSIOLOGY

Each kidney is composed of approximately a million nephrons, each consisting of a glomerulus and renal tubule. The glomerulus is made of a tuft of capillaries and a central region of mesangium. The capillaries arise from the afferent arteriole and join to form the efferent arteriole. The capillary wall consists of fenestrated endothelium, glomerular basement membrane and foot processes (podocytes) of visceral epithelial cells. The basement membrane is made of type IV collagen, laminin and heparan sulfate proteoglycan. The Bowman space leads into the proximal tubule that has an initial convoluted portion, then the straight segment, descending and ascending limbs of the loop of Henle and the distal tubule

(Fig. 17.1). Six to eight distal tubules join to form the collecting ducts that finally enter the renal pelvis.

The early part of the distal tubule on its ascent from the medulla to the cortex lies near the glomerulus of the same nephron. The cells of the tubule in contact with the afferent arteriole are denser than the rest and called macula densa. The smooth muscle cells of the afferent arteriole, in this region, contain prominent cytoplasmic granules that are the site of renin activity. The juxtaglomerular apparatus (JGA) is composed of afferent and efferent arterioles, the macula densa and lacis cells located between these structures. The JGA is involved in systemic blood pressure regulation, electrolyte homeostasis and tubuloglomerular feedback.

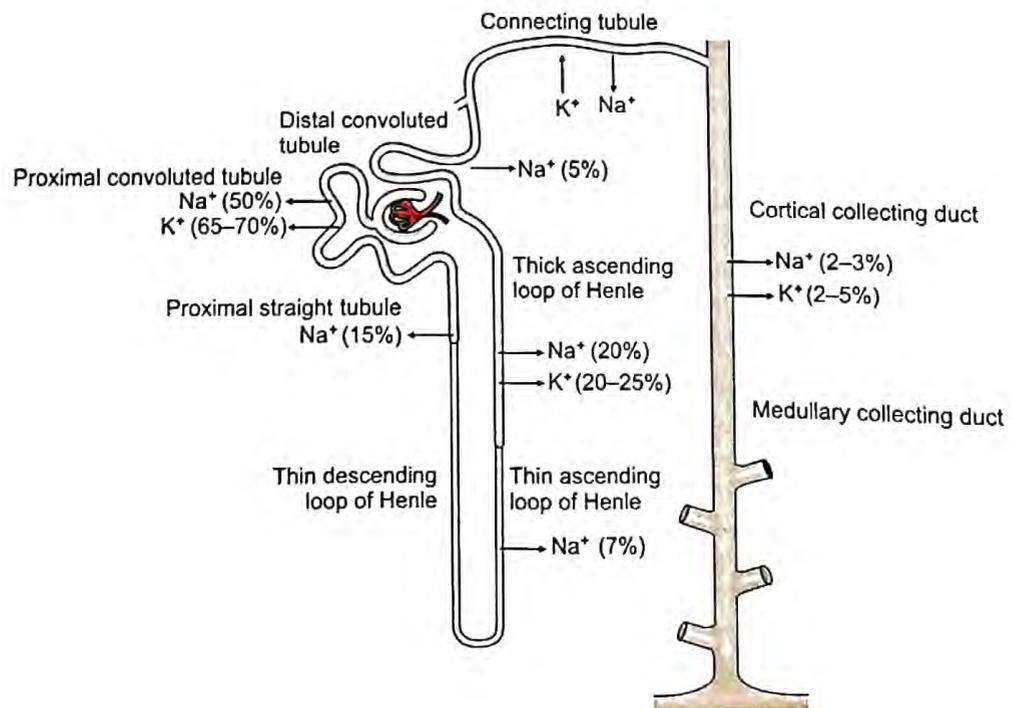


Fig. 17.1: Renal tubular handling of sodium and potassium. The major sites of reabsorption are shown, with percentage of filtered cation in parenthesis

Renal Physiology

Glomerular filtration depends upon the higher pressure in afferent arterioles. The filtration barrier is constituted by the endothelium with slit pores, basement membrane and podocytes of visceral epithelial cells. Filtration of solutes depends upon their molecular size, shape and electrical charge. The filtrate from the glomerular capillaries passes from the Bowman capsule into the proximal convoluted tubule, loop of Henle, distal tubule and collecting ducts. The filtrate contains all the diffusible and ultrafiltrable substances present in plasma. Small quantities of protein are usually present, but are reabsorbed in proximal tubule. Bulk of the glomerular filtrate is reabsorbed into the peritubular capillaries and only 0.5% is excreted as urine.

Tubular Reabsorption

The proximal tubules reabsorb about 80% of the glomerular filtrate. Approximately 65% of sodium is reabsorbed in the proximal tubule, through several active transport systems. Sodium transport is dependent on the parallel transport of bicarbonate, chloride, amino acids and glucose. Tubular reabsorption of sodium and other permeable solutes is promoted by the phenomenon of solvent drag during transport of water across the tubular epithelium. Figure 17.1 indicates the principal sites of reabsorption of sodium and potassium.

The glomerular filtration rate is regulated by tubuloglomerular feedback that depends upon the functional integrity of the JGA. Increased delivery of chloride to the macula densa results in local activation of renin-angio-

tensin mechanism. The renin-angiotensin-aldosterone system, prostaglandins and natriuretic peptides are involved in sodium handling. Potassium is completely reabsorbed in the proximal tubule; the amount seen in urine depends upon its secretion in the distal tubule.

Distal tubules and collecting ducts are responsible for urinary acidification, concentration and regulation of sodium balance. Exchange of potassium or hydrogen ions for sodium takes place in the distal tubules under the regulation of aldosterone. Antidiuretic hormone mediates absorption of water through insertion of 'water channels' (aquaporins) on the luminal surface of cells in the collecting tubules.

Renal Acidification

The kidney helps in regulation of acid-base balance by maintaining plasma bicarbonate concentration at 22–26 mEq/L. Depending on dietary protein intake, children produce about 1–3 mEq/kg/day of nonvolatile acids. Filtered bicarbonate is almost completely reabsorbed, 85 to 90% in the proximal tubules and the rest in distal tubules and collecting ducts. Bicarbonate, consumed in the buffering of nonvolatile acids, is regenerated by the renal excretion of titrable acid and ammonia. Chronic acidosis augments the production of ammonia and thus elimination of acid. Figures 17.2 and 17.3 demonstrate the chief mechanisms involved in the reabsorption of bicarbonate and excretion of protons in the proximal and distal tubules, respectively.

The reabsorption of filtered bicarbonate as well as excretion of acid is mediated by tubular secretion of hydrogen

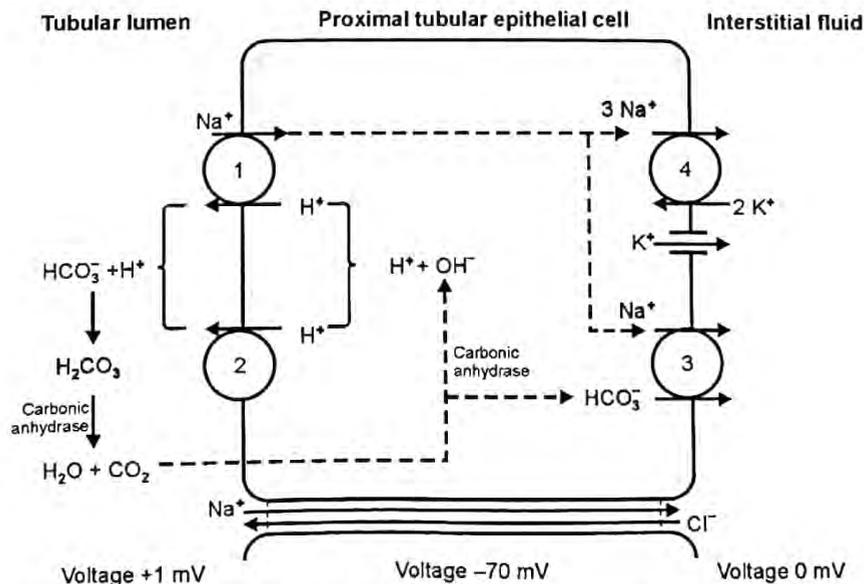


Fig. 17.2: Reabsorption of bicarbonate in the proximal tubule. Protons (H^+) are secreted into the lumen through the actions of the sodium (Na^+) H^+ antiporter (1) and the H^+ ATPase (2). Secreted H^+ combines with HCO_3^- to form H_2CO_3 , which, under the action of luminal membrane carbonic anhydrase dissociates to H_2O and CO_2 . The CO_2 travels across the membrane into the cell where it combines with OH^- to generate HCO_3^- . The HCO_3^- and Na^+ cross the basolateral membrane using the Na^+/HCO_3^- symporter (3). Na^+ also exits the cell via the Na^+/K^+ ATPase (4). Electrogenic H^+ secretion generates a small lumen positive voltage, which creates current flow across the paracellular pathway

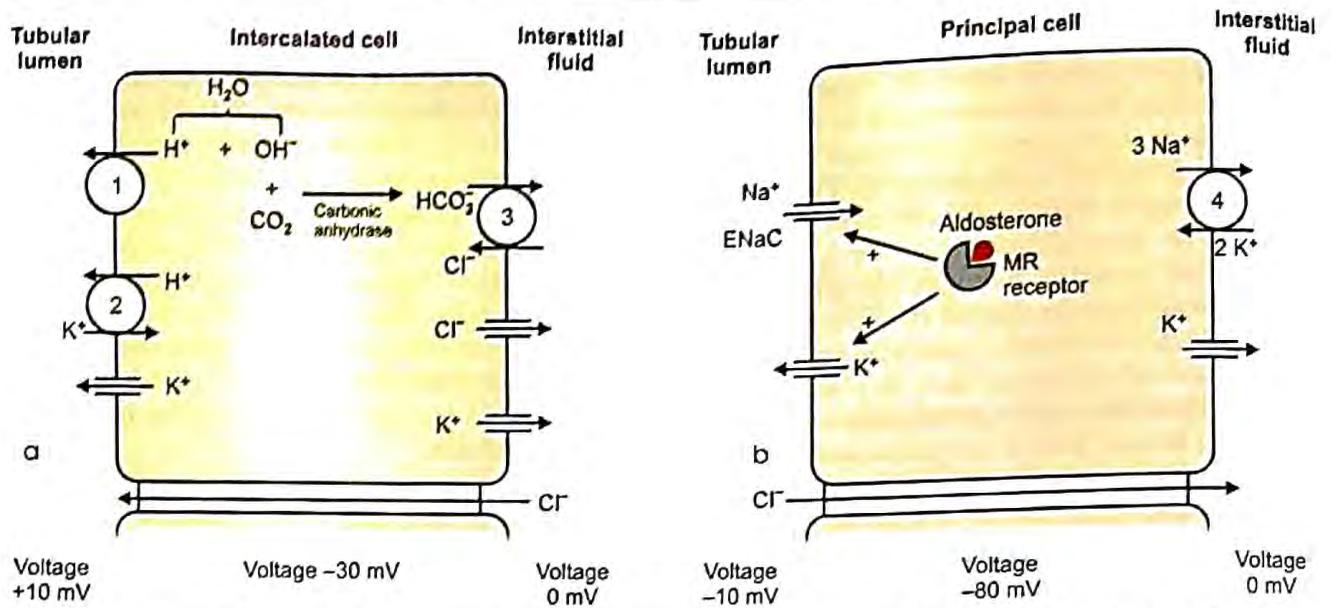


Fig. 17.3: Mechanism of acidification and potassium excretion in the distal renal tubules. (a) The intercalated cells of the cortical collecting ducts secrete H^+ through the H^+ ATPase (1) and H^+/K^+ ATPase (2), independent of Na^+ transport. The hydroxyl (OH^-) ions generated in the cell through H^+ secretion exit the cell by the HCO_3^-/Cl^- exchanger (3). The secreted H^+ is buffered by luminal ammonia forming NH_4^+ and phosphate (titrable acids), to prevent a drop in luminal pH that would prevent further H^+ secretion. (b) Principal cells mediate sodium (Na^+) absorption and potassium (K^+) transport. The apical membrane contains an amiloride sensitive Na^+ channel (epithelial sodium channel, ENaC); Na^+ exits basolaterally via Na^+/K^+ ATPase (4). Sodium transport creates a lumen negative transepithelial potential that increases the rate of H^+ secretion by intercalated cells. Aldosterone binds to the mineralocorticoid (MR) receptor and enhances Na^+ absorption and H^+ and K^+ secretion.

ions (H^+). In the proximal tubule, filtered HCO_3^- combines with H^+ to form H_2CO_3 that rapidly dissociates to H_2O and CO_2 (catalyzed by carbonic anhydrase at the brush border of the tubular basement membrane) (Fig. 17.2). CO_2 diffuses along its concentration gradient into the tubular cell, combining with H_2O to generate HCO_3^- that is absorbed by the peritubular capillaries. The proximal tubule reabsorbs 80–90% of the filtered HCO_3^- ; the remainder is reabsorbed distally. In the distal tubule, the secreted H^+ ions combine with the major urinary buffers, sodium hydrogen phosphate (Na_2HPO_4) and ammonia (NH_3) to form NaH_2PO_4 and NH_4^+ (measured in urine as titratable acidity and ammonium ion, respectively) (Fig. 17.3). The distal nephron generates and maintains a steep pH gradient between the blood and urine, but its capacity to secrete H^+ ions is small. Thus, even a slight increase in distal HCO_3^- delivery results in increase in urine pH. Extracellular fluid volume and potassium balance also regulate H^+ secretion and HCO_3^- reabsorption.

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Development of Structure and Function

The fetal kidneys are lobulated structures that ascend from the pelvis to their normal position between 6 and 9 weeks of gestation. These kidneys can be visualized on antenatal ultrasound by 12–13 weeks. The kidneys grow steadily in

size between 12 and 40 weeks, with the renal length increasing from about 1.0 to 2.7 cm. The fetal bladder is visualized by 10–14 weeks, and its capacity increases steadily to about 50 mL at term. Beyond 16 weeks, the amniotic volume is principally dependent on urine production.

Glomerular Filtration

Glomerular filtration begins at 5–9 weeks' gestation, initiating urine formation. The fetal kidney receives about 2–4% of cardiac output, which increases in neonates to 15–18%. Serum creatinine level is high at birth, reflecting maternal values, but falls rapidly to 0.3–0.5 mg/dL by the end of first week. Most (92%) neonates pass urine within the first 48 hours. The GFR is low at birth (15–20 mL/min/1.73 m² in the first 3 days in term, 10–15 mL/min/1.73 m² in preterm) but increases to 35–45 mL/min/1.73 m² at 2 weeks and 75–80 mL/min/1.73 m² by 2 months.

Tubular Function

Tubular function contributes to urine formation around 14 weeks' gestation. Postnatal tubular maturation follows a pattern similar to GFR but its maturation is delayed. Infants have reduced sodium and bicarbonate reabsorption and limited ability for hydrogen ion excretion. The pH of urine in newborns is high for the degree of acidemia.

Urine Osmolality

The capacity of the kidneys to concentrate or dilute urine is limited in neonates. An infant can concentrate his urine

to a maximum of 700–800 mOsm/kg whereas the older child can achieve 1200–1400 mOsm/kg. Growing babies utilize most of the protein available for growth rather than catabolize to urea. Decreased production and excretion of urea result in a relatively hyposmolar interstitium and reduced urinary concentration. The newborn can dilute urine to a minimum of 50 mOsm/kg, like an older child. However, the time taken to excrete a water load is longer. Thus, delayed feeding and overdiluted or concentrated feeds are potentially harmful.

Maturation of Renal Function

Renal function continues to improve during the first two years of life, at the end of which, various parameters of renal function approach adult values, if corrected to standard surface area. Structural growth parallels the functional maturation.

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DIAGNOSTIC EVALUATION

Clinical Features of Renal Disease

Hematuria

Gross hematuria in acute GN is typically smoky brown or cola colored. Bright red blood suggests a nonglomerular cause, as in renal or vesical calculi. Gross hematuria is rare in UTI. Other conditions which might impart a red color to urine include hemoglobinuria, myoglobinuria, porphyria and ingestion of beetroot.

Edema

Acute GN presents with facial puffiness and gross hematuria; the edema does not pit readily on pressure. If fluid intake is not restricted, the edema may increase and involve hands, feet and legs. In nephrotic syndrome, edema develops insidiously, starting with eyelid puffiness most noticeable in the morning. Over a period of several days, there is pitting edema over the feet and legs. Facial swelling is often mistaken for allergy or insect bite.

Oliguria

Oliguria, defined as urine volume less than 0.5 mL/kg/ hr, commonly results from gastroenteritis and hypo-volemia. Oliguria is an important feature of moderate or severe acute GN, acute tubular necrosis and conditions causing severe glomerular injury (e.g. HUS, vasculitis).

Abnormalities of Micturition

A poor urinary stream in boys, especially in presence of a full bladder, suggests obstruction, most commonly due

to posterior urethral valves. Persistent dribbling indicates abnormal ureteric insertion distal to bladder neck. Infants with meningomyelocele should be evaluated for bladder dysfunction. Dysuria, flank pain and ureteric colic suggest UTI or urinary tract calculi.

Polyuria, Polydipsia

Impaired urinary concentration is a feature of obstructive uropathy and primary or secondary tubulointerstitial disorders. Polyuria is also present in conditions associated with deficiency or resistance to antidiuretic hormone, diabetes mellitus, hypokalemia (e.g. distal renal tubular acidosis) and hypercalcemia.

Enuresis

Primary monosymptomatic enuresis needs to be distinguished from patients with dysfunctional voiding. Most children with nocturnal enuresis have no evidence of renal disease. Urinalysis and culture are recommended in patients with secondary enuresis.

Hypertension

Assessment of blood pressure is necessary in all children, and especially those with disorders of the kidneys or urinary tract. Symptomatic hypertension is chiefly due to a renal parenchymal or renovascular cause; endocrine conditions are uncommon.

Growth Retardation, Anemia

Physical retardation is a feature of advanced chronic kidney disease (CKD, stages 3–5) and tubular disorders. Normocytic normochromic anemia is striking in patients with advanced CKD. Patients with unexplained anemia should be evaluated for a renal disease.

Abdominal Mass

Multicystic renal dysplasia, polycystic kidneys, renal vein thrombosis, hydronephrosis (due to pelviureteric or lower urinary tract obstruction) and Wilms' tumor may result in palpable masses.

Examination of Urine

Urinalysis is an important step for diagnosis of renal disease. Evaluation includes microscopic examination of the uncentrifuged as well as centrifuged specimen and semiquantitative or quantitative detection of different substances.

Collection of Specimen

The first morning specimen is preferred since it is relatively concentrated. While a clean container is sufficient, specimens for culture should be collected in a sterile container. After cleaning the perineum with soap and water, a 'clean catch' sample is collected. If facilities for immediate processing are not available, the specimen is stored at 4°C for 12–14 hours.

It is difficult to obtain satisfactory specimens in children below 2 years old. Urine may be collected using a sterile bag that is applied after local cleaning and removed soon after the void. These specimens should not be used for culture. Other reliable ways for obtaining urine specimens in infants include percutaneous suprapubic aspiration or transurethral catheterization.

Specific Gravity

Specific gravity is measured using either refractometer or hydrometer; the former is convenient, requires less volume of urine and gives accurate values. The early morning urine specific gravity should exceed 1.015.

pH

Urine is collected in a capped syringe, if pH can be measured promptly. If measurement is likely to be delayed, urine should be collected under paraffin. Urine pH is lowest in the fasting, early morning specimen and increases following meals.

Protein

Proteinuria is an important marker of renal injury. Detection of 3–4+ albuminuria suggests glomerular disease. Low molecular weight proteinuria, including lysozyme, β_2 microglobulin, neutrophil gelatinase associated lipocalin and retinol-binding protein, suggest tubular injury. Dipstick methods (Uristix) for proteinuria are convenient and reliable. Composite strips for pH, glucose, hematuria, leukocyte esterase and nitrite are also available. Proteinuria can also be semiquantitatively tested using the boiling and sulfosalicylic acid tests.

Reducing Substances

Reducing substances can be estimated by Benedict test or dipsticks based on the glucose oxidase method, both of which produce a graded color change.

Microscopic Examination

A fresh, well-mixed specimen is examined for cellular elements, crystals and casts. Alternatively, urine is centrifuged at 1500 rpm for 10 min; urine is decanted and the cell pellet resuspended in 0.3–0.5 mL urine. Evaluation for hematuria, defined as more than 5 red cells/hpf in a centrifuged specimen is abnormal. Red cell casts indicate glomerular inflammation (Fig. 17.4). Leukocytes may occasionally be absent despite significant bacteriuria. On the other hand, isolated presence of leukocytes is not specific for UTI, and may be noted in interstitial nephritis, stones and high fever. The detection of bacteriuria in fresh, uncentrifuged urine is significant.

Blood Tests

Blood levels of creatinine and urea are used to assess renal function. The normal levels of serum creatinine are 0.2–0.5 mg/dL in children below 6 yr and 0.4–0.8 mg/dL in older children. Blood urea ranges between 20 and 35 mg/dL during childhood. However, it is important to realize the limitations of these investigations. Values of blood urea or creatinine do not increase even when glomerular filtration rate is reduced by 50%. The level of serum creatinine is dependent on muscle mass and is, therefore, low in malnutrition. Bilirubin may interfere with creatinine measurements. Blood urea levels are low on a protein deficient diet and high with tissue breakdown, trauma,

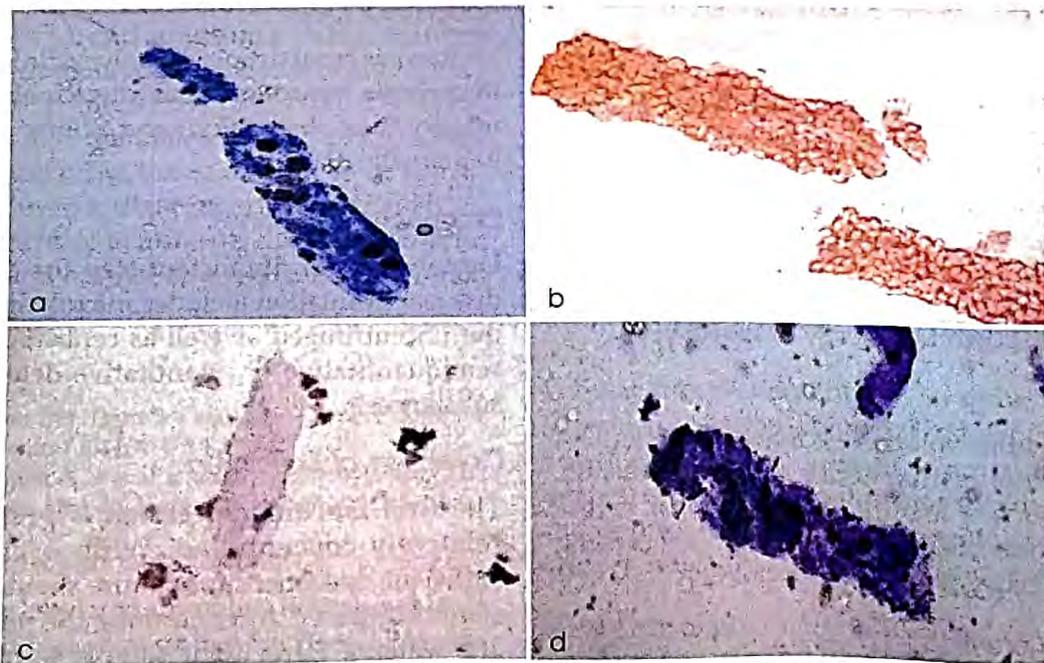


Fig. 17.4: Appearance of casts on urine microscopic examination. (a) White blood cell casts; (b) Red blood cells casts; (c) Hyaline cast; (d) Granular cast

gastrointestinal bleeding and use of corticosteroids. Estimation of blood levels of cystatin C, which does not depend on the nutritional status, is considered a sensitive indicator of glomerular function.

Other specific investigations include albumin, cholesterol, antistreptococcal antibody titers, complement, immunoglobulins and autoantibodies. Estimation of blood pH, bicarbonate, electrolytes and osmolality is important in patients with tubular disorders and/or renal failure.

Glomerular Filtration Rate (GFR)

While clearance of inulin is regarded as the reference for estimating GFR, the test is cumbersome. Measurement of the creatinine clearance is adequate for assessing GFR in most cases.

Creatinine Clearance

Creatinine clearance depends on the body size; the values are normalized to surface area. The normal creatinine clearance is 80–120 mL/minute per 1.73 m². GFR can be estimated from serum creatinine (mg/dL) and patient height (cm). The value of the constant *k* ranges between 0.41 and 0.43.

$$\text{GFR (mL/minute per 1.73 m}^2\text{)} = \frac{k \times \text{height}}{\text{Serum creatinine}}$$

Radionuclide Clearance

Disappearance curves of the radionuclides, ¹²⁵I-iothalamate, ^{99m}Tc-diethylenetriaminepentaacetic acid (DTPA) or ⁵¹Cr-ethylenediaminetetraacetic acid (EDTA) following its IV injection can be used to accurately compute GFR.

Tests of Tubular Function

Table 17.1 lists some important evaluations useful in diagnosing disorders of tubular function.

Table 17.1: Investigations for evaluation of tubular diseases

Substrate	Test
Phosphate	Tubular reabsorption of phosphate Tubular maximum for reabsorption/GFR Blood parathormone
Glucose	Renal threshold and tubular maximum for glucose reabsorption
Amino acids	Clearance of amino acid
Bicarbonate	Blood anion gap Fractional excretion of bicarbonate
H ⁺	Minimum urinary pH Urine anion gap; urine osmolal gap Urine to blood (U–B) CO ₂ gradient
Water	Maximum urine osmolality Water deprivation test Plasma ADH
Sodium	Urinary sodium excretion Plasma renin, aldosterone

ADH: Antidiuretic hormone; GFR: Glomerular filtration rate

Water Deprivation Test

Following a few hours of fluid deprivation, desamino-8-D-arginine vasopressin (DDAVP) is administered nasally (5–10 µg in neonates and infants, 20 µg in children) or by IM injection (0.4–1.0 µg in infants and young children, 2 µg in older children). Urine is collected every hour for the next 2–3 hour. Following administration of DDAVP, patients with nephrogenic diabetes insipidus fail to show a rise of urine osmolality that remains below 300 mOsm/kg (normal >800 mOsm/kg). Those with deficiency of the antidiuretic hormone concentrate urine appropriately following DDAVP administration.

Radionuclide Imaging

Imaging of the kidney and urinary tract has been simplified by radionuclide methods. Radionuclide procedures are noninvasive, highly sensitive and expose patients to less radiation compared to radiocontrast studies. The compounds, labeled with radioactive ^{99m}technetium, commonly used include dimercaptosuccinic acid (DMSA), DTPA and mercaptotriacylglycine (MAG-3). Following IV injection, DMSA attains high concentration in the renal cortex and provides very high quality images of renal morphology. This is useful in detection and follow-up of renal parenchymal defects associated with urinary tract infections (Fig. 17.5a).

DTPA is freely filtered by the glomeruli with no tubular reabsorption or excretion. A DTPA renogram is useful for evaluating perfusion and function of each kidney. Obstruction to the urine flow can be diagnosed by studying the effect of IV frusemide. Normally, there is prompt washout of the radionuclide, but this clearing may not occur in subjects with upper urinary tract obstruction (Fig. 17.5b). Renal arterial narrowing results in reduced renal blood flow and an abnormal pattern on DTPA renogram. This effect is accentuated by administration of angiotensin-converting enzyme inhibitors, thus increasing its sensitivity in diagnosis of renal artery stenosis. MAG-3 provides highly satisfactory information on renal structure and function.

^{99m}Tc-labeled radionuclide scan can be used instead of the radiocontrast micturating cystourethrogram. The procedure is sensitive for detecting vesicoureteric reflux with minimal radiation exposure. However, this procedure does not provide sufficient anatomic details of bladder and urethra to recommend its use for initial evaluation of patients with suspected urinary tract obstruction, nor grading of vesicoureteric reflux.

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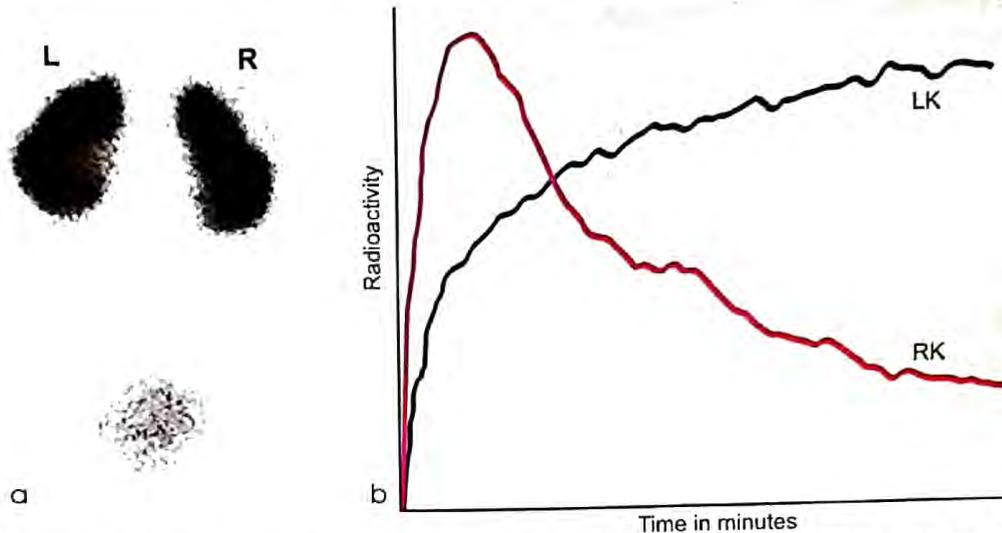


Fig. 17.5: (a) ^{99m}Tc -DMSA scintigraphy showing midzonal scars and loss of volume in the right kidney. The left kidney is normal; (b) Renal dynamic scan with diuretic was performed in a 6-week-old newborn with isolated left hydronephrosis. The excretion of the tracer on the left side is sluggish and unchanged with administration of diuretic, suggesting an obstructive pattern of excretion, as seen with pelviureteric junction obstruction

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HEMATURIA

The presence of blood in urine imparts it a color, which includes various shades of deep red, smoky brown, cola-color and faint pink. Parents may mistake very concentrated urine for that containing blood. Microscopic examination of urine will show red blood cells. Reagent-coated dipsticks detect free hemoglobin and myoglobin. Red urine may be present in porphyria and following beetroot ingestion. Urine appears orange-colored after administration of rifampicin or pyridium. Uric acid and xanthine crystals may also impart a pink tinge to the nappy.

In children, the commonest cause of gross hematuria is postinfectious GN (Table 17.2). Urinary tract stones are

not infrequent. Gross hematuria is rare in acute pyelonephritis. Conditions that cause persistent microscopic hematuria include idiopathic hypercalciuria, benign familial hematuria, Alport syndrome, IgA nephropathy and membranoproliferative GN.

Diagnostic Evaluation

A history of pain in the flank or suprapubic region, dysuria and edema should be obtained. Physical examination includes assessment of growth and features of acute or chronic kidney disease such as edema, hypertension, unexplained pallor, bony abnormalities and abdominal mass. An audiogram and a detailed eye examination may be needed. Figure 17.6 shows an algorithm for evaluation of patients with hematuria.

A fresh specimen is examined for red cells, red cell casts and protein. Absence of large number of red cells in bloody urine suggests hemoglobinuria (intravascular hemolysis)

Table 17.2: Causes of hematuria

Glomerular

Postinfectious glomerulonephritis (GN)
IgA nephropathy
Henoch-Schönlein nephritis
Membranoproliferative GN
Rapidly progressive GN

Uncommon

Lupus nephritis
Other vasculitides, e.g. microscopic polyangiitis
Membranous nephropathy
Familial benign hematuria
Alport syndrome

Non-glomerular

Hypercalciuria
Renal calculi
Urinary tract infection
Hemorrhagic cystitis
Trauma, exercise
Cystic renal disease
Interstitial nephritis

Uncommon

Vascular malformations
Coagulation disorders
Thrombocytopenia
Nutcracker syndrome
Renal or bladder malignancy

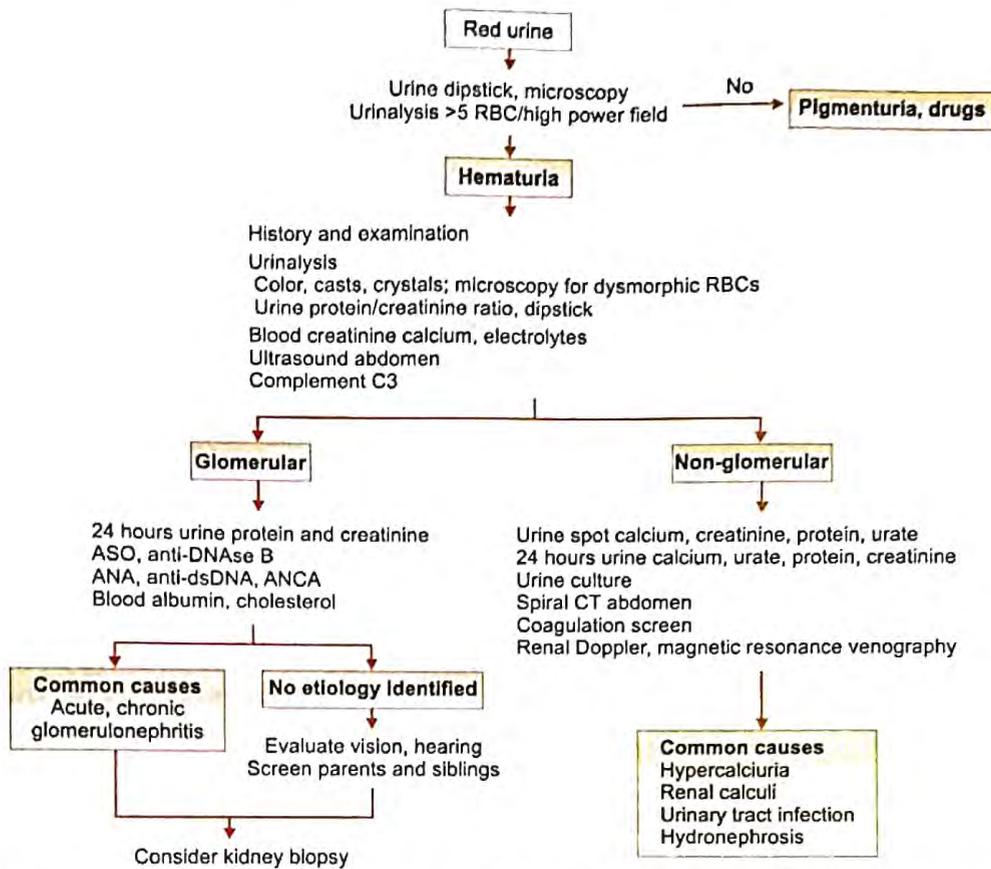


Fig. 17.6: Approach to evaluation of a patient with hematuria. The initial step in evaluation attempts to distinguish glomerular from nonglomerular causes of hematuria (see Table 17.3). Estimation of complement C3 is an important screening test for postinfectious glomerulonephritis. Patients with persistent glomerular hematuria might require kidney biopsy and/or screening for familial causes. ASO antistreptolysin O; ANA antinuclear antibody; anti-dsDNA anti-double-stranded DNA antibody; ANCA antineutrophil cytoplasmic antibody

or myoglobinuria. In glomerular disease, urine shows dysmorphic red cells, of different shapes, whereas in bleeding from renal pelvis or the lower urinary tract, the red cells maintain normal morphology (Fig. 17.7 and Table 17.3). Presence of significant proteinuria (2+ or more) and/or red cell casts suggests glomerular disease. Hypercalciuria should be screened by determination of urinary calcium to creatinine ratio on one or more random samples.

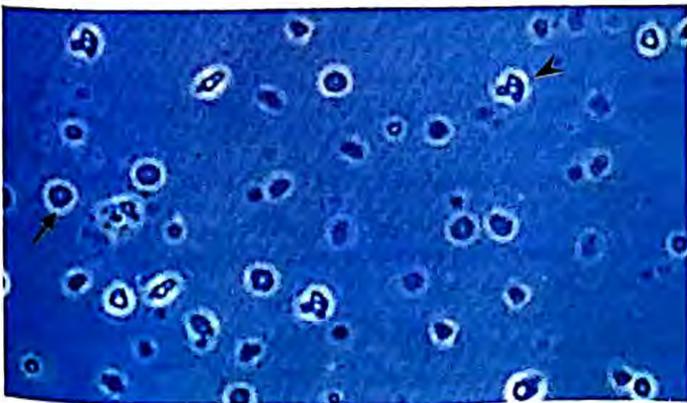


Fig. 17.7: Phase contrast microscopy showing dysmorphic red cells (arrowhead). Normal red cells are also seen (arrow)

A plain X-ray film of the abdomen and abdominal ultrasound is done to exclude major renal and urinary tract anomalies and calculi. Blood levels of creatinine are measured; specialized blood tests depend on the likely clinical etiology. Surgical conditions that cause hematuria can be diagnosed by appropriate imaging. Invasive procedures such as cystoscopy are rarely indicated.

In a significant proportion, isolated microscopic hematuria spontaneously disappears over a period of several years. Other family members may have similar urinary abnormalities. If there is no family history, a renal biopsy is not urgently indicated and the patient kept under observation.

Renal Biopsy

Renal biopsy should be done, if hematuria is associated with persistent or heavy (3+ or more) proteinuria, history of renal disease in the family or evidence of chronic kidney disease in the patient, or if renal impairment or hypertension are seen on follow-up. A biopsy is also considered in children showing persistent microscopic hematuria for two or more years even in the absence of the above features. This procedure is necessary to diagnose IgA nephropathy, Alport syndrome, thin basement membrane

Table 17.3: Features that distinguish glomerular from non-glomerular hematuria

Features	Glomerular causes	Non-glomerular causes
Dysuria	No	Suggests urethritis or cystitis
Systemic complaints	Edema, pharyngitis, rash, arthralgia	Fever (urinary tract infection), loin pain (calculi)
Family history	Deafness, renal failure (Alport syndrome)	Calculi (hypercalciuria)
Hypertension, edema	Common	Rare
Abdominal mass	Absent	Wilms tumor, obstructive uropathy
Urine color	Brown, tea, cola	Bright red, clots
Proteinuria	2+ or more	Trace, 1+
Dysmorphic RBC	>20%	<15%
RBC casts	Common	Absent
Crystals	Absent	May suggest calculi

RBC: Red blood cells

disease (typically presents as familial benign hematuria) and chronic GN. The biopsy is evaluated by light, immunofluorescence and electron microscopy.

Alport Syndrome

This condition is inherited in an X-linked manner, although autosomal transmission is known. Mutations in the gene encoding alpha subunit of collagen IV (*COL4A*) result in persistent microscopic hematuria, moderate proteinuria and progressive kidney failure. A significant proportion show high frequency sensorineural deafness; ocular defects (lenticonus, cataract, macular changes) are often associated. Ultrastructural examination of renal biopsy shows variable thickness of glomerular basement membrane with lengths of marked attenuation to areas of lamination. Therapy is supportive, including the use of angiotensin-converting enzyme inhibitors. The majority of male patients (X-linked illness; hemizygous mutations in *COL4A5* gene) show progression to end stage kidney disease. The course the illness in patients with autosomal recessive illness (mutation in *COL4A3* or *COL4A4*) is also rapid.

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PROTEINURIA

The glomerular capillaries provide an effective barrier to filtration of proteins. Small amounts of protein are filtered but almost completely reabsorbed by the proximal tubule. Detection of more than trace amounts of protein in the urine is abnormal. However, the degree of proteinuria does not always reflect the severity of glomerular abnormality. Massive proteinuria occurs in minimal change nephrotic syndrome, in which glomeruli are normal or show mild

changes. Persistent and heavy proteinuria, especially if associated with hematuria, should be promptly evaluated.

Quantitation of Proteinuria

Protein excretion at 100–1000 mg/m²/day indicates mild to moderate proteinuria; more than that is heavy (nephrotic range) proteinuria. Accurate quantitative measurements of 24 hours urinary protein are not needed, if semiquantitative tests are done on a concentrated (first morning) specimen. Normally, the protein to creatinine ratio, in the first morning urine specimen, is below 0.2 (mg/mg); a ratio of 0.2–2 indicates mild to moderate and >2 heavy proteinuria. The latter usually corresponds to 3+ or 4+ reaction on boiling or dipstick test.

Important causes of asymptomatic proteinuria include orthostatic proteinuria, chronic glomerular diseases, reflux nephropathy, renal hypoplasia and rarely renal tubular disorders (Table 17.4). In orthostatic (postural) proteinuria,

Table 17.4: Conditions presenting with proteinuria

Glomerular proteinuria

Nephrotic syndrome (minimal change disease, focal segmental glomerulosclerosis, congenital nephrotic syndrome)

Membranous

Hepatitis B and C nephropathy, HIV nephropathy

Reflux nephropathy

Amyloidosis

Associated hematuria: Postinfectious glomerulonephritis, IgA nephropathy, Henoch-Schönlein nephritis, lupus nephritis, C3 glomerulopathy, Alport syndrome

Nonglomerular proteinuria

Drug induced nephropathy (analgesics)

Heavy metal nephropathy (e.g. gold, lead, cadmium)

Renal tubular acidosis

Interstitial nephritis, pyelonephritis

Intermittent or transient proteinuria

Postural (orthostatic)

Fever

Exercise

protein is absent in urine specimen collected after overnight recumbence. Continued follow-up is necessary until proteinuria disappears.

A renal biopsy is indicated in presence of persistent or heavy proteinuria. Long-term observation is necessary to monitor clinical course and renal function. The underlying cause is treated, where possible. Low salt diet and prolonged treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are effective in reducing glomerular proteinuria.

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ACUTE GLOMERULONEPHRITIS

Acute glomerulonephritis (GN) is characterized by abrupt onset of hematuria, oliguria, edema and hypertension. The clinical severity varies. Mild disease may go undetected; severe cases have anuria, hypertensive encephalopathy and heart failure. Poststreptococcal GN is the most common cause of acute GN in India (Table 17.5). Key investigations include renal function tests, urinalysis, serum complement C3 and titers of antistreptolysin. Renal biopsy is required, if the presentation or course suggests a diagnosis other than poststreptococcal GN (Table 17.6).

Poststreptococcal Glomerulonephritis

Acute GN following infection by group A beta-hemolytic streptococci is a common disorder. Streptococcal infection of the throat or skin precedes the onset of nephritis by 1 to 4 weeks. Only a few strains of streptococci are

Table 17.5: Etiology of the acute nephritic syndrome

Postinfectious

Streptococci, staphylococci, pneumococci, meningococci, *Treponema pallidum*, *Salmonella*, leptospira

Plasmodium malariae, *P. falciparum*, toxoplasma, filaria

Hepatitis B and C, cytomegalovirus, parvovirus, Epstein-Barr virus, coxsackievirus, echovirus, varicella

Associated with severe infections; infection of shunts, prostheses, bacterial endocarditis

Systemic vasculitis

Henoch-Schönlein purpura

Microscopic polyarteritis, Wegener granulomatosis

Others

Membranoproliferative glomerulonephritis

IgA nephropathy

Hereditary nephropathy

Systemic lupus erythematosus

Table 17.6: Indications for renal biopsy in acute glomerulonephritis

Systemic features. Fever, rash, joint pain, heart disease

Absence of serologic evidence of streptococcal infection; normal levels of C3 in the acute stage of illness

Mixed features of glomerulonephritis and nephrotic syndrome

High blood levels of urea or presence of anuria requiring dialysis (rapidly progressive GN)

Delayed resolution

Oliguria, hypertension and/or azotemia persisting past 7–10 days

Gross hematuria persisting past 3–4 weeks

Nephrotic range proteinuria beyond 2 weeks

Low C3 levels beyond 12 weeks

Persistent proteinuria beyond 6 months

nephritogenic, e.g. types 4 and 12 causing pharyngitis and type 49 causing pyoderma.

Pathology

On light microscopy, glomeruli are enlarged and ischemic and capillary loops narrowed, making glomeruli appear bloodless (Fig. 17.8a); there is proliferation of mesangial cells and neutrophil infiltration. Immunofluorescence shows granular deposits of IgG and complement (C3) along capillary walls (Fig. 17.8b). Electron microscopy shows deposits (humps) on the subepithelial side of the glomerular basement membrane.

Clinical Features

Poststreptococcal GN affects school-age children, more commonly boys and is uncommon below 3 yr. Subclinical episodes are more common than overt disease, especially during epidemics. The onset is rapid, with puffiness around the eyes and pedal edema. Urine is cola-colored; hematuria is brief, often lasting only a few hours and does not persist beyond 1–2 weeks. While the degree of oliguria correlates with the disease severity, anuria is uncommon. Hypertension, present in over half the patients, resolves with loss of edema. Atypical presentations include (i) convulsions due to hypertensive encephalopathy; (ii) left ventricular failure and pulmonary edema, due to malignant hypertension and hypervolemia; (iii) acute kidney injury; and (iv) nephrotic syndrome.

Laboratory Findings

Urine shows 1–2+ protein with red cells, and red cell and granular casts. White cells indicate glomerular inflammation and should not be regarded as evidence of UTI. Hemodilution may result in normocytic anemia; ESR is raised. Blood levels of urea and creatinine are elevated reflecting renal impairment; hyponatremia and hyperkalemia occur with continuing oliguria. Chest X-ray may show prominent vascular markings suggesting hypervolemia.

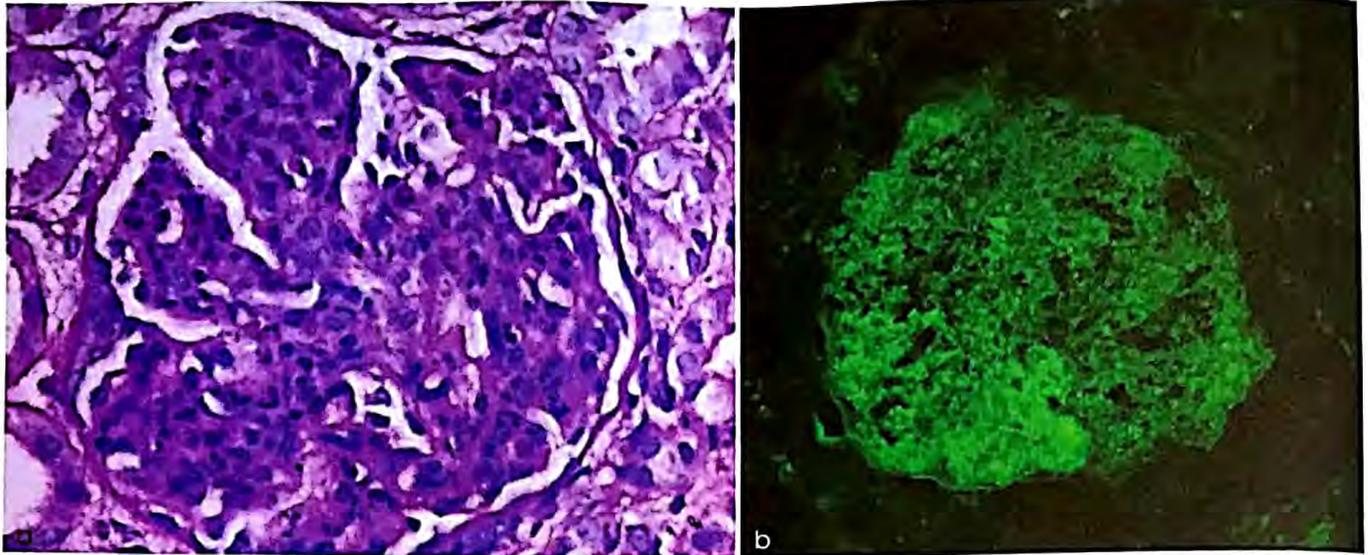


Fig. 17.8: (a) Poststreptococcal GN. Moderately severe proliferation and exudative changes with infiltration of neutrophils. A few open capillary lumina are seen; (b) Immunofluorescence examination showing extensive fine granular deposition of IgG along the capillary wall and in mesangium with a starry sky appearance

Serologic evidence for streptococcal infection is present in most patients with pharyngitis, though antibiotic therapy may blunt this response. ASO titer is increased in more than 80% patients; anti-DNase B is elevated in cases of streptococcal skin infection. The titers decrease within 4–6 weeks. The level of serum C3 is low in 90% patients but normalizes by 8–12 weeks. Persistent low C3 levels indicate other forms of GN.

Management

Patients with mild oliguria and normal blood pressure can be managed at home. Close attention to blood pressure and dietary intake is essential. Treatment with penicillin has no effect on the course of the disease, but may be given, if active pharyngitis or pyoderma is present. The principles of management of patients with severe oliguria and acute kidney injury are discussed later.

Diet: The intake of sodium, potassium and fluids is restricted until blood levels of creatinine reduce and urine output increases. Overhydration may increase the risk of hypertension and precipitate left ventricular failure. Patients with azotemia require accurate measurement of urine output and daily weight, and restriction of fluid intake to an amount equal to insensible losses and 24 hr urine output.

Diuretics: Patients showing modest edema are treated with oral furosemide at a dose of 1–3 mg/kg; the edema disappears with the return of renal function. Therapy with IV furosemide (2–4 mg/kg) is necessary in patients with pulmonary edema.

Hypertension: Mild hypertension may be controlled by restriction of salt and water intake. Effective anti-hypertensive agents include amlodipine, nifedipine or diuretics. Beta-blockers and angiotensin-converting

enzyme inhibitors carry risk of hyperkalemia. Patients with hypertensive emergencies need prompt treatment with IV nitroprusside or labetalol.

Left ventricular failure: Hypertension should be controlled and IV furosemide given to induce diuresis, leading to improvement in heart failure. If diuresis is not noted, dialysis is initiated. Respiratory support with positive end-expiratory pressure may be needed.

Prolonged oliguria: Treatment, as outlined above, should be continued and levels of blood urea, creatinine and electrolytes monitored. Dialysis is required in children with severe renal failure and prolonged oligoanuria, fluid overload and life-threatening electrolyte disturbances. Occurrence of secondary infections should be avoided.

Outcome and Prognosis

Acute poststreptococcal GN has an excellent prognosis in childhood. The symptoms begin to resolve in the first week with loss of edema and fall in blood pressure. Gross hematuria and significant proteinuria disappear within 2 weeks, although microscopic hematuria and slight proteinuria may persist for several months. Hypertension subsides within 2–3 weeks, but rarely may persist for several weeks. Patients with acute GN of nonstreptococcal etiology have variable and unpredictable outcome. These cases need close follow-up over several years with periodic urinalyses and measurements of blood pressure.

Renal biopsy: A biopsy is rarely indicated in those suspected to have poststreptococcal GN except when renal function is severely impaired beyond 7–10 days or serum C3 remains depressed beyond 12 weeks. Patients with features of a systemic illness (e.g. systemic lupus) require a kidney biopsy (Table 17.6).

Crescentic Glomerulonephritis

Rapidly progressive GN (RPGN) is defined as an acute nephritic illness accompanied by rapid loss of renal function over days to weeks. The histopathological correlate is the presence of crescents (crescentic GN) involving 50% or more glomeruli (Fig. 17.9) suggesting severe glomerular injury. The chief forms of RPGN are: (i) immune complex crescentic GN (immunofluorescence showing immunoglobulin and C3 deposits; normal or low C3), (ii) pauci-immune crescentic GN (related to small vessel vasculitis; positive antineutrophil cytoplasmic antibodies; scant immune deposits) and (iii) anti-glomerular basement membrane GN (with anti-GBM antibodies; linear IgG deposits). There is satisfactory clinicopathologic correlation and patients with extensive histological changes have poor outcomes. Renal biopsy should be performed in all patients with severe nephritic features, which do not resolve within 1–2 weeks.

The outcome is related to histological severity and prompt institution of therapy. Satisfactory results have been obtained with initial administration of IV and oral corticosteroids and IV cyclophosphamide, followed by maintenance immunosuppression for 2–3 years. Prompt plasmapheresis is recommended for patients with pauci-immune crescentic GN and Goodpasture syndrome.

Nephritis in Henoch-Schönlein Purpura

Henoch-Schönlein purpura (HSP) is the most common vasculitis in children (Fig. 17.10). Mild renal involvement indicated by microscopic hematuria and mild proteinuria is common. Serum IgA levels may be elevated. Renal biopsy shows mesangial proliferation with mesangial deposition of IgA. Most patients recover without any specific treatment. However, long-term observation is necessary to detect insidious renal damage. Rarely, a

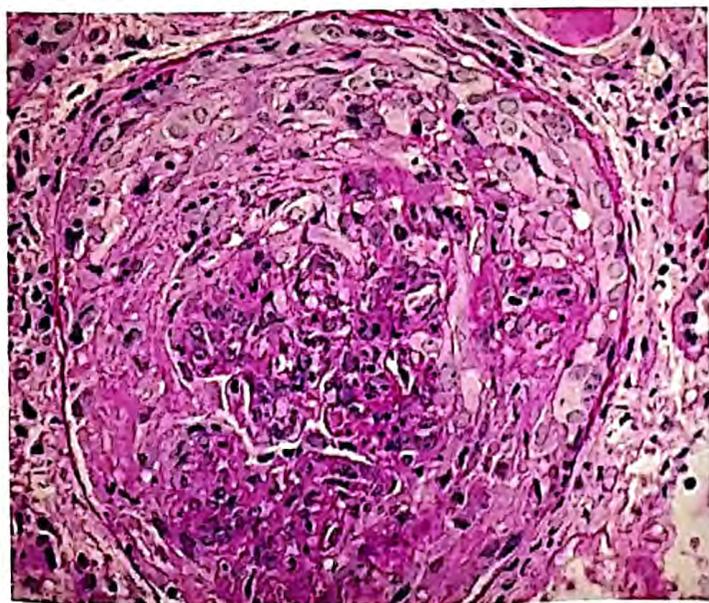


Fig. 17.9: Large cellular crescent with compression of glomerular tuft (Masson trichrome $\times 200$)



Fig. 17.10: Henoch-Schönlein purpura in a 6-year-old girl admitted with severe abdominal pain. Note purpuric rash over the lower limbs

patient may present with nephritic or nephrotic syndrome, hypertension, azotemia and crescentic GN. Therapy with a combination of oral/IV corticosteroids and cyclophosphamide initially, followed by maintenance steroids and azathioprine is recommended. Long-term outcome depends on the severity of renal manifestations.

Immunoglobulin A Nephropathy

Predominant deposition of IgA in the glomeruli, chiefly in the mesangium and occasionally in capillary walls is characteristic. The usual clinical manifestation is recurrent episodes of gross hematuria following upper respiratory infections; each episode lasts for 2–5 days. An acute nephritic or nephrotic syndrome is rarely the initial manifestation. Renal histology shows mesangial proliferation of varying severity. Patients with hematuria and non-nephrotic proteinuria are treated using angiotensin-converting enzyme inhibitors. Therapy with corticosteroids and alkylating agents is indicated in patients with nephrotic range proteinuria, deranged renal function or those with severe histological changes.

Lupus Nephritis

Patients with systemic lupus erythematosus variably present with asymptomatic proteinuria and/or hematuria, acute nephritic syndrome and nephrotic syndrome. Renal biopsy may show almost normal glomeruli, focal or diffuse proliferative GN or membranous nephropathy. Immunofluorescence studies show mesangial and capillary wall deposits of all immune reactants (full-house deposition). Antinuclear and double-stranded DNA autoantibodies are present in most cases with lupus nephritis; C3 levels are reduced.

Remissions and relapses and progressive renal damage are characteristic. Infections and end stage renal disease are the chief cause of mortality.

C3 Glomerulopathy

C3 glomerulopathy (C3G) comprises glomerulonephritis secondary to uncontrolled activation of the alternate complement pathway, characterized histologically by predominant deposits of C3. In most cases, complement dysregulation is caused by the C3 nephritic factor, an autoantibody that binds to C3 convertase, stabilizing it against inactivation by factor H (FH). This results in uncontrolled activation of C3. Patients usually show a membranoproliferative pattern of injury, with lobulation and mesangial interposition with thickening of capillary walls, which appear split on silver methanamine staining. Immunofluorescence shows isolated or predominant C3 deposits in basement membrane, mesangium and/or capillaries. Based on electron microscopy, C3G is classified as dense deposit disease (ribbon-like electron dense osmophilic material in the glomerular basement membrane) and C3 glomerulonephritis (C3GN; deposits in mesangium, subepithelial and/or subendothelial locations).

Most patients present with proteinuria, gross or persistent microscopic hematuria, hypertension and/or renal failure. Diagnosis is suggested by renal histology and persistently low serum C3. Management comprises reduction of proteinuria and control of hypertension using ACE inhibitors. Immunosuppression with prednisolone and mycophenolate mofetil is proposed, but most patients show progressive renal disease. There is a high risk of recurrence of C3G in allografts.

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NEPHROTIC SYNDROME

Nephrotic syndrome is characterized by massive proteinuria, hypoalbuminemia and edema; hyperlipidemia is often associated. Some patients show hematuria and hypertension. Heavy proteinuria (more than 1 g/m²/day) is the underlying abnormality, leading to hypoalbuminemia (serum albumin below 2.5 g/dL). The resultant fall in plasma oncotic pressure leads to interstitial edema and hypovolemia. This stimulates the renin-angiotensin-aldosterone axis and antidiuretic hormone

secretion that enhances sodium and water retention. The pathogenesis of edema may, however, be different in patients with significant glomerular lesions, who show primary sodium retention and expanded intravascular volume. Hypoalbuminemia also induces hepatic synthesis of β -lipoproteins resulting in hypercholesterolemia.

More than 90% of childhood nephrotic syndrome is primary (or idiopathic). Other causes such as amyloidosis, vasculitis, systemic lupus erythematosus, postinfectious GN and hepatitis B nephropathy are infrequent. Nephrotic syndrome in children can be divided into two groups based on renal histology: (i) minimal change nephrotic syndrome (MCNS); and (ii) nephrotic syndrome with significant lesions (Table 17.7).

Steroid-sensitive nephrotic syndrome (which is usually MCNS) has a satisfactory long-term outcome. In contrast, the steroid-resistant form (usually associated with significant glomerular lesions) has less satisfactory course and a significant proportion show progressive renal failure.

STEROID-SENSITIVE NEPHROTIC SYNDROME

MCNS accounts for 80% cases of nephrotic syndrome in children. Renal biopsy does not show significant abnormalities on light microscopy (Fig. 17.11a). Electron microscopy shows nonspecific obliteration of epithelial foot processes. Immunofluorescence studies do not demonstrate deposition of immune reactants except occasional mesangial IgM. On the other hand, patients with focal segmental glomerulosclerosis (FSGS) show evidence of sclerosis involving a segment of the glomerular tuft (Fig. 17.11b).

The pathogenesis of MCNS is obscure. There is evidence to suggest perturbation of cell-mediated

Table 17.7: Features of idiopathic nephrotic syndrome

Features	Minimal lesion	Significant lesions
Age at onset	2–6 years	Older children
Sex incidence	Higher in boys	Equal
Hematuria	Rare	Usual
Blood pressure	Normal	Normal or increased
GFR	Normal	Normal or decreased
Renal biopsy	Normal glomeruli; mild mesangial proliferation; often IgM deposits	Changes of varying severity; C3, immunoglobulin deposits
Serum C3	Normal	Low in MPGN
Selectivity of proteinuria	High	Low
Response to steroids	Remission in >95%	Unsatisfactory
Prognosis	Good; relapses stop by second decade	Variable progression of renal damage

MPGN: Membranoproliferative glomerulonephritis

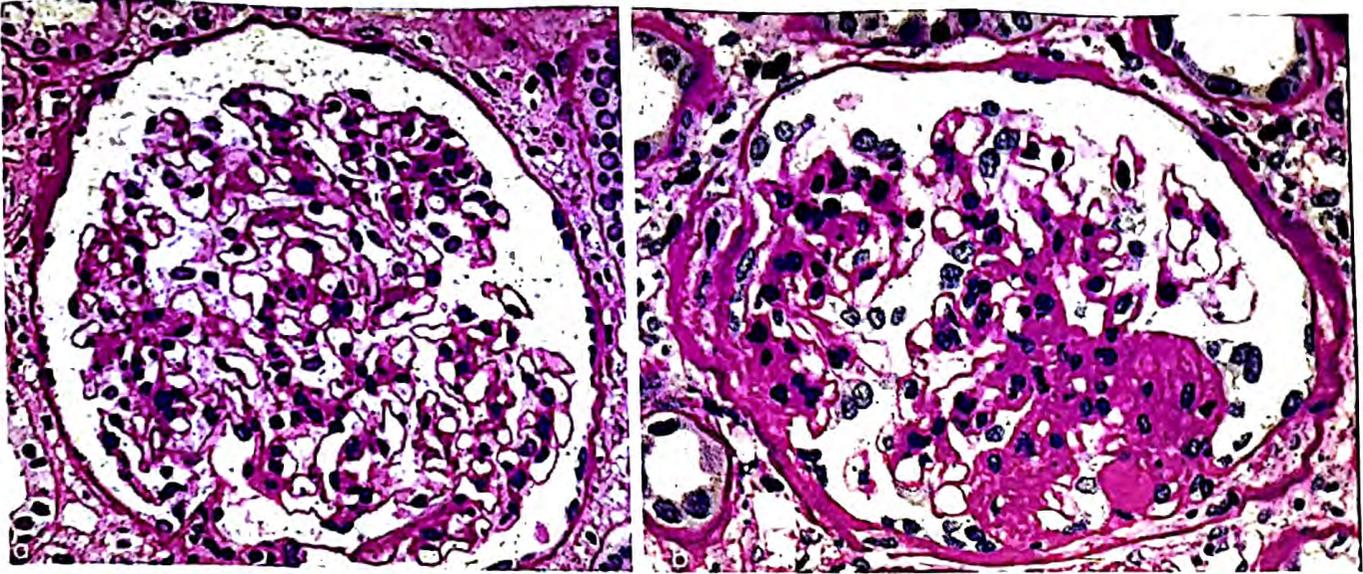


Fig. 17.11: (a) Renal histology in a 4-year-old boy with steroid-dependent nephrotic syndrome. There is normal morphology of glomerular capillary loops, mesangial matrix and cells suggestive of minimal change disease; (b) Histological features in a 6-year-old girl with steroid-resistant nephrotic syndrome secondary to focal segmental glomerulosclerosis. Note the hilar sclerosis involving large areas of the glomerulus and adhesions to the Bowman's capsule

immunity, which through yet undefined mechanisms alters the permselectivity of the glomerular filter, resulting in proteinuria. A significant proportion of patients shows Th2 polarization; some also show perturbation in the T-regulatory/Th17 axis.

Clinical Features

The onset is insidious with edema first noticed around the eyes and subsequently on legs. It is soft and pits easily on pressure. Gradually, edema becomes generalized, with ascites, hydrothorax and hydrocele (Fig. 17.12). With



Fig. 17.12: An 8-year-old boy with steroid-dependent nephrotic syndrome. Anasarca is seen affecting upper limbs (including dorsa of hands), trunk and ascites. Note the cushingoid features and striae on lower abdominal wall and upper legs

increasing edema, urine output may fall. The blood pressure is usually normal; sustained elevation suggests the possibility of significant glomerular lesions. The bloated appearance and relative well-being of the child is misleading and after the loss of edema, severe muscle wasting is revealed. Infections may be present at the onset and during relapses.

Laboratory Findings

Urine examination shows heavy (3–4+) proteinuria. Gross hematuria or persistent microscopic hematuria suggests the likelihood of significant glomerular lesions; hyaline and granular casts are present. Serum albumin is low and values below 1 g/dL are often obtained. Hypercholesterolemia may impart a milky appearance to the plasma. Blood urea and creatinine values are within the normal range except when there is hypovolemia and fall in renal perfusion.

Blood levels of IgG are low and those of IgM elevated; C3 level is normal. The severity of glomerular damage is reflected in the passage of proteins of large molecular weight, chiefly globulin.

Evaluation at onset of nephrotic syndrome includes: (i) urinalysis for proteinuria, red cells, casts; (ii) blood levels of urea, creatinine, albumin, cholesterol; (iii) complete blood counts; and (iv) tuberculin test. Depending on clinical and laboratory findings, the following additional tests may be required: (i) C3 and antistreptolysin O (if gross or persistent microscopic hematuria); (ii) chest X-ray (positive tuberculin test or history of contact with tuberculosis); (iii) hepatitis B surface antigen (recent jaundice, raised levels of transaminases); (iv) antinuclear antibodies (suspected systemic lupus erythematosus); and (v) urine culture (suspected urinary tract infection).

A renal biopsy is not required to confirm the diagnosis of MCNS prior to starting treatment. A biopsy is recommended in children with atypical features at the onset (age below 12 months, gross or persistent microscopic hematuria, low blood C3, hypertension or impaired renal function). Patients who continue to show nephrotic range proteinuria despite appropriate steroid therapy require a biopsy to determine the underlying disorder.

Management of Initial Episode

The child should receive a high protein diet. Salt is restricted to the amount in usual cooking with no extra salt given. Any associated infection is treated. Patients should be screened for tuberculosis. Diuretics are administered, only if edema is significant. They should be used cautiously and overzealous fluid loss avoided. Frusemide (1–4 mg/kg/day in 2 divided doses) alone or with an aldosterone antagonist, spironolactone (2–3 mg/kg/day in 2 divided doses) is adequate. Therapy with corticosteroids results in abolition of proteinuria (remission) usually by 10–14 days, diuresis and loss of edema.

The first episode of nephrotic syndrome should be treated adequately, both in terms of dose and duration of corticosteroids, since this is considered an important determinant of long-term course. Only prednisolone and prednisone are of proven benefit in the treatment of proteinuria. Either of these agents is given at a dose of 60 mg/m²/day (maximum 60 mg) in single or divided doses for 6 weeks, followed by 40 mg/m² (maximum 40 mg) as a single morning dose on alternate days for the next 6 weeks. Therapy with corticosteroids is then stopped. Extending initial therapy beyond 12 weeks increases the risk of corticosteroid toxicity without significant benefits, and is not recommended.

Parent Education

The parents should be explained about the disease and the usual outcome and their cooperation ensured. They are taught how to examine urine for protein, which should be done periodically to detect a relapse early. During the periods of remission, no dietary restrictions are imposed.

Subsequent Course

A small proportion of patients have only a single episode of the illness, while the majority shows relapses. Some patients have three or less relapses in a year (infrequent relapsers), while others have four or more relapses (frequent relapsers) (Table 17.8). About 15% remain in remission while on prednisolone therapy and relapse whenever the dose is reduced or within 2 weeks of its discontinuation (steroid dependent). About 10% patients either do not respond to the initial treatment with prednisolone, or do so transiently and later cease to respond (steroid resistant).

Table 17.8: Definitions regarding course of nephrotic syndrome

Remission: Urine albumin nil or trace (or proteinuria <4 mg/m²/hr) for 3 consecutive early morning specimens

Relapse: Urine albumin 3+ or 4+ (or proteinuria >40 mg/m²/hr) for 3 consecutive early morning specimens, having been in remission previously

Frequent relapses: Two or more relapses in initial six months or four or more relapses in any 12 months

Steroid dependence: Two consecutive relapses when on alternate day steroids or within 14 days of its discontinuation

Steroid resistance: Absence of remission despite therapy with daily prednisolone at a dose of 60 mg/m²/day for 4 weeks and alternate day for next 4 weeks

Management of Relapse

Relapses are often triggered by minor infections. Symptomatic therapy of infectious illness might result in remission of low grade (1–2+) proteinuria. However, persistence of 3–4+ proteinuria requires treatment for relapse. Prednisolone is given at a dose of 60 mg/m²/day until protein is negative/trace for three consecutive days, and then on alternate days at a dose of 40 mg/m² for 4 weeks. Thus, treatment for a relapse usually lasts for 5–6 weeks.

The first 2–3 relapses are treated in the manner described above. Once the pattern of relapses is known, therapy is individualized. Patients with infrequent relapses continue to receive treatment for individual relapses as outlined above.

Frequent Relapses and Steroid Dependence

Patients with frequent relapses or steroid dependence require prolonged treatment in order to maintain disease remission.

Long-term Alternate Day Prednisolone

Following treatment of a relapse, the dose of prednisolone is tapered to maintain the patient in remission; usually a small dose is given on alternate days for 9–18 months (Table 17.9). This strategy is effective in maintaining remission in many patients. Since infections precipitate relapses, administering the same small dose daily for 5–7 days starting at onset of infections may prevent relapses. Relapses, while on this therapy, are treated as described above. Patients with repeated relapses, while on long-term therapy, should be considered for treatment with a steroid-sparing agent.

Steroid-Sparing Agents

The additional use of an alternative agent should be considered in patients with: (i) prednisolone threshold (for maintaining remission) higher than 0.5–0.7 mg/kg on alternate days, or (ii) features of corticosteroid toxicity (growth failure, hypertension, cataract). The agents used, usually in successive order, are listed below and in Table 17.9.

Table 17.9: Therapy for steroid-sensitive nephrotic syndrome

Agent	Dose	Duration	Adverse effects
Prednisolone	0.3–0.7 mg/kg on alternate days	9–18 months	Cushingoid body habitus, hypertension, short stature, cataract, hirsutism
Levamisole	2–2.5 mg/kg on alternate days	1–2 years	Leukopenia, rash, flu-like symptoms
Cyclophosphamide*	2–2.5 mg/kg/day	12 weeks	Leukopenia; alopecia; gonadal toxicity; nail discoloration. (Hemorrhagic cystitis; nausea and vomiting are more common with IV administration)
Mycophenolate mofetil	600–1000 mg/m ² /day or 20–25 mg/kg/day	1–3 years	Gastrointestinal discomfort, diarrhea; leukopenia
Cyclosporine (CyA)* Tacrolimus (Tac)*	CyA: 4–5 mg/kg/day Tac: 0.1–0.2 mg/kg/day	12–36 months	Acute and chronic nephrotoxicity, elevated transaminases (both agents); hirsutism, gum hyperplasia, hypertension or hyperlipidemia (CsA > Tac); hyperglycemia, neurotoxicity with headache and seizures (Tac > CsA)
Rituximab*	375 mg/m ² IV once a week	1–2 doses	Infusion reactions (fever, rash, bronchospasm); neutropenia

* Preferred earlier, if relapses are life-threatening (associated with peritonitis, other serious infections or thrombosis) or in presence of significant steroid toxicity

Levamisole: This immunomodulator is effective in reducing relapses in patients with frequent relapsing or steroid-dependent nephrotic syndrome. After inducing remission, levamisole is administered at a dose of 2–2.5 mg/kg on alternate days. Alternate day prednisolone is given in decreasing doses, until a dose of 0.3–0.5 mg/kg is reached, for 3–6 months; it is occasionally possible to discontinue steroids altogether. Treatment with levamisole is given for 1–2 year or longer. The chief side effect is leukopenia, which should be monitored every 2 months; others include flu-like symptoms and rash.

Cyclophosphamide: Treatment with cyclophosphamide and alternate day prednisolone is effective in many patients with frequent relapsing or steroid-dependent nephrotic syndrome. A 12-week course of treatment may induce long-lasting remission in 30–40% cases. Side effects include leukopenia, nausea and vomiting; a high fluid intake is ensured to prevent hemorrhagic cystitis. There is risk of gonadal toxicity and malignancies, although at the doses and duration used, these risks are minimal. The alkylating agent, chlorambucil has significant additional toxicities and a low margin of safety, and is not recommended.

Mycophenolate mofetil: Prolonged treatment with this agent is useful in reducing relapse rates and corticosteroid sparing. The lack of renal, hemodynamic and metabolic toxicity makes it an alternative to calcineurin inhibitors. Chief side effects include gastrointestinal discomfort, diarrhea and leukopenia. The dose of the medication is 600–1000 mg/m²/day or 20–25 mg/kg/day in two divided doses for 12–36 months. Tapering doses of prednisolone are given for ~6 months.

Cyclosporine and tacrolimus: Therapy with either of these agents is indicated in patients that fail to benefit with other

steroid-sparing agents or show high steroid threshold with steroid toxicity. Cyclosporine A or tacrolimus is administered, in two divided doses, for 12–24 months aiming for respective trough levels of 80–120 ng/mL and 3–7 ng/mL. Both agents have strong steroid-sparing potential, with steroid discontinuation achieved in most patients over 6–9 months.

Adverse effects are common and include acute and chronic nephrotoxicity. A renal biopsy is done after 2–3 years of continuous therapy. Patients receiving cyclosporine have cosmetic side effects (hirsutism, gum hyperplasia), hypertension and hypercholesterolemia. Treatment with tacrolimus is associated with risk of hyperglycemia, elevated transaminases, diarrhea, tremors, headache and seizures.

Rituximab: This monoclonal anti-CD20 antibody has been used with success in patients with steroid dependent nephrotic syndrome, with remission lasting 6–18 months. This agent appears to be useful in patients who fail to respond or show toxicity with other therapies.

Complications in Nephrotic Syndrome

The patient should be maintained in remission, as far as possible. Relapses should be promptly treated so that the child does not develop more than minimal edema.

Edema

Edema is controlled with salt restriction and oral hydrochlorothiazide or frusemide for a few days. Salt must not be totally stopped and the usual amounts used in cooking should be allowed. For massive edema, higher doses of frusemide along with spironolactone are needed. Infusion of albumin is necessary in cases where serum albumin levels are low causing poor renal perfusion and oliguria.

Infections

Nephrotic syndrome and steroid therapy render children susceptible to infections. Infections with *S. pneumoniae*, gram-negative organisms and varicella are common. Children present with serious infections, e.g. peritonitis, cellulitis, pneumonia and meningitis. Peritonitis may manifest with low grade fever, diarrhea and abdominal discomfort. Patients with varicella should receive oral acyclovir for 7 days; severe illness requires administration of IV acyclovir. Immunization with pneumococcal and varicella vaccines is advised once the patient is off steroids for 4 weeks.

Thrombotic Complications

Patients with nephrotic syndrome are at risk for thrombosis involving renal, pulmonary and cerebral veins. Aggressive use of diuretics, venepuncture of deep veins and hypovolemia increase the risk of this complication. Treatment with low molecular weight heparin followed by oral anticoagulants is recommended.

Hypovolemia and Acute Renal Failure

Hypovolemia may occur during a severe disease relapse or following administration of diuretics, particularly in children with poor oral intake, diarrhea and vomiting. Features include abdominal pain, lethargy, dizziness and leg cramps, tachycardia, hypotension, delayed capillary refill, low volume pulses and clammy distal extremities. Elevated ratio of blood urea to creatinine, high hematocrit, urine sodium <20 mEq/L, fractional excretion of sodium 0.2–0.4% and urinary potassium index [$\text{urine K}^+ / (\text{urine K}^+ + \text{urine Na}^+)$] >0.6 suggest the presence of hypovolemia. Therapy with diuretics should be discontinued. Patients require rapid infusion of normal saline (10–20 mL/kg) over 20–30 min. Those who do not respond to two boluses of saline should receive infusion of 5% albumin (10–15 mL/kg) or 20% albumin (0.5–1 g/kg).

Steroid Toxicity

Repeated and prolonged courses of steroids often result in significant toxicity, characterized by cushingoid features, short stature, hypertension, osteoporosis and subcapsular cataract. Timely use of steroid sparing agents (levamisole, alkylating agents, cyclosporin) is recommended.

Long-term Outcome

Children with MCNS usually have an excellent prognosis. The frequency of relapses decreases with time and a majority of patients outgrow the condition by adulthood. It is unfortunately not possible to predict when a particular patient will stop getting relapses. The mortality rate of 1–4% is associated with infections and hypovolemia that should be preventable.

STEROID-RESISTANT NEPHROTIC SYNDROME

Steroid resistance is diagnosed, if there is lack of remission despite treatment with prednisolone, at a dose of 2 mg/kg/day (60 mg/m²/day) for 4 weeks followed by 1.5 mg/kg (40 mg/m²) on alternate days for another 4 weeks. Care is taken to exclude systemic infections (e.g. peritonitis, cellulitis, respiratory tract infections), which might result in persistent proteinuria. The management of these patients is difficult, with patients showing a variable response to immunosuppression, adverse effects of prolonged therapy and risk of progressive renal damage.

Baseline assessment of renal function, blood levels of albumin and cholesterol, and estimation of proteinuria (24 hours quantitation) guides evaluation. Patients should be evaluated for secondary causes. Children with steroid resistance should undergo renal biopsy before instituting specific treatment. While patients with minimal change disease show satisfactory response to therapy, the presence of FSGS with chronic tubulointerstitial changes is associated with less satisfactory outcomes. Patients should also undergo testing for hepatitis B surface antigen, anti-HCV IgG and HIV.

About 20–30% patients with familial and sporadic steroid resistant nephrotic syndrome have homozygous or compound heterozygous mutations in genes encoding podocyte proteins, including podocin (*NPHS2*), nephrin (*NPHS1*) and Wilms tumor (*WT1*) genes. Mutations in more than 70 genes are known to be associated with steroid resistance. Next-gen sequencing using targeted gene or whole exome approach is useful in screening. These patients are unresponsive to immunosuppressive medications, progress rapidly to end stage renal disease and unlike nongenetic FSGS (which recurs after transplantation), does not recur in allografts. Where facilities exist, mutational analysis should be offered to patients with (i) congenital nephrotic syndrome (onset below 3 months of age), (ii) family history of SRNS, (iii) sporadic initial steroid resistance that does not respond to therapy with calcineurin inhibitors, and (iv) girls with steroid resistant FSGS.

Management

Patients with steroid-resistant nephrotic syndrome secondary to minimal change disease, FSGS or mesangio-proliferative GN are treated similarly. The chief factor predicting renal outcome is the response of proteinuria to therapy, rather than the renal histology. The aim of therapy is thus to induce and maintain remission of proteinuria, while avoiding medication related adverse effects. Most regimens use a combination of an immunosuppressive agent with prednisolone (given on alternate days) and an angiotensin-converting enzyme inhibitor (Table 17.10). The best results are obtained with regimens combining calcineurin inhibitors (cyclosporine or tacrolimus) and tapering doses of corticosteroids. Although the aim of

Table 17.10: Agents for management of steroid-resistant nephrotic syndrome

Agent	Dose	Duration	Efficacy	Adverse effects
Calcineurin Inhibitors				
Cyclosporine	4–5 mg/kg/day	12–36 months	50–80%	See Table 17.9
Tacrolimus	0.1–0.2 mg/kg/day	12–36 months	70–85%	
Cyclophosphamide				
Intravenous	500–750 mg/m ²	8 pulses	40–50%	Leukopenia; alopecia; nausea and vomiting; gonadal toxicity; hemorrhagic cystitis
Oral	2–2.5 mg/kg/day	12 weeks	20–25%	
High dose corticosteroids with cyclophosphamide				
Methylprednisolone	20–30 mg/kg IV	'Pulses' on alternate days × 6	30–35%	Hypertension, hypokalemia, hyperglycemia, steroid psychosis, systemic infections
Prednisolone	Tapering doses*	18 months		Side effects of cyclophosphamide and prolonged steroid therapy
Cyclophosphamide	2–2.5 mg/kg/day*	12 weeks		

*Prednisolone 1.5 mg/kg on alternate days × 4 weeks; 1.25 mg/kg × 4 weeks; 1 mg/kg × 4 months; 0.5–0.75 mg/kg × 12–18 months

**Cyclophosphamide is administered during 3–15 weeks

treatment is the achievement of complete remission, occurrence of partial remission is also satisfactory. Patients who respond to treatment do so within 3–6 months.

Adjunctive therapy with angiotensin-converting enzyme inhibitors (e.g. enalapril 0.3–0.6 mg/kg/day, ramipril 6 mg/m²/day) is associated with decrease in proteinuria and control of hypertension. Adverse effects include dry cough, hyperkalemia and decline in renal function. Angiotensin receptor blockers (e.g. losartan, valsartan) may be used in case of persistent dry cough with ACE inhibitors, or as add-on therapy for better antiproteinuric effect. Therapy with HMG coenzyme-A reductase inhibitors is advised for subjects with persistent hypercholesterolemia.

Hypertension must be controlled and infections managed appropriately. Edema is minimized with judicious use of diuretics. The use of intravenous albumin is indicated in cases with (i) symptomatic hypovolemia, (ii) symptomatic edema or (iii) marked ascites that is causing respiratory compromise. In cases with hypovolemia, 10–20 mL/kg of 4.5–5% albumin should be infused. Severe symptomatic edema or ascites may be treated with 0.75–1 g/kg of 20% albumin, infused over 2 hours, to expand the circulating volume followed by furosemide 1 mg/kg. Close monitoring is essential to avoid fluid overload and pulmonary edema.

Congenital Nephrotic Syndrome

Congenital nephrotic syndrome present in the first 3 months of life with anasarca, hypoalbuminemia and oliguria. The etiology of congenital nephrotic syndrome is heterogeneous. The 'Finnish' form of the disease is inherited in an autosomal recessive manner, with mutations in the gene encoding nephrin (*NPHS1*). The characteristic renal histology with microcystic dilation of proximal tubules is seen after a few months of life,

although ultrastructural abnormalities of the glomerular basement membrane are present at birth. Elevated levels of alpha-fetoprotein (AFP) in maternal serum and amniotic fluid enable antenatal screening. The clinical course is complicated by failure to thrive, recurrent infections, hypothyroidism and progression to renal failure by 2–3 years.

Patients with Denys-Drash syndrome show mutations in the *WT1* gene, congenital nephrotic syndrome, male pseudohermaphroditism and high risk of bilateral Wilms' tumor. Renal histology is characterized by diffuse mesangial sclerosis and there is progressive renal failure.

Other causes of congenital nephrotic syndrome include infections (congenital syphilis, cytomegalovirus disease, toxoplasmosis) and mutations in *PLCE1* or *NPHS2* genes; rarely renal histology may be normal (minimal change nephrotic syndrome) or show focal segmental glomerulosclerosis. Therapy of patients with congenital nephrotic syndrome includes appropriate nutrition, control of edema, thyroxin supplements and reduction of proteinuria through ACE inhibitors and/or indomethacin.

Regular use of IV albumin infusions (every 2–3 weeks) avoids marked hypoalbuminemia and reduces the need for hospitalization for managing anasarca.

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CHRONIC GLOMERULONEPHRITIS

Chronic GN is not a single disease entity, but comprises advanced stages of several forms of GN. In most cases, the glomerular disease is primary and not part of a systemic disorder. However, chronic GN may occur in systemic lupus erythematosus, microscopic polyarteritis, familial nephropathies and nephropathies due to drugs and toxins. Variable glomerular deposition of immunoglobulin, complement and fibrin is found on immunofluorescence studies. Renal biopsy examination in early stages shows several patterns, while later the histologic changes are nonspecific. Most glomeruli are sclerosed with corresponding tubular, interstitial and vascular changes.

Clinical Features

The patient may be asymptomatic and the disease detected on routine urine examination. Others may show failure to thrive, persistent anemia, moderate to severe hypertension, edema, nocturia, microscopic or gross hematuria, bone pains and deformities.

Differential Diagnosis

It might be difficult to distinguish chronic from acute GN. The presence of anemia, growth retardation, hypertensive retinopathy, left ventricular hypertrophy and radiological skeletal changes indicate impaired renal function of long duration. Examination of the renal biopsy is valuable.

Urinalysis shows proteinuria, hematuria, white cells and casts. Urine specific gravity is fixed and low (around 1.010). Blood urea and creatinine levels are raised and the glomerular filtration rate less than 30 mL/min/1.73 m². Ultrasonography shows small kidneys with regular outline.

Management

There is no specific treatment for chronic GN. Treatment with immunosuppressive drugs does not offer any benefit. The blood pressure should be controlled and infections treated. If renal function is compromised, the treatment is that of advanced chronic kidney disease.

INTERSTITIAL NEPHRITIS

This is focal or diffuse inflammatory reaction of renal interstitium with secondary involvement of tubules and rarely, glomeruli. Acute interstitial nephritis is usually due to infections or drugs (e.g. ampicillin, cephalosporins). Common causes of chronic interstitial nephritis include urinary tract obstruction and vesicoureteric reflux. Interstitial nephritis may be a feature of a systemic disorder (e.g. systemic lupus, vasculitis, associated with uveitis); autoantibodies to tubular basement membrane are found in some cases.

The clinical features are nonspecific and include abdominal pain, anorexia, pallor, headache and edema. Hypertension is absent. The presence of progressive renal

insufficiency associated with satisfactory urine output, and minimal urinary abnormalities suggest the diagnosis. Leukocytes and eosinophils are frequently seen in the urine.

A renal biopsy establishes the diagnosis and helps assess severity. Drug-related interstitial nephritis is treated with stoppage of the offending drug; treatment with corticosteroids is beneficial. The treatment of chronic interstitial nephritis is symptomatic.

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URINARY TRACT INFECTIONS

Urinary tract infection (UTI) is a common medical problem in children, affecting 3–10% girls and 1–3% boys. They are an important cause of morbidity and might result in renal damage, often in association with vesicoureteric reflux (VUR). During infancy, UTIs are equally common in boys and girls because the route of infection is often hematogenous and boys have a higher incidence of urinary tract anomalies. Beyond infancy, the incidence is higher in girls.

Microbiology

UTIs are chiefly caused by *E. coli* the predominant periurethral flora, others include *Klebsiella*, *Enterobacter* and *Staphylococcus saprophyticus*. *Proteus* and *Pseudomonas* infections occur following obstruction or instrumentation; *Candida* infection occurs in immunocompromised children or after prolonged antimicrobial therapy.

Predisposing Factors

Recurrent UTIs are observed in 30–50% children, usually within 3 months of the first episode. Predisposing factors for recurrent UTI include female sex, age below 6 months, obstructive uropathy, severe vesicoureteric reflux (VUR), voiding dysfunction, constipation and repeated catheterization, e.g. for neurogenic bladder. Children with malnutrition and those receiving immunosuppressive therapy are also susceptible.

Clinical Features

Neonates show features of sepsis with fever, vomiting, diarrhea, jaundice, poor weight gain and lethargy. The older infant has unexplained fever, frequent micturition and occasionally convulsions. Gross hematuria is uncommon. The presence of crying or straining during voiding, dribbling, weak or abnormal urine stream and palpable bladder suggest urinary obstruction.

It is difficult to distinguish between infection localized to the bladder (cystitis) and upper tracts (pyelonephritis). The distinction is not necessary since most UTI in children below 5 years of age involve the upper tracts. Patients with

high fever ($>39^{\circ}\text{C}$), systemic toxicity, persistent vomiting, dehydration, renal angle tenderness or raised creatinine are considered as *complicated*. Patients with low grade fever, dysuria, frequency and urgency and absence of symptoms of complicated UTI are considered to have *simple UTI*. This distinction is important for purposes of therapy.

Important features on evaluation include history of straining at micturition, incontinence or poor urinary stream, voiding postponement and surgery for meningo-myelocele or anorectal malformation. Finding of palpable kidney(s), distended bladder, tight phimosis or vulval synechiae and neurological deficit in lower limbs suggest a predisposing cause.

Diagnosis

The diagnosis of UTI is based on growth of significant number of organisms of a single species in the urine. Significant bacteriuria is a colony count of $>10^5/\text{mL}$ of a single species in a clean catch sample. Urine may be obtained by suprapubic bladder aspiration or urethral catheterization in children below 2 years. Any colonies on suprapubic aspiration and $>50,000/\text{mL}$ on urethral catheterization are considered significant. The occurrence of significant bacteriuria in absence of symptoms is termed *asymptomatic bacteriuria*.

The presence of >10 leukocytes per mm^3 in fresh uncentrifuged sample, or >5 leukocytes per high power field in centrifuged sample is useful for screening. Dipstick examination, combining leukocyte esterase and nitrite, has moderate sensitivity and specificity for detecting UTI.

Treatment

Once UTI is suspected, a urine specimen is sent for culture and treatment started. *Infants below 3 months of age and children with complicated UTI should initially receive parenteral antibiotics*. The initial choice of antibiotics is empiric and is modified once culture result is available. While a third generation cephalosporin is preferred, therapy with a single daily dose of aminoglycoside is also safe and effective (Table 17.11). Once oral intake improves and symptoms abate, usually after 48–72 hours, therapy is switched to an oral antibiotic. The duration of treatment for complicated UTI is 10–14 days. Older infants and patients with simple UTI should receive treatment with an oral antibiotic for 7–10 days. Adolescents with cystitis may receive shorter duration of antibiotics, lasting 72 hours. *Patients with asymptomatic bacteriuria do not require treatment*.

All children with UTI are encouraged to take enough fluids and empty the bladder frequently. Routine alkalization of the urine is not necessary. With appropriate therapy, fever and systemic toxicity reduce and urine culture is sterile within 24–36 hours. Failure to obtain such results suggests either lack of bacterial sensitivity to the medication or presence of an underlying anomaly of the urinary tract. A repeat urine culture is not required during

Table 17.11: Antimicrobials for treatment of UTI

Medication	Dose (mg/kg/day)
Parenteral	
Ceftriaxone	75–100, in 1–2 divided doses IV
Cefotaxime	100–150, in 2–3 divided doses IV
Amikacin	10–15, single dose IV or IM
Gentamicin	5–6, single dose IV or IM
Coamoxiclav	50–75 of amoxicillin, in 2 divided doses IV
Oral	
Cefixime	8–10, in 2 divided doses
Coamoxiclav	30–50 of amoxicillin, in 2 divided doses
Ciprofloxacin	10–20, in 2 divided doses
Ofloxacin	15–20, in 2 divided doses
Cephalexin	50–70, in 2–3 divided doses

or following treatment, unless symptoms fail to resolve despite 72 hours of therapy symptoms recur, or contamination of the initial culture is suspected.

Imaging Studies

Following treatment of the first episode of UTI, plans are made for evaluation of the urinary tract. The aim of imaging studies is to identify urologic anomalies that predispose to pyelonephritis, such as obstruction or vesicoureteric reflux, and detect evidence of renal scarring. Renal ultrasonography is useful in detecting hydronephrosis or anomalies of the urinary bladder and may be performed even during therapy for UTI. Micturating cystourethrogram is necessary for the diagnosis and grading of VUR (Fig. 17.13) and defines urethral and bladder anatomy. This procedure may be performed 2–4 weeks after treatment of the UTI. DMSA scintigraphy detects cortical scars, which are regions of decreased uptake with loss of renal contours or presence of cortical thinning with decreased volume (Fig. 17.5a). In order to distinguish scars from reversible changes of pyelonephritis, this procedure is done 3–4 months after therapy for UTI.

These investigations should be performed judiciously, such that sufficient evaluation is done but at minimum risks of radiation exposure. The recommendations of the Indian Society of Pediatric Nephrology on evaluation following the first UTI are summarized in Table 17.12. All infants (<1 year) require evaluation using ultrasonography, MCU and DMSA scan, since they are at the highest risk of UTI recurrence and scarring. Early detection of high grade VUR or obstructive uropathy allows interventions to prevent progressive kidney damage. Imaging is less aggressive in older children, but patients with recurrent UTI require detailed evaluation for anomalies.

Preventing Recurrent UTI

Prophylactic antibiotics are administered to young infants until results of imaging are available. The medication used should be effective, nontoxic and not alter the gut flora or

Table 17.12: Evaluation following the first episode of urinary tract infection

Age	Evaluation*
Below 1 year	Ultrasound Micturating cystourethrogram (MCU) Dimercaptosuccinic acid (DMSA) renal scan
1–5 years	Ultrasound DMSA scan MCU, if ultrasound or DMSA scan is abnormal
Above 5 years	Ultrasound If ultrasound abnormal: MCU and DMSA scan

*Patients with recurrent UTI need detailed evaluation with ultrasonography, DMSA scan and MCU

Table 17.13: Antimicrobials for prophylaxis of urinary tract infections

Medication	Dose (mg/kg/day)	Remarks
Cotrimoxazole	1–2 of trimethoprim	Avoid in infants <3-mo-old, glucose-6-phosphate dehydrogenase (G6PD) deficiency
Nitrofurantoin	1–2	May cause vomiting and nausea; avoid <3-mo-old, G6PD deficiency, renal insufficiency
Cephalexin	10	Drug of choice in first 3–6 months of life
Cefadroxil	5	Alternative agent in early infancy

Usually given as single bedtime dose

induce bacterial resistance (Table 17.13). The medication is given as a single bedtime dose. Long-term antibiotic prophylaxis is also recommended in patients with VUR and in those with frequent febrile UTI (3 or more episodes in a year), even if the urinary tract is normal.

Circumcision reduces the risk of recurrent UTI in infant boys, and might have benefits in patients with high grade VUR. Children with recurrent UTI and/or VUR might have dysfunctional voiding and require appropriate advice. Constipation should be managed with dietary modifications and medications as required. Some patients may require bladder retraining, anticholinergic medications and/or clean intermittent catheterization.

Suggested Reading

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VESICoureTERIC REFLUX

Vesicoureteric reflux (VUR) refers to the retrograde flow of urine from bladder to ureters and pelvis at rest or during micturition. Pathogenic organisms that might be present in the bladder can gain access to the renal parenchyma, initiate inflammation and renal scarring (*reflux nephropathy*). VUR may be an isolated anomaly (primary) or associated with other anomalies of the urinary tract (secondary).

VUR is present in 30–35% of children with febrile UTI and is a major risk factor for acute pyelonephritis and reflux nephropathy. The latter may result in hypertension, renal insufficiency and cause morbidity during pregnancy.

Two techniques are commonly used to detect VUR. The radiocontrast MCU is commonly used since in addition to showing VUR it provides excellent anatomical details (Fig. 17.13). The severity of VUR is graded from I to V (Fig. 17.14). Isotope radionuclide cystography is more sensitive for detecting VUR and causes less radiation exposure but provides fewer anatomical details.

Management

The proposed guidelines for management of VUR are outlined in Fig. 17.15. Randomized trials suggest that antibiotic prophylaxis have a modest benefit in reducing the risk of recurrent UTI. Continuous antibiotic prophylaxis is recommended as the initial treatment for all children with VUR since it reduces periurethral colonization and, thereby, the risk of recurrent UTI. Cotrimoxazole or nitrofurantoin is given as a bedtime dose. Since the risk of recurrent UTI and renal scarring is



Fig. 17.13: Micturating cystourethrogram showing bilateral grade V vesicoureteric reflux in a girl with recurrent UTI. Note the dilatation, tortuosity of ureters and cupping of the calyces

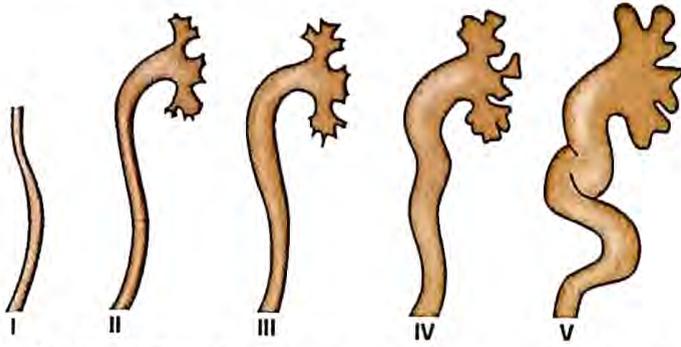


Fig. 17.14: Grading of vesicoureteric reflux (VUR) on micturating cystourethrogram. *Grade I:* VUR does not reach the renal pelvis; *Grade II:* VUR extending up to the renal pelvis without dilatation of pelvis or calyceal fornices; *Grade III:* VUR extending up to the kidney, with mild dilatation or tortuosity of the ureter and renal pelvis, and no or minor blunting of the calyceal fornices; *Grade IV:* Moderate dilatation or tortuosity of the ureter, renal pelvis and fornices, with complete obliteration of the sharp angles of the calyceal fornices, but normal appearance of the papillary impressions; *Grade V:* Gross dilatation and tortuosity of the ureter, renal pelvis and calyces, with loss of papillary impressions on calyces

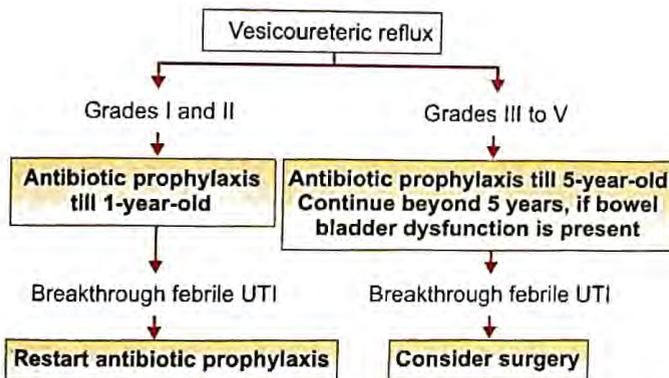


Fig. 17.15: Management of vesicoureteric reflux. Medical therapy is based on the principle that VUR resolves over time, and prophylactic antibiotics maintain urine sterility and prevent infections while awaiting spontaneous resolution. Reflux takes longer to resolve, if associated with bowel bladder dysfunction or if high grade reflux is present; such patients require prolonged prophylaxis. Surgical correction of VUR is indicated, if breakthrough infections occur, since significant parenchymal injury may occur with pyelonephritis

low after 4–5 years of age, prophylaxis may be discontinued in children older than 5 years with normal bowel and voiding habits, even if mild to moderate reflux persists.

Other measures to be instituted include a liberal fluid intake, regular and complete bladder emptying and local toilet. Constipation should be avoided. A close follow-up is required for occurrence of breakthrough UTI.

The indications for surgical correction of primary VUR are limited and include poor compliance or intolerance to medical treatment. Patients with grades III to V reflux may be offered surgical repair, if they have breakthrough febrile UTI, if parents prefer surgical intervention to

prophylaxis, or in patients who show deterioration of renal function. Ureteric reimplantation has cure rates of 95–97%.

The precise indication for endoscopic submucosal injection of dextranomer/hyaluronic acid copolymer (Deflux) at ureteric orifices is not defined. While results are satisfactory in centers with expertise, a significant proportion of patients, particularly those with bowel bladder dysfunction, may show persistence and/or recurrence of reflux.

Follow-up

Repeat imaging is required after 18–36 months in patients with grades III–V VUR. Radionuclide cystogram, with lower radiation exposure and higher sensitivity, is preferred for follow-up evaluation. Urinalysis and measurement of height, weight and blood pressure are done annually. Urine cultures are obtained, if the patient has symptoms of UTI.

Screening of Siblings and Offspring

VUR is inherited in an autosomal dominant manner with incomplete penetrance; almost one-third siblings and offspring of patients show VUR. Ultrasonography is recommended to screen for presence of reflux; further imaging is performed, if ultrasonography is abnormal.

Outcome

Primary VUR tends to resolve by 6–10 years of age. Factors favoring resolution are younger age and low grade and unilateral VUR. The rate of resolution is 70–90% for grades I–III and 10–35% for higher grades.

Reflux Nephropathy

This is characterized by renal cortical scarring, predominantly at the poles. The underlying calyces lose their normal concave shape and show clubbing. Such scarring occurs early in life when the kidneys are still growing. Reflux nephropathy is an important cause of hypertension and end stage renal disease in children.

Suggested Reading

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ACUTE KIDNEY INJURY

Acute kidney injury (AKI) or acute renal failure (ARF) denotes an acute impairment of renal function resulting in retention of nitrogenous wastes and other metabolic derangements. Oliguria or anuria is a prominent feature, though rarely urine output may be normal.

Definition and Classification

In the absence of a standard definition of ARF, the term acute kidney injury (AKI) is proposed to reflect the entire spectrum of the disorder. Patients are diagnosed to have AKI, if there is abrupt reduction in kidney function, defined as either (i) absolute increase in serum creatinine of more than or equal to 0.3 mg/dL over 48 hours, or a percentage increase of more than or equal to 50% from baseline in last 7 days, or (ii) reduction in urine output (less than 0.5 mL/kg/hr for >6 hours). The inclusion of both an absolute and a percentage change in creatinine allows for variations related to age, gender and body mass index. Table 17.14 shows the classification of AKI.

Incidence and Etiology

The etiology of AKI is classified as prerenal, intrinsic renal or postrenal (Table 17.15). The chief causes of AKI include acute tubular necrosis (ATN) secondary to hypovolemia, sepsis and nephrotoxic agents, acute glomerulonephritis and hemolytic uremic syndrome (HUS). Postrenal failure is consequent to mechanical obstruction in the collecting system. In developing countries, common causes include septicemia with multiorgan failure, HUS, gastroenteritis with dehydration, postinfectious and crescentic GN and intravascular hemolysis. In developed countries, AKI follows major surgical procedures, HUS and severe systemic infections.

Pathophysiology

Prerenal failure is secondary to systemic hypovolemia or renal hypoperfusion, where renal tubular injury leads to marked decline in glomerular filtration and renal blood flow, often by 50 to 75%. Leakage of glomerular filtrate

back into the circulation across the damaged tubular epithelium and tubular obstruction from impaction of casts and cellular debris results in oliguria. While early stages are rapidly reversible by infusion of fluids, prolonged or severe ischemia may lead to acute tubular necrosis. Nephrotoxic agents cause uniform epithelial damage, especially in the proximal tubules, without disruption of tubular basement membrane.

In acute tubular necrosis, examination may be normal except for dehydration. The oliguric phase lasts about 3–10 days, during which period the biochemical and clinical abnormalities gradually worsen, more rapidly if infection, trauma and bleeding are associated. Subsequently, urine output increases steadily. A diuretic phase may be observed, usually lasting for a week, during which large amounts of water and electrolytes may be lost.

Approach to Evaluation

History provides clues to the underlying cause of AKI. It is important to examine for prerenal factors that lead to renal hypoperfusion. A history of diarrhea, vomiting, fluid or blood loss is taken and assessment of fluid intake in the previous 24 hours made. In patients with nephrotoxicity or intravascular hemolysis, urine output is often not diminished (nonoliguric renal failure).

Laboratory evaluation (Table 17.16) includes blood counts and estimation of blood levels of urea, creatinine, electrolytes, pH and bicarbonate and urinalysis. In prerenal azotemia, the renal tubular function is intact and reabsorption of water and sodium is increased. The urine is concentrated with low sodium content. Impaired tubular function in intrinsic renal failure results in increased sodium excretion and failure to concentrate urine. Determination of urine sodium and osmolality and fractional excretion of sodium help in differentiating functional oliguria (prerenal) from established (intrinsic) renal failure. Ultrasonography is a useful imaging tool in renal failure since it allows visualization of the pelvicalyceal system and assessment of the renal size, structural anomalies and calculi, and does not depend on renal function.

Most patients with AKI do not require a renal biopsy. Indications for biopsy are: (i) rapidly progressive or

Table 17.14: Staging of acute kidney injury (AKI), based on KDIGO criteria*

Stage	Serum creatinine	Urine output
1	Increase in serum creatinine of ≥ 0.3 mg/dL over 48 hours or $\geq 150\%$ to 200% (1.5- to 2-fold) from baseline in last 7 days	Less than 0.5 mL/kg per hour for >6 hours
2	Increase in serum creatinine to more than 200% to 300% (>2- to 3-fold) from baseline	Less than 0.5 mL/kg per hour for >12 hours
3** hours	Increase in serum creatinine to more than 300% ≥ 4.0 mg/dL with acute increase of ≥ 0.5 mg/dL)	Less than 0.3 mL/kg per hour for 24 hours, or anuria for 12 (>3-fold) from baseline (or serum creatinine

*Only one criterion (creatinine or urine output) should be fulfilled to qualify for a stage

**Patients receiving renal replacement therapy (RRT) are considered in stage 3

KDIGO: Kidney Disease Improving Global Outcomes

Table 17.15: Important causes of acute kidney injury**Prerenal failure**

Hypovolemia (dehydration, blood loss, diabetic ketoacidosis)
 Third space losses (septicemia, nephrotic syndrome)
 Congestive heart failure
 Perinatal asphyxia
 Drugs (ACE inhibitors, diuretics)

Intrinsic renal failure

Acute tubular necrosis
 Prolonged prerenal insult (*see above*)
 Medications: Aminoglycosides, radiocontrast, NSAIDs
 Exogenous toxins: Diethylene glycol, methanol
 Intravascular hemolysis, hemoglobinuria
 Tumor lysis syndrome
 Hemolytic uremic syndrome: Infection associated, atypical
 Glomerulonephritis (GN)
 Postinfectious GN
 Systemic disorders: SLE, Henoch-Schönlein syndrome, microscopic polyangiitis
 Membranoproliferative GN
 Interstitial nephritis (drug-induced, idiopathic)
 Bilateral renal vessel occlusion (arterial, venous)

Postrenal failure

Posterior urethral valves, urethral stricture
 Bilateral pelviureteric junction obstruction
 Ureteral obstruction (stenosis, stone, ureterocele)
 Neurogenic bladder

NSAIDs: Nonsteroidal anti-inflammatory drugs; SLE: Systemic lupus erythematosus

nonresolving glomerulonephritis; (ii) AKI associated with underlying systemic disorder, e.g. lupus erythematosus, Henoch-Schönlein purpura; (iii) suspected interstitial nephritis; (iv) clinical diagnosis of acute tubular necrosis or HUS, if significant dysfunction persists beyond 2–3 weeks; (v) underlying cause of AKI not apparent on clinical features and investigations. Patients with severe azotemia might require dialysis prior to biopsy to reduce the risk of bleeding. Figure 17.16 indicates representative diagnoses on histology.

Occasionally, a patient with undetected chronic kidney disease may present for the first time with acute onset of oliguria. History of previous renal disease may be present. The presence of the following suggests the possibility of chronic kidney disease: (i) retarded physical growth, (ii) severe anemia, (iii) hypertensive retinopathy, (iv) hypocalcemia, hyperphosphatemia and high parathormone, (v) radiologic features of mineral bone disease and (vi) small kidneys on imaging.

Management

Prompt clinical and laboratory evaluation is necessary. Management includes treatment of life-threatening complications, maintenance of fluid and electrolyte balance and nutritional support. Evaluation for complications

Table 17.16: Investigations in patients with acute kidney injury**Complete blood counts**

Blood: Urea, creatinine, sodium, potassium, calcium, phosphate, pH, bicarbonate

Urinalysis; culture

Urine: Sodium, osmolality, fractional excretion of sodium

Chest X-ray (for fluid overload, cardiomegaly)

Abdominal ultrasonography

Investigations to determine cause

Peripheral smear examination, platelet and reticulocyte count, complement (C3), LDH levels; stool shigatoxin (suspected hemolytic uremic syndrome)

Blood ASO, C3, antinuclear antibody, antineutrophil cytoplasmic antibody (suspected acute, rapidly progressive GN)

Doppler ultrasonography (suspected arterial, venous thrombosis)

Renal biopsy (specific diagnosis feasible)

includes measurement of blood pressure, search for signs of congestive heart failure, fluid overload, acidosis and anemia. Complications such as dehydration or fluid overload, hypertension, heart failure, severe anemia, hyperkalemia and acidosis require urgent treatment.

Fluid Repletion

Prerenal ARF responds to fluid replacement with improved renal perfusion and increased urine output. Dehydration is corrected by infusion of 20–30 mL/kg of normal saline or Ringer's lactate over 45–60 min. If hemorrhage accounts for vascular collapse, blood transfusion should be given. Potassium should not be administered until urine flow is established; care is taken to avoid overhydration. Patients with renal hypoperfusion, in whom the only reason for oliguria is intravascular volume depletion, respond to fluids with increase in urine output (~2 mL/kg over 2–3 hours). Appropriate fluid therapy should be continued. However, if no diuresis occurs despite correction of dehydration, frusemide (1–2 mg/kg IV) may be given. If these measures fail to induce diuresis, a diagnosis of AKI is likely.

Fluid Restriction

In patients with AKI, fluid retention may result from excessive oral or parenteral fluids, and leads to edema, hypertension and heart failure. Daily fluid requirement is restricted to insensible water losses (300–400 mL/m²), urine output and extrarenal fluid losses. This is usually given orally; intravenous fluids are not required.

Intake–output monitoring, daily weight, physical examination and serum sodium guide fluid management. If fluid in an appropriate volume and composition is given, the patient should lose 0.5–1% of weight every day and serum sodium should stay within normal range. A rapid weight loss and rising sodium suggest inadequate fluid replacement, while absence of weight loss and low serum sodium indicate fluid excess.

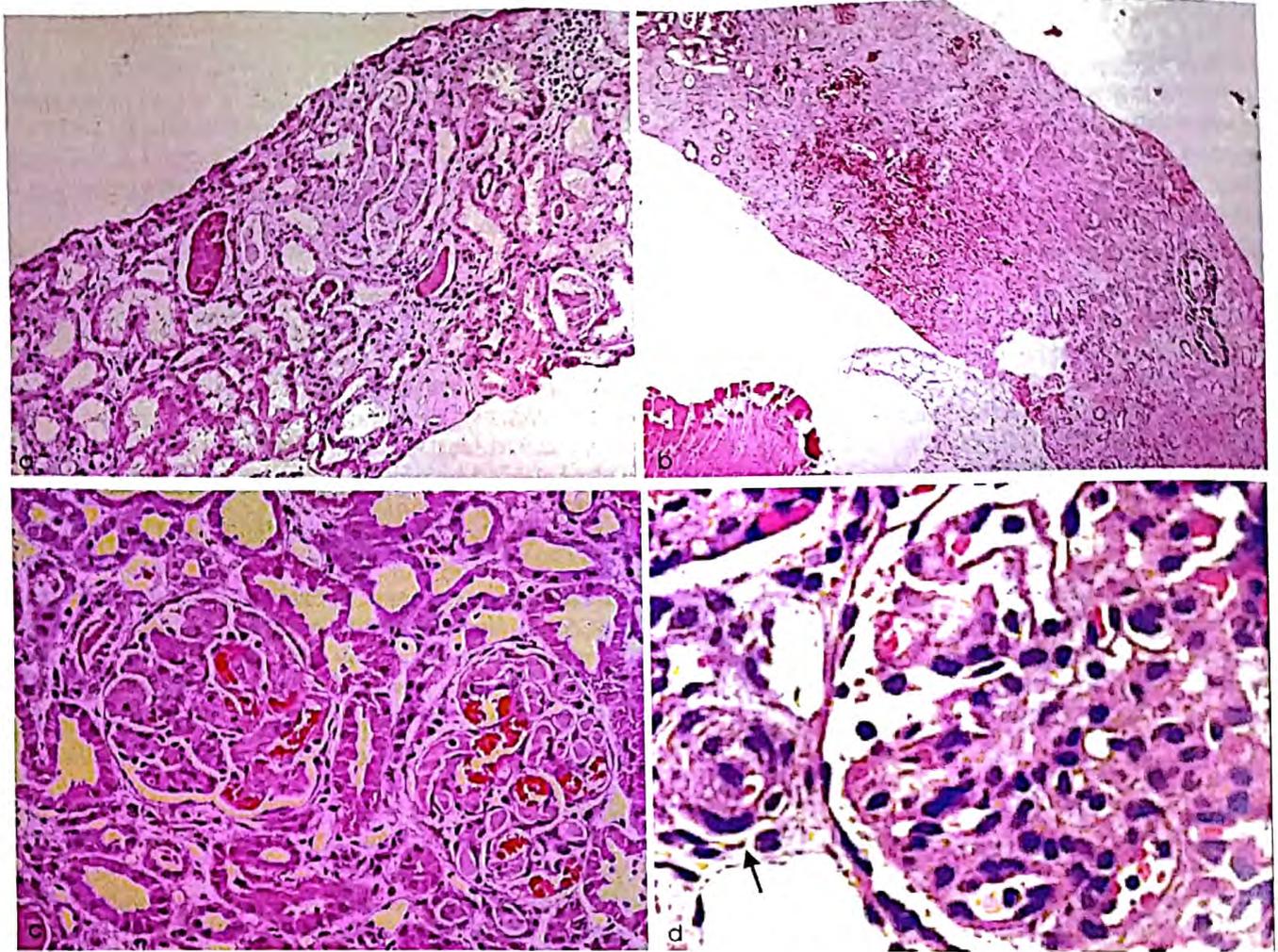


Fig. 17.16: Photograph of kidney biopsy showing (a) Acute tubular necrosis/injury in the form of simplification of proximal tubular epithelium along with fine granular casts in some tubular lumina (H & E 200 \times); (b) Patch of acute cortical necrosis involving glomeruli, tubules and interstitium with adjacent relatively preserved cortical parenchyma (H & E 40 \times); (c) Thrombotic microangiopathy, suggested by glomeruli with marked endothelial swelling, capillary lumina occluded by fibrin thrombi and mesangiolysis; (d) Thrombotic microangiopathy, suggested by glomeruli showing endothelial swelling and detachment, widened subendothelial spaces, and arterioles showing intimal hyperplasia, endothelial swelling and lumen occluded by platelet thrombi (arrow)

Diet

Patients with AKI have increased metabolic needs and are usually catabolic. Adequate nutritional support with maximization of caloric intake should be achieved as early as possible. A diet containing 1.0–1.2 g/kg of protein in infants and 0.8–1.2 g/kg in older children and a minimum of 60–80 Kcal/kg is recommended. Energy requirements are met by addition of carbohydrates and fat in the diet. Vitamin and micronutrient supplements are provided. In patients with oligoanuria and fluid overload, daily caloric requirement cannot be met due to fluid restriction. Once dialysis is initiated, dietary protein, fluid and electrolyte intake should be increased.

General Measures

Patients with AKI are managed under intensive care conditions. Accurate records of intake and output and daily weight should be maintained. Urine should be

collected by condom drainage; bladder should preferably not be catheterized. The risk of infection is high and appropriate preventive measures are necessary. Prophylactic antibiotics are not recommended, but infections should be promptly managed.

Drugs that increase severity of renal damage, delay recovery of renal function or reduce renal perfusion, e.g. aminoglycosides, radiocontrast media, NSAIDs, amphotericin B, ACE inhibitors and indomethacin should be avoided. Standard charts are used for modifying the dose and dosing interval of antibiotics, depending on the severity of renal injury. While diuretics may transiently improve urine output, they do not affect renal function or acute outcomes. Their utility is limited to settings where high urine flow is required to prevent intratubular precipitation (intravascular hemolysis, hyperuricemia, myoglobinuria) and patients with pulmonary edema awaiting dialysis.

Dopamine at low doses causes renal vasodilatation and may induce a modest natriuresis and diuresis. However, it has no beneficial effect on the outcome of AKI, and may be associated with transient tachyarrhythmia or tissue ischemia. Hence, its use for prevention or treatment of acute tubular necrosis is not recommended. The role of other medications, including fenoldopam, atrial natriuretic peptide and calcium channel blockers is investigational.

Treatment of Complications

In a child with ARF, immediate attention is directed towards detection and management of life-threatening complications. Table 17.17 lists important complications and measures for their management. Children with pulmonary edema and congestive cardiac failure may require endotracheal intubation and assisted ventilation. Severe acidosis is treated by administration of sodium bicarbonate, and, if persistent, dialysis.

Infections, including respiratory and urinary tract, peritonitis and septicemia, are important causes of death. Procedures should be performed with aseptic techniques, IV lines carefully watched, skin puncture sites cleaned, and long-term catheterization of the bladder avoided.

Specific Therapy

Patients with atypical HUS benefit from plasma exchanges. Immunosuppressive medications and plasma exchange are useful in dialysis-dependent patients with vasculitis, crescentic GN or systemic lupus erythematosus. If

interstitial nephritis is suspected, the offending agent should be withdrawn and oral corticosteroids given.

Dialysis

AKI requiring dialysis can be managed with multiple modalities, including peritoneal dialysis, intermittent hemodialysis and continuous hemofiltration or hemodiafiltration. The purpose of dialysis is to remove endogenous and exogenous toxins and maintain fluid, electrolyte and acid-base balance until renal function recovers.

Indications for dialysis include persistent hyperkalemia (>6.5 mEq/L), fluid overload (pulmonary edema, severe hypertension), uremic encephalopathy, severe metabolic acidosis (bicarbonate <10 – 12 mEq/L) and hyponatremia (<120 mEq/L) or hypernatremia. The decision to institute dialysis should be based on assessment of the patient and keeping in view the likely course of AKI. *Dialysis should begin early to prevent life-threatening complications.*

The choice of dialysis modality is influenced by several factors, including goals of dialysis, the advantages and disadvantages of each modality and institutional resources (Table 17.18).

Peritoneal dialysis: Peritoneal dialysis does not require vascular access and sophisticated equipment and is easy to perform even in neonates. It is often the initial renal replacement therapy of choice in sick and unstable infants. Peritoneal access is obtained using a stiff catheter and trocar,

Table 17.17: Management of complications

Complication	Treatment	Remarks
Fluid overload	Fluid restriction. Insensible losses (400 mL/m ² /day); add urine output and other losses; 5% dextrose for insensible losses; N/5 saline for urine output	Monitor other losses and replace as appropriate; prefer oral to parenteral fluids; consider dialysis
Pulmonary edema	Oxygen; furosemide 2–4 mg/kg IV	Monitor using CVP; consider dialysis
Hypertension	<i>Symptomatic.</i> Sodium nitroprusside 0.5–8 µg/kg/minute infusion; furosemide 2–4 mg/kg IV; nifedipine 0.3–0.5 mg/kg oral/sublingual <i>Asymptomatic.</i> Nifedipine, amlodipine, prazosin, labetalol, clonidine	In emergency, reduce blood pressure by one-third of the desired reduction during first 6–8 hours, one-third over next 12–24 hours and the final one-third slowly over 2–3 days
Metabolic acidosis	Sodium bicarbonate (IV or oral), if bicarbonate levels <18 mEq/L	Watch for fluid overload, hypernatremia, hypocalcemia; consider dialysis
Hyperkalemia	Calcium gluconate (10%) 0.5–1 mL/kg over 5–10 minutes IV Salbutamol 5–10 mg nebulized Dextrose (10%) 0.5–1 g/kg and insulin 0.1–0.2 U/kg IV Sodium bicarbonate (7.5%) 1–2 mL/kg over 15 min Calcium or sodium resonium (Kayexalate) 1 g/kg	Stabilizes cell membranes; prevents arrhythmias Shifts potassium into cells Requires monitoring of blood glucose Shifts potassium into cells; less efficient Given orally or rectally, can be repeated 4–8 hours
Hyponatremia	Fluid restriction; if sensorial alteration or seizures 3% saline 6–12 mL/kg over 30–90 min	Hyponatremia is usually dilutional; 12 mL/kg of 3% saline raises sodium by 10 mEq/L
Severe anemia	Packed red cells 3–5 mL/kg; consider exchange transfusion	Monitor blood pressure, fluid overload
Hyperphosphatemia	Phosphate binders (calcium carbonate, acetate; aluminum hydroxide)	Avoid high phosphate products: Milk products, high protein diets

Table 17.16: Comparison of modalities of dialysis for kidney injury

Features	Peritoneal dialysis	Hemodialysis	Continuous renal replacement therapy
Availability; ease of performance	++	+	-
Technical expertise required	-	+	++
Vascular access required	-	+	+
Anticoagulation required	-	+	++
Slow and continuous removal of fluid and toxins without dysequilibrium	+	-	+
Rapid clearance of toxins, fluid	-	++	+
Achieve desired fluid removal	+/-	+	++
Feasible in hemodynamically unstable patients	+	-	+
Cost	-	+	++

or a soft silastic catheter (see Chapter 29). The abdominal skin is prepared as for a surgical procedure. Dialysis fluid is infused 30–50 mL/kg, left in the peritoneal cavity for 30–60 min and then drained using siphon effect (Fig. 17.17a). Initially 30–40 cycles are carried out. Commercially available dialysates are lactate based and with a dextrose concentration of 1.7%. In patients with fluid overload, the concentration of dextrose is increased to 2.5–3% to facilitate ultrafiltration. Potassium is not added in the first 5–10 cycles, to enable correction of hyperkalemia. Later, 3–4 mEq/L potassium chloride is added to the dialysate. The results of peritoneal dialysis are gratifying. In acute tubular necrosis, often a single dialysis is adequate. The procedure can be repeated, if necessary.

The most important complication is peritonitis. Meticulous aseptic precautions will minimize its incidence. Stiff catheters should be removed after 48–72 hours, beyond which the risk of infection is very high. The risk of injury to viscera and infections is considerably less with soft silastic (Tenckhoff or Cook) catheters, which, therefore, can be used for prolonged periods. While the standard (double-cuff) Tenckhoff catheter needs to be placed surgically, a temporary (peel away) catheter is inserted bedside. The use of an automated cycler is preferred to manual peritoneal dialysis.

Hemodialysis: Hemodialysis is efficient for correction of fluid and electrolyte abnormalities. It is expensive to

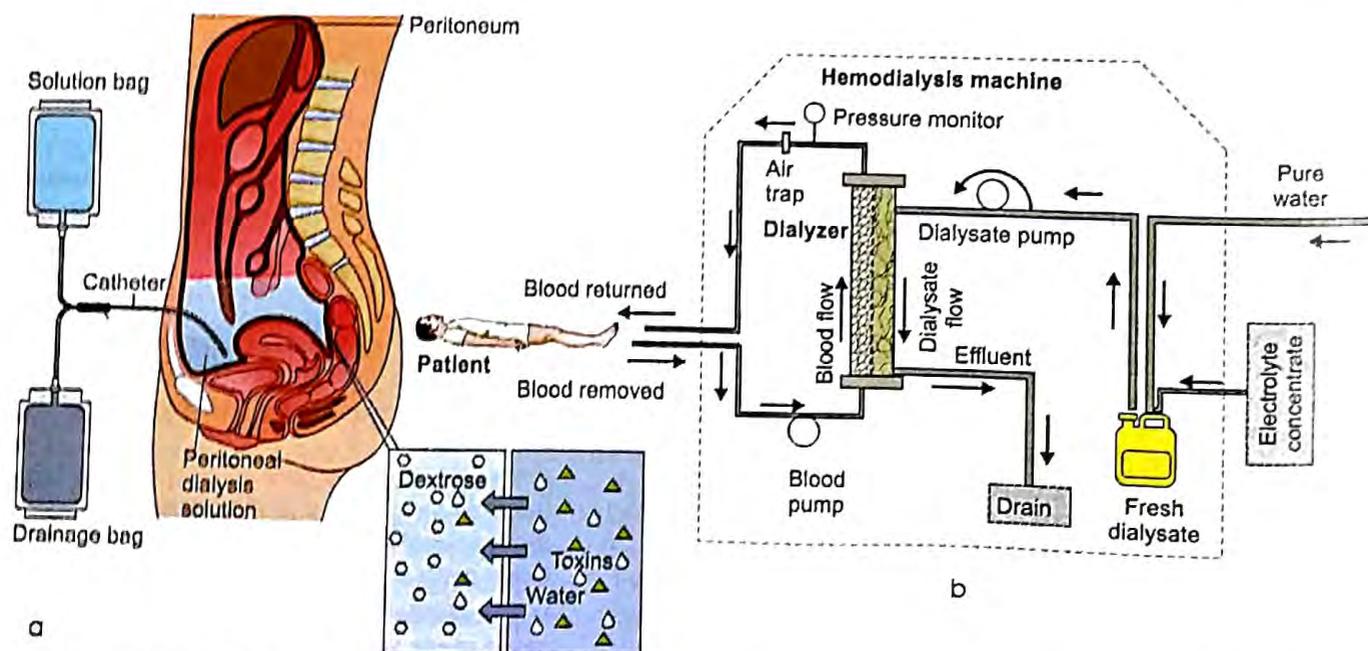


Fig. 17.17: Modalities of dialysis for acute kidney injury. (a) Peritoneal dialysis is based on solute exchange and water transfer across the peritoneal membrane, driven by the concentration gradient and high dextrose content of the dialysate. (b) Hemodialysis requires blood to be pumped outside the body via a large bore double lumen catheter, followed by the exchange of solute and ultrafiltration of water across a synthetic hemodialyser membrane into a dialysate; the purified blood is then returned into the bloodstream via the same catheter

institute, and requires expertise and skilled nursing. The procedure might not be suited for patients with hemodynamic instability, bleeding tendency and in young children with difficult vascular access.

The equipment required are the hemodialysis machine, pediatric dialyzer with tubings and dialysate fluid (Fig. 17.17b). These dialyzers are available in different sizes (0.5–1.5 m²) and selection depends upon patient size and ultrafiltrate properties. Vascular access is necessary for removing and returning large quantities of blood required for the procedure. This is usually achieved using a double lumen catheter inserted into the internal jugular, femoral or subclavian vein. Most children are maintained on a hemodialysis regimen of 3–4 hours, three times a week. Sick patients with fluid overload benefit from daily dialysis initially.

Continuous renal replacement therapies (CRRT): CRRT is any extracorporeal blood purification therapy intended to substitute for impaired renal function over an extended period of time and applied for, or aimed at being applied for, 24 hours a day. Various modalities include [continuous arteriovenous hemofiltration (CAVH)], [continuous venovenous hemofiltration (CVVH)], continuous venovenous hemodiafiltration (CVVHDF) and slow continuous ultrafiltration (SCUF). These therapies are useful when large amount of fluids have to be removed in sick and unstable patients. CVVH is preferred modality in AKI secondary to major surgical procedures, burns, heart failure and septic shock, especially when conventional hemodialysis or intermittent peritoneal dialysis is not possible.

Slow long extended daily dialysis (SLEDD): Sick patients often benefit from hybrid treatments that combine the advantages of CRRT and feasibility of hemodialysis. SLEDD is done daily for an extended but limited period (8–10 hours) using low dialysate flow rates and at the same time minimizing the cost and technical complexities of CRRT.

Outcome

AKI carries a mortality of 20–40%, chiefly related to the underlying etiology and duration of renal failure. Patients with septicemia and HUS with prolonged anuria are associated with poor prognosis. The outcome in crescentic GN and vasculitis depends on the severity of the renal injury and promptness in initiation of specific therapy. The outlook is satisfactory in acute tubular necrosis without complicating factors. Other factors associated with poor outcome include delayed referral, presence of complicating infections and cardiac, hepatic or respiratory failure. Maintenance of nutrition and prevention of infections is crucial in improving outcome.

Acute Renal Failure in Newborn

Newborns are at high risk of AKI. Important causes include: (i) perinatal hypoxemia, associated with birth asphyxia or respiratory distress syndrome; (ii) hypo-

volemia secondary to dehydration, intraventricular hemorrhage, heart disease and postoperatively, (iii) sepsis with hypoperfusion; (iv) delayed initiation and inadequacy of feeding in early neonatal period; (v) increased insensible losses (due to phototherapy, radiant warmers, summer heat), twin-to-twin transfusions and placental hemorrhage; (vi) nephrotoxic medications, e.g. aminoglycosides, indomethacin; maternal intake of ACE inhibitors, nimesulide; and (vii) renal vein thrombosis, e.g. in infants of diabetic mothers, severe birth asphyxia, dehydration, polycythemia and catheterization of umbilical veins. AKI may occasionally be the first manifestation of a congenital anomaly of the urinary tract.

Renal failure is suspected in the presence of oliguria (urine output <0.5 mL/kg/hr) or blood creatinine >1.2 mg/dL. Serum creatinine levels are high at birth (reflecting maternal levels) and decrease to below 0.5 mg/dL by 5–7 days of age. Failure of reduction or rise of serum creatinine indicates impaired renal function.

The principles of management are similar to that for older children. Fluid should be limited to insensible (30 mL/kg/day for full-term, 50–100 mL/kg/day for preterm neonates), gastrointestinal and renal losses. Extremely premature neonates nursed in radiant warmers require extra fluids. Systolic blood pressure more than 95–100 mm Hg may need treatment.

Extra care should be taken while dialyzing neonates; peritoneal dialysis is technically easier and preferred. However, sudden distention of peritoneal cavity may cause respiratory embarrassment or apnea. Hypothermia should be avoided by carefully warming the dialysis fluid. A number of drugs are dialyzable and appropriate amounts should be added to supplement for their losses.

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HEMOLYTIC UREMIC SYNDROME

Hemolytic uremic syndrome is a heterogeneous group of disorders that are a common cause of AKI in children. They are characterized by microangiopathic hemolytic anemia, thrombocytopenia and acute renal insufficiency. Two broad subgroups are recognized; the first is more common, occurs in young children and is associated with shiga toxin producing enteropathogens (shiga toxin-associated HUS), whereas the second is uncommon, affects

children of all ages and is associated with abnormalities of the alternative complement pathway (complement associated or atypical HUS).

Shigatoxin-Associated HUS

Verotoxin-producing *E. coli* (in North America and Europe; most commonly O157:H7; O104:H4 in a recent epidemic) and *Shigella dysenteriae* 1 (in south Asia) cause the diarrheal prodrome preceding HUS. Cytotoxin-mediated injury to endothelium in the renal microvasculature leads to localized coagulation and fibrin deposition. As red cells and platelets traverse these damaged vessels, they are injured and sequestered. Though the brunt of the microvascular injury is on the kidney, other organs especially the brain may be affected. Since chiefly shigatoxins 1 and 2 are implicated, the illness is also called shigatoxin *E. coli*-related hemolytic uremic syndrome (STEC-HUS).

Atypical HUS

This condition often lacks the prodromal history of diarrhea or dysentery, but may be triggered by minor infections. The onset may be insidious or present with a rapidly progressive illness. Microangiopathic lesions chiefly affect interlobular arteries and result in severe hypertension and progressive renal insufficiency. Predisposing factors include mutations in regulators of the complement pathway (factors H, I and B, C3, membrane cofactor protein and thrombomodulin), and antibodies against complement factor H.

Clinical and Laboratory Features

Children of all ages may be affected. Following a prodrome of acute diarrhea, dysentery or a febrile illness, patients show sudden onset of pallor and oliguria. Blood pressure may be high. Focal or generalized seizures and alteration of consciousness are common. Many patients do not show a prodromal illness.

The blood film shows broken and distorted red cells, increased reticulocyte count and high blood levels of LDH. Coombs' test is usually negative except in *S. pneumoniae* associated HUS where the test is positive. Thrombocytopenia is usually present; neutrophilic leukocytosis is seen in patients with shigellosis. Urine shows microscopic hematuria and mild proteinuria. Blood levels of urea and creatinine reflect the severity of renal failure. In patients with STEC-HUS, establishing etiology requires either stool culture or PCR for STEC or ELISA for shigatoxin. Serum complement C3 levels are low in some patients with atypical HUS. Detailed analysis of components of the alternative complement pathway and its regulators is recommended in all patients with atypical HUS.

On renal biopsy, the endothelial cells are swollen and separated from the basement membrane with accumulation of foamy material in the subendothelial space

(Figs 17.16c and d). The capillary lumen is narrowed by swollen endothelial cells, blood cells and fibrin thrombi. Arterioles may show similar changes. Patchy or extensive renal cortical necrosis may be present. *HUS is diagnosed on clinical and laboratory features, and a renal biopsy is rarely required.*

Treatment

Treatment includes management of complications of renal failure, treatment of hypertension and correction of anemia. Proper nutrition must be ensured. Peritoneal or hemodialysis may be necessary to prevent complications of renal insufficiency. Repeated plasma exchange with infusion of fresh frozen plasma is recommended for patients with atypical HUS. Plasma exchanges are initiated as early as possible, performed daily until hematological remission, and then less frequently. Patients with anti-factor H antibodies benefit from immunosuppression with agents that reduce antibody production. The use of eculizumab, a high affinity monoclonal antibody targeted against C5, benefits patients with HUS associated with activation of the complement cascade. While effective in ensuring hematological and renal remission, the medication is not available in the country.

Outcome

Mortality during the acute episode of shigatoxin associated HUS is low. On follow-up, 20–30% patients show varying degree of residual renal damage. Factors suggestive of poor outcome include oligoanuria for more than 2 weeks, severe neurological involvement and presence of cortical necrosis. The acute and long-term outcome in atypical HUS is unsatisfactory, though the prognosis has improved with supportive measures. Recurrent episodes of HUS may occur, including in the allograft after renal transplantation.

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CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD) is defined as kidney damage lasting for at least 3 months, as characterized by structural or functional abnormalities of the kidney with or without decreased glomerular filtration rate (GFR). Abnormalities may include structural malformations (e.g. hydronephrosis, single kidney), pathological conditions

Table 17.19: Stages of chronic kidney disease (CKD)

GFR, mL/min/1.73 m ²	NKF-KDOQI stage	Description	KDIGO stage	Description
>90	1	Kidney damage with normal or increased GFR	G1	Normal or high
60–89	2	Kidney damage with mild reduction of GFR	G2	Mildly decreased
45–59	3	Moderate reduction of GFR	G3a	Mildly to moderately decreased
30–44			G3b	Moderately to severely decreased
15–29	4	Severe reduction of GFR	G4	Severely decreased
<15	5	Kidney failure	G5	Kidney failure
<15, on dialysis	5D	Kidney failure, dialysis dependence		

KDIGO Kidney diseases improving global outcomes; NKF-KDOQI: National Kidney Foundation-Kidney Disease and Outcome Quality Initiative
In the absence of evidence of kidney damage, GFR category G1 or G2 do not fulfil the criteria for CKD

Severity of disease is additionally expressed as albuminuria, categorized as follows: (i) A1: normal to mildly increased (urine protein to creatinine ratio, Up/Uc <150 mg/g); (ii) A2: moderately increased (Up/Uc 150–500 mg/g) and (iii) A3: severely increased (Up/Uc >500 mg/g)

(e.g. focal segmental glomerulosclerosis) and markers of kidney damage such as abnormal urinalysis (hematuria, proteinuria) or biochemistry (persistently increased serum creatinine). CKD is divided into 5 stages, based on level of GFR estimated from level of serum creatinine and height using the modified Schwartz formula (Table 17.19). Since renal maturation increases from infancy to reach adult values at the age of 2 years, CKD stages apply only to children beyond >2-year-old. Terms such as chronic renal failure and end stage renal disease are avoided. Important conditions resulting in CKD are listed in Table 17.20. Congenital abnormalities of the kidney and urinary tract (CAKUT) are the leading causes of CKD in childhood.

Pathophysiology and Clinical Features

The term CKD implies permanent decrease in renal function. Most children with CKD stage 1–3 (GFR more than 30 mL/min/1.73 m²) are asymptomatic; reduction of GFR below this level is associated with symptoms. *Regardless of the etiology, once there is a critical loss of nephron mass, the renal failure is progressive and manifests with similar symptoms.* Loss of urinary concentrating ability results in

frequent passage of urine, nocturia and increased thirst. Anemia that is usually normocytic and normochromic is chiefly due to reduced renal erythropoietin production. Mild hemolysis and blood loss from gastrointestinal tract may also contribute.

Resistance to the action of growth hormone, the levels of which are increased, is considered to be responsible for growth failure. Anorexia, malnutrition and skeletal deformities contribute to growth retardation. Abnormalities in metabolism of calcium and phosphate and bone disease results from hyperphosphatemia, lack of renal formation of 1, 25-dihydroxyvitamin D₃, deficiency of calcium, chronic acidosis and secondary hyperparathyroidism.

The blood pressure may be increased and optic fundi show hypertensive retinopathy. Severe proximal muscle weakness, peripheral neuropathy, itching, purpura and pericarditis are late features. Infections are common and may acutely worsen renal function.

Investigations

The patient should be investigated to find the cause of renal failure and detect reversible factors (e.g. urinary tract obstruction, UTI, severe hypertension, drug toxicity and dehydration). Appropriate imaging studies are done. Blood counts and levels of urea, creatinine, electrolytes, pH, bicarbonate, calcium, phosphate, alkaline phosphatase, parathormone (PTH), protein and albumin are obtained. Levels of ferritin and transferrin saturation are obtained in patients with anemia. GFR can be estimated based on serum creatinine and height (p 465); its accurate assessment by creatinine clearance or radionuclide methods is rarely necessary.

Management

Optimal management of CKD involves a team approach involving pediatric nephrologist, specialist nurse, dietitian, social worker and orthopedic surgeon. The

Table 17.20: Common causes of chronic kidney disease

Glomerulonephritis: Idiopathic (e.g. focal segmental glomerulosclerosis); secondary (systemic lupus erythematosus, IgA nephropathy, microscopic polyarteritis, Henoch-Schönlein purpura)

Reflux nephropathy: Primary, secondary

Obstructive uropathy: Posterior urethral valves, pelviureteric junction obstruction, renal stones

Developmental anomalies: Bilateral renal hypoplasia, dysplasia

Familial nephropathy: Nephronophthisis, Alport syndrome, polycystic kidneys

Others: Hemolytic uremic syndrome, amyloidosis, renal vein thrombosis, renal cortical necrosis

management of CKD focuses on the following principles: (i) Treatment of reversible conditions; (ii) Retarding the progression of kidney disease, with particular attention to control of hypertension and proteinuria; (iii) Anticipation and prevention of complications of CKD; (iv) Optimal management of complications, including anemia, mineral bone disease, malnutrition, growth failure and metabolic acidosis; and (v) Identification of children in whom renal replacement therapy (RRT) is anticipated; adequate counseling and preparation of the family for RRT.

At the initial stages, management aims at maintaining nutrition and retarding progression of the renal failure. Later, treatment of complications and renal replacement therapy in the form of dialysis or transplantation is required.

Treatment of Reversible Renal Dysfunction

Common conditions with potentially recoverable kidney function include an obstruction to the drainage, recurrent urinary tract infections with vesicoureteric reflux and decreased renal perfusion due to renal arterial stenosis. Care should be taken to avoid AKI that may follow the administration of nephrotoxic drugs, herbal medications and radiocontrast agents, and occur with hypoxic injury due to inadequate hydration during or following surgery.

Retarding Progression of Renal Failure

Hypertension and proteinuria lead to increased intraglomerular perfusion, adaptive hyperfiltration and progressive renal injury. Hypertension should be adequately controlled. Long-term therapy with angiotensin-converting enzyme inhibitors has been shown to reduce proteinuria and may retard progression of renal failure. Strict control of blood pressure to 50th to 75th centile for age, gender and height, is useful in delaying progression. Children with proteinuria should be treated with an ACE inhibitor or an angiotension receptor blocker (ARB) because of their antiproteinuric effect. Therapy with lipid lowering agents and correction of anemia, shown to be useful in retarding progression of CKD in adults, may also have utility in children.

Diet

Careful attention to diet is essential. Recommended daily amounts of calories should be ensured. A diet high in polyunsaturated fats, such as corn oil and medium chain triglycerides and complex carbohydrates is preferred. Water restriction is usually not necessary, except in ESRD or presence of fluid overload. Excessive use of diuretics, overzealous restriction of salt and gastroenteritis may lead to dehydration that should be corrected.

Proteins: The protein intake should be 1–2 g/kg/day; proteins consumed should be of high biologic value. Restriction of protein intake is not required.

Sodium: Since renal regulation of sodium reabsorption is impaired, its dietary intake needs to be individualized. Some infants are polyuric and lose large amounts of

sodium requiring its supplementation. Children with chronic glomerulonephritis retain sodium and water, which contributes to hypertension. These patients require salt and water restriction and may benefit from diuretics.

Potassium: Renal regulation of potassium balance is maintained until very late, but the capacity to rapidly excrete a potassium load is reduced. Dietary items with large potassium content should be avoided.

Calcium and phosphorus: Calcium supplements are given as calcium carbonate or acetate. Excessive consumption of dairy products should be avoided to restrict phosphate intake.

Vitamins: Vitamins B₁, B₂, folic acid, pyridoxine and B₁₂ are supplemented.

Hypertension

Hypertension in patients with proteinuria and glomerular filtration rate >30 mL/min/1.73 m² should preferably be treated with angiotensin-converting enzyme inhibitors (e.g. enalapril). Beta-adrenergic blockers (atenolol) and calcium channel antagonists (nifedipine, amlodipine) are also effective; the latter are the preferred initial choice in CKD stage 4–5 (GFR <30 mL/min/1.73 m²). Treatment with loop diuretics is beneficial in those with fluid overload. Patients with severe hypertension, uncontrolled with the above medications, may require additional therapy with clonidine or prazosin.

Anemia

Anemia generally develops when the GFR falls below 30 mL/min/1.73 m². Iron deficiency, indicated by low levels of transferrin saturation (<20%) and ferritin (<100 ng/dL), is the most common underlying contributing factor. Therapy with iron (elemental iron 4–6 mg/kg per day) should be initiated in such cases. Iron replete patients with pernicious anemia should receive therapy with recombinant human erythropoietin 50–150 U/kg/dose given subcutaneously or intravenously 2–3 times a week. The dose of erythropoietin should be adjusted to achieve target hemoglobin of 11–12 g/dL. Patients should receive iron and micronutrient supplements concomitantly. Patients on hemodialysis should receive intravenous iron supplementation. Inadequate response to erythropoietin may occur due to iron, folate or vitamin B₁₂ deficiency, chronic infection, aluminum toxicity and severe hyperparathyroidism. Patients with hemoglobin level below 6 g/dL should receive leukocyte-poor, packed red cell transfusions. Blood is transfused slowly, since it may aggravate hypertension and heart failure.

Infections

Urinary tract and other infections should be promptly treated with effective and least toxic drugs. The dosage of most drugs requires modification (reduction of dosage

and/or increase in dosing interval), depending on the severity of renal failure.

Growth

Optimization of caloric and protein intake and treatment of mineral bone disease is important. Administration of recombinant human growth hormone at 0.024–0.070 mg/kg subcutaneously once a day, 6–7 times a week (max 0.35 mg/kg/week) improves growth velocity in children with chronic renal failure. Early recognition and management of malnutrition, mineral bone disease, metabolic acidosis and electrolyte disturbances should take precedence over the institution of therapy with growth hormone. The goal of therapy is to achieve the patient's genetic height potential.

Mineral Bone Disease

Mineral bone disease (MBD) is a serious problem in children as it occurs during the period of active growth (Fig. 17.18). Its prevention and adequate treatment is crucial. The proximal nephron is the chief site of synthesis of 1,25-dihydroxyvitamin D₃ (calcitriol), the most potent metabolite of vitamin D. Its decreased production is an important factor in the pathogenesis of secondary hyperparathyroidism in CKD. Recent studies also show a high incidence of vitamin D deficiency among children with CKD. With reduction of renal function, phosphate balance is initially maintained by its increased excretion from the normal nephrons. However, when the GFR falls below 25%, blood phosphate levels rise.

The symptoms of are vague and nonspecific. Bone pain, muscle weakness, growth retardation and skeletal deformities are prominent. Blood examination shows

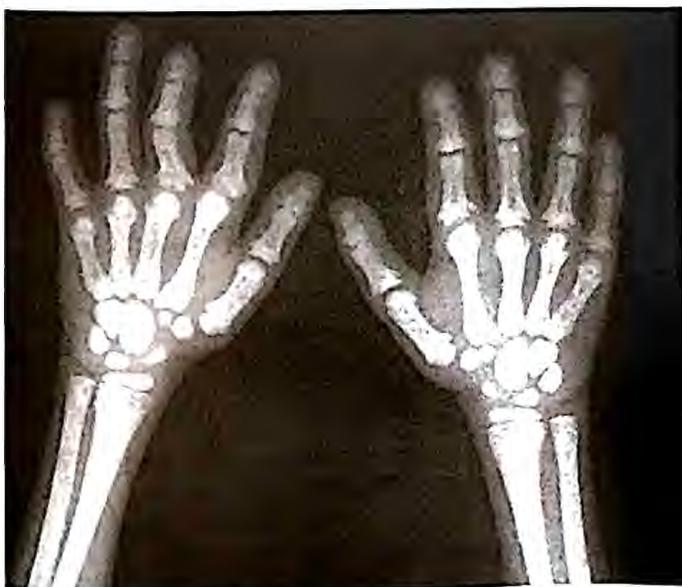


Fig. 17.18: Mineral bone disease associated with hyperphosphatemia and secondary hyperparathyroidism in a 12-year-old girl on chronic hemodialysis. Note the osteopenia and bone resorption in terminal phalanges of the fingers

hypocalcemia, hyperphosphatemia and raised levels of alkaline phosphatase and PTH. X-rays reveal changes suggestive of rickets. Radiologic features of secondary hyperparathyroidism are initially seen in the phalanges and clavicles.

The goals of early intervention are to maintain normal bone mineralization and growth, avoid hyperphosphatemia and hypocalcemia, and prevent or reverse increased PTH secretion. Treatment is based on dietary restriction of phosphate, and administration of phosphate binders and vitamin D. When serum phosphate exceeds the target range, phosphate containing food (e.g. dairy products) are restricted. Oral phosphate binders, calcium carbonate or acetate (0.5–1 g/day with meals) reduce intestinal absorption of dietary phosphate. Since aluminum accumulation may increase the risk of bone disease and encephalopathy, prolonged administration of aluminum hydroxide as a phosphate binder is avoided. Sevelamer, a calcium and aluminum free ion-exchange resin that binds phosphorus within the intestinal lumen, is a safe and effective alternative to calcium containing phosphate binders.

The first steps in managing elevated levels of PTH in children with CKD are correction of underlying nutritional deficiency of vitamin D deficiency and management of hyperphosphatemia. If the PTH still remains elevated after these measures, therapy with activated vitamin D should be started. Vitamin D analogs with short half-life (calcitriol, 20–50 ng/kg/day or 1 α -hydroxy D₃, 25–50 ng/kg/day) are preferred. Excessive vitamin D intake may cause hypercalcemia, hypercalciuria and elevation of calcium phosphorus product, which should be monitored.

Osteotomy may be required to correct bony deformities.

Immunization

Patients with CKD should receive all routine vaccines. Apart from the regular immunization, children with CKD should also receive vaccines against pneumococcal, chickenpox and hepatitis A and B infections, especially if prepared for transplantation. Immunization is scheduled so as to complete live vaccinations prior to transplantation. Primary as well as booster doses of inactivated vaccines can be given 6 months after transplant.

Long-term Care

The rate of progression of chronic renal injury is variable. In some disorders (e.g. hemolytic uremic syndrome, crescentic GN), stage V CKD is present within a few weeks or months. In others (e.g. reflux nephropathy and some forms of chronic GN), the decline in renal function is slow. Patients showing a rapid deterioration of renal function should be evaluated for potentially reversible complications (infection, urinary outflow obstruction, fluid loss, hypertension and use of nephrotoxic drugs).

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RENAL REPLACEMENT THERAPY

Preparation of a child for end stage care should be discussed in advance with the family members. The financial resources and the family support available should be addressed. Initiation of dialysis should be considered when the glomerular filtration rate (GFR) falls below 12 mL/min/1.73 m² body surface area and is strongly recommended when the GFR is <8 mL/min/1.73 m². However, the well-being of the patient is more important than the estimated GFR for deciding when dialysis should begin. The presence of fluid overload, hypertension, gastrointestinal symptoms, growth retardation and neurological consequences of uremia influence the decision to initiate RRT.

The different forms of renal replacement therapy are chronic peritoneal dialysis, hemodialysis and renal transplantation. In children with stage V CKD (ESRD), transplantation is the desired form of therapy. While chronic dialysis is life sustaining, it is inferior to renal transplantation in providing adequate renal replacement. Transplantation is associated with significant survival advantage, decreased risks of hospitalization and improved quality of life.

Chronic Peritoneal Dialysis (PD)

Chronic PD is done through a Tenckhoff catheter tunneled through the abdominal wall into the peritoneum. Chronic PD can be done manually (ambulatory PD) or with the help of an automaticycler (cyclic PD). The duration of dialysis is usually 10–12 hours a day during which 4–6 cycles are performed. Chronic PD is preferred to chronic hemodialysis since it is done at home, without the need for hospital visits. Patients on chronic PD have less restriction on fluid and caloric intake; control of hypertension is better and hematocrit is maintained. The success of chronic PD, however, relies upon the motivation of families to carry out the procedure.

Chronic Hemodialysis (HD)

HD is mostly carried out in the hospital setting. These children require vascular access either an arteriovenous



Fig. 17.19: Hemodialysis in a patient with end-stage renal disease. Note the vascular access through a catheter in the internal jugular vein, hemodialysis machine and the dialyzer (solid arrow)

fistula or graft, or a double lumen indwelling catheter in a central vein (internal jugular vein preferred). Dialysis is done for 3–4 hours/session, with a frequency of 3 sessions/week. During a hemodialysis session, blood is circulated through an extracorporeal circuit that includes a hollow fiber dialyzer (artificial kidney) (Fig. 17.19). Anti-coagulation of the circuit is achieved by systemic heparinization. The procedure requires technical expertise and need for continuous monitoring.

Renal Transplantation

The feasibility and efficacy of renal transplantation as standard therapy for ESRD in children is well established. Advances in surgical skills, availability of better immunosuppressive medications and ability to prevent and treat infections, have improved the short- and long-term outcome. The usual immunosuppressive therapy is a combination of a calcineurin inhibitor (cyclosporin or tacrolimus), purine synthesis inhibitor (azathioprine or mycophenolate mofetil) and prednisolone. Long-term allograft survival is better with live compared to deceased donors. Following successful renal transplantation, the child can lead a normal life and resume physical activity and schooling. The allograft survival varies between 10 and 20 years.

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DISORDERS OF RENAL TUBULAR TRANSPORT

In comparison to glomerular diseases, tubular disorders are less common. Early and correct diagnosis is essential since specific management is possible in many cases. The diagnosis of a *primary* tubular disorder implies that there

is no significant impairment of glomerular function or tubulointerstitial inflammation. A tubular disorder may be congenital or acquired and involve a single function of a tubule (renal glucosuria, nephrogenic diabetes insipidus) or multiple functions (Fanconi syndrome).

Initial Evaluation

Children with primary defects in tubular function usually present during infancy. Table 17.21 shows important clinical features of patients with such disorders. Most renal tubular disorders can be diagnosed following careful interpretation of urine and plasma biochemistry, key investigations are listed in Table 17.1.

Renal Tubular Acidosis (RTA)

RTA encompasses conditions characterized by a defect of renal acidification, which result in hyperchloremic metabolic acidosis and inappropriately high urine pH. Defects in tubular transport result in reduced proximal tubular reabsorption of bicarbonate (HCO_3^-), the distal secretion of protons (hydrogen ion, H^+) or both, leading to impaired capacity for net acid excretion and persistent hyperchloremic metabolic acidosis. The plasma anion gap [$\text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-)$] is in the normal range (8–12 mEq/L). The renal function is normal or only mildly impaired.

Two main forms are recognized: Distal RTA (type 1) and proximal RTA (type 2). Another variety (type 4) distinguished by the presence of hypoaldosteronism and hyperkalemia is less common in children.

Distal RTA

Distal (type 1) RTA is due to defective secretion of H^+ in the distal tubule, in the absence of significant decrease in

Table 17.21: Presenting features in tubular disorders

Growth retardation, failure to thrive
Delayed gross motor milestones
Polyuria, excessive thirst
Recurrent episodes of dehydration, vomiting, fever
Rickets, bone pains
Episodic weakness
Constipation
Craving for salt and savory foods

glomerular filtration rate. Patients with distal RTA are unable to excrete ammonium (NH_4^+) ions adequately, and the urine pH cannot reach maximal acidity (i.e. remains >5.5) despite acidemia, indicating low H^+ concentration in the collecting duct. Hypokalemia is caused by increased urinary losses of potassium and aldosterone stimulation by urinary Na^+ loss and volume contraction, leading to further increase in tubular K^+ secretion.

The condition is often sporadic, but may be inherited (dominant, recessive or X-linked). Important forms are listed in Table 17.22. The disease may be associated with systemic diseases (systemic lupus erythematosus, Wilson disease) or secondary to renal disease (obstructive uropathy, reflux nephropathy) or drug toxicity (lithium, analgesics, amphotericin B).

Presenting features: Children present with failure to thrive, polyuria, polydipsia, hypokalemic muscle weakness and rickets. Ultrasonography may show nephrocalcinosis (Fig. 17.20). Patients with incomplete forms of distal RTA may present with nephrolithiasis or incidentally detected nephrocalcinosis.

Table 17.22: Inherited forms of renal tubular acidosis (RTA)

Type of RTA	Associated disorders
Type 1 (distal)	Hemolytic anemia Early hearing loss Normal hearing; delayed hearing loss
Type 2 (proximal), isolated	Ocular abnormalities (band keratopathy, cataracts, glaucoma); defective dental enamel; intellectual impairment; basal ganglia calcification
Type 2, Fanconi syndrome	Dent disease Cystinosis Tyrosinemia type 1 Fanconi-Bickel syndrome Wilson disease Galactosemia Hereditary fructose intolerance Lowe syndrome Glycogen storage disease type I Mitochondrial disorders
Type 3 (combined)	Osteopetrosis; blindness, deafness
Type 4 (hyperkalemic)	Congenital adrenal hyperplasia Pseudohypoaldosteronism (PHA) PHA type 2, Gordon syndrome



Fig. 17.20: Medullary nephrocalcinosis. Ultrasonography in a 3-year-old boy with distal renal tubular acidosis shows hyperechoic medulla

Diagnosis: Biochemical abnormalities include hyperchloremic metabolic acidosis, hypokalemia, increased urinary excretion of calcium and decreased urinary citrate. Urinary net acid excretion (titratable acid and ammonium) is markedly reduced. Despite moderate to severe acidosis, patients cannot lower urine pH below 5.3. Measurement of the difference between urinary and blood CO_2 , during the passage of alkaline urine, is a reliable indicator of distal tubular acidification. Normally, the difference is more than 20 mm Hg, provided the urine pH is >7.5 . In children with distal RTA, the urine to blood CO_2 gradient is reduced below 10 mm Hg. Table 17.23 shows useful tests for the evaluation of patients with RTA. Hearing evaluation should be performed in all patients with idiopathic distal RTA.

Patients with incomplete forms of distal RTA show normal levels of serum pH and bicarbonate. The defect in distal acidification can be demonstrated by the fludrocortisone frusemide test. Hypercalciuria and hypocitraturia are associated.

Treatment: Hypokalemia should be treated before correction of acidosis. Acidosis is treated by administration of sodium bicarbonate (initially 2–3 mEq/kg in divided doses), its dose titrated to blood levels of bicarbonate. Alkali requirements decrease beyond 5 years of age. Treatment of acidosis reduces potassium losses and promotes growth and healing of rickets. Some patients require prolonged potassium replacement. Vitamin D supplements are not required. If hypercalciuria persists, administration of thiazides may be considered.

Proximal (Type 2) RTA and Fanconi Syndrome

Proximal RTA is due to reduced proximal tubular reabsorption of bicarbonate with marked bicarbonaturia. Once the plasma bicarbonate falls below 16 mEq/L, it is mostly reabsorbed. At steady state, daily acid loads are excreted successfully and the distal acidification mechanism is intact. Thus, children with proximal RTA have less severe acidosis than distal RTA.

Pathophysiology: The primary defect in proximal RTA is reduced renal threshold for bicarbonate, resulting in bicarbonaturia. Proximal RTA may represent isolated or generalized proximal tubular dysfunction (Table 17.22). The latter, termed Fanconi syndrome, is characterized by tubular proteinuria and aminoaciduria and variable degrees of bicarbonaturia, phosphaturia, electrolyte wasting and glucosuria. Fanconi syndrome may be (i) idiopathic, or secondary to (ii) a metabolic disorder (Table 17.23), (iii) drugs (ifosfamide, aminoglycosides, cisplatin), (iv) toxins (cadmium, lead, mercury) and (v) tubulointerstitial nephritis.

Clinical features: Failure to thrive and physical retardation are the chief clinical features. Irritability, anorexia and listlessness may be present. Rickets is rare in isolated proximal RTA but common in Fanconi syndrome. Those with secondary Fanconi syndrome may have features of the underlying disorder. Nephrocalcinosis and urolithiasis

Table 17.23: Investigations to differentiate types of renal tubular acidosis (RTA)

	<i>Proximal RTA</i>	<i>Classic distal RTA</i>	<i>Type 4 RTA</i>
Plasma potassium	Normal or low	Normal or low	High
Urine pH (during acidosis)	<5.5	>5.5	<5.5
Urine anion gap	Positive	Positive	Positive
Urine ammonium	Low	Low	Low
Fractional bicarbonate excretion	$>10\text{--}15\%$	$<5\%$	$>5\text{--}10\%$
U-B PCO_2 mm Hg	>20	<10	>20
Urine calcium	Normal	High	Normal or low
Other tubular defects	Often present	Absent	Absent
Nephrocalcinosis	Absent	Present	Absent
Bone disease	Common	Often present	Absent

U-B PCO_2 : Urine to blood PCO_2 gradient

are not seen. Symptoms related to hypokalemia (weakness, paralysis) are uncommon.

Diagnosis: Table 17.23 shows the features that allow proximal RTA to be distinguished from other forms of RTA. The blood pH and HCO_3^- levels are low and urine pH relatively alkaline. However, if the blood HCO_3^- falls below 14–16 mEq/L, urine pH falls to <5.5. Urinary calcium and citrate excretion is normal. Demonstration of its high fractional excretion of bicarbonate (>15%), at plasma bicarbonate level 20–22 mEq/L is confirmatory.

Evaluation of other proximal tubular functions is essential. This includes an assessment of phosphate excretion and evaluation for aminoaciduria, glucosuria and low molecular weight proteinuria. Estimation of calcium excretion and examination for rickets is important. Disorders that are associated with Fanconi syndrome should be screened for, including cystinosis, Lowe syndrome, galactosemia and Wilson disease.

Treatment: The correction of acidosis requires administration of 5–20 mEq/kg of alkali daily. Part of the alkali is replaced as potassium citrate. Since administration of large amounts of alkali results in bicarbonate wasting, it is prudent to give a modest amount of sodium bicarbonate (5–8 mEq/kg/day in divided doses) along with restriction of dietary sodium. The latter causes contraction of extracellular fluid volume and increased proximal bicarbonate reabsorption. Administration of hydrochlorothiazide has a similar effect. Children with Fanconi syndrome also need supplements of phosphate (neutral phosphate, Joulie solution). Treatment with vitamin D is necessary in children with rickets.

Cystinosis: This autosomal recessive disorder presents in infancy with features of severe Fanconi syndrome. The underlying defect is in the lysosomal membrane protein (cystinosin) that transports cystine from lysosomes into the cytosol. This leads to very high levels of free lysosomal cystine, which is deposited as crystals in the cornea, conjunctiva, bone marrow, leukocytes and lymph nodes. Tubular handling of cystine is normal. The most common form of cystinosis is the infantile nephropathic form in which patients present in early infancy. Later, patients show photophobia and enlarged liver and spleen; some have blond hair.

Diagnosis is indicated by the presence of cystine crystals in cornea on slit-lamp microscopy (Fig. 17.21). Elevated levels of cystine in polymorphonuclear leukocytes or cultured fibroblasts are confirmatory. Prenatal diagnosis requires measurement of cystine level in chorionic villi or cultured amniotic fluid cells.

Correction of metabolic acidosis and replacement of electrolytes is essential. Early therapy with oral cysteamine may retard progression of systemic disease. Topical therapy is essential to prevent corneal deposits. Long-term complications include hypothyroidism and diabetes



Fig. 17.21: Slit-lamp examination of the cornea in a 4-year-old girl with cystinosis; diffuse crystal deposition is noted

mellitus. If untreated, most patients show progression to end stage renal failure by late childhood.

Lowe syndrome: This X-linked condition presents within the first few months of life with Fanconi syndrome, severe rickets, ocular defects (congenital cataracts, buphthalmos, corneal degeneration, strabismus), neonatal or infantile hypotonia, rickets, seizures, developmental delay and mental impairment. Hypercalciuria may be prominent. Diagnosis is confirmed by either mutational analysis of the affected gene (*OCRL*) or measurement of the activity of the enzyme (phosphatidylinositol bisphosphate 5-phosphatase) in cultured fibroblasts. Chronic tubular injury leads to glomerulosclerosis and progressive renal insufficiency. Most children die in early childhood.

Hyperkalemic (Type 4) RTA

Hyperkalemia with distal RTA occurring due to aldosterone resistance or deficiency is termed type 4 RTA. Aldosterone directly stimulates the proton pump, increases Na^+ absorption resulting in negative intratubular potential and increases urinary K^+ losses; and stimulates basolateral Na^+/K^+ ATPase. Hence, aldosterone deficiency or resistance is expected to cause hyperkalemia and acidosis. Maximally acidic urine (<5.5) can be formed, indicating the ability to establish a maximal H^+ gradient. However, the rate of ammonium excretion is low. Aldosterone deficiency without renal disease may occur with Addison disease, or following adrenal necrosis or tuberculosis. Aldosterone resistance may occur with chronic renal insufficiency such as obstructive uropathy or interstitial nephritis or with use of certain drugs (e.g. amiloride, spironolactone, ACE inhibitors, heparin, NSAIDs, calcineurin inhibitors).

The autosomal recessive form of pseudohypoaldosteronism (PHA type 1) should be considered in infants presenting with salt loss, hypotension, hyperkalemia and metabolic acidosis. Patients with PHA type 2 have hypertension, acidosis and hyperkalemia with hyporeninemic hypoaldosteronism.

Nephrogenic Diabetes Insipidus

Congenital nephrogenic diabetes insipidus is an inherited disorder of water reabsorption, caused by resistance to the action of ADH on its receptor. Absorption of water in the distal tubules and collecting ducts is significantly impaired. The defect usually involves the arginine vasopressin receptor 2 (*AVPR2*) gene on the X chromosome. Less commonly, the disease is inherited in an autosomal recessive manner due to mutations in the gene encoding aquaporin 2.

The usual history is of a boy who, within a few weeks of life, shows failure to thrive, excessive thirst, recurrent episodes of dehydration and unexplained fever. The infant continues to have increased or normal urine output even when dehydrated. Constipation is common. Polyuria, polydipsia and nocturnal enuresis are striking in older children. Recurrent episodes of dehydration and rapid rehydration may lead to neurological injury with intracranial calcification, seizures and psychomotor dehydration.

Hypernatremia (serum sodium often more than 170 mEq/L), with low urine sodium is characteristic. Correspondingly, serum chloride and osmolality are high. The urine osmolality is inappropriately low (usually below 150–200 mOsm/kg) for the elevated plasma osmolality. Further, urine osmolality does not increase despite administration of DDAVP. This allows nephrogenic diabetes insipidus to be differentiated from deficiency of the ADH (central diabetes insipidus). The latter show normal response to DDAVP with increase in urine osmolality to more than 600–800 mOsm/kg. Tubular unresponsiveness to ADH may also occur as part of chronic pyelonephritis, obstructive uropathy, sickle cell disease, lithium toxicity, hypercalcemia, hypokalemia and tubulointerstitial disease.

Treatment consists of increased fluid intake and sodium restriction to reduce the osmolar load. Administration of hydrochlorothiazide (2–3 mg/kg/day), alone or in combination with amiloride (20 mg/1.73 m²/day), reduces polyuria and leads to clinical improvement. Indomethacin may also reduce urine volume, but its use is limited beyond infancy.

Renal Glucosuria

Renal glucosuria is an autosomal recessively transmitted, isolated defect of tubular glucose transport. It is recognized by the presence of glucose in the urine, despite normal blood glucose levels. Glucose metabolism and other renal tubular transport mechanisms are normal. Several members of a family may be affected. The disorder is asymptomatic and benign, and does not require treatment.

Type A defects are characterized by generalized decrease in capacity of tubules to reabsorb glucose, and a low tubular maximum for glucose. In type B defects, the tubular maximum for glucose is normal, but the capacity of individual nephrons to reabsorb glucose is affected

variably. In type O defects, there is no tubular reabsorption of glucose.

Bartter Syndrome

Bartter syndrome is an autosomal recessive disorder characterized by hypokalemia and metabolic alkalosis, resulting from excessive chloride, potassium and sodium wasting in the thick ascending limb of the loop of Henle. Clinical features include failure to thrive, polyuria, polydipsia and recurrent episodes of dehydration. Vomiting, constipation, muscle weakness and cramps are other manifestations. Patients show marked hypokalemia with high urinary potassium and hypochloremic metabolic alkalosis. Volume contraction leads to increase in levels of plasma renin and aldosterone. Elevated urinary levels of chloride (>20–30 mEq/L) are characteristic.

Several subtypes of Bartter syndrome are recognized, differing in their molecular basis and clinical severity. The condition may occasionally present in the neonatal period with history of maternal polyhydramnios and postnatal polyuria, dehydration and nephrocalcinosis; some have sensorineural deafness.

Bartter syndrome should be differentiated from other conditions with persistent hypokalemic metabolic alkalosis (e.g. cystic fibrosis, recurrent vomiting, inherited forms of hypertension and Gitelman syndrome) by the presence of normal blood pressure and high urinary chloride and calcium excretion.

Therapy is directed towards replacement of urinary losses of fluid, sodium, potassium and chloride. Most patients require supplements of potassium chloride (1–3 mEq/kg/day). Despite supplementation, serum potassium rarely returns to normal range. Use of prostaglandin synthase inhibitors (indomethacin 2–3 mg/kg/day or ibuprofen 20–30 mg/kg/day) is beneficial. Potassium sparing diuretics and ACE inhibitors have been used with modest benefit in correcting hypokalemia.

Gitelman Syndrome

Hypokalemia, hypomagnesemia and metabolic alkalosis may be caused by Gitelman syndrome, an autosomal recessive condition characterized by a defect in the apical thiazide sensitive sodium chloride cotransporter (NCCT) in the distal tubules. Clinical and laboratory features are milder than in Bartter syndrome. Patients present in adolescence or adulthood with episodes of muscle weakness, cramps, tetany, vomiting or fatigue. Polyuria and failure to thrive are less pronounced.

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NEPHROLITHIASIS AND NEPHROCALCINOSIS

Renal calculi are uncommon in children and occur usually in the setting of an underlying metabolic abnormality. Symptoms include dysuria, hypogastric pain, hematuria and occasionally urinary infections. Nephrocalcinosis refers to formation of crystalline deposits within the renal parenchyma, presenting as enhanced renal echogenicity, which may be cortical, medullary or diffuse. Table 17.24 lists common underlying metabolic causes. Urinary tract infection, particularly with urease producing organisms like *Proteus*, favors precipitation of magnesium ammonium phosphate and calcium phosphate (struvite stones). Progressive renal impairment may occur in patients with nephrocalcinosis, untreated obstruction or recurrent UTI.

Evaluation

Ultrasonography detects most radiopaque and radiolucent calculi and nephrocalcinosis. High resolution computerized tomography detects even minute calculi. Plain radiographs and intravenous pyelography are rarely required; the latter is useful only if suspecting radiolucent or low density stones (uric acid, xanthine), duplex system or obstruction, particularly in a young child where performing CT would necessitate sedation. However, high resolution ultrasonography may overdiagnose nephrocalcinosis, particularly in newborns where physiologically increased echogenicity or deposition of Tamm-Horsfall protein is mistaken for medullary nephrocalcinosis.

Investigations aiming at detecting abnormalities show a metabolic cause in 50% patients. Initial investigations

Table 17.24: Underlying metabolic abnormalities in children with nephrolithiasis or nephrocalcinosis

Hypercalciuria with hypercalcemia

- Vitamin D overdose
- Primary hyperparathyroidism
- Production of PTH related peptide (malignancy, sarcoidosis)

Hypercalciuria with normal serum calcium

- Idiopathic hypercalciuria
- Familial hypophosphatemia with hypercalciuria
- Distal renal tubular acidosis
- Dent disease
- Barter syndrome with/without sensorineural deafness
- Autosomal dominant hypocalcemia with hypercalciuria
- Familial hypomagnesemia, hypercalciuria and nephrocalcinosis
- Lowe syndrome
- Furosemide use

Miscellaneous causes

- Primary hyperoxaluria (type I, type II)
- Cystinuria
- Abnormal purine, pyrimidine metabolism: Lesch-Nyhan syndrome, glycogenosis type 1, xanthinuria
- Melamine toxicity

should include renal function tests, blood levels of calcium, phosphorus, uric acid, pH and bicarbonate. Detection of specific crystals in the urine may suggest an etiology (Fig. 17.22). High (>5.5) urine pH in first morning sample suggests defective tubular acidification. Quantitation of calcium, oxalate and uric acid in timed urine collections evaluates excretion of solutes as compared to normal individuals. Alternatively, solute excretion is expressed as a ratio to urinary creatinine in spot samples. Patients with hypercalciuria require evaluation for hypercalcemia (intact PTH, 25-hydroxyvitamin D) and for association with incomplete distal renal tubular acidosis, hypomagnesemia, hypophosphatemic rickets and abnormalities of the thyroid hormone. Where available, stone analysis is performed using X-ray diffraction or infrared spectroscopy.

Idiopathic Hypercalciuria

This is the *most common underlying cause* in patients with nephrolithiasis, but may alternatively present with microscopic and gross hematuria. A family history of hematuria or nephrolithiasis is often present. Urinary calcium to creatinine ratio in the early morning 'spot' urine serves as a screening test. The upper limit of normal in children over 2 years is 0.2 (mg/mg). The diagnosis is confirmed by an accurate measurement of 24 hours urinary calcium; values greater than 4 mg/kg/day are abnormal. *Blood levels of calcium and magnesium are normal.* Idiopathic hypercalciuria should be distinguished from hypercalciuria secondary to persistent hypercalcemia (e.g. hyperparathyroidism, vitamin D toxicity) or associated with renal tubular acidosis. A high fluid intake and diet low in animal protein and salt is advised. Therapy with thiazide diuretics, which reduces urinary calcium excretion, may be required.

Endemic Vesical Calculi

Vesical calculi are usually single stones, detected in young boys (<5-year-old) in some regions of the country, e.g. Rajasthan, Andhra Pradesh and North-Eastern states, and in neighboring countries, e.g. Pakistan and Afghanistan. These stones are composed of ammonium acid urate and calcium oxalate. Risk factors include consumption of a predominantly cereal (wheat or jowar) based diet, which has low amounts of calcium and phosphate and high oxalate content. Recurrent diarrheal episodes contribute by causing dehydration and an acidic, concentrated urine. A high intake of dairy products and animal proteins has led to a decline in the prevalence of these stones. Treatment requires suprapubic cystolithotomy; these stones rarely recur.

Primary Hyperoxaluria

Primary hyperoxaluria type 1 is an autosomal recessive disorder of glyoxylate metabolism with deficient activity

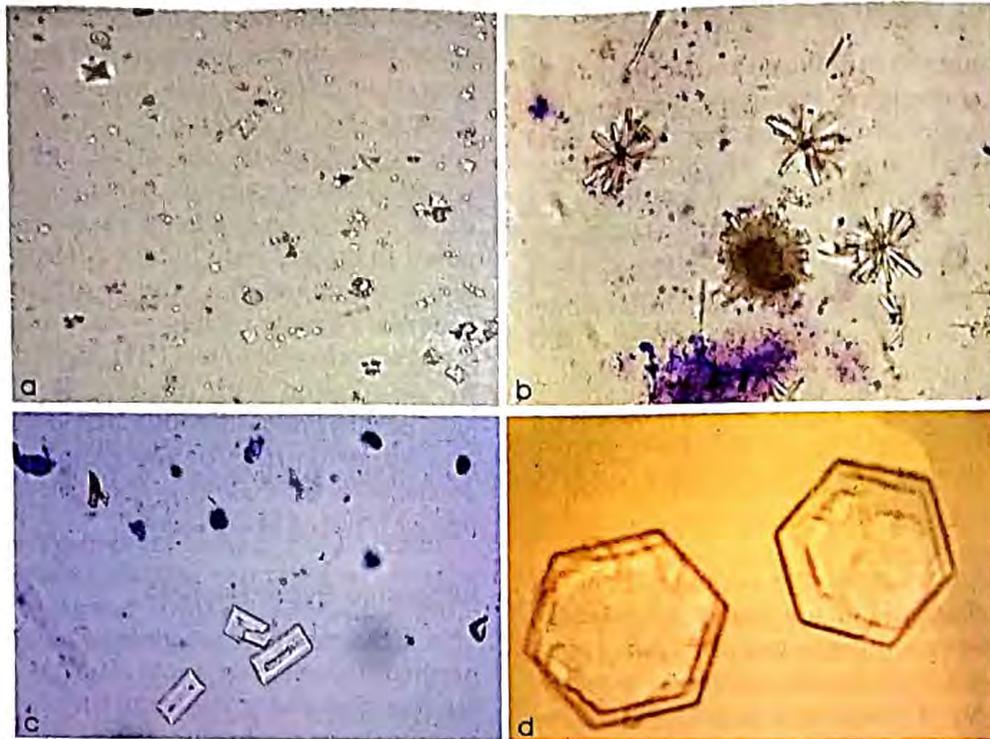


Fig. 17.22: Morphology of urine crystals may suggest etiology of renal stones. (a) Envelope-shaped oxalate dihydrate crystals; (b) Florets of calcium phosphate; (c) Coffin lid-shaped triple phosphate; (d) Hexagonal cystine crystals

of the liver-specific enzyme, alanine glyoxylate aminotransferase causing overproduction of endogenous oxalate, which manifests as renal stones and/or nephrocalcinosis. Precipitation of oxalate also affects the eyes, heart, bones and bone marrow. The diagnosis is suggested by elevated oxalate in plasma and/or urine, and confirmed by deficient activity of the enzyme on liver biopsy and sequencing of the affected gene, *AGXT*. Treatment is supportive; some patients with partial deficiency benefit from pyridoxine supplementation. Patients presenting in childhood progress to end-stage renal disease by adolescence and require combined liver kidney transplantation.

Cystinuria

This autosomal recessive disorder is characterized by impaired proximal tubular reabsorption of cystine and dibasic amino acids (ornithine, lysine and arginine). Supersaturation of urine with cystine crystals may lead to formation of recurrent radiopaque calculi and account for 10% of cases presenting in childhood. The diagnosis is suggested by presence of hexagonal crystals in urine, urinary excretion of specific amino acids (as above) and positive urine nitroprusside cyanide test. Confirmation requires quantification of urinary cystine excretion (24 hr or cystine:creatinine ratio), stone analysis or genetic testing. A high fluid intake and urinary alkalization help, since cystine is poorly soluble at normal urinary pH but dissolves well at pH >8.0. Agents such as penicillamine and tiopronin prevent formation of calculi by cleaving

disulfide bonds of cystine to form the more soluble homodimer, cysteine.

Management of Renal Calculi

Stones less than 5–7 mm in size may pass spontaneously. Extracorporeal shock wave lithotripsy (ESWL) may suffice for small stones. Percutaneous nephrolithotomy may be appropriate in patients with relative contraindication for ESWL or with stones too large for lithotripsy. Ureteroscopy is useful for distal and mid-ureteric calculi. Open surgery is necessary for stones more than 3 cm in size or those with associated pelviureteric junction obstruction.

UTI should be treated and an adequate fluid intake ensured. Patients with idiopathic hypercalciuria may benefit from a low salt intake; dietary calcium restriction is not necessary. Persistent hypercalciuria is treated with oral potassium citrate, an inhibitor of crystallization. Thiazide diuretics reduce urine calcium excretion; their long-term use is, however, restricted due to side effects. Prolonged alkali supplementation is necessary in patients with distal RTA.

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ENURESIS

Enuresis is defined as normal, nearly complete evacuation of the bladder at a wrong place and time at least twice a month after 5 years of age. Enuresis should be differentiated from continuous or intermittent incontinence or dribbling. The bed is usually soaking wet in enuresis, compared to incontinence in which there is loss of urine without normal emptying of the bladder. Enuresis is usually functional while continuous or daytime incontinence is often organic.

More than 85% children attain complete diurnal and nocturnal control of the bladder by 5 years of age. The remaining 15% gain continence at approximately 15% per year, such that by adolescence only 0.5–1% children have enuresis. Up to the 11th year, enuresis is twice as common in boys as it is in girls; thereafter, the incidence is similar or slightly higher in girls.

Enuresis is called primary when the child has never been dry and secondary when bed wetting starts after a minimum period of 6 months of dryness at night. It is termed monosymptomatic, if it is not accompanied by any lower urinary tract symptoms and nocturnal, if it occurs only during sleep. Children with *monosymptomatic nocturnal enuresis* require no further evaluation.

Etiology

Maturation delay is the most likely cause of nocturnal enuresis, suggested by high spontaneous cure rates with increasing age. Other reasons that have been attributed include a lack of circadian rhythm of secretion of the antidiuretic hormone (ADH), inadequate sleep arousal, urinary tract infections, bladder bowel dysfunction and stressful events.

Evaluation

Less than 5% patients with nocturnal enuresis have an organic basis. A careful history helps determine whether the enuresis is primary or secondary, whether any daytime symptoms are present and whether any voiding difficulty is present. In cases of secondary enuresis, history should be taken to rule out acute stressful conditions, polyuria and features of bladder irritability such as frequency and urgency. Physical examination should focus on spinal anomalies.

If the child has a normal urinary stream with no daytime symptoms suggestive of a voiding disorder and normal physical examination, the child does not require extensive evaluation. Clinical and neurological examination excludes an anatomical or neurological cause for incontinence.

A voiding diary with frequency and volume charting of urine output and fluid intake for at least 2 days, with a record of daytime accidents, bladder symptoms and bowel habits for at least 7 days is useful. It helps detect children with non-monosymptomatic enuresis or polydipsia, provides information on nocturnal polyuria (such children benefit from desmopressin) and helps monitor compliance

to instructions and response to therapy. Urinalysis rules out infection, proteinuria and glucosuria. Additional diagnostic and invasive procedures, including ultrasonography and MCU, are limited to patients with suspected neurological or urological dysfunction.

Treatment

The decision for treatment should be guided by the degree of concern and motivation on the part of the child rather than the parents. General advice should be given to all enuretic children, but active treatment need not begin before the age of 6 years. Caffeinated drinks like tea, coffee and sodas should be avoided in the evening. Adequate fluid intake during the day as 40% in the morning, 40% in the afternoon and 20% in the evening is recommended.

The firstline of treatment is usually non-pharmacological, comprising motivational therapy and use of alarm devices. *Motivational therapy* alone is successful in 25% patients. The child is reassured and provided emotional support. Every attempt is made to remove any feeling of guilt. The benign nature of the disorder is explained to the child and parents using diagrams, if required, to explain the probable basis of the disorder. The child is encouraged to assume active responsibility, including keeping a dry night diary, voiding urine before going to bed and changing wet clothes and bedding. Dry nights should be credited with praise and encouraging words from the parents. Punishments and angry parental responses should be avoided.

Behavioral modification is encouraged to achieve good bladder and bowel habits. The child is encouraged to void frequently enough to avoid urgency and daytime incontinence and to have a daily bowel movement. Bladder training exercises have not been shown to be useful in improving the functional bladder capacity.

Alarm therapy involves the use of a device to elicit a conditioned response of awakening to the sensation of a full bladder. The alarm device consists of a small sensor attached to the child's underwear, or a mat under the bedsheet and an alarm attached to the child's collar or placed at the bedside. When the child starts wetting, the sensors are activated causing the alarm to ring. The child should awaken to the alarm, void in the toilet and reattach the alarm; a parent should ensure the child does not merely wake to switch off the alarm. The alarm is best used after 7 years of age and is successful in about two-thirds of children; one-third of children may relapse. While alarm systems are available in India, the ordinary alarm clock may be used to wake the child to void in the toilet at a critical time when the bladder is full and the child is still dry. The combination of motivational and alarm therapy is successful in up to 60–70% of children.

Pharmacotherapy is considered, if enuresis persists despite institution of alarm, regular voiding habits, exclusion or treatment of constipation and exclusion of

postvoid residual urine or dysfunctional voiding. Cardiac arrhythmias are a rare but serious adverse event effect of tricyclic antidepressants, which are, therefore, not recommended. Anticholinergic drugs reduce uninhibited bladder contractions and are useful in children who have significant daytime urge incontinence besides nocturnal enuresis. The usual dose is 5 mg for oxybutynin or 2 mg for tolterodine at bedtime, given above 6 years of age. Desmopressin (DDAVP, 0.2–0.4 mg orally; oral melt 120–240 µg) works by reducing the volume of urine. Its rapid onset of action makes it a satisfactory choice for special occasions like staying out for the night. Relapse rates are high after stopping the medication.

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CONGENITAL ABNORMALITIES OF KIDNEY AND URINARY TRACT

Congenital abnormalities of kidney and urinary tract (CAKUT) are common and account for about 25% cases of CKD in children.

Single Kidney

In unilateral renal agenesis, one kidney fails to form while the other is normal in size, position and function. Agenesis may occur due to primary failure of formation of the ureteric bud or its inability to engage with the renal mesenchyme. The condition may occur sporadically or as part of syndromes such as brachio-otorenal, DiGeorge, Fanconi anemia, Fraser or nail-patella syndromes. Renal agenesis is asymptomatic, usually detected incidentally on ultrasonography. Usually, there is compensatory hypertrophy of the normal kidney. A DMSA scan helps in ruling out scarring due to associated vesicoureteric reflux or an ectopic kidney. Children with single kidney should avoid contact sports. While affected patients are expected to maintain glomerular function, they require annual monitoring for hypertension and proteinuria.

Fetuses with bilateral renal agenesis or hypoplasia rarely survive to term. Lack of fetal urine production leads to oligohydramnios and limb anomalies. Neonates show low set ears, flat nose, prominent epicanthic folds and small chin (Potter facies). Pulmonary hypoplasia is the usual cause of death.

Renal Dysplasia

Renal dysplasia implies abnormal development of renal parenchyma. Primitive ducts surrounded by connective tissue, metaplastic cartilage, poorly differentiated glomeruli and dilated tubules are present. Bilateral total renal dysplasia is fatal in the neonatal period.

Multicystic dysplastic kidney: A multicystic dysplastic kidney (MCDK) is an enlarged nonfunctioning kidney with cysts of varying sizes resulting from abnormal differentiation of the metanephros. Affecting 1 in 2400 to 4300 live births, it is the most common cystic renal malformation in children. Ultrasonography shows characteristic findings, including multiple thin-walled noncommunicating cysts of varying size, in an enlarged kidney without identifiable parenchyma or renal pelvis (Fig. 17.23).

Most patients with MCDK have a normal contralateral kidney showing compensatory hypertrophy. However, 20–40% cases may show associated abnormalities of the contralateral genitourinary tract, such as vesicoureteric reflux or pelviureteric junction obstruction. A DMSA scan confirms that the affected kidney is nonfunctional and rules out reflux-associated scarring of the contralateral kidney. Children with MCDK require regular monitoring by ultrasound to ensure compensatory hypertrophy of the normal kidney and progressive involution of the affected kidney, which is undetectable by 5–7 years of age in most cases. Progressive renal impairment is seen, only if other abnormalities are associated. The risk of malignant transformation (Wilms' tumor) and hypertension is negligible. Nephrectomy is not indicated except in presence of severe hypertension, suspected malignancy, or a large kidney that fails to involute.

Obstructive Uropathy

Obstructive anomalies of the urinary tract are an important cause of irreversible renal damage in childhood. The common lesions include pelviureteric junction obstruction, vesicoureteric junction obstruction and posterior urethral valves. Diagnosis is suspected on antenatal ultrasonography or following presentations with dribbling of urine, poor urinary stream, fever and/or urinary tract infections. Chronic obstruction results in dysfunction of distal tubules with impaired urinary concentration and acidification,



Fig. 17.23: Multicystic dysplastic kidney. Multiple, thin-walled and noncommunicating cysts involve the left kidney on postnatal ultrasound at one month age

leading to polyuria, polydipsia, failure to thrive, refractory rickets and systemic acidosis.

Pelviureteric junction (PUJ) obstruction: Stenosis of the PUJ may be unilateral or bilateral. Obstruction is more common in boys and in presence of ectopic, malrotated or horseshoe kidney. It may present as an asymptomatic flank mass, or with upper abdominal pain, UTI or hematuria. Ultrasonography shows a dilated renal pelvis without ureteric dilatation. Radionuclide (DTPA) renal scan shows impaired drainage of the affected kidney which does not improve despite administration of a diuretic. Where scintigraphy is not available, intravenous pyelography shows renal pelvis dilatation with an abrupt cut-off at the PUJ. Mild cases are followed up with ultrasound. Surgical treatment by pyeloplasty is indicated if the relative function of the affected kidney is impaired. Nephrectomy may be required for a kidney with extremely poor function that does not improve despite temporary nephrostomy, severe hypertension or recurrent urinary infections.

Posterior urethral valves: These are an important cause of distal urinary tract obstruction in boys. The usual presenting features are dribbling, abnormal urinary stream, palpable bladder and recurrent UTI. The presence of severe obstruction *in utero* may lead to renal dysplasia, with mild to moderate renal dysfunction at birth. Antenatal ultrasound shows bilateral hydronephrosis with or without a thick-walled bladder and oligohydramnios. The diagnosis is confirmed on MCU, which shows dilated posterior urethra and valves at its junction with the anterior urethra. The bladder is enlarged and may show diverticuli and trabeculations; secondary vesicoureteric reflux is common.

Endoscopic fulguration of the valves is performed as early as possible. Alternatively, temporary urinary diversion by vesicostomy or bilateral ureterostomies is necessary. Long-term follow-up is necessary since a significant proportion of patients show progressive kidney disease. Bladder dysfunction is common, with delayed continence or incontinence, poor bladder sensation and a poorly compliant low capacity bladder. If pharmacotherapy fails, patients may require clean intermittent catheterization and occasionally bladder augmentation.

Phimosis: Up to the age of 2 years, the prepuce cannot be fully retracted because of congenital adhesions with the glans. The diagnosis of phimosis should thus be made with caution in young children. Indications for therapy include recurrent balanoposthitis, forceful/difficult urination, paraphimosis or recurrent urinary tract infections.

Ureterocele: This is a congenital condition in which the terminal part of the ureter distends within the bladder to form a sac-like pouch. Symptoms include recurrent urinary infections, abdominal pain and urolithiasis. Ureteroceles

are commonly associated with duplex systems, particularly in girls. Endoscopic deroofing is the treatment of choice.

Miscellaneous

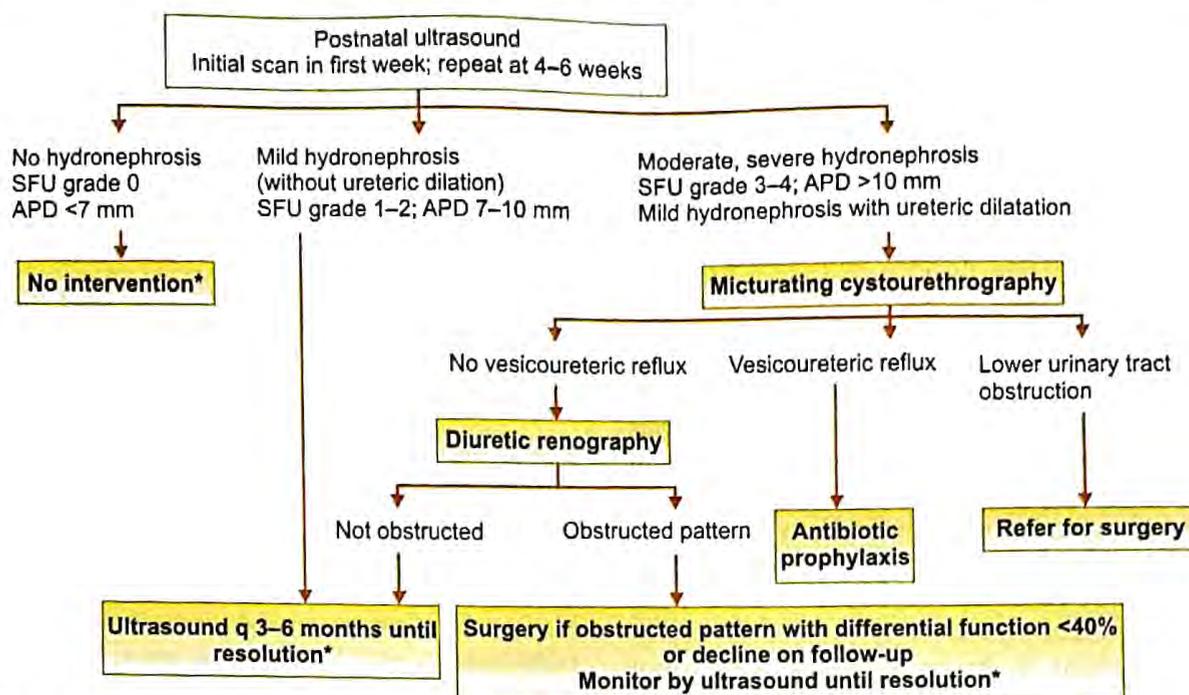
Renal ectopia, renal fusion: An ectopic kidney may lie in the pelvis or the iliac fossa. It may be structurally normal or hypoplastic. The patient may be asymptomatic, or have abdominal discomfort or dysuria. A horseshoe kidney results from fusion of identical poles of both kidneys. Patients with horseshoe kidney show vesicoureteric reflux in 30% cases.

Renal duplication: A duplex (duplicated) system is a kidney with two pyelocalyceal systems. In patients with partial or incomplete duplication, either a single or bifid ureter is present; in those with complete duplication, two ureters from the affected side empty separately into the bladder. Evaluation consists of imaging of the upper tract (ultrasonography, DTPA renal scan, intravenous pyelography) to evaluate for obstruction and lower tract (MCU) for vesicoureteric reflux.

ANTENATAL HYDRONEPHROSIS

Extensive use of antenatal ultrasonography has led to increasing detection of CAKUT. On antenatal ultrasound, hydronephrosis is identified in 4–5% pregnancies. However, the majority of cases of antenatal hydronephrosis resolve without sequelae, representing transient physiological obstruction or stasis. Patients require monitoring by ultrasound during the antenatal period for progressive worsening and association with oligohydramnios, which suggests severe lower urinary tract obstruction. A postnatal ultrasound is recommended during the first week of life and on day 1 in severe cases. Neonates with posterior urethral valves, solitary kidney or bilateral hydronephrosis and impaired renal function require prompt management. Neonates showing significant unilateral or bilateral dilatation should undergo a MCU at 4–6 weeks of life to detect vesicoureteric reflux; if reflux is ruled out, a diuretic renal dynamic (DTPA) scan may be required done to detect significant PUJ or VUJ obstruction and evaluate differential renal function. Most cases with mild to moderate hydronephrosis require only ultrasound monitoring and show spontaneous resolution by 2–5 years of age. Surgery is indicated in presence of obstructive drainage pattern associated with low differential function, and/or recurrent UTI. Infants with vesicoureteric reflux should receive continuous antibiotic prophylaxis.

Figure 17.24 shows a proposed algorithm for postnatal evaluation and management of antenatally detected hydronephrosis. Parents of infants with antenatal hydronephrosis should be counseled regarding increased risk of urinary tract infections and their prompt management.



*Parents of infants with hydronephrosis should be counseled regarding the risk of urinary tract infections

Fig. 17.24: Postnatal evaluation in patients with antenatal hydronephrosis. A postnatal ultrasound is recommended at 3–7 days except in suspected lower urinary tract obstruction, where it is done earlier. Postnatal hydronephrosis is classified using Society for Fetal Urology (SFU) grade or renal pelvic anteroposterior diameter (APD). Infants with normal findings should undergo a repeat study at 4–6 weeks. Patients with isolated mild hydronephrosis (unilateral or bilateral) should be followed with sequential ultrasounds, at 3 and 6 months, followed by 6–12 monthly until resolution; those with worsening hydronephrosis require closer evaluation. Patients with higher grades of hydronephrosis or dilated ureter(s) are screened for underlying obstruction or vesicoureteric reflux. Diuretic renography is useful in detecting pelviureteric junction or vesicoureteric junction obstruction and determining the need for surgery.

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CYSTIC KIDNEY DISEASES

Polycystic kidney disease and nephronophthisis are relatively common and glomerulocystic kidney disease is increasingly diagnosed. Better delineation using high resolution ultrasonography or MRI and identification of genetic loci have enabled accurate diagnosis and management for these conditions.

Polycystic Kidneys

Polycystic kidneys are inherited in either the autosomal dominant or autosomal recessive form, with distinctive features. Autosomal recessive polycystic kidney disease (ARPKD), caused by mutations in *PKHD1* gene encoding fibrocystin or polyductin, is characterized by fusiform

dilation of collecting tubules which are arranged radially from the cortex to medulla. Affected children often present in the neonatal period with oliguria, respiratory insufficiency and palpable kidneys. ARPKD is sometimes diagnosed in young children presenting with hypertension, renal insufficiency and enlarged kidneys, or with portal hypertension due to associated congenital hepatic fibrosis. Ultrasonography shows enlarged 'bright' kidneys, usually without visible cysts (Fig. 17.25a). Contrast-enhanced computerized tomography (CT) reveals a characteristic striate pattern of contrast excretion on delayed films.

The autosomal dominant form (ADPKD) is caused by mutations in the *ADPKD1* (chromosome 16) or *ADPKD2* (chromosome 4) genes encoding polycystins 1 and 2, respectively, membrane proteins that regulate tubular and vascular development in various tissues. The condition usually presents beyond the third decade of life with episodic hematuria, hypertension, palpable kidneys and gradual decline in renal function, but may be detected in childhood. Ultrasonography shows multiple cysts in each kidney (Fig. 17.25b). Associated findings include cysts in the liver, spleen and pancreas, mitral valve prolapse and berry aneurysms of the cerebral arteries. Ultrasonography often reveals cysts in the kidneys in one affected parent unless they are younger than 30 years, in which case

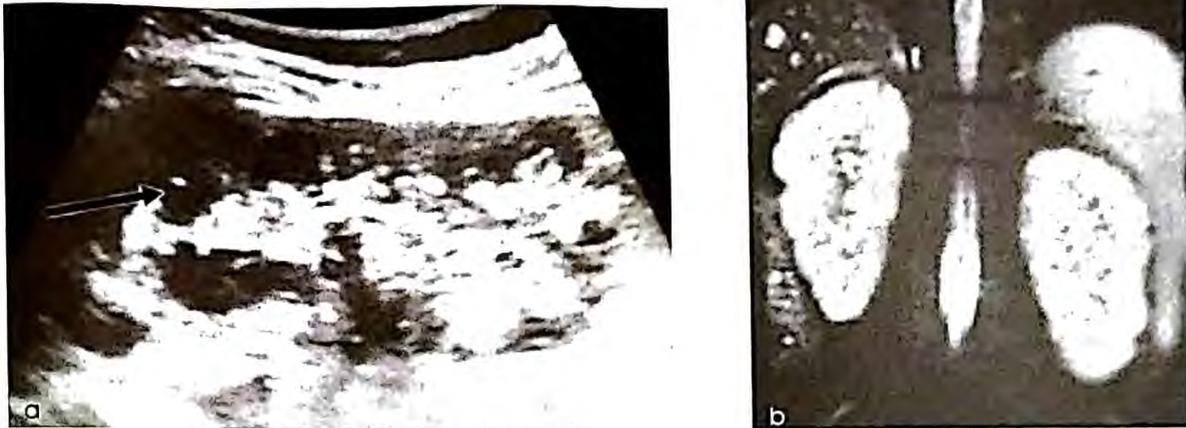


Fig. 17.25: Findings on ultrasonography in polycystic kidney disease. (a) Note bulky enlarged kidney with increased echogenicity, loss of corticomedullary differentiation and occasional visible cyst (arrow) in a child with autosomal recessive polycystic kidney disease; (b) Renal architecture is disorganized by multiple irregular cysts of varying sizes in autosomal dominant polycystic kidney disease; also note the foci of calcification

grandparents should be screened; rare cases are due to *de novo* mutations. Therapy with angiotensin-converting enzyme inhibitors helps control hypertension and limits hyperfiltration and proteinuria. The role of inhibitors of the mTOR pathway (sirolimus and everolimus) and V2 receptor antagonists (tolvaptan) is being explored.

Glomerulocystic Kidney Disease

The predominant finding in glomerulocystic kidney disease (GCKD) is cysts involving glomeruli, diagnosed most definitely on renal biopsy. Ultrasonography shows small subcortical cysts with increased kidney echogenicity and loss of cortical medullary differentiation. The condition may occur sporadically, with autosomal dominant inheritance, as a part of known syndromes (tuberous sclerosis, trisomy 13) or in association with other renal diseases such as dysplasia, ADPKD or ARPKD. Mutations in the hepatocyte nuclear factor β gene lead to the renal cysts and diabetes syndrome, characterized by GCKD, maturity onset diabetes and genitourinary abnormalities.

Nephronophthisis–Medullary Cystic Disease Complex

This group includes recessively inherited cystic disorders caused by mutations in genes, named *NPHP 1–9*, encoding

cytosolic proteins called nephrocystins. Patients with nephronophthisis present during the first decade of life with polydipsia, polyuria or enuresis, growth retardation and renal insufficiency, acidosis and anemia. Extrarenal features may include retinitis pigmentosa; ocular motor apraxia, hypotonia and cerebellar or midbrain abnormalities (Joubert syndrome); skeletal chondrodysplasia (Jeune syndrome); and hepatic fibrosis with pancreatic dysplasia.

The diagnosis of nephronophthisis is supported by the ultrasound or CT finding of small kidneys with corticomedullary cysts and poor corticomedullary differentiation. Renal histology shows cysts involving the collecting ducts, tubular dilatation with atrophy and interstitial fibrosis. While medullary cystic kidney disease is histologically indistinguishable from nephronophthisis, the disease is inherited in an autosomal dominant manner, and presentation is delayed to adulthood.

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Endocrine and Metabolic Disorders

PSN Menon • Anurag Bajpai

GENERAL PRINCIPLES

Endocrine glands play a crucial role in the maintenance of body physiology and homeostasis. The hypothalamic-pituitary axis regulates most endocrine organs including thyroid, adrenals and gonads, and processes like growth, puberty, and regulation of salt and water homeostasis.

Structure and Mechanism of Action

Hormones are chemicals secreted by endocrine glands into bloodstream that act at sites distant from the site of their origin. Hormones are derived either from amino acids (e.g. peptide hormones, glycoproteins, thyroxine and epinephrine) or cholesterol (e.g. steroid hormones, vitamin D, adrenal and gonadal steroids). The peptide hormones (e.g. parathyroid hormone, growth hormone and insulin) do not bind to circulating binding proteins resulting in their rapid elimination with a short half-life. These hormones are destroyed in the stomach often by gastric acid and hence cannot be administered orally. They do not cross the plasma membrane, but act on membrane receptors. The steroid hormones, on the other hand, bind to circulating proteins and have a longer half-life. They traverse cell membranes and act on intracellular receptors. They are readily absorbed after oral intake. Hormone receptors may be extracellular (e.g. peptide hormones) or intracellular (e.g. steroid and thyroid hormones). Binding of hormones to the extracellular receptors activates a catalytic process resulting in the production of second messengers that induce structural changes in intracellular proteins, culminating in the hormone effect (Fig. 18.1). Steroids and thyroxine act on intracellular receptors (Fig. 18.2). The resulting hormone-receptor complex binds to the hormone response elements in the target gene, resulting in regulation of transcription. The effect of these hormones is hence slower than those acting through extracellular receptors.

Regulation and Metabolism

Hormone secretion is regulated by a feedback system that includes regulatory hormones, hormone levels and

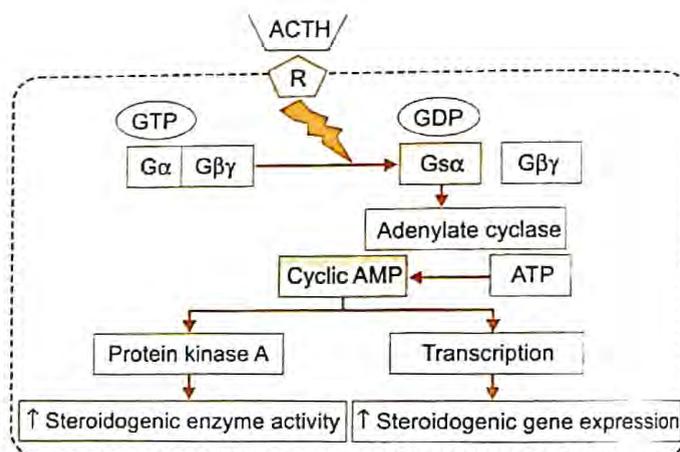


Fig. 18.1: Mechanism of action of extracellular G-protein coupled adrenocorticotrophic hormone (ACTH) receptor. Note that ACTH has a small extracellular receptor (R). Activation of the ACTH receptor stimulates G-protein, G α subunit by hydrolyzing guanosine triphosphate (GTP) to guanosine diphosphate (GDP), resulting in increased intracellular cyclic AMP that stimulates steroidogenesis by activating cyclic AMP-dependent kinases. AMP adenosine monophosphate, ATP adenosine triphosphate

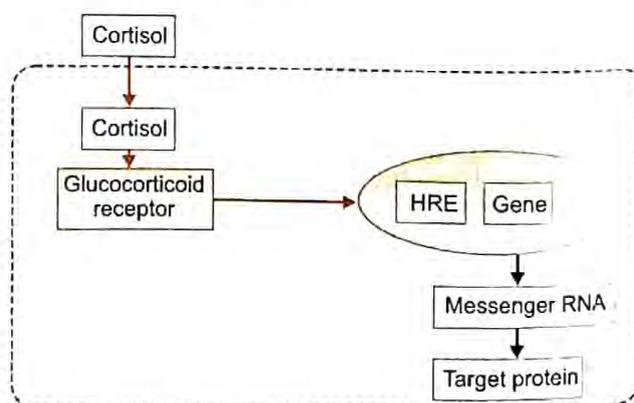


Fig. 18.2: Mechanism of action of intracellular cortisol receptor. HRE hormone response element

hormone effects. The feedback operates at the level of the endocrine gland as well as the hypothalamic-pituitary axis. Plasma enzymes rapidly inactivate the peptide

hormones, shortening their duration of action. Steroid hormones are slowly metabolized by the liver and excreted in the urine. Urinary analysis for steroid hormones thus provides an indirect outline about their synthesis and metabolism. Activation of hormones (e.g. androgen to estrogen, testosterone to dihydrotestosterone and calcitriol to calcitriol) is vital for the action of some hormones. Inactivation of hormones at the site of action prevents their excess effects (e.g. inactivation of cortisol by 11 β -hydroxysteroid dehydrogenase prevents its action on mineralocorticoid receptor). Peripheral conversion also plays an important role in hormone function (e.g. conversion of thyroxine to triiodothyronine).

Assessment of Hormone Action

Endocrine assessment relies on the estimation of basal hormone levels (e.g. thyroid disorders), their metabolites (e.g. urinary metabolites in adrenal disorders), hormone effects (e.g. insulin-like growth factor-1 levels in growth hormone deficiency and urinary osmolality for diabetes insipidus), stimulation tests in deficiency states (e.g. growth hormone deficiency and adrenal insufficiency) and suppression tests in excess states (e.g. growth hormone excess and Cushing syndrome). Pulsatile secretion of hormones makes the assessment of many hormones by a single blood test arduous. Pooled samples (three blood samples drawn at 0, 15 and 30 minutes) are mandatory for hormones such as gonadotropins, prolactin and cortisol.

The feedback mechanism also guides the assessment of endocrine disorders. As discussed earlier, in primary organ failure, pituitary hormones are elevated through a feedback regulation loop (e.g. thyroid-stimulating hormone in primary hypothyroidism, luteinizing hormone and follicle-stimulating hormone with gonadal failure and adrenocorticotropic hormone with adrenal failure, whereas low pituitary hormone levels suggest probable hypothalamic or pituitary dysfunction). The feedback mechanism also provides the basis for dynamic endocrine tests for diagnosis of hormone excess states (e.g. dexamethasone suppression test for Cushing syndrome and glucose suppression test for growth hormone excess).

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DISORDERS OF PITUITARY GLAND

Physiology

The anterior and posterior parts of pituitary gland are distinct both in embryology and function. The anterior pituitary develops from the Rathke's pouch. Posterior pituitary originates from the infundibulum, which is a downgrowth from the floor of the diencephalon. The principal hormones produced by the anterior pituitary are thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), growth hormone (GH) and prolactin (PRL). These hormones regulate the actions of target organs—adrenals by ACTH, thyroid by TSH and gonads by LH and FSH. The secretion of anterior pituitary hormones is regulated by hypothalamic peptides: Growth hormone releasing hormone (GHRH), somatostatin, dopamine, gonadotropin-releasing hormone (GnRH), corticotropin-releasing hormone (CRH) and thyrotropin-releasing hormone (TRH), and also by hormones produced by the target glands. Posterior pituitary hormones (arginine vasopressin or AVP and oxytocin) are secreted by neurons in the hypothalamic nuclei. AVP (antidiuretic hormone, ADH) is the key regulator of body water and osmolality.

Growth Hormone Deficiency

Growth hormone deficiency (GHD) may be caused by congenital malformations of central nervous system (CNS), genetic defects or acquired neurological insults (Table 18.1). Children with GHD have normal growth at birth. Growth retardation becomes apparent by the age of one year. Crowding of midfacial structures with a round

Table 18.1: Etiology of growth hormone deficiency

Congenital

Genetic defects

Isolated GH deficiency

Type I: Autosomal recessive

Type II: Autosomal dominant

Type III: X-linked recessive

Multiple pituitary deficiencies

Type I: Autosomal recessive

Type II: X-linked

Idiopathic GH releasing hormone deficiency

Developmental defects: Pituitary aplasia or hypoplasia, anencephaly, holoprosencephaly, midfacial anomalies, septo-optic dysplasia

Acquired

Tumors: Hypothalamic, pituitary or other intracranial tumors
Irradiation

Infections: Encephalitis, meningitis, tuberculosis, toxoplasmosis

Infiltration: Histiocytosis, hemochromatosis, sarcoidosis

Injury: Perinatal insult (breech), head injury, surgery

Vascular: Aneurysm, infarction



Fig. 18.3: A 6-year-old girl with short stature due to growth hormone deficiency. Note the immature facies, midfacial hypoplasia and cherubic appearance

facies, depressed nasal bridge, single central incisor tooth, micropenis, undescended testis and mild obesity are common clinical features (Fig. 18.3). Body proportions are normal. The development of teeth is delayed. The facial appearance is 'doll-like' and these children look much younger than their actual age. Bone age is delayed. Newborns may present with severe hypoglycemic seizures due to concomitant ACTH deficiency. Associated gonadotropin deficiency causes delay in sexual development and small genitalia.

Resistance to GH action (GH insensitivity or Laron syndrome) presents with almost similar features with severe growth retardation and elevated baseline GH levels.

Approach to Diagnosis of Short Stature and GHD

Growth failure may occur as part of any long-standing systemic illness. Chronic systemic disorders and nutritional deficiencies (including malabsorption) have predominant effect on weight and height is less affected initially. Thus weight age is substantially lower than height age. On the contrary, endocrine causes like GHD, hypothyroidism and pseudohypoparathyroidism mainly affect height resulting in disproportionately low height age (see Chapter 2).

Evaluation

History: Perinatal history, birth weight and length should be recorded. History of birth asphyxia, breech presentation, neonatal hypoglycemia, micropenis and prolonged jaundice should alert the pediatrician for the possibility of GHD. Features of chronic infections, cardiopulmonary disorders, malabsorption and raised intracranial tension

should be looked for in all short children. Presence of polyuria and polydipsia suggests diabetes insipidus, diabetes mellitus and/or renal tubular acidosis. Constipation, delayed milestones, lethargy and cold intolerance indicate hypothyroidism. Family history of short stature and/or delayed puberty suggests the possibility of familial short stature or constitutional delay of growth and puberty.

Examination: Anthropometric assessment (weight, height, weight for height and head circumference) provides crucial inputs for the diagnosis. Body proportions help in identifying skeletal dysplasia. Increased upper to lower segment (US: LS) ratio is observed in hypothyroidism, achondroplasia (Fig. 18.4) or Turner syndrome while reduced US: LS ratio is seen in disorders such as Morquio syndrome and spondyloepiphyseal dysplasia. Body proportions are normal in GHD.

The clinician should also look for specific clinical features of an underlying etiology such as GHD, hypothyroidism, Turner syndrome and rickets (Table 18.2). Evaluation for dysmorphism, skeletal deformities and pubertal staging (sexual maturity rating) is essential for diagnosis.

Investigations: Laboratory evaluation of short stature is best done by a stepwise application of diagnostic tests to determine the etiology (Fig. 18.5).

Step 1: The first step in investigation is to rule out common treatable causes. This involves exclusion of malnutrition, chronic systemic illnesses and recurrent infections by appropriate tests such as complete blood counts, erythrocyte sedimentation rate, chest X-ray, serum



Fig. 18.4: Achondroplasia: Note the abnormal body proportions and the characteristic facies.

Table 18.2: Pointers to the etiology of short stature

Pointer	Etiology
Midline defects, micropenis	Growth hormone deficiency
Rickets	Renal failure, malabsorption, renal tubular acidosis
Pallor	Renal failure, malabsorption, nutritional anemia
Malnutrition	Protein energy malnutrition, malabsorption, celiac disease, cystic fibrosis
Obesity	Hypothyroidism, Cushing syndrome, Prader-Willi syndrome, pseudohypoparathyroidism
Metacarpal shortening	Turner syndrome, pseudohypoparathyroidism
Cardiac murmur	Turner syndrome, congenital heart disease
Mental retardation	Hypothyroidism, Down syndrome, Turner syndrome, pseudohypoparathyroidism

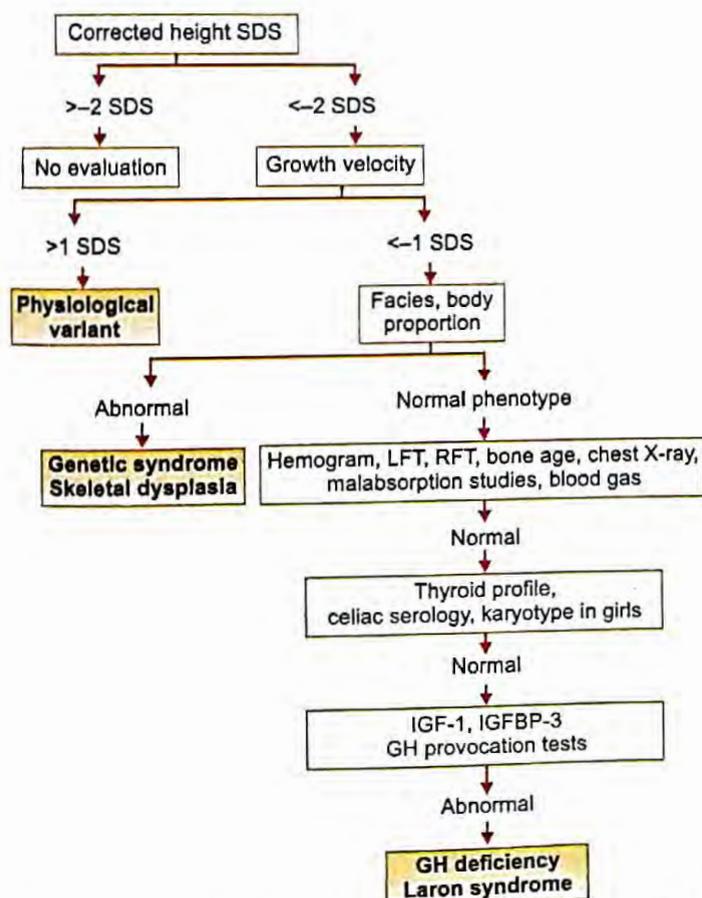


Fig. 18.5: Approach to a child with short stature. GH growth hormone; IGF-1 insulin-like growth factor-1; IGFBP-3 IGF binding protein-3; LFT liver function tests; RFT renal function tests; SDS standard deviation score

electrolytes, liver and renal function tests and venous blood gases (renal tubular acidosis). Estimation of skeletal maturation (bone age) forms an important aspect of evaluation of short stature.

Step 2: The next step in evaluation involves evaluation for hypothyroidism (free T4 and TSH), celiac disease (tissue transglutaminase antibody) and Turner syndrome (karyotype in all girls).

Step 3: Evaluation for GH-IGF (insulin-like growth factor) axis is performed after common causes of growth retardation are excluded. This is important as systemic illness and hypothyroidism influence the GH-IGF axis. Random or fasting blood GH level measurements do not confirm the diagnosis of GHD, as GH hormone secretion is pulsatile. The diagnosis of GHD requires pharmacologic stimulation tests. GHD is suspected when the peak level of GH is less than 10 ng/mL following stimulation. The common provocative agents used are insulin, glucagon, clonidine or GHRH. Levels of IGF-1 and IGF binding protein-3 (IGFBP-3) are helpful to diagnose GHD and Laron syndrome. GHD may be associated with other pituitary hormone deficiencies and appropriate investigations should be carried out to detect deficiency of these hormones, if GHD is present. CT or MRI scans of hypothalamic and pituitary regions are essential to rule out developmental or acquired neurological lesions.

Management

General measures: Management of short stature involves correction of the underlying cause and provision of adequate nutrition intake. Patients should be advised diet rich in protein and calorie content. They should be encouraged to increase their physical activity. Iron and vitamin deficiencies should be corrected, if present. Zinc supplementation (10 mg/day for 3–6 months) may help in improving growth in patients with idiopathic short stature.

Specific therapy: Initiation of specific treatment is effective in restoring growth in hypothyroidism (thyroxine), celiac disease (gluten-free diet) and renal tubular acidosis (bicarbonate supplements). A short course of testosterone helps boys with constitutional delay of growth and puberty. Treatment of genetic syndromes and skeletal dysplasias is extremely difficult. Some of them do respond to GH therapy. Surgical techniques for bone lengthening (e.g. Ilizarov procedure) have been used with variable success in selected forms of skeletal dysplasia.

Growth hormone: GH is highly effective patients with GHD. GH therapy may result in increase in final height by 20–30 cm from pretreatment levels. The treatment is given as daily night-time injections (25–50 µg/kg/day) till epiphyses close. GH therapy is monitored by assessment of physical growth and bone age measurements. Lab parameters are often not helpful to monitor GH therapy, even though IGF-1 levels have been tried. The treatment is expensive and all efforts should be made to

Table 18.3: Indications for growth hormone therapy

Growth hormone deficiency in children and adults
Turner syndrome
Chronic renal insufficiency
Prader-Willi syndrome
Small for gestational age who fail to catch-up in growth by 2–3 years of age
<i>SHOX</i> gene mutations and Leri-Weill dyschondrosteosis
Noonan syndrome
Idiopathic short stature

ensure that treatment is given regularly for at least 2 years. The role of GH is expanding with increasing use in other disorders with short stature such as Turner syndrome, chronic renal failure, small for gestational age infants who fail to catch-up, Russell-Silver syndrome, Prader-Willi syndrome and idiopathic short stature (Table 18.3).

Growth Hormone Excess

Excess of GH during childhood may result in somatic overgrowth or gigantism. Increased GH secretion after the fusion of skeletal epiphyses causes features of acromegaly. Coarse features with prominent jaw, broad nose, large tongue, bushy eyebrows, thick skin and dorsal kyphosis are characteristic. Headache and visual field defects (bitemporal hemianopia and enlargement of the blind spot) are common.

Diagnosis: The diagnosis is based on clinical examination, serial photographs of the child, growth assessment and investigations. X-rays may show tufting of the phalanges and increased heel pad thickness. MRI of brain helps to confirm and determine the extent of the tumor. IGF-1 is the best screening test for GH excess. Non-suppressible GH levels confirm the diagnosis after a glucose challenge.

Pituitary gigantism is rare in children. It may be the only clue to an underlying pituitary adenoma, which may be associated with isolated or multiple endocrine abnormalities in the setting of multiple endocrine neoplasia or McCune-Albright syndrome.

Differential diagnosis: GH excess differs from Sotos syndrome (cerebral gigantism), which is characterized by large size at birth, excessive growth in early childhood, and advanced height, weight and bone ages. The skull is large with prominent forehead and jaw, high-arched palate, hypertelorism and antimongoloid slant of the palpebral fissure. Tall stature due to hereditary tall stature, obesity, precocious puberty, Marfan syndrome and homocystinuria should be ruled out by appropriate tests.

Management: Medical management involves the use of long-acting somatostatin analogs such as octreotide. The GH receptor antagonist, pegvisomant is also useful in treatment. Partial or complete resection of pituitary adenoma is indicated, if there is evidence of raised intracranial tension.

Diabetes Insipidus

Polyuria (urine output >5 mL/kg/hr or 2 L/m²/day) is an important pediatric problem and may be the only manifestation of a serious disease such as diabetes insipidus, diabetes mellitus, brain tumor and renal tubular acidosis. Polyuria may result from increased solute load or impaired renal concentrating capacity (Table 18.4).

Diabetes insipidus (DI) is an important cause of polyuria. DI presents with low urine osmolality (<600 mOsm/kg) in association with high plasma osmolality (>300 mOsm/kg or serum sodium >146 mEq/L). DI may be due to decreased production of vasopressin (central DI) or its action (nephrogenic DI). Dehydration is unusual unless there is an abnormality of thirst mechanism. However, infants are at a high risk of developing hypernatremic dehydration.

Central DI: This is commonly associated with an intracranial pathology (Table 18.4). Craniopharyngioma may present with DI, growth retardation and skull calcification. Germinoma located in the pituitary stalk may be missed on routine brain scans, emphasizing the need to repeat neuroimaging, if no cause is found. Malformations of the CNS such as septo-optic dysplasia and holoprosencephaly display central DI and deficiency of anterior pituitary hormones. Histiocytosis is the

Table 18.4: Causes of polyuria

Increased fluid load

- Iatrogenic
- Compulsive water drinking

Increased solute load

- Osmotic diuresis:* Diabetes mellitus, mannitol treatment
- Salt loss:* Adrenal insufficiency, diuretics, cerebral salt wasting, aldosterone resistance

Impaired urinary concentration

Inefficient ADH action (diabetes insipidus, DI)

Central DI (neurogenic DI)

- Genetic defects
- Malformations: Septo-optic dysplasia, holoprosencephaly, anencephaly
- CNS insults: Head trauma, neurosurgery, infection, brain death
- Infiltrative disorders: Sarcoidosis, histiocytosis
- Space occupying lesions: Craniopharyngioma, germinoma

Nephrogenic DI

- Genetic: X-linked (V2 receptor), AR and AD (aquaporin defect)
- Acquired: Hypokalemia, hypercalcemia, obstructive uropathy, nephrocalcinosis

Tubulopathy

- Renal tubular acidosis
- Bartter syndrome
- Gitelman syndrome

AD: Autosomal dominant; ADH: Antidiuretic hormone; AR: Autosomal recessive

commonest infiltrative disorder associated with central DI. Neurological infections including tuberculosis may manifest with central DI later.

Nephrogenic DI: This results from inherited or acquired resistance to vasopressin. Congenital nephrogenic DI due to mutation in vasopressin receptor (V2) presents in infancy with failure to thrive, recurrent fever and dehydration. Polyuria is often absent in this setting. Hypokalemia and hypercalcemia are important causes of nephrogenic DI.

Water Balance and Differential Diagnosis of Polyuria

Maintenance of water balance involves regulation of urine output and thirst. Thirst is controlled by hypothalamus. Urine output is determined by solute load, hydration status and urine concentration capacity. Fluid homeostasis involves close interaction of arginine vasopressin (AVP), renin-angiotensin-aldosterone system and atrial natriuretic peptide (ANP). Vasopressin is secreted by hypothalamus in response to osmotic signals and acts on the V2 receptors in collecting duct to increase free water resorption. The renin-angiotensin-aldosterone system is central to the regulation of sodium, fluid and blood pressure.

Diabetes mellitus: Diabetes mellitus presents with polydipsia, polyphagia, recurrent infections and weight loss in addition to polyuria.

Renal disorders: Polyuria is common in obstructive uropathy. It is often the presenting feature of tubular disorders such as renal tubular acidosis (RTA), Bartter syndrome and Gitelman syndrome. These conditions are associated with severe failure to thrive and rickets.

Inefficient aldosterone action: These include adrenal insufficiency, isolated aldosterone deficiency or aldosterone resistance. They present with hyponatremia, hyperkalemia and dehydration. The condition may be lethal. Failure to thrive is common. Pigmentation is characteristic of adrenal insufficiency. Polyuria and salt wasting in the neonatal period should prompt evaluation for congenital adrenal hyperplasia (CAH). Genital ambiguity in girls is a clue to the diagnosis of CAH.

Excessive water drinking (psychogenic polydipsia): The condition is rare and a diagnosis of exclusion.

Evaluation

Subjective estimates of urine output and nocturia may suggest polyuria; however, these cannot substitute for measurement of 24-hour urine output and fluid intake. Urine output in excess of 2 L/m²/day or 5 mL/kg/hr confirms polyuria (Fig. 18.6).

Clinical: Diabetes mellitus is suggested by polyphagia, recurrent infections and failure to thrive. Renal tubular acidosis should be suspected when acidotic breathing,

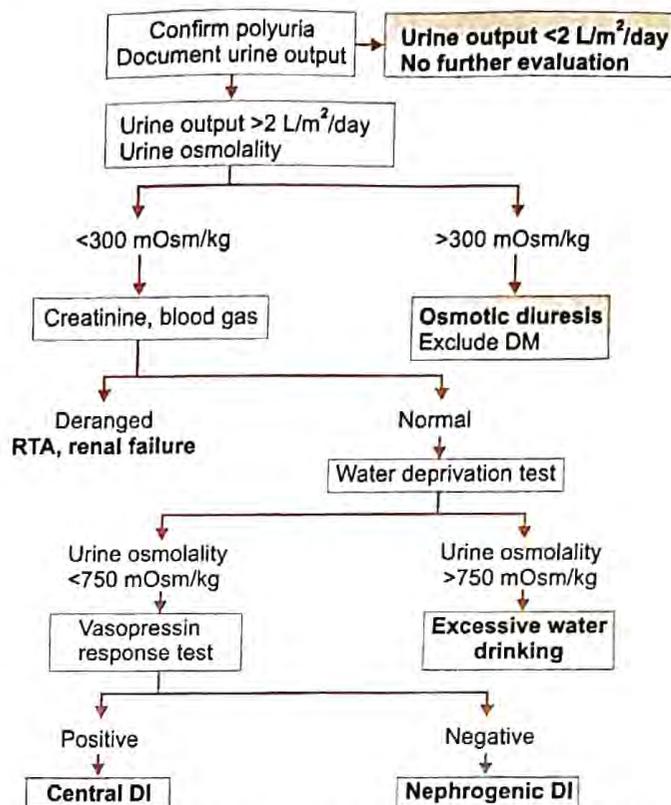


Fig. 18.6: Approach to a child with polyuria. DI diabetes insipidus; DM diabetes mellitus; RTA renal tubular acidosis

bony deformities or muscle weakness are present. Neurological and fundus examination should be performed. Careful search for features of histiocytosis (e.g. ear discharge, proptosis, rash, organomegaly, lymphadenopathy, bony defects and seborrheic dermatitis) is essential (Table 18.5).

Investigations: Initial investigations should include testing for urine sugar and early morning specific gravity or osmolality. Blood gases, urea, electrolytes, calcium and creatinine should be estimated. High plasma osmolality (>300 mOsm/kg or sodium >146 mEq/L) with low urine osmolality (<300 mOsm/kg and urine specific gravity <1.005) suggest the diagnosis of DI, which needs further classification on the basis of response to AVP. Patients with normal plasma osmolality and low urine osmolality

Table 18.5: Pointers to diagnosis of polyuria

Feature	Diagnosis
Cleft lip, cleft palate	Hypopituitarism
Metabolic bone disease	Renal tubular acidosis (RTA), renal failure
Growth failure	Nephrogenic diabetes insipidus, RTA, congenital adrenal hyperplasia, Bartter syndrome
Rash, ear discharge	Histiocytosis
Pigmentation	Adrenal insufficiency
Genital ambiguity	Congenital adrenal hyperplasia

(<300 mOsm/kg) should undergo water deprivation test. Urinary osmolality >300 mOsm/kg (specific gravity >1.010) excludes the possibility of complete DI.

MRI of the hypothalamic-pituitary region and anterior pituitary hormone evaluation should be done in central DI. Evaluation of nephrogenic DI includes renal imaging and serum electrolytes.

Water deprivation test: This test is indicated in children with polyuria with low urinary osmolality and normal plasma osmolality. The aim is to increase plasma osmolality above 300 mOsm/kg (or serum sodium above 146 mEq/L) to allow the opportunity for maximal renal concentration. Renal failure and RTA should be excluded before the test. Water deprivation test is not required in the presence of hyponatremia. It should be done on an inpatient basis due to the risk for dehydration.

Water deprivation is started early in the morning. The child is weighed and target weight loss calculated (5% of total body weight). Body weight, urine output and urine and blood osmolality are monitored hourly. The test is stopped when urine osmolality increases above 750 mOsm/kg or specific gravity is more than 1.010 excluding DI. The test is also discontinued when serum sodium is above 146 mEq/L (target achieved) or weight loss is more than 5% (risk of dehydration). Urine osmolality below 300 mOsm/kg in the presence of plasma osmolality above 300 mOsm/kg confirms DI and needs evaluation by a formal vasopressin test. Partial forms of DI may have urine osmolality between 300 and 750 mOsm/kg and also require to be evaluated.

Vasopressin response test: This test is performed to differentiate central DI from nephrogenic DI. Urine osmolality is measured one and four hours after vasopressin injection (0.1 unit/kg). An increase in urine osmolality by more than 50% of baseline level is diagnostic of central DI while a smaller increase suggests nephrogenic DI.

Management

Management of polyuria is guided by the underlying cause. Treatment of underlying diabetes mellitus (insulin), adrenal insufficiency (hydrocortisone) and renal tubular acidosis (bicarbonate supplementation) is effective in reducing urine output. Behavioral therapy is recommended for psychological polydipsia.

Central DI: Central DI is managed with vasopressin analogs. Desmopressin (DDAVP), a vasopressin analog has high potency and prolonged duration of action. It can be given by intranasal (2.5–10 µg 12 hourly), or sublingual or oral (50–200 µg 12 hourly) route. Patients with idiopathic DI should be followed for evolving brain tumors.

Nephrogenic DI: Hydrochlorothiazide and amiloride combination (1–2 mg/kg/day of thiazide) reduces urine output by 40%. Addition of indomethacin to this regimen

reduces urine output by 50–70%. This should be combined with salt restriction and reduction in solute load.

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DISORDERS OF THYROID GLAND

Physiology

Biosynthesis of thyroid hormones involves interaction of iodine, tyrosine, thyroglobulin and the enzyme, thyroid peroxidase. Thyroid peroxidase is the rate-limiting enzyme in thyroid hormone synthesis. This process is regulated by TSH (Fig. 18.7). TSH secretion is, in turn, under the direct control of the thyrotropin-releasing hormone (TRH) released from the hypothalamus and feedback control of thyroxine. Thyroid hormones bind to intracellular receptors and activate transcription factors. Most triiodothyronine (T_3) in the circulation is produced by peripheral conversion of thyroxine (T_4) by the enzyme monodeiodinase. This process is stimulated in thyroid hormone-depleted states as a protective mechanism to produce more T_3 . Thus T_3 levels are the last to fall in hypothyroidism, and are not a reliable indicator of the disease.

Thyroid hormones play an active role in the regulation of somatic and intellectual growth, intermediary metabolism and thermoregulation. There is a critical phase in the early neonatal period for the effect of thyroid hormone on mental development. This underscores the need for early diagnosis and appropriate management of congenital hypothyroidism. TSH levels increase immediately after birth, resulting in increase in T_3 and T_4 levels, and reach their maximum by 24 hours. Their levels fall to normal in the next few weeks. TSH levels should

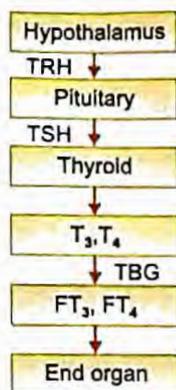


Fig. 18.7: Regulation of hypothalamic–pituitary–thyroid axis. FT₃ free triiodothyronine; FT₄ free thyroxine; T₃ triiodothyronine; T₄ thyroxine; TBG thyroxine binding globulin; TRH thyrotropin-releasing hormone; TSH thyroid-stimulating hormone

thus be estimated after 48 hours after birth as a part of neonatal screening for congenital hypothyroidism.

Assessment of Thyroid Function

Thyroid function is assessed by serum TSH and free and/or total T₄ and T₃. TSH is the most sensitive indicator of primary (thyroidal) hypothyroidism, but is not as helpful in the diagnosis of central (pituitary or hypothalamic) hypothyroidism. Serum T₄ level is a better indicator of thyroid status than serum T₃ due to increased conversion of T₄ to T₃ during thyroid-depleted states. Considering the variability in the levels of circulating thyroxine-binding globulin (TBG), estimation of free thyroid hormones is superior to total hormone levels in the diagnosis of hypothyroidism. Low free T₄ (FT₄) and low TSH levels suggest central hypothyroidism, while low FT₄ levels with high TSH levels indicate primary hypothyroidism. Persistent elevation of TSH in the presence of normal FT₄ suggests subclinical hypothyroidism. Elevated FT₄ and undetectable TSH levels imply a hyperthyroid state.

Hypothyroidism

Hypothyroidism is caused by defects in the hypothalamic–pituitary axis (central hypothyroidism), thyroid gland (primary hypothyroidism) or the peripheral sensitivity to thyroxine (Table 18.6).

Congenital Hypothyroidism

Congenital hypothyroidism is the most common preventable cause of mental retardation. Congenital hypothyroidism is more commonly reported in India (1 in 1000 newborns) compared to western countries (1 in 4000).

Etiology: With wider coverage of iodine supplementation program, the incidence of iodine deficiency has declined and thyroid dysgenesis has emerged as the most common cause of congenital hypothyroidism in India (75% of all cases). The disorder encompasses a spectrum ranging from

Table 18.6: Etiology of hypothyroidism

Primary (thyroid, >95%)

Autoimmune thyroiditis

Enzyme defects: Trapping, organification, thyroglobulin synthesis, deiodination

Iodine deficiency: Endemic goiter

Dysgenesis: Aplasia, dysplasia, ectopia

Thyroid injury: Surgery, radiation, infection

Goitrogens: Thiocyanates, thionamides, lithium, amiodarone

Transient causes: Maternal TSH receptor blocking antibody, iodine excess, maternal antithyroid drug

Secondary or tertiary (hypothalamus or pituitary, <5%)

Malformations: Septo-optic dysplasia, holoprosencephaly

Genetic defects

CNS insults: Trauma, surgery, radiation, infection

CNS tumors: Craniopharyngioma, germinoma

Peripheral (extremely rare)

Resistance to thyroxine

CNS: Central nervous system; TSH: Thyroid-stimulating hormone

complete agenesis, partial agenesis to ectopic thyroid. Increased incidence of thyroid dysgenesis is noted in Down syndrome. Biosynthetic defects include disorders affecting iodine transport, peroxidation, thyroglobulin synthesis and deiodination. Pendred syndrome, a disorder of the pendrin gene, is associated with decreased intracellular transport of iodine and deafness. Nongoitrous congenital hypothyroidism is known to be associated with genes *TSHR*, *PAX8* and *TSHB*. Transient congenital hypothyroidism may occur following transplacental passage of TSH receptor blocking antibodies, iodine exposure and treatment with antithyroid drugs (e.g. amiodarone).

Clinical features: Features of congenital hypothyroidism are nonspecific and often difficult to identify in the neonatal period. They become prominent with increasing age. However, the window period for neurological intervention would have elapsed in most children by that time. This underscores the need for neonatal screening for congenital hypothyroidism. Clinical manifestations include hoarse cry, facial puffiness, umbilical hernia, hypotonia, mottling of skin and lethargy (Fig. 18.8). Prolonged jaundice, constipation and unexplained hypothermia may also indicate hypothyroidism. Open posterior fontanel is an important indicator of congenital hypothyroidism (Table 18.7).

Evaluation: History of maternal thyroid disease or ingestion of antithyroid medications should be probed. Family history of hypothyroidism suggests dysmorphogenesis, while recurrent transient hypothyroidism indicates a disease related to maternal TSH receptor antibody. Residence in iodine deficient area may suggest the diagnosis of iodine deficiency. Presence of goiter



Fig. 18.8: Congenital hypothyroidism: Note the characteristic facial features

Table 18.7: Clinical features of hypothyroidism

Congenital	Acquired
Open posterior fontanel	Growth retardation
Umbilical hernia	Delayed skeletal maturation
Characteristic edematous facies	Delayed dental development
Constipation	Delayed puberty
Pallor	Myopathy and pseudohypertrophy
Hypothermia	Enlarged sella
Large tongue	Pseudotumor cerebri
Rough dry skin	
Hypotonia	
Large abdomen	

should prompt evaluation for transplacental passage of antithyroid drugs or disorders of thyroid hormone biosynthesis. Hypoglycemia, micropenis and midline facial defects suggest hypothalamic-pituitary causes.

Investigations: Initial investigations in a child with high TSH levels include evaluation of radionuclide uptake and ultrasound of thyroid to confirm the presence of thyroid gland. Thyroid dysgenesis is diagnosed, if no thyroid tissue is visualized on ultrasound. Radiotracer uptake study with radioactive iodine or technetium is done as soon as the diagnosis of primary congenital hypothyroidism is established (Fig. 18.9). Children with absent

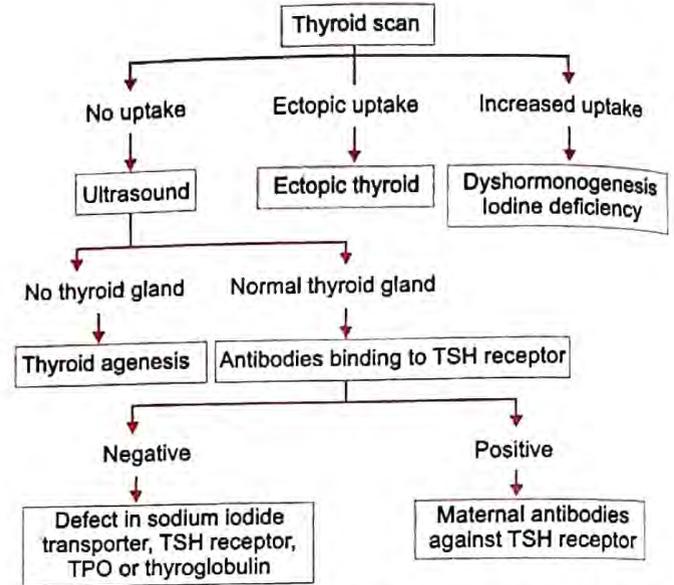


Fig. 18.9: Approach to diagnosis of congenital hypothyroidism. TPO thyroid peroxidase; TSH thyroid-stimulating hormone

radiotracer uptake but normal thyroid on ultrasound may have defects in iodine transport, TSH receptor abnormalities or transplacental passage of TSH blocking antibody. Increased radioactive tracer uptake suggests iodine deficiency or dyshormonogenesis (Table 18.8). Children with low TSH levels should be worked up for other pituitary defects.

Management: Thyroid replacement should be started straightaway after diagnosis. In central hypothyroidism, cortisol replacement should precede thyroid replacement as it could precipitate adrenal insufficiency. Thyroxine (T_4) is initiated at a dose of 10–15 $\mu\text{g}/\text{kg}/\text{day}$. T_4 and TSH levels are expected to normalize over one week and one month, respectively, with this treatment. FT_4 and TSH should be measured at each visit. Thyroxine dose should be adjusted to achieve FT_4 levels in the upper normal range for the age. TSH levels may remain high for up to two years in children with reset hypothalamic-pituitary axis. Lifelong thyroid replacement is required in most cases. In suspected transient congenital hypothyroidism, thyroid replacement should be stopped for one month at the age of 3 years. Treatment is not required, if follow-up thyroid functions are normal.

Table 18.8: Comparison of different forms of primary congenital hypothyroidism

Type	Goiter	Radioactive iodine uptake	Urine iodine	Thyroid on ultrasound	Diagnostic investigation
Dysgenesis/agenesis	No	No	Normal	Absent	Radionuclide scan
Ectopic	No	Ectopic	Normal	Absent	Radionuclide scan
Iodine deficiency	Yes	High	Low	Eutopic	Urine iodine
TSHRAb*	No	No	Normal	Eutopic	Antibody
Enzyme defects	Yes	Normal	Normal	Eutopic	Perchlorate discharge

*TSHRAb antibody to TSH receptor

Outcome: Early diagnosis and treatment following neonatal screening has resulted in normal intellectual outcomes. Outcome is, however, poor in children with congenital hypothyroidism who have been diagnosed beyond the neonatal period. Mental retardation and short stature are common sequels.

Screening: Difficulty in early identification of congenital hypothyroidism and the disastrous consequences of delayed diagnosis have led to neonatal screening for hypothyroidism. Screening programs use dried blood sample collected at postnatal age of 2 to 4 days. The most commonly used strategy screens first for TSH. Care should be taken to use appropriate cutoff for TSH levels as per age. Higher levels of TSH are used initially as cutoff for treatment (more than 40 mU/L). TSH-based screening has higher sensitivity compared to T_4 -based approach. However, TSH-based approach does not identify central hypothyroidism. T_4 first approach can identify these children, but has the disadvantage of missing cases with compensated hypothyroidism.

Acquired Hypothyroidism

Etiology: Autoimmune thyroiditis is the most common cause of acquired hypothyroidism. This is more common in girls. Goiter is often nodular and firm unlike the soft and uniform goiter seen in dysmorphogenesis. Anti-thyroid peroxidase (anti-TPO) antibodies are usually present. Autoimmune thyroiditis may be associated with other autoimmune endocrinopathies such as adrenal insufficiency, type 1 diabetes mellitus and hypoparathyroidism. Rarely, congenital abnormalities, e.g. thyroid dysgenesis or an inborn error of thyroid hormone synthesis may become evident in older children and adolescents. Iodine deficiency and goitrogens are other causes of primary hypothyroidism in older children. Secondary hypothyroidism due to combined hypothalamic-pituitary defects could be a manifestation of neurological insults or tumors.

Clinical features: Features of acquired hypothyroidism are subtle compared to congenital hypothyroidism. Often short stature may be the only manifestation. Cold intolerance, lethargy, constipation, delay in dentition and poor school performance may suggest hypothyroidism. All children with unexplained developmental delay, mental subnormality and short stature should be evaluated for hypothyroidism. Most patients with hypothyroidism have delayed puberty; however, uncontrolled long-standing hypothyroidism may trigger precocious puberty in girls. Goiter is common in iodine deficiency, chronic lymphocytic thyroiditis and dysmorphogenesis. Hypothyroidism is associated with Down syndrome, Turner syndrome, celiac disease and type 1 diabetes. Children with these disorders should be periodically screened for hypothyroidism even in the absence of symptoms.

Evaluation: Severe short stature and intellectual disability suggest missed congenital hypothyroidism. A firm and non-nodular goiter implies iodine deficiency or disorder of thyroid hormone synthesis; firm nodular goiter indicates autoimmune thyroiditis. Family history of acquired hypothyroidism suggests autoimmune thyroiditis. Children with central hypothyroidism should be evaluated for other pituitary hormone deficiencies including MRI of the hypothalamic-pituitary region. Antibodies to thyroid peroxidase enzyme (anti-TPO) should be estimated in acquired primary hypothyroidism.

Management: Treatment of acquired hypothyroidism should be gradual. A dose of 100 $\mu\text{g}/\text{m}^2/\text{day}$ is recommended (Table 18.9). In long-standing cases, initial treatment should be started at 25–50% of these doses with gradual build up every 3–4 weeks. Thyroxine should be given in empty stomach in the morning. Follow-up should be done every three months during the first two years of therapy and six monthly thereafter. The doses should be modified to maintain TSH levels in the normal range. Most children require lifelong therapy.

Subclinical Hypothyroidism

Mild elevations of TSH (below 10 mU/L) with normal FT_4 levels are frequently observed in children especially with obesity. The clinical relevance of subclinical hypothyroidism is unclear. In most cases, these findings reverse over a period of three to six months and do not require treatment. Treatment should be considered in children with thyromegaly, presence of anti-TPO antibodies, or family history of hypothyroidism.

Goiter

Goiter refers to the enlargement of the thyroid gland. From a clinical standpoint, thyromegaly is diagnosed when the lateral lobe of the thyroid is larger than the terminal phalanx of the thumb of the child (Fig. 18.10).

Etiology Goiter may be associated with diminished, normal or increased thyroid function (Table 18.10). Thyroid enlargement may represent increase in size in response to compensatory TSH secretion (hypothyroidism), infiltration (autoimmune thyroiditis, neoplasms or hemochromatosis), or presence of TSH receptor stimulating antibodies (Graves disease). Important causes

Table 18.9: Recommended dose schedule of thyroxine

Age	Thyroxine dose, $\mu\text{g}/\text{kg}/\text{day}$
Neonatal period	10–15
1–6 months	6–10
1–5 years	4–6
5–12 years	3–5
12–18 years	2–3
>18 years	1–2



Fig. 18.10: Diffuse goiter in a child due to dysmorphogenesis

Table 18.10: Causes of goiter

Inflammatory: Acute suppurative thyroiditis, subacute thyroiditis

Infiltration: Autoimmune thyroiditis, neoplasm, hemochromatosis

Increased TSH levels: Dysmorphogenesis, iodine deficiency, unilateral agenesis

TSH stimulating antibody: Graves disease

Colloid goiter

of congenital goiter include maternal antithyroid medications, dysmorphogenesis and iodine deficiency. Autoimmune thyroiditis is the most common cause in older children, followed by iodine deficiency, dysmorphogenesis and Graves disease. Differential diagnosis includes diffuse nodular goiter, benign adenoma, thyroid cyst and occasionally, a carcinoma.

Evaluation: Goiter is usually classified as diffuse or nodular goiter. Either form can be produced by autoimmune thyroiditis and colloid goiter. An acutely painful thyroid enlargement is usually due to hemorrhage or active inflammation, whereas a firm goiter is characteristic of chronic lymphocytic thyroiditis. Multinodular goiter may be seen in chronic lymphocytic thyroiditis, iodine deficiency and colloid goiter. Isolated enlargement of one lobe indicates hemiagenesis. Diffuse goiter in the newborn may be due to Graves disease, dysmorphogenesis or administration of goiterogenic drugs. Investigations should include thyroid function tests. Anti-TPO antibodies should be measured to identify autoimmune thyroiditis. Positive anti-TPO antibodies indicate a risk of hypothyroidism, even if the thyroid

functions are normal. Ultrasound and fine needle aspiration should be performed, if no clue to etiology is identified.

Management: Treatment should be directed to the cause (antithyroid medications in Graves disease; thyroxine in hypothyroidism). Children with autoimmune thyroiditis should be followed with annual thyroid function tests. Suppressive thyroxine therapy for euthyroid goiter is of limited benefit and is best avoided. Surgery is indicated, only if goiter is large enough to cause respiratory embarrassment.

Solitary Thyroid Nodule

Identification of solitary thyroid nodule in children should alert to the possibility of thyroid malignancy (up to 20% cases). A well-circumscribed nodule is usually due to a benign cyst. Pointers towards malignancy include a firm nodule with limited mobility and associated lymph node enlargement. Children with solitary thyroid nodule should undergo ultrasound-guided fine needle aspiration to exclude an underlying malignancy.

Iodine Deficiency Disorders

The term 'iodine deficiency disorders (IDD)' refers to the wide-spectrum of effects of iodine deficiency on growth and development.' These include endemic goiter, endemic cretinism and impaired mental function in children and adults with goiter and increased rates of stillbirth and perinatal and infant mortality. Correcting iodine deficiency can prevent these conditions. Endemic goiter is present when the prevalence of goiter in a defined population exceeds 5%. Endemic goiter is graded by the method suggested by World Health Organization (WHO) (Table 18.11). Screening of estimates of iodine intake are usually derived from 24-hour urinary iodine excretion values or urinary iodine concentration expressed in relation to creatinine concentration as given in Table 18.12.

Endemic goiter: This does not differ from nontoxic diffuse sporadic goiter and the diagnosis is established by epidemiologic criteria. Usually, TSH is elevated with low T_4 and T_3 levels.

Table 18.11: Estimation of thyroid size by palpation

Stage 0	No goiter
Stage 1A	Goiter detectable only by palpation and not visible even when the neck is fully extended
Stage 1B	Goiter palpable but visible only when the neck is fully extended (this stage also includes nodular glands, even if not goitrous)
Stage 2	Goiter visible when the neck is in normal position; palpation not needed for diagnosis
Stage 3	Very large goiter, which can be recognized at a considerable distance

Table 18.12: Classification of severity of iodine deficiency

Iodine deficiency	None	Mild	Moderate	Severe
Median urine iodine, µg/L	>100	50–99	20–49	<20
Goiter prevalence	<5%	5–20%	20–30%	>30%
Neonatal thyroid stimulating hormone, >5 mU/L whole blood	<3%	3–20%	20–40%	>40%
Cretinism	None	None	Present	Present

Assessment of iodine deficiency disorders and monitoring their elimination: A guide for programme managers. 3rd ed. 2007, WHO

Endemic cretinism: This is a disorder associated with endemic goiter and severe iodine deficiency with characteristic clinical features, which include deaf–mutism, squint, mental retardation and characteristic spastic or rigid neuromotor disorder. Two types of endemic cretinism are described. Neurological cretinism is characterized by deaf–mutism, squint, proximal spasticity and rigidity (more in the lower extremities), disorders of stance and gait with preservation of vegetative functions, occasional signs of cerebellar or oculomotor disturbance and severe mental deficiency. Retarded psychomotor development, severe short stature, coarse facial features and myxedema without deaf–mutism characterize myxedematous cretinism. Iodine deficiency is also associated with poor school performance in children and recurrent pregnancy loss in women.

Prevention and control: Iodine deficiency disorders are best prevented as treatment is usually ineffective. Iodinated salt or iodized oil are highly efficacious in preventing iodine deficiency. Treatment of endemic cretinism may eliminate signs of hypothyroidism but neuromotor and intellectual deficiency are irreversible. Surgical removal of large goiters is indicated only to relieve airway obstruction or for cosmetic reasons.

The National Goiter Control Programme of the Ministry of Health and Family Welfare in India began in 1962 with establishment of salt iodination plants. The program is directed towards control of iodine deficiency disorders and ensuring that only iodized salt is used in India. The recommended daily intake of iodine is 40–120 µg for children up to the age of 10, 150 µg for older children and adults and an additional 25 µg and 50 µg during pregnancy and lactation, respectively. Based on an assumption of a mean intake of salt of 5 g/day, the recommended level of iodination is one part of iodine in 25,000 to 50,000 parts of salt.

Hyperthyroidism

Hyperthyroidism is relatively uncommon in children. It is most commonly seen in young girls, caused by Graves disease (Table 18.13).

Clinical features: The condition should be suspected in children with weight loss with increased appetite, tremors, diarrhea, warm extremities, increased sweating and anxiety. Inability to concentrate, personality changes, mood instability and poor school performance are

Table 18.13: Etiology of hyperthyroidism

Infancy

- Transplacental passage of thyroid antibodies
- TSH receptor activating mutation

After infancy

- Graves disease (TSH receptor stimulating antibody)
- Release of preformed thyroid hormone: Subacute thyroiditis
- Toxic thyroid nodule, toxic multinodular goiter
- Iatrogenic
- Pituitary resistance to T₃

common. Examination reveals firm homogeneous goiter. Eye signs are relatively uncommon compared to adults and are related to sympathetic over-activity (lid lag, ophthalmoplegia, absence of wrinkling) or autoimmune infiltration (chemosis, proptosis). Tachycardia, cardiac arrhythmia and high output cardiac failure may occur.

Diagnosis: The diagnosis is confirmed by the demonstration of elevated serum free T₄ and T₃ levels. The presence of goiter, infiltrative eye signs and hyperthyroidism are suggestive of Graves disease. Absence of goiter should raise the possibility of transient hyperthyroidism as part of autoimmune thyroiditis. Differentiating thyrotoxicosis from thyroiditis is important, as antithyroid drugs are not required in children with thyroiditis who may progress to hypothyroidism. Diffusely increased radiotracer uptake is suggestive of Graves disease while reduced uptake is characteristic of thyroiditis.

Management: Antithyroid drugs are ineffective in the acute phase due to lag period in their onset of action. Propylthiouracil is contraindicated in children due to hepatotoxicity. Treatment should be started with methimazole (0.5–1.0 mg/kg/day) in 3–4 divided doses. Beta-blockers (propranolol 2 mg/kg/day in two divided doses) are effective in ameliorating of sympathetic symptoms. Iodinated contrast (idopate 0.001 µg/kg/day) and Lugol iodine (5% iodine and 10% potassium iodide; 126 mg/mL iodine, 1 drop 8 hourly) are effective in reversing of features of hyperthyroidism. Prednisolone (1–2 mg/kg/day) inhibits peripheral conversion of T₄ to T₃ and is useful in treatment of hyperthyroid storm. Cardiac failure refractory to these measures requires treatment with digitalis.

Surgery and radioiodine ablation should be considered in patients with failure of medical management. Patients

with large or toxic nodular goiter require partial or total thyroidectomy. Radioiodine (^{131}I) is now increasingly used in the management of childhood Graves disease.

Neonatal Hyperthyroidism

One percent of babies born to mothers with Graves disease show fetal thyrotoxicosis and cardiac failure. Management includes maternal antithyroid drugs and digitalization. This usually occurs within the first week of life but may be delayed, if mother is on antithyroid medications or has concomitant TSH receptor blocking antibody. Treatment should include antithyroid drugs, propranolol and corticosteroids. The condition is self-limiting and resolves over 3–6 months.

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DISORDERS OF CALCIUM METABOLISM

Physiology

Calcium homeostasis involves interaction of gastrointestinal absorption, bone resorption and renal excretion. Most (99%) body calcium is stored in the bone and is in constant equilibrium with serum calcium. Parathyroid hormone (PTH), vitamin D and calcitonin are the key regulators of calcium metabolism (see Fig. 6.7). The body senses calcium levels using calcium-sensing receptors present in the parathyroid gland and kidney. Reduced action of the receptor in the presence of low serum calcium level increases PTH secretion and inhibits renal calcium excretion.

PTH increases serum calcium by stimulating bone resorption (osteoblast), calcitriol production (proximal tubule) and renal calcium resorption (distal tubule). Calcitriol is the only hormone that regulates intestinal calcium absorption. Calcitriol is formed by activation of vitamin D in the liver (25-hydroxylation) and kidney (1 α -hydroxylation). Sunlight is the major source of vitamin D with minor contribution from dietary sources. 1 α -hydroxylase enzyme in the kidneys is the rate-limiting step of calcitriol synthesis. Calcitonin, secreted by the parafollicular cells of thyroid in response to elevated calcium levels, lowers serum calcium levels by decreasing bone resorption and increasing urinary calcium excretion. It has a minor role on calcium homeostasis.

Hypocalcemia

Hypocalcemia (total calcium <8 mg/dL) is an important metabolic disorder. Estimation of ionic calcium is important for confirmation of hypocalcemia (ionic calcium <1.1 mmol/L).

Clinical Features

In the neonatal period, subtle clinical features like lethargy, jitteriness and poor feeding are characteristic of hypocalcemia. Seizures are common and hypocalcemia is the commonest biochemical abnormality associated with neonatal seizures.

In the post-neonatal period, the commonest presentation is tetany (simultaneous contraction of groups of muscles). This is most commonly observed in hands (adduction of thumbs along with extension of the proximal interphalangeal joints and flexion of distal interphalangeal joints) and feet (flexion and internal rotation of lower limbs) resulting in carpopedal spasm. In milder cases, latent tetany can be detected by tests of neuromuscular excitability. Tapping the facial nerve at the angle of jaw results in contraction of facial muscles (Chvostek sign). Inflating blood pressure cuff above the systolic blood pressure for more than 5 minutes triggers spasm of the hand muscles (Trousseau sign). Hypocalcemia should be considered in children with seizures, dilated cardiomyopathy and unexplained stridor.

The diagnosis is confirmed by the demonstration of prolonged QT interval on ECG, as suggested by Q_0T_c more than 0.2 seconds, where $Q_0T_c = Q_0T \div \sqrt{RR}$

Q_0T = Interval from beginning of Q wave to beginning of T wave; RR = RR interval

Etiology

Hypocalcemia may be caused by chelation of calcium or inefficient action of PTH or vitamin D (Table 18.14).

PTH related: Inefficient PTH action caused by decreased production (hypoparathyroidism) or action (pseudohypoparathyroidism) is an important cause of hypocalcemia. High phosphate levels due to impaired phosphaturic

Table 18.14: Etiology of hypocalcemia**Deficiency of ionic calcium (chelation)**

Phosphate load
Tumor lysis
Rhabdomyolysis
Top feeds

Total calcium deficiency

PTH deficiency (hypoparathyroidism)
Aplasia: DiGeorge syndrome
Autoimmune: Polyglandular endocrinopathy types I and II
Infiltration: Wilson disease, hemochromatosis, thalassemia
Transient: Hypomagnesemia, maternal hyperparathyroidism, post-surgery
PTH resistance (pseudohypoparathyroidism)
Vitamin D deficiency
Nutritional
1 α -hydroxylase deficiency: Renal failure, VDDR type I
Calcitriol resistance: VDDR type II
Increased inactivation: Phenytoin, phenobarbitone
PTH: Parathyroid hormone; VDDR: Vitamin D-dependent rickets

action of PTH characterize these disorders. Hypoparathyroidism may occur as part of congenital malformation or acquired destruction of the parathyroid glands. Autoimmune hypoparathyroidism is the most common form in older children and frequently associated with autoimmune polyendocrinopathy type 1.

DiGeorge syndrome characterized by abnormal development of third and fourth pharyngeal pouches is caused by deletion of part of chromosome 22q. This results in maldevelopment of thymus (resulting in T cell immunodeficiency), parathyroid glands (resulting in hypoparathyroidism), heart (resulting in conotruncal defects) and face (abnormal facies). Activating mutation of calcium-sensing receptor is associated with low PTH and calcium levels with paradoxically increased urinary calcium excretion (familial hypercalciuric hypocalcemia).

Hypomagnesemia is an important cause of transient hypoparathyroidism and should be excluded in children with refractory hypocalcemia.

PTH resistance (pseudohypoparathyroidism, PHP): This is caused by an inactivating mutation in the gene encoding for stimulatory subunit of G protein (G_{α}). This presents with clinical features of hypoparathyroidism in the wake of elevated PTH levels. PHP may be associated with the phenotype of Albright hereditary osteodystrophy such as round facies, brachydactyly, short stature, obesity, short fourth and fifth metacarpals (brachymetacarpia), osteodystrophy and heterotopic ossification.

Vitamin D related: Vitamin D deficiency (nutritional, malabsorption), decreased 1 α -hydroxylase action (renal failure, vitamin D-dependent rickets type I), increased inactivation of vitamin D (antiepileptic drugs) and

calcitriol resistance (vitamin D-dependent rickets type II) are associated with hypocalcemia. Phosphate levels are low due to secondary hyperparathyroidism. Vitamin D deficiency is the most common cause of hypocalcemia in children. Rickets may be absent. Maternal vitamin D deficiency is common in India and results in reduced calcium and vitamin D stores in children. These infants develop hypocalcemia during periods of rapid bone growth (4–8 weeks of life). Vitamin D-dependent rickets presents with early onset severe hypocalcemia and rickets.

Increased chelation: Increased calcium binding results in reduction of ionic calcium and features of hypocalcemia. This is most commonly related to high phosphate levels (renal failure or release of intracellular phosphate due to hemolysis, tumor lysis or rhabdomyolysis). Increased phosphate levels in cow milk and commercial formula is an important cause of neonatal hypocalcemia. Metabolic or respiratory alkalosis increases albumin binding of calcium resulting in hypocalcemia.

Evaluation

Evaluation is directed towards identification of etiology and assessment of the severity of illness.

Clinical: Detailed history of the age of onset, presenting features, frequency of episodes of hypocalcemia and family history should be obtained. Neonates should be screened for prematurity, birth asphyxia, maternal hyperparathyroidism and initiation of top feeds. Congestive cardiac failure, recurrent infections and abnormal facies are suggestive of DiGeorge syndrome.

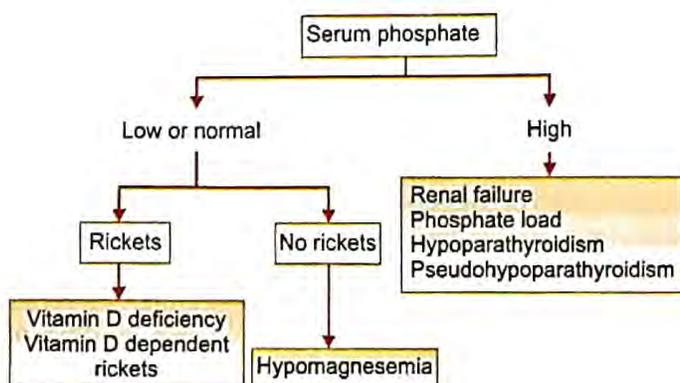
Investigations: Initial evaluation should include serum phosphate levels, renal and liver function tests and serum alkaline phosphatase (Table 18.15 and Fig. 18.11). Phosphate regulation is dependent on PTH and inefficient PTH action results in hyperphosphatemia. Hypocalcemia due to decreased vitamin D action is associated with secondary hyperparathyroidism and low phosphate levels. Thus hypocalcemia with hyperphosphatemia in the absence of phosphate load (exogenous or tissue lysis) and normal renal function suggests parathyroid insufficiency. Hypomagnesemia should be considered in patients with refractory hypocalcemia and normal or low phosphate levels. 25-hydroxyvitamin D levels should be measured in children with rickets to identify vitamin D deficiency.

Management

In children with severe hypocalcemia (ionic calcium <0.8 mmol/L), parenteral calcium should be administered (2 mL/kg intravenously over 5–10 min) after obtaining blood sample for calcium. Calcium gluconate (10%, 9 mg calcium per mL) is the preparation of choice. Care should be taken to administer the drug slowly (to avoid cardiac effects) and avoid extravasation (to prevent skin necrosis).

Table 18.15: Laboratory features of common causes of hypocalcemia

Disorder	Phosphate	25-hydroxyvitamin D	Parathyroid hormone (PTH)
Vitamin D deficiency	Low, normal	Low	High
Renal failure	High	Normal	High
Hypoparathyroidism	High	Normal	Low
Pseudohypoparathyroidism	High	Normal	High
Hypomagnesemia	Low, normal	Normal	Low

**Fig. 18.11:** Evaluation of a child with hypocalcemia

Parenteral calcium should be started at a dose of 80 mg/kg/day and should be gradually tapered over two days. The management of nutritional and refractory rickets is given in Chapter 8.

Hypercalcemia

Hypercalcemia (serum calcium >11 mg/dL) is rare in children. Its causes include increased bone resorption (hyperparathyroidism, malignancy and immobilization) or excessive vitamin D action (iatrogenic excess and increased 1α -hydroxylase activity).

Etiology: Hyperparathyroidism is the commonest cause of chronic hypercalcemia in children. Homozygous inactivating mutations of the calcium-sensing receptor present with severe neonatal hyperparathyroidism and hypocalciuria. Parathyroid adenoma is rare before the age of 10 years. Rarely, hypercalcemia may be associated with other conditions, e.g. Williams syndrome (supravalvular aortic stenosis, abnormal facies) or hypophosphatasia (inactivating mutation of alkaline phosphatase). Vitamin D-related hypercalcemia occurs in children receiving parental vitamin D or inadvertently high doses of oral vitamin D. Increased 1α -hydroxylase activity may occur in patients with granulomatous diseases (tuberculosis, sarcoidosis) or fat necrosis.

Clinical features: They are often nonspecific, including muscular weakness, anorexia, nausea, vomiting, constipation, polydipsia and polyuria. Ectopic calcification in the kidney, basal ganglia and skin are common. Bony deformities and pathological fractures may be present. Infants present with failure to thrive, poor feeding, hypotonia and seizures. Serum total and ionized calcium levels are elevated with low levels

of phosphate. Hyperparathyroidism is associated with elevated levels of PTH.

Management: Treatment of acute hypercalcemia involves high fluid intake followed by diuresis (furosemide 1 mg/kg). Bisphosphonates and antiresorptive agents are indicated, if there is no response to these measures. Hemodialysis may be required in refractory cases. Surgical exploration is indicated in all cases of hyperparathyroidism. Short course of glucocorticoids (prednisolone 2 mg/kg/day for 3 weeks) is indicated in children with iatrogenic vitamin D excess or increased 1α -hydroxylase action (fat necrosis or sarcoidosis).

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DISORDERS OF ADRENAL GLANDS

Physiology

Adrenal cortex produces three important groups of hormones—glucocorticoids, mineralocorticoids and androgens. The process of steroidogenesis involves conversion of cholesterol to steroid hormones through a series of enzymatic processes. Cholesterol is transferred into the mitochondria in a process mediated by the steroidogenic acute regulatory protein (StAR), an ACTH-dependent protein. The most clinically relevant step in steroidogenesis is 21-hydroxylation mediated by the enzyme 21-hydroxylase (P450c21). This step is crucial for the production of cortisol and aldosterone (Fig. 18.12).

Cortisol, the major glucocorticoid hormone has an important role in intermediary metabolism causing increased blood glucose levels and enhanced catabolism of proteins and lipids.

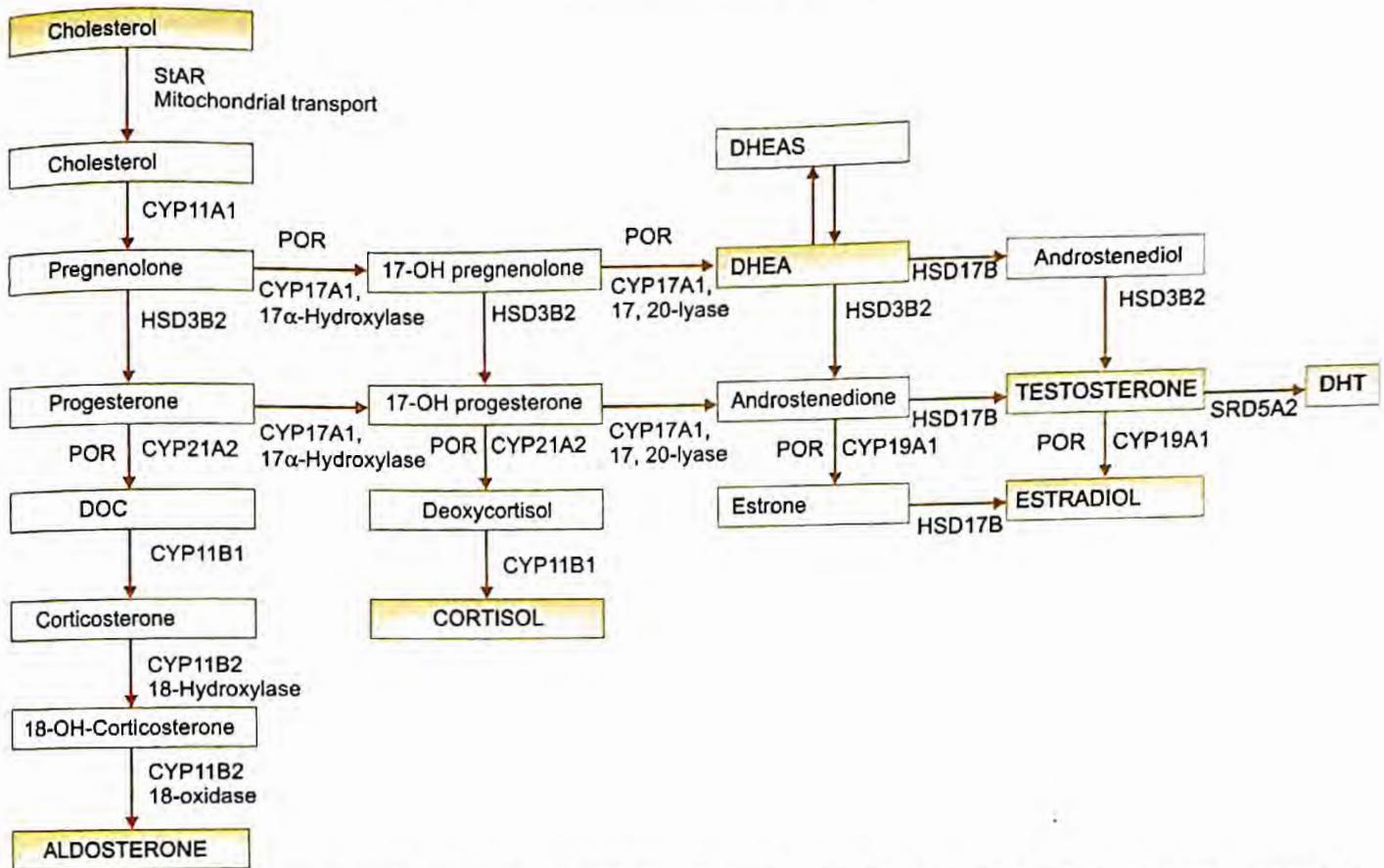


Fig. 18.12: Pathways of steroid biosynthesis. The key enzymes mediating synthesis of principal steroids are named according to their site of action and the nomenclature of cytochrome P450 enzymes. StAR steroidogenic acute regulatory protein; DOC deoxycorticosterone; DHEA dehydroepiandrosterone; DHEAS DHEA sulfate; DHT dihydrotestosterone. The enzyme nomenclature: CYP11A1: P450 side chain cleavage enzyme, P450_{sc} or 20,22-desmolase; HSD3B2: 3 β -hydroxysteroid dehydrogenase type 2; CYP17A1: 17 α -hydroxylase or 17,20 lyase; CYP21A2: 21-hydroxylase; CYP11B1: 11 β -hydroxylase; CYP11B2: This has 3 actions—11 β -hydroxylase, 18-hydroxylase and 18-oxidase; POR: P450 oxidoreductase, CYP19A1: Aromatase, HSD17B: 17 β -hydroxysteroid dehydrogenase, SRD5A2: 5 α -reductase type 2

Aldosterone acts on distal renal tubules and collecting ducts of kidneys to promote sodium and fluid reabsorption. Aldosterone deficiency causes urinary salt-wasting resulting in salt-wasting crisis (hyponatremia, hyperkalemia and metabolic acidosis).

Adrenal androgens are necessary for the development of pubic and axillary hair in girls.

Adrenocorticotrophic hormone (ACTH), a polypeptide secreted by the anterior pituitary, is the major regulator of glucocorticoid and androgen synthesis. Intravascular volume, serum potassium levels and renin-angiotensin system are the chief regulators of aldosterone synthesis. ACTH has only a minor role in aldosterone regulation. ACTH deficiency as in secondary adrenal insufficiency is, therefore, not associated with salt-wasting. ACTH secretion is stimulated by hypothalamic corticotropin-releasing hormone (CRH) and suppressed by cortisol as part of a feedback loop.

Adrenocortical Hyperfunction—Cushing Syndrome

The most common disorder of adrenocortical hyperfunction is Cushing syndrome. The term Cushing disease refers to

hypercortisolism caused by an ACTH-producing pituitary tumor. Classic features of Cushing syndrome such as central obesity, striae, moon facies and buffalo hump are rare in children (Fig. 18.13). Growth failure and obesity are common; other features include hypertension, hirsutism, delayed puberty, behavioral problems, bone pain and muscle weakness.

Etiology: Cushing syndrome may be caused by increased endogenous production or exogenous administration (Table 18.16). Prolonged steroid treatment is the commonest cause of childhood Cushing syndrome. Increased adrenal glucocorticoid production may be related to increased ACTH levels or represent autonomous adrenal hyperfunction. Adrenal pathology is more likely in young children, while pituitary causes are common after puberty. Ectopic ACTH production is rare in children.

Evaluation: Investigations are directed towards confirming the diagnosis of Cushing syndrome and finding the etiology. Commonly used screening tests include assessment of diurnal cortisol rhythm, overnight



Fig. 18.13: Cushing disease secondary to pituitary adenoma. Note the moon face and hypertrichosis over forehead and upper lip

Table 18.16: Etiology of Cushing syndrome

ACTH-dependent causes

Hypothalamic lesions: Increased corticotropin production
 Pituitary lesions: Microadenoma, macroadenoma
 Ectopic lesions: Neuroblastoma, carcinoid tumor, Wilms tumor

ACTH independent causes

Adrenal carcinoma, adenoma
 Pigmented nodular hyperplasia
 McCune-Albright syndrome

Exogenous administration

Glucocorticoids
 ACTH
 ACTH adrenocorticotrophic hormone

dexamethasone suppression test (cortisol levels after a single midnight dose of dexamethasone 0.3 mg/m²; maximum dose 1 mg) and 24-hour urine free cortisol (Table 18.17). The diagnosis is confirmed with low dose dexamethasone suppression test (serum cortisol after dexamethasone 5 µg/kg every 6 hours for two days).

The most important part of evaluation of a child with Cushing syndrome is to differentiate ACTH-dependent causes from autonomous adrenal steroid production (Table 18.18). ACTH levels differentiate ACTH-independent (ACTH levels <5 pg/mL) from ACTH-dependent conditions (ACTH levels >15 pg/mL). Ectopic ACTH production should be suspected in children with extremely high ACTH levels (>100 pg/mL). High dose dexamethasone suppression test is based on the principle that high doses of this agent suppress ACTH production in individuals with pituitary lesions but not in those with ectopic ACTH production (Fig. 18.14).

Adrenal tumors in children are usually large and identifiable on ultrasound. Magnetic resonance imaging of the hypothalamic-pituitary region should be performed in children with ACTH-dependent Cushing syndrome. Inferior petrosal sinus sampling is the test for identifying the source of ACTH production and should be performed in children with ACTH-dependent Cushing syndrome with normal neuroimaging.

Management: Resection of adrenal lesion is recommended for adrenal adenoma and carcinoma. Prolonged cortisol excess causes suppression of the normal contralateral adrenal gland. This mandates close monitoring for adrenal insufficiency in the perioperative period. Adrenal carcinoma is highly malignant and has a high rate of recurrence. Pigmented nodular hyperplasia should be

Table 18.17: Screening tests for Cushing syndrome

Test	Sensitivity	Specificity	Cut-off level	Comments
Morning cortisol	Low	Low	>10 µg/dL	Not recommended
Overnight dexamethasone suppression test	High	Low	>5 µg/dL	Screening test
Urine free cortisol	High	High	>75 µg/m ² /day	Screening test*
Low dose dexamethasone suppression test	High	High	>5 µg/dL	Diagnostic test

*Diagnostic of Cushing syndrome, if level is greater than 3 to 4 times the normal range

Table 18.18: Laboratory findings of common causes of Cushing syndrome

Disorder	Urinary free cortisol	High dose dexamethasone suppression test	Adrenocorticotrophic hormone (ACTH)
<i>Adrenal lesion</i>			
Pituitary lesion	High	Not suppressed	Low
Microadenoma	High	Suppressed	High
Macroadenoma	High	Not suppressed	High
<i>Ectopic ACTH</i>	High	Not suppressed	High
<i>Exogenous</i>	Low	Not suppressed	Low

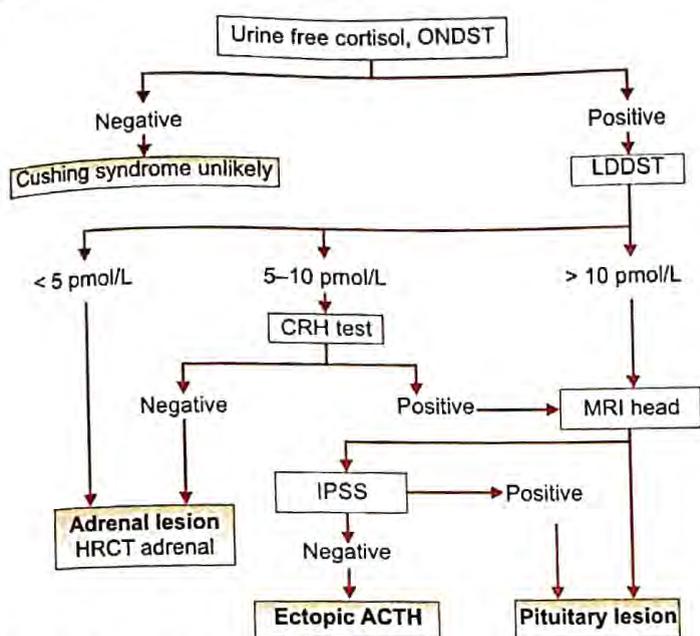


Fig. 18.14: Approach to Cushing syndrome in children. ACTH adrenocorticotropic hormone; CRH corticotropin-releasing hormone; HRCT high resolution computed tomography scan; IPSS inferior petrosal sinus sampling; LDDST low dose dexamethasone stimulation test; ONDST overnight dexamethasone stimulation test

treated with bilateral adrenalectomy. Trans-sphenoidal resection of pituitary adenoma is recommended for Cushing disease.

Medical management of Cushing syndrome with inhibitors of steroidogenesis (ketoconazole, aminoglutethimide, cyproheptadine, metyrapone and mitotane) has been tried with variable results.

Aldosterone Excess

Hyperaldosteronism is associated with fluid and sodium retention along with increased urinary loss of potassium. The chief clinical features of primary hyperaldosteronism are hypertension and hypokalemic alkalosis. Primary hyperaldosteronism due to increased adrenal aldosterone production is extremely rare. Secondary hyperaldosteronism results from factors that activate the renin-angiotensin system.

Etiology: Primary hyperaldosteronism may be caused by diffuse hyperplasia or adenoma. Glucocorticoid-remediable aldosteronism (GRA), a genetic disorder involving chimeric fusion of CYP11B1 promoter and the coding region of CYP11B2, results in regulation of aldosterone secretion by ACTH and thereby, hyperaldosteronism. Primary hyperaldosteronism should be differentiated from secondary hyperaldosteronism (renal failure, congestive cardiac failure, liver disease and nephrotic syndrome, and apparent and real mineralocorticoid excess (Table 18.19).

Table 18.19: Etiology of hyperaldosteronism

Primary hyperaldosteronism

Adenoma, hyperplasia
Glucocorticoid remediable hyperaldosteronism

Secondary hyperaldosteronism

Renal artery stenosis, renin-secreting tumor
Cardiac failure, nephrotic syndrome, liver disease

Other causes of excessive mineralocorticoid action

Apparent mineralocorticoid excess (deficiency of 11β -hydroxysteroid dehydrogenase)
Liddle syndrome
Congenital adrenal hyperplasia due to deficiency of 17α -hydroxylase or 11β -hydroxylase

Evaluation: Hypokalemic alkalosis in a child with low renin hypertension should prompt evaluation for true or apparent aldosterone excess. High aldosterone level in this setting is suggestive of primary hyperaldosteronism or GRA. Decrease in aldosterone levels and resolution of clinical and laboratory features after dexamethasone suppression suggests GRA; no effect is seen in primary hyperaldosteronism. Diagnosis of primary hyperaldosteronism should be confirmed by adrenal imaging.

Management: Hyperaldosteronism should be managed with salt restriction and aldosterone antagonist (spironolactone, eplerenone). Physiological hydrocortisone replacement suppresses ACTH secretion in glucocorticoid remediable aldosteronism resulting in resolution of hyperaldosteronism and hypertension. Surgery is the treatment of choice for adrenal adenoma.

Pheochromocytoma

Pheochromocytoma is a catecholamine-secreting tumor, arising from chromaffin cells of adrenal medulla. It can also arise from the abdominal sympathetic chain, peri-adrenal area, or in the thoracic cavity. The condition is rare in children and coexists with other syndromes such as neurofibromatosis, von Hippel-Lindau disease and multiple endocrine neoplasia type II. Compared to adults, pheochromocytoma is more likely to be bilateral and associated with underlying genetic anomaly in children.

Clinical features: Excessive secretion of catecholamines results in hypertension, which is usually sustained and often paroxysmal. The clinical symptoms include headache, palpitation, pallor, sweating, nausea, vomiting, visual disturbances and occasionally convulsions.

Evaluation: The diagnosis should be considered only after other common causes of childhood hypertension such as renal parenchymal disorders, renal artery stenosis and coarctation of aorta have been excluded. Diagnosis is established by demonstration of increased urinary excretion of catecholamines and their derivatives.

Ultrasound, CT scan, MRI scan and ^{123}I metaiodobenzylguanidine (MIBG) scintigraphy are used for localization. Often the tumors are multiple.

Management: Surgery is the treatment of choice. Transabdominal exploration of all the sites with removal of tumors is advocated. Preoperative alpha blockade is needed using phenoxybenzamine and prazosin. Recently, calcium channel blocking agents have been used successfully.

Adrenal Insufficiency

Adrenal insufficiency may be related to adrenal defects (primary adrenal insufficiency; autoimmune destruction, infection, steroidogenic defect, hemorrhage), decreased ACTH production (secondary adrenal insufficiency) or ACTH resistance.

Etiology: Autoimmune adrenal dysfunction is the commonest cause of primary adrenal failure (Addison disease) beyond infancy. Autoimmune adrenal failure is often associated with autoimmune polyendocrinopathy type 1 and 2. Infections due to tuberculosis and human immunodeficiency virus (HIV) are known to result in primary adrenal failure. Adrenal hemorrhage in the setting of meningococcal and other bacterial infections (Waterhouse-Friderichsen syndrome) is an important cause of adrenal insufficiency. Congenital adrenal hyperplasia (CAH) due to deficiency of 21-hydroxylase or 3β -hydroxysteroid dehydrogenase and deficient steroidogenesis due to defective steroidogenic acute regulatory protein (StAR; causing lipoid CAH) are the chief causes in the neonatal period.

Secondary adrenal insufficiency is caused by congenital malformations (holoprosencephaly, midline defects), genetic defects or acquired insults (neurosurgery, tumor, radiation). This is usually associated with other anterior pituitary hormone deficiencies as well. In secondary adrenal insufficiency, mineralocorticoid function is preserved, as ACTH does not regulate aldosterone secretion. Thus, salt-wasting is not observed. Prolonged steroid treatment is associated with suppression of the hypothalamic-pituitary axis resulting in adrenal insufficiency after discontinuation of medications. Again, mineralocorticoid activity is preserved in these patients.

Clinical features: Adrenal insufficiency presents with slowly progressive lethargy, vomiting, salt craving, fatigue, postural hypotension, hypoglycemia and episodes of shock during severe illness. The concomitant presence of shock, hyponatremia, hyperkalemia and hemoconcentration is characteristic of acute adrenal insufficiency and warrants immediate steroid replacement. Primary adrenal insufficiency is characterized by hyperpigmentation due to elevated levels of melanocyte-stimulating hormone. Hyperpigmentation is present in sun-exposed areas such as elbows and palmar creases and areas that are normally

hyperpigmented such as areola and genitalia. Pigmentation is absent in children with secondary adrenal insufficiency.

Evaluation: All patients suspected to have adrenal insufficiency should undergo urgent testing for serum electrolytes and blood sugar. Basal levels of cortisol are low but can be in the normal range. Elevated plasma renin activity indicates mineralocorticoid deficiency. ACTH stimulation test (cortisol estimation 60 minutes after 0.25 mg of intramuscular or intravenous ACTH injection) is the best test for adrenocortical reserve. Serum cortisol levels lower than 18 $\mu\text{g}/\text{dL}$ are suggestive of adrenal insufficiency.

The next step in evaluation of adrenal insufficiency is estimation of ACTH levels. Elevated ACTH levels suggest primary adrenal pathology while low levels points towards pituitary defect. Further evaluation of primary adrenal insufficiency includes abdominal CT scan and workup for tuberculosis.

Management: The initial management of salt-wasting crisis includes correction of shock by fluid boluses. Hydrocortisone is given immediately at a dose of 50 mg/m^2 , followed by 100 $\text{mg}/\text{m}^2/\text{day}$ in four divided doses. Frequent monitoring of hemodynamic parameters, urine output and serum electrolytes are required. Once the child is hemodynamically stable, hydrocortisone is tapered to the physiological dose (10 $\text{mg}/\text{m}^2/\text{day}$). Fludrocortisone acetate (0.1 mg/day) is added once hydrocortisone dose is $<50 \text{ mg}/\text{m}^2/\text{day}$.

Long-term management of adrenal insufficiency requires lifelong replacement of glucocorticoids and mineralocorticoids. Parents should be educated about the need for increasing dose during periods of stress. The dose of glucocorticoid should be increased 2–3 times in conditions of minor stress (fever and mild infection) and 4–5 times in severe stress (severe infection or surgery). These doses should continue throughout the period of stress. Patients with secondary adrenal insufficiency require lower dose of glucocorticoids (6–10 $\text{mg}/\text{m}^2/\text{day}$); mineralocorticoid replacement is not necessary.

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH), a group of autosomal recessive defects in steroid synthesis, is characterized by deficiency of adrenocortical hormones on one hand and excess of steroid precursors on the other (Fig. 18.12). CAH is the commonest adrenal disorder in childhood.

21-hydroxylase Deficiency

21-hydroxylase deficiency is the commonest form of CAH accounting for over 90% of all cases. This disorder is associated with diminished synthesis of the cortisol and aldosterone. Low cortisol levels stimulate ACTH

synthesis. Elevated ACTH level causes accumulation of steroid precursors (e.g. dehydroepiandrosterone, androstenedione and 17-hydroxyprogesterone). Depending on the severity of enzyme deficiency, the disease forms a spectrum of presentation as highlighted below.

Salt-wasting form: These patients are the most severely affected and present in the neonatal period with virilization and salt-wasting. Abnormal genital appearance should prompt the diagnosis in girls. Diagnosis is often missed in boys as they lack specific clinical features. They present after second week of life with failure to thrive, polyuria, hyperpigmentation and shock. Early diagnosis is mandatory to prevent mortality. 21-hydroxylase deficiency should be suspected in neonates with ambiguous genitalia, polyuria, shock, recurrent vomiting and features of sepsis with negative septic screen. The diagnosis is confirmed by measurement of blood levels of 17-hydroxyprogesterone (17-OHP). If these tests are not available, the child should be managed empirically in the lines of adrenal insufficiency.

Simple virilizing form: A subset of patients with 21-hydroxylase deficiency (25%) synthesizes enough aldosterone to prevent adrenal crisis. These patients have features of androgen excess in the form of virilization in girls and peripheral precocious puberty in boys (Fig. 18.15).

Non-classic form: This disorder is associated with partial 21-hydroxylase deficiency. Clinical manifestations are related to mild hyperandrogenism that presents with hirsutism, acne and menstrual irregularity in adolescents.

Diagnosis: Diagnosis of the salt-wasting form is established by demonstration of extreme elevation of 17-OHP levels (10000–20000 ng/dL, normal <90 ng/dL) in presence of clinical and laboratory features of adrenal insufficiency. 17-OHP levels are elevated to a lesser extent



Fig. 18.15: Congenital adrenal hyperplasia secondary to 21-hydroxylase deficiency. Note the clitoral hypertrophy, hyperpigmentation and increased rugosity of the labial folds giving a male appearance to the female genitalia

Table 18.20: Comparison of commonly used steroid preparations

Preparation	Potency (compared to hydrocortisone)			Biological half-life
	Glucocorticoid	Mineralocorticoid	Growth inhibitory	
Hydrocortisone	1	1	1	6 hours
Cortisone	0.8	1.25	1.25	5 hours
Prednisolone	4	0.25	8	8 hours
Dexamethasone	20	0	40	12 hours
Fludrocortisone	0.1	100	0.1	12 hours

in those with simple virilizing and non-classic forms. The best method of diagnosing these patients is the estimation of 17-OHP levels before and 60 minutes after an intramuscular injection of ACTH (0.25 mg).

Management: These patients require lifelong steroid replacement therapy. Patients with salt-wasting and virilizing forms are treated with hydrocortisone (10–15 mg/m²/day) and fludrocortisone (0.1 mg/day). After completion of growth and pubertal development, synthetic glucocorticoid preparations (dexamethasone, prednisolone) can be used (Table 18.20).

Other Variants

Enzyme deficiencies other than 21-hydroxylase deficiency account for less than 10% of cases of CAH (Table 18.21). Patients with 11-hydroxylase deficiency and 17-hydroxylase deficiency present with hypertension and are managed with hydrocortisone alone. Deficiencies of StAR and 3-hydroxysteroid dehydrogenase manifest as salt-wasting crisis and require therapy with mineralocorticoid.

Suggested Reading

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Table 18.21: Comparison of common variants of congenital adrenal hyperplasia

Enzymes deficient	Androgen levels	Blood pressure	Clinical presentation		Laboratory diagnosis	Treatment
			Boys	Girls		
21-hydroxylase						
Salt-wasting	High	Low	Precocious puberty	Ambiguity of genitalia	17-OHP*	Hydrocortisone Fludrocortisone
Simple virilizing	High	Normal	Precocious puberty	Ambiguity of genitalia	17-OHP*	Hydrocortisone
Non-classic	High	Normal	Normal	Hirsutism	17-OHP*	Hydrocortisone Fludrocortisone
11β-hydroxylase	High	High/Normal [§]	Precocious puberty	Ambiguity of genitalia	DOC	Hydrocortisone Spironolactone
3β-hydroxysteroid dehydrogenase	Variable [#]	Low	Ambiguity of genitalia	Ambiguity of genitalia	ACTH stimulation test**	Hydrocortisone Fludrocortisone
17α-hydroxylase/17-lyase	Low	High [§]	Ambiguity of genitalia	Delayed puberty	DOC	Hydrocortisone Fludrocortisone
StAR	Low	Low	Ambiguity of genitalia	Delayed puberty	Low 17-OHP	Hydrocortisone Fludrocortisone

DOC: Deoxycorticosterone; StAR: Steroidogenic acute regulatory protein; 17-OHP: 17-hydroxyprogesterone

* Basal and ACTH stimulated

§ BP is high due to mineralocorticoid effect of DOC; however, BP may be normal

Due to peripheral conversion of dehydroepiandrosterone (DHEA)

** Ratio of pregnenolone, progesterone, 17-hydroxypregnenolone to 17-OHP and DHEA to androstenedione following ACTH stimulation test

OBEESITY

The incidence of childhood obesity has increased rapidly in the last decade. The prevalence of overweight and/or obesity in Indian children is around 20% posing significant risk of lifestyle diseases in future.

Criteria for Diagnosis of Obesity

Obesity implies excessive fat and not merely excess weight. As methods of measuring body fat are cumbersome and expensive, several clinical and anthropometric parameters are used as markers of obesity.

Body mass index: Body mass index (BMI) is the most widely used parameter to define obesity. It takes into account weight as well as the height. It is calculated by the formula:

$$\text{BMI} = \text{Weight (kg)} \div \text{height (m}^2\text{)}$$

Children with BMI more than 85th percentile for age are considered overweight while those with more than 95th percentile for age are obese. BMI is a good indicator of body fat but is unreliable in short muscular individuals. BMI greater than 99th percentile (120% of 95th percentile) implicate severe obesity. The cutoffs for obesity should take into consideration the local population. As the aim of assessing BMI is to identify individuals at risk for metabolic complications, lower BMI cutoffs have been recommended for Indian adults (23 kg/m² for overweight and 27 kg/m² for obesity). Thus the use of CDC charts would underestimate the problem of obesity in Indian children and IAP 2015 growth charts should preferably be used for defining obesity.

Weight for height: This compares the child's weight to the expected weight for his/her height and is useful in children below 2 years of age (see Chapter 2). Weight for height more than 120% is diagnosed as obesity.

Skinfold thickness: Skinfold thickness measured over the subscapular, triceps or biceps regions is an indicator for subcutaneous fat. Age specific percentile cut-offs should be used with values more than 85th percentile being abnormal.

Waist circumference and waist hip ratio: Waist circumference is measured at the minimum circumference between the iliac crest and the rib cage. Hip circumference is measured at the maximum protuberance of the buttocks, and the waist hip ratio (WHR) may be calculated from these values. Waist circumference itself is a satisfactory marker of abdominal adiposity, a risk factor for metabolic and cardiovascular effects of obesity. Waist circumference greater than 75% is a risk factor for metabolic complications. WHR is probably a more refined method but is not age-independent; norms for Indian children are not available.

Etiology

In most children with obesity, environmental and the hereditary factors play the major role. Underlying etiology is identified in a few cases (<1%). The causes of childhood obesity are classified in Table 18.22.

Constitutional obesity: Most children with obesity do not have an organic cause. This is caused by imbalance in

Table 18.22: Etiology of obesity**Constitutional**

Environmental factors (95% cases)

Pathological

Endocrine: Cushing syndrome, deficiency of growth hormone, hypothyroidism, pseudohypoparathyroidism

Hypothalamic: Head injury, infection, brain tumor, radiation, after neurosurgery

Drugs: Antiepileptic drugs, steroids, estrogen

Genetic syndromes: Prader-Willi, Laurence-Moon-Bardet-Biedl, Beckwith-Wiedemann, Carpenter syndromes

Monogenic disorders: Leptin deficiency, or resistance, abnormalities of melanocortin-4 receptor and proconvertase

energy intake and expenditure. These children are tall for age, a factor that differentiates them from pathological obesity. They have proportional obesity and normal development. It is important to identify this subgroup of children to avoid unnecessary investigations.

Endocrine causes: Growth failure, developmental delay and dysmorphism in an obese child denote an endocrine etiology. Cushing syndrome is characterized by central obesity, hypertension, and striae with retarded skeletal maturation. Hypothyroidism is an extremely rare cause of isolated obesity and other features such as developmental delay and coarse skin are always present. In GH deficiency and pseudohypoparathyroidism, growth retardation and hypocalcemia are dominant clinical features and obesity is a less prominent sign.

Genetic syndromes: Several genetic syndromes have obesity as their major clinical feature. Many of these syndromes are associated with hypogonadism or hypotonia (Prader-Willi, Carpenter and Laurence-Moon-Bardet-Biedl syndromes).

Hypothalamic obesity: CNS insults due to surgery, radiation, tumors and trauma result in rapid onset obesity. These disorders are associated with excessive appetite, signs and symptoms of CNS involvement and other hypothalamic-pituitary defects.

Monogenic obesity: Monogenic obesity represents a very small proportion of children with obesity. They are more likely when the obesity is morbid, has an early onset of obesity and strong family history. Leptin deficiency was the first monogenic cause of obesity identified. Inefficient leptin action (deficiency or resistance) results in uncontrolled appetite and obesity. Abnormalities in mineralocorticoid receptor and proconvertase are associated with obesity. Melanocortin-4 receptor (MC4-R) defects are the commonest monogenic form of obesity and are associated with growth acceleration.

Drugs: Commonly used drugs associated with obesity include corticosteroids, antipsychotics (olanzapine,

risperidone), antidepressants (paroxetine) and anti-epileptics (valproic acid, lamotrigine).

Evaluation

Initial evaluation is guided to differentiate constitutional from pathological obesity (Table 18.23). Normal growth, generalized pattern and lack of developmental delay or dysmorphism imply constitutional obesity, which does not need extensive investigations.

History: Family history of obesity and its complications should be recorded. Detailed history of physical activity, dietary recall and periods of inactivity should be assessed. Increased appetite in a child with recent onset obesity may indicate the possibility of a hypothalamic lesion. Features of raised intracranial tension along with history of neurologic infection, head trauma or neurosurgery suggest the prospect of an underlying neurologic cause for obesity. Intake of drugs linked with development of obesity such as steroids and antiepileptics should be probed.

Examination: Look for features of endocrinopathies, dysmorphic syndromes and complications such as hypertension and acanthosis nigricans (Fig. 18.16). Special emphasis should be given to sexual maturity and ocular examination. Hypogonadism is an important feature of obese children with Laurence-Moon-Bardet-Biedl and Prader-Willi syndromes (Figs 18.17, 18.18 and Tables 18.24, 18.25). Parents of obese girls are often concerned about

Table 18.23: Differentiating features of constitutional and pathological obesity

Feature	Constitutional	Pathological
Pattern	Generalized	Central
Growth rate	Accelerated	Retarded
Skeletal maturation	Advanced	Retarded
Dysmorphic features	Absent	May be present
Endocrine features	Absent	May be present

**Fig. 18.16:** Acanthosis nigricans on the back of neck in a girl with obesity



Fig. 18.17: Laurence-Moon-Bardet-Biedl syndrome. Note the central obesity and hypoplastic genitalia



Fig. 18.18: Laurence-Moon-Bardet-Biedl syndrome. Note the polydactyly

Table 18.24: Clues to the diagnosis to obesity

Disorder	Features
Delayed puberty	Laurence-Moon-Bardet-Biedl syndrome, Prader-Willi syndrome
Retinitis pigmentosa, polydactyly	Alstrom syndrome, Laurence-Moon-Bardet-Biedl syndrome
Short hand and feet	Prader-Willi syndrome
Buffalo hump and striae	Cushing syndrome
Short fourth metacarpals	Pseudohypoparathyroidism, Turner syndrome
Developmental delay	Prader-Willi syndrome, hypothyroidism, pseudohypoparathyroidism

Table 18.25: Features of common causes of obesity

Disorder	Features
Prader-Willi syndrome	Infantile hypotonia, hyperphagia, almond-shaped eyes, acromicria, hypogonadism and behavioral abnormalities
Laurence-Moon-Bardet-Biedl syndrome	Hypogonadism, retinitis pigmentosa, polydactyly, renal abnormalities and intellectual disability
Beckwith-Wiedemann syndrome	Macrosomia at birth, organomegaly, ear lobe creases, macroglossia, abdominal wall defects and hemihypertrophy
Cushing syndrome	Hirsutism, central obesity, growth retardation, striae, buffalo hump, hypertension and myopathy
Hypothyroidism	Growth retardation, coarse facies, developmental delay
Pseudohypoparathyroidism	Tetany, round facies, short fourth metacarpal, cutaneous calcifications

premature thelarche. While this may reflect central isosexual precocious puberty caused by obesity, it is most likely due to increased fat. These conditions are distinguished by approximating the thumb and index finger around the nipple. Lack of resistance during this procedure indicates lipomastia while breast nodule can be felt as an area of resistance. Obese boys frequently present with concerns of small penile size. This is usually due to penis being buried in the suprapubic pad. Stretched penile length should be measured after pressing the suprapubic pad of fat to ascertain the actual size of penis.

Investigations: No workup is required in children with normal growth, facies, development and pubertal development. Thyroid profile and evaluation for Cushing syndrome should be done in the presence of growth failure and/or characteristic clinical features. The effects of obesity on endocrine functions should be considered while interpreting laboratory reports. Mildly elevated TSH levels with normal FT_4 are common in obese children. This is not the cause of obesity and should not be treated unless TSH is persistently elevated. Cortisol levels may be mildly elevated in obese children and should not be mistakenly diagnosed as Cushing syndrome. Genetic testing for Prader-Willi syndrome should be done in the presence of facial features, history of infantile hypotonia and growth failure. Monogenic causes of obesity should be considered only in the presence of clinical features or pointers to diagnosis.

Complications

Childhood obesity is associated with significant complications (Table 18.26).

Table 18.26: Complications of obesity

Category	Complications
Metabolic	Insulin resistance, type 2 diabetes, metabolic syndrome, hyperandrogenism
Cardiovascular	Hypertension, dyslipidemia, atherosclerosis
Gastrointestinal	Non-alcoholic fatty liver disease, gallstones, gastroesophageal reflux
Skeletal	Blount's disease, slipped capital femoral epiphysis, fractures
Respiratory	Obstructive sleep apnea, hypoventilation syndrome
Neurological	Benign intracranial hypertension

Endocrine system: Endocrine complications are the most important adverse effects of childhood obesity. Central to this is the development of insulin resistance caused by overspill of fat and its deposition in liver and skeletal muscle. Insulin resistance predisposes to development of type 2 diabetes, polycystic ovarian disease, metabolic syndrome and non-alcoholic fatty liver disease. Hyperandrogenism is a common feature in obese girls. Obesity has also been associated with accelerated growth, skeletal maturation and early puberty in girls.

Cardiovascular system: Obese children have a higher prevalence of dyslipidemia, hypertension and atherosclerosis. Importantly hypertension may be masked, requiring repeat blood pressure measurements. Childhood obesity is associated with increased risk of adult coronary disease.

Central nervous system: Benign intracranial hypertension is common in children with obesity and presents with headache and vomiting.

Orthopedics: Obese children have a higher risk of flat foot, Blount disease (tibia vara), fractures, genu valgum and osteoarthritis. The most debilitating complication is slipped capital femoral epiphysis. This presents with dull aching pain in knee, hip or groin with abnormal gait. Blount disease presents with progressive bowing of legs and knee pain. X-ray of knee and hip should be done in obese children with recurrent pain in hip or knee or abnormal gait.

Respiratory system: Obese children are at risk of respiratory distress and bronchial asthma. Obesity predisposes to the development of obstructive sleep apnea and hypoventilation syndrome.

Gastrointestinal system: Obesity is associated with gastroesophageal reflux disease and non-alcoholic fatty liver disease. Fatty liver is present in 40% of children with obesity but elevated serum transaminases occur only in 25% of these children. Gallstones are noted in 2% children with obesity. Rapid weight fluctuations are associated with the gallstone disease. Gallstone should be suspected in an obese child with recurrent abdominal pain, jaundice, nausea and intolerance to fatty foods.

Psychological issues: Obesity is associated with increased prevalence of mood disorders. This represents intrinsic effects of obesity and psychological effects of bullying.

Assessment of Complications

The high incidence of complications in obese children calls for regular follow-up screening. Investigations should include a baseline oral glucose tolerance test using blood sugar levels fasting and 2 hours after 1.75 g/kg glucose (maximum 75 g), lipid profile and liver function tests. Age appropriate cutoffs should be used for these investigations (Table 18.27). These tests should be repeated every 3 years, if normal. Fasting insulin has limited role and is not routinely required. Mildly elevated liver transaminases are common in obese children; persistent elevation beyond twice the upper limit indicates non-alcoholic steatohepatitis. Children with elevated transaminases should undergo ultrasound abdomen and work-up for other causes of hepatic dysfunction (hepatitis B and C, Wilson disease and autoimmune hepatitis). Sleep studies may be required in the presence of snoring, daytime somnolence or lethargy.

Management

Management of childhood obesity is challenging with major impetus on lifestyle measures (Fig. 18.19). Specific management is available for only a few situations. Diet, activity and behavioral measures are the cornerstone of

Table 18.27: Pediatric cutoffs for investigations for assessment of obesity complications

Investigation	Normal	Borderline	Abnormal
Blood glucose (fasting)	<100 mg/dL	100–125 mg/dL	>126 mg/dL
Blood glucose (2 hours after glucose)	<140 mg/dL	140–199 mg/dL	>200 mg/dL
Total cholesterol	<170 mg/dL	170–199 mg/dL	>200 mg/dL
LDL-cholesterol	<110 mg/dL	110–129 mg/dL	>130 mg/dL
Triglyceride	<90 mg/dL	90–129 mg/dL	>139 mg/dL
HDL-cholesterol	>45 mg/dL	40–45 mg/dL	<40 mg/dL
Serum aspartate aminotransferase (AST or SGOT)	<40 IU/L	40–80 IU/L	>80 IU/L

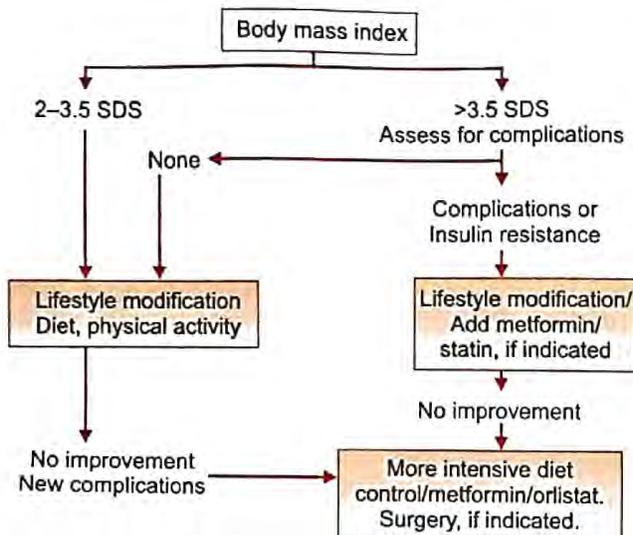


Fig. 18.19: Approach to management of obesity. SDS standard deviation score

therapy; measures such as drug therapy and surgery are reserved for morbid cases.

The management of obesity is a challenge, requiring multidisciplinary approach involving physicians, nutritionists and physical trainers. The goal is to bring BMI within the normal range for age and gender. Excessive and rapid weight loss adversely affects the growth of the child and should be avoided. In most children, weight stabilization is the initial aim; weight loss should not exceed 1 kg per month. The child and parents are counseled that there is no quick fix solution for obesity. The focus is on changing the lifestyle of the child without recourse to drugs and surgery.

Lifestyle Measures

The cornerstone to management is lifestyle measures. The whole family is encouraged to follow a healthy lifestyle as a unit; focusing on the child alone is often counterproductive.

Nutritional therapy: The child should be advised to stick to regular meals. Skipping breakfast and snacking in between meals should be discouraged. The caloric intake should be reduced by 20%. Overzealous restriction and fad diets are not recommended. Food pyramid and 'traffic light' approach for diet may be used to highlight healthy eating pattern. Special emphasis is laid on fixed portion size, decreased junk food consumption, avoiding television viewing while eating, and increased fruit consumption.

Physical activity: Periods of inactivity should be reduced along with increase in physical activity. Screen time (time spent on watching television, computer and mobile devices) is restricted to less than one hour a day. Increase in routine activities like household chores and walking to school should be encouraged. A plan of enjoyable activity

like dancing, sports and running should be made to ensure a minimum of 30 minutes daily. Weight bearing exercises and over-regimented schedule should be avoided.

Specific Management

Specific treatment should be initiated in children with hypothyroidism, GH deficiency and Cushing syndrome. Children with mildly elevated TSH level do not need treatment. Obese children with Prader-Willi syndrome and growth failure may benefit from GH therapy. Octreotide is effective in hypothalamic obesity while the use of leptin is reserved for leptin deficiency.

Treatment of Complications

Complications should be treated early to avoid long-term adverse effects. Metformin is indicated in children with insulin resistance and type 2 diabetes, non-alcoholic fatty liver disease and polycystic ovarian disease. Statins are the drug of choice for children with persistent dyslipidemia. Treatment of non-alcoholic fatty liver disease includes the use of metformin, vitamin E and pioglitazone. Girls with polycystic ovarian syndrome may benefit from lifestyle modifications, metformin, oral contraceptives and antiandrogens. Medroxyprogesterone acetate is beneficial in children with obesity—hypoventilation syndrome while continuous positive airway pressure may be used in obstructive sleep apnea.

Medical Management for Obesity

Orlistat is the only drug approved for use in children with obesity. The drug inhibits gastric lipase resulting in reduced absorption of fat with modest weight loss. The major side effects are abdominal pain, bloating, steatorrhea and leakage of oil. The medicine should be combined with fat-soluble vitamins. Newer agents include MC4 receptor modulators, GLP1 analogs and endocannabinoid agonists.

Surgical Management

Bariatric surgery is considered in severe obesity when other measures fail. The intervention is preferred after achieving final height to avoid potential adverse growth effects. Bariatric surgery is a major surgical undertaking, and should be viewed as a potentially life-saving and not just a cosmetic procedure. Patients need to adhere to strict dietary restriction for life. Laparoscopic adjustable banding is the recommended procedure in children. Malabsorptive procedures and gastric sleeve are not recommended for children.

Suggested Reading

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DISORDERS OF THE GONADAL HORMONES

Puberty

Puberty is the phase of life when secondary sexual characteristics appear and mature, and capability of reproduction is attained. Deviations from the normal pattern of puberty have major diagnostic and therapeutic implications.

Physiology

Puberty involves development of primary (testicular and penile growth in boys and breast, ovarian and uterine growth in girls) and secondary sexual characteristics (pubic and axillary hair growth, change of voice in boys, acne and axillary odor). Sex hormones (estrogen in girls and testosterone in boys) play an important role in the development of primary sexual characteristics, while adrenal androgens are involved in the development of secondary sexual characteristics in girls.

Kisspeptin, a hypothalamic peptide, is the key regulator of puberty. Acting as the 'on-off switch' of puberty, kisspeptin initiates GnRH pulses. Initially, GnRH pulses occur only during nights followed by secretion during both day and night. This leads to increase in the levels of gonadotropins, and thereby, sex hormones. LH is a better indicator of pubertal status compared to FSH. Pulsatile secretion of GnRH makes basal gonadotropin levels an unreliable indicator of pubertal status. The hypothalamic-pituitary-gonadal axis is under feedback control. Thus secretion of LH is inhibited by testosterone and estrogen produced by the Leydig cells and theca cells, respectively. Inhibin produced by the Sertoli and granulosa cells inhibits FSH production.

Patterns of Pubertal Development

The pattern of pubertal development is different in girls and boys. Puberty starts at around the age of 10 years in girls (range 8–12 years) and is completed over 5 years. Breast enlargement (thelarche) is the first event followed by the development of pubic hair (pubarche) and onset of menstrual cycles (menarche). Breast development may be asymmetrical in the initial phase. Menarche usually occurs 2 years after thelarche usually during stage III and IV. Pubertal development is closely linked to remaining growth potential of the child. Thus a girl is expected to gain around 20 cm from breast stage II development and 5–8 cm after achieving menarche. Discordant pubertal development (menarche within one year of thelarche) suggests a hyperestrogenic state with withdrawal bleeding.

In boys, puberty starts with testicular enlargement at 11.5 years (range 9 to 14 years). This is followed by penile enlargement and pubarche; spermarche occurs by 14 years. Peak growth velocity in boys correlates to testicular volume of 10 mL.

Assessment of Puberty

The stage of pubertal assessment is assessed using Tanner staging system (Figs 5.1, 5.2). Breast development beyond Tanner II in girls and testicular volume greater than 4 mL indicates the onset of puberty. Maximum growth spurt occurs during early puberty in girls (Tanner II-III) compared to boys where it occurs later (Tanner III-IV) (Table 18.28). Menstrual periods are irregular in the first few years before attainment of regular ovulatory cycles. It is important to differentiate adrenarche (pilosebaceous development related to increase in adrenal steroids) from gonadarche (genital development related to increase in GnRH) in girls.

Precocious Puberty

Pubertal onset before the age of 8 years in girls and 9.5 years in boys is suggestive of precocious puberty. Precocious puberty may be due to stimulation of the hypothalamic-pituitary axis (gonadotropin-dependent precocious puberty) or autonomous sex hormone production (gonadotropin-independent).

Precocious Puberty in Girls

Precocious puberty is common in girls and may represent a normal variation in the age at onset of puberty. In most cases, puberty is slowly progressive with no long-term adverse effect. Endocrine workup should be restricted to girls with progressive forms of puberty.

Gonadotropin-dependent precocious puberty (central precocious puberty) is much more common than gonadotropin-independent precocious puberty (Table 18.29). In more than 90% cases, no underlying cause is identified. It may be caused by a variety of pathologies of the central nervous system. Hypothalamic hamartoma, a neuronal migration defect, is the commonest cause of organic central precocious puberty. The disorder presents with early onset and rapid progression of puberty, seizures and uncontrolled laughter episodes (gelastic epilepsy).

Table 18.28: Comparison of pattern of pubertal development in boys and girls

	Girls	Boys
Onset	10–12 years	12–14 years
First sign	Breast development	Testicular enlargement
Growth spurt	Tanner II and III	Tanner III and IV
Sexual maturity	Menarche 14 years	Spermarche 14–15 years

Table 18.29: Etiology of precocious puberty in girls**Gonadotropin-dependent or central precocious puberty**

Idiopathic

Tumors: Hamartoma, pituitary adenoma, craniopharyngioma, glioma

Infections: Neurotuberculosis, meningitis

Injury: Head trauma, neurosurgery, cranial irradiation

Malformation: Arachnoid cyst, hydrocephalus, septo-optic dysplasia

Gonadotropin-independent or peripheral precocious puberty

Hypothyroidism

Ovarian estrogen: McCune-Albright syndrome, cyst, tumor, aromatase excess

Adrenal estrogen: Estrogenic adrenal adenoma

Exogenous estrogen exposure

Incomplete variants

Isolated thelarche

Isolated pubarche (adrenarche)

Isolated menarche

Gonadotropin-independent precocious puberty (peripheral precocious puberty) is rare and usually caused by estrogenic ovarian cysts. Fluctuating pubertal development and early vaginal bleeding (due to hyperestrogenic state) is common. The condition is usually self-resolving and there is no need for treatment. Recurrent ovarian cysts should raise the possibility of McCune-Albright syndrome, a somatic activating mutation of stimulatory G protein,

which presents with a constellation of cutaneous (multiple café au lait spots), skeletal (multiple fibrous dysplasia) and endocrine abnormalities (hyperthyroidism, rickets and GH excess). Precocious puberty occurs at an early age and is rapidly progressive. Prolonged untreated primary hypothyroidism may induce early puberty due to action of TSH on FSH receptor. Delayed bone age and growth are characteristics.

Evaluation

Aims of evaluation include confirmation of diagnosis, identification of underlying etiology and determination of prognosis and treatment (Fig. 18.20).

Clinical: History should include the onset, progression and extent of puberty. Exposure to steroids, estrogens and androgens should be enquired. Family history of precocious puberty and early menarche points towards idiopathic central precocious puberty. Features of hypothyroidism should be assessed. Advanced growth is characteristic of precocious puberty; growth retardation indicates hypothyroidism or concomitant GH deficiency. Examination of vaginal mucosa for estrogen effect provides clues regarding the pubertal status of the patient. Red, glistening vaginal mucosa suggests lack of estrogens while pink mucosa with mucus is indicative of estrogen effect. Abdominal examination for adrenal or ovarian mass should be done. Features of McCune-Albright syndrome include café au lait spots, polyostotic fibrous dysplasia, bony deformities and polyendocrinopathy.

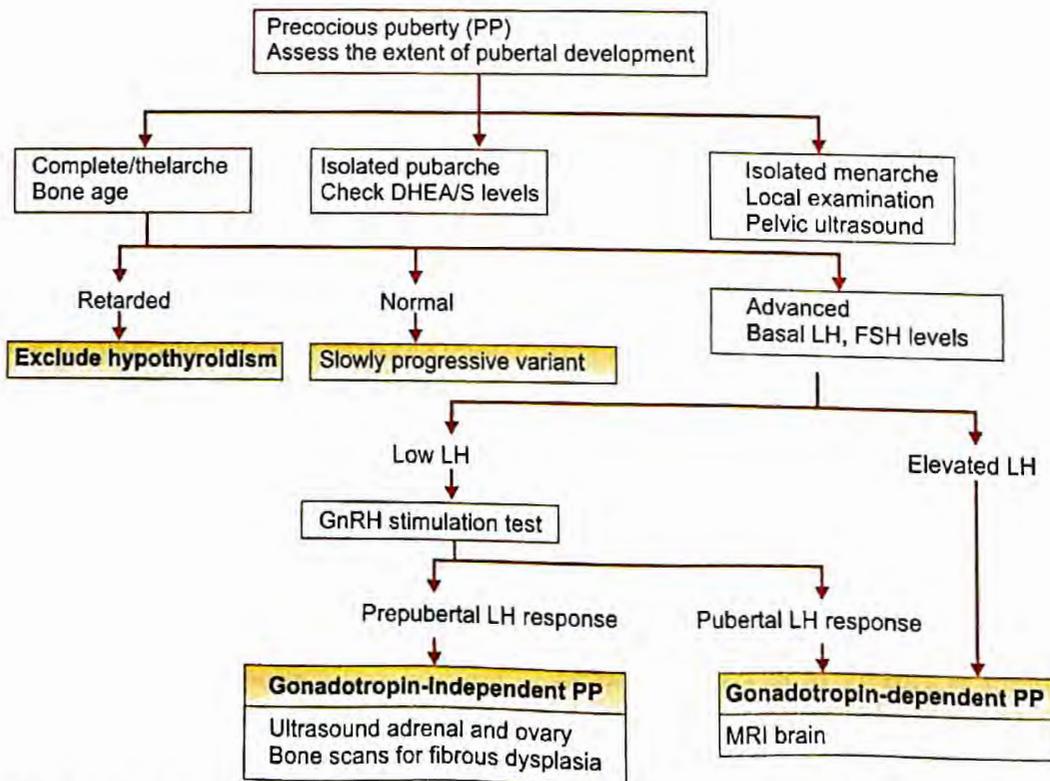


Fig. 18.20: Approach to precocious puberty in girls. DHEA/S dehydroepiandrosterone sulfate; FSH follicle-stimulating hormone; GnRH gonadotropin-releasing hormone; LH luteinizing hormone; MRI magnetic resonance imaging

Investigations: Assessment of pubertal status is based on basal or stimulated gonadotropin levels. Pooled gonadotropin levels are preferred due to their pulsatile secretion. LH is a better indicator compared to FSH, since the former increase significantly during puberty. LH levels in the pubertal range (>0.6 mU/L with LH/FSH ratio >1) is suggestive of development of puberty.

Bone age helps in assessing the height compromise and in predicting final height. Advanced bone age (more than two years ahead of chronological age) suggests progressive precocious puberty, while normal bone age indicates slowly progressive puberty. Retarded growth and skeletal maturation is diagnostic of hypothyroidism. Thyroid function should be assessed to rule out hypothyroidism in these girls.

MRI of brain should be done in girls with onset of puberty <6 years of age, rapid progression and associated neurological features. Ultrasound of abdomen and pelvis helps in diagnosing follicular cysts and ovarian and adrenal mass. Girls with prepubertal LH levels should undergo ultrasound of ovary and adrenals (for ovarian cyst and adrenal tumor) and skeletal survey (fibrous dysplasia).

Management

Aims of management include treatment of underlying cause, management of associations, puberty suppression and achievement of target height potential. The significant long-term consequence of precocious puberty is short stature. Growth is accelerated at presentation. This is associated with disproportionately advanced bone age resulting in premature epiphyseal fusion culminating in compromised final height.

Gonadotropin-dependent precocious puberty: Drugs used for pubertal suppression include medroxyprogesterone acetate (MPA), cyproterone and GnRH analogs. MPA does not improve height outcome and is considered in girls with intellectual disability where final height is not important. Long-acting GnRH analogs are the only agents effective in improving height outcome. They cause sustained stimulation and desensitization of pituitary leading to reversal of pubertal changes. GnRH analogs should be considered in girls with early onset (before 6 years of age) rapidly progressive puberty and height compromise (bone age to chronological age difference more than two years). The treatment is discontinued at the chronological age of 11 years and bone age of 12.5 years.

Gonadotropin-independent precocious puberty: Thyroxine replacement reverses the pubertal changes of hypothyroidism. Treatment for McCune-Albright syndrome is directed towards inhibiting estrogen production (aromatase inhibitors: anastrozole, letrozole) or estrogen action (tamoxifen, estrogen receptor antagonist: fulvestrant). Size and morphological features guide treatment of ovarian cysts.

Incomplete Variants of Precocious Puberty

These disorders represent normal variants and do not require specific treatment. Their identification helps in restricting the extent of diagnostic workup and counseling.

Isolated thelarche: Isolated breast development may represent isolated thelarche or first manifestation of central precocious puberty. Bone age, gonadotropin levels and pelvic ultrasound help in differentiating the two conditions. Normal growth, prepubertal LH, age appropriate bone age and small uterine size suggest isolated thelarche. These children usually present around the age of 1–2 years and show gradual regression of thelarche by 5 years of age.

Isolated adrenarche: Premature adrenarche refers to development of pubic hair and acne in the absence of breast development or menarche. Most cases are physiological variants. Rarely, androgen excess due to adrenal (21-hydroxylase deficiency, 11 β -hydroxylase deficiency, adrenal tumor) or ovarian (tumor, polycystic ovarian disease) causes may be identified. Normal bone age and absence of virilization suggest premature adrenarche and no treatment.

Isolated menarche: Vaginal bleeding in the absence of thelarche is against the diagnosis of gonadotropin-dependent precocious puberty. Vaginal bleeding occurs early in course of estrogen excess states like ovarian cysts, hypothyroidism and McCune-Albright syndrome. Vaginal bleeding without breast development requires evaluation of local causes (infection, foreign body, sexual abuse or tumors).

Precocious Puberty in Boys

Precocious puberty is less common in boys, but when present is usually associated with significant pathology. This mandates prompt evaluation and treatment of all boys with precocious puberty.

Etiology

Gonadotropin-dependent and independent precocious puberty accounts for similar number of cases (Table 18.30).

Gonadotropin-dependent precocious puberty: The etiology is similar to girls, except that organic causes are common. Hypothalamic hamartoma, craniopharyngioma, hydrocephalus and tubercular meningitis are important causes (Figs 18.21 and 18.22). These disorders are associated with increase in testicular volume and elevated basal and GnRH-stimulated LH.

Gonadotropin-independent precocious puberty: This is caused by increased androgen production by testis and adrenals, with prepubertal LH levels. Adrenal overproduction due to CAH is the chief cause of peripheral precocious puberty in boys; adrenal tumors are rare. Human chorionic gonadotropin (hCG) secreting tumors

18

of the liver, mediastinum or brain may present with precocious puberty. Testotoxicosis, associated with constitutional activation of LH receptor, presents with early onset gonadotropin-independent precocious puberty. Androgen-secreting testicular tumors present with precocious puberty and unilateral testicular enlargement.

Table 18.30: Etiology of precocious puberty in boys

Gonadotropin-dependent or central precocious puberty

Idiopathic

Central nervous tumors: Hamartoma, craniopharyngioma, glioma

Infections: Tubercular meningitis

Injury: Head trauma, surgery, radiation

Malformation: Arachnoid cyst, hydrocephalus

Gonadotropin-independent or peripheral precocious puberty

Congenital adrenal hyperplasia: 21-hydroxylase deficiency, 11 β -hydroxylase deficiency

Adrenal tumors: Adenoma, carcinoma

Testicular tumors: Seminoma, germinoma

Testotoxicosis: Activation of LH receptor

hCG secreting tumor: Germinoma, hepatoblastoma

Exogenous androgen exposure: Testosterone cream

hCG: Human chorionic gonadotropin, LH: Luteinizing hormone

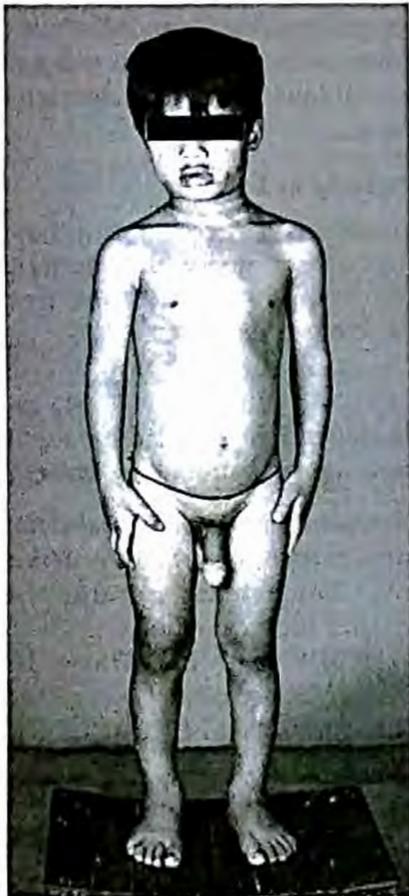


Fig. 18.21: Central precocious puberty secondary to hypothalamic hamartoma

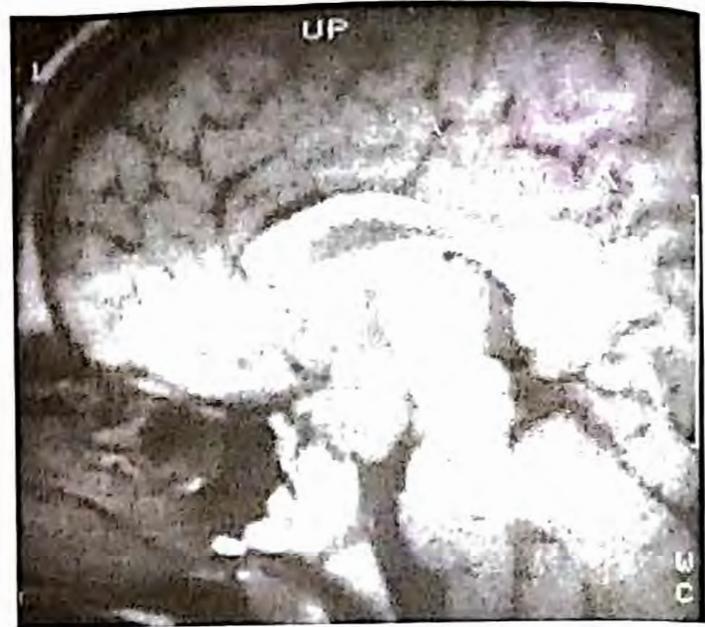


Fig. 18.22: MRI scan showing an isodense mass suggestive of hypothalamic hamartoma

Evaluation

Evaluation is directed towards confirming the diagnosis and establishing the underlying cause.

Clinical: History should include age at onset and progression of puberty, neurological features, family history of precocious puberty and androgen exposure. Detailed anthropometric and neurological examination is performed. Features of CAH (hyperpigmentation, hypertension) should be identified. Estimation of testicular volume is an integral part of assessment. Prepubertal testicular volume (<4 mL) is characteristic of CAH and adrenal tumors; unilateral enlargement is seen in testicular tumors.

Investigations: Initial investigations include LH, FSH and testosterone levels and bone age. All patients with pubertal LH levels should undergo MRI of brain. In the presence of prepubertal LH levels, imaging for adrenals (preferably CT scan) and 17-hydroxyprogesterone levels should be done. The levels of hCG should be estimated, if these investigations are noncontributory (Fig. 18.23).

Management

Management of central precocious puberty includes treatment of underlying pathology and GnRH analog therapy. GnRH analog should be continued till the age of 12 years. CAH is managed with hydrocortisone and fludrocortisone. Surgery is the treatment of choice for adrenal and testicular tumors, while radiotherapy is effective in hCG-secreting tumors. Aromatase inhibitors and antiandrogens are indicated in testotoxicosis.

Delayed Puberty

Delayed puberty is more common in boys than in girls. Most children with delayed puberty have constitutional

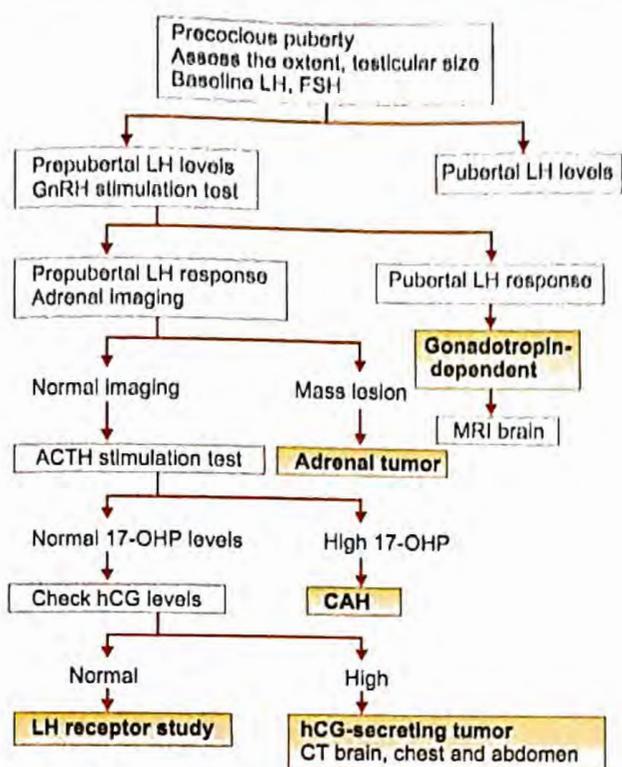


Fig. 18.23: Approach to precocious puberty in boys. ACTH adrenocorticotropic hormone; CAH congenital adrenal hyperplasia; CT computed tomography; FSH follicle-stimulating hormone; GnRH gonadotropin-releasing hormone; hCG human chorionic gonadotropin; LH luteinizing hormone; MRI magnetic resonance imaging; 17-OHP 17-hydroxyprogesterone

delay emphasizing the need for watchful monitoring and conservative approach.

Delayed Puberty in Girls

Delayed puberty in girls is defined as lack of secondary sexual characteristics by the age of 13 years. Absence of menarche by the age of 16 years, or 5 years after onset of puberty indicates pubertal delay.

Etiology

Delayed puberty may be caused by defects in the hypothalamic-pituitary axis, ovaries or genital tract (Table 18.31). Defects in the hypothalamic-pituitary axis are associated with low gonadotropin levels (hypogonadotropic hypogonadism). This may be related to reversible causes such as systemic diseases, malnutrition, eating disorders, hyperprolactinemia and hypothyroidism. Irreversible defects include destruction of the hypothalamic-pituitary axis by infection, surgery, radiation or tumor. Defective smell sensation, low GnRH levels and hypogonadotropic hypogonadism characterize Kallmann syndrome, a neuronal migration defect due to mutation of *KAL1* gene. Hypergonadotropic hypogonadism is associated with defective estrogen production

Table 18.31: Etiology of delayed puberty in girls

Hypogonadotropic hypogonadism

Transient

Systemic disorders: Renal failure, liver disease, celiac disease, renal tubular acidosis, cystic fibrosis

Nutritional disorders: Malnutrition, anorexia nervosa

Endocrine disorders: Hypothyroidism, hyperprolactinemia, type 1 diabetes

Permanent

Isolated hypogonadotropic hypogonadism

Genetic: *KAL1*, GnRH receptor, LH, FSH, *DAX1* mutations

Dysmorphic syndromes: CHARGE, Prader-Willi, Laurence-Moon-Bardet-Biedl

Multiple pituitary hormone deficiencies

Malformations: Holoprosencephaly, septo-optic dysplasia, midline defects

Genetic disorders: *PROP1*, LH gene deletions

Brain tumors: Craniopharyngioma, germinoma, glioma

Brain injury: Surgery, infection, radiation, trauma

Infiltrative disorders: Histiocytosis, autoimmune disorders

Hypergonadotropic hypogonadism

Gonadal dysgenesis: Turner syndrome, *SRY* deletion, trisomy 18, 13, 21

Steroidogenic defects: *STAR*, 17 α -hydroxylase, 17 β -hydroxysteroid dehydrogenase or aromatase deficiency

Ovarian insults: Surgery, radiation, alkylating agents, infections

Autoimmune ovarian failure: Autoimmune polyendocrinopathy

Gonadotropin resistance: LH and FSH receptor mutations

Isolated amenorrhea

Structural malformations: Müllerian agenesis, vaginal septum, imperforate hymen

Inefficient androgen action: Complete androgen insensitivity syndrome

DAX1: Dosage sensitive sex reversal; FSH: Follicle-stimulating hormone; GnRH: Gonadotropin-releasing hormone; LH: Luteinizing hormone; *KAL1*: Kallmann syndrome gene 1; *STAR*: Steroidogenic acute regulatory protein; *SRY*: Sex determining region on Y chromosome

by ovaries and elevated gonadotropin levels. Causes include Turner syndrome, ovarian failure and enzymatic defects in estrogen synthesis.

Evaluation

Goals of evaluation include identification of constitutional delay, organic etiology requiring neuroimaging and decision regarding treatment.

Clinical: Family history of delayed puberty provides a clue to constitutional delay in puberty. Patients are screened for chronic systemic or neurological diseases, Turner syndrome or hypothyroidism, and poor olfactory sensation. Amenorrhea with normal secondary sexual characteristics indicates anatomical defects.

Investigations: Workup is directed towards screening for systemic disorders (liver, renal or gastrointestinal disease), followed by estimation of FSH levels and karyotype. Steroidogenic defects are likely, if karyotype and pelvic ultrasound are normal. In patients with low/normal FSH

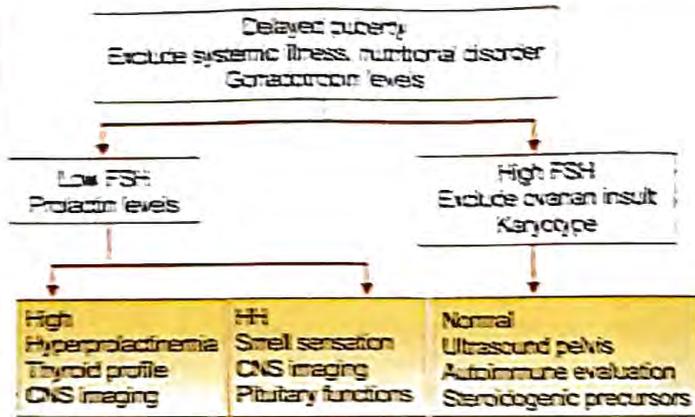


Fig. 18.24: Approach to delayed puberty in girls. CNS central nervous system; HH hypogonadotropic hypogonadism; FSH follicle-stimulating hormone

levels, prolactin and thyroid profile is measured to exclude reversible causes (Fig. 18.24). Neuroimaging and pituitary function tests should be done, if these levels are normal.

Management

All patients with hypergonadotropic hypogonadism and irreversible hypogonadotropic hypogonadism need hormone replacement. Hormone replacement should be deferred till the bone age of 12 years to avoid deleterious effects on height. The goal of treatment is to initiate and maintain sexual characteristics and to prevent osteoporosis. Treatment should be started with low dose estrogens (2 µg ethinylestradiol, 0.3 mg conjugated estrogen or 0.1 mg estradiol valerate every day) and gradually increased every 3 months till adult doses (20 µg of ethinylestradiol, 1.25 mg of conjugated estrogen or 1 mg estradiol valerate daily by 2 years) are reached. Medroxyprogesterone acetate (5–10 mg from day 11 to 21) should be added two years after initiation of treatment or when withdrawal bleeding occurs.

Delayed Puberty in Boys

Delayed puberty is more common in boys than girls and is usually due to a constitutional delay. Lack of pubertal changes by the age of 14 years is suggestive of delayed puberty in boys.

Etiology

Constitutional delay in growth and puberty is the commonest cause of delayed puberty in boys (Table 18.32). They have growth retardation and delayed bone age. Family history of delayed puberty is present. Gonadotropin levels are prepubertal similar to hypogonadotropic hypogonadism.

Hypogonadotropic hypogonadism: This may be reversible due to systemic illnesses or permanent due to neurological insult (e.g. infection, surgery, radiation or tumor). Kallmann syndrome is an important cause of isolated gonadotropin deficiency and presents with impaired smell sensation.

Table 18.32: Etiology of delayed puberty in boys

Hypogonadotropic hypogonadism

Transient
Constitutional delay of puberty and growth
Systemic disorders: Renal failure, liver disease, celiac disease, renal tubular acidosis, cystic fibrosis
Nutritional disorders: Malnutrition, anorexia nervosa, bulimia nervosa
Endocrine disorders: Hypothyroidism, hyperprolactinemia, type 1 diabetes mellitus

Permanent

Isolated hypogonadotropic hypogonadism

Genetic disorders: KAL1, GnRH receptor, LH, FSH, DAX1 mutations

Dysmorphic syndromes: CHARGE, Prader-Willi, Laurence-Moon-Bardet-Biedl, Robinow

Multiple pituitary hormone deficiencies

Malformations: Holoprosencephaly, septo-optic dysplasia, midline defects

Genetic disorders: PROP1, LH gene deletions

Brain tumors: Craniopharyngioma, germinoma, glioma

CNS insults: Surgery, infection, radiation, trauma

Infiltrative disorders: Histiocytosis, sarcoidosis, hemo chromatosis

Hypergonadotropic hypogonadism

Chromosomal abnormalities: Klinefelter syndrome, gonadal dysgenesis

Steroidogenic defects: StAR, 17 α -hydroxylase, 17 β -hydroxysteroid dehydrogenase deficiency, Smith-Lemli-Opitz syndrome
Testicular insults: Radiotherapy, chemotherapy, trauma, torsion, infections

Malformations: Vanishing testis syndrome, cryptorchidism

Inefficient testosterone action: 5 α -reductase deficiency

Resistance to testosterone action: Androgen insensitivity syndrome

DAX1 dosage sensitive sex reversal; FSH follicle-stimulating hormone; GnRH gonadotropin-releasing hormone; LH luteinizing hormone; KAL1 Kallman syndrome gene 1, StAR steroidogenic acute regulatory protein

Delayed puberty is common in Prader-Willi, Laurence-Moon-Bardet-Biedl, Noonan and Robinow syndromes.

Hypergonadotropic hypogonadism (testicular failure) may be due to chromosome abnormalities (e.g. Klinefelter syndrome), partial gonadal dysgenesis, steroidogenic defects and acquired testicular injury (infection, radiation, or chemotherapy) (Fig. 18.25).

Evaluation

Clinical: Family history of delayed puberty suggests constitutional delay in puberty. History of delayed growth spurt with continued growth in adult years and late onset of shaving in father and brothers is common. Patients are examined for features of systemic disease(s); history of head injury, neurosurgery and intracranial space occupying lesions suggest a defect in the hypothalamic-pituitary axis.



Fig. 18.25: Klinefelter syndrome. Note the tall stature and gynecomastia

Investigations: Initial step includes estimation of LH, FSH and testosterone levels. Elevated gonadotropin levels (hypergonadotropic hypogonadism) should be followed by karyotype (Klinefelter syndrome) and evaluation for biosynthetic defects. Boys with low LH and FSH levels may have constitutional delay in puberty or hypogonadotropic hypogonadism. They may be distinguished by hCG stimulation test or GnRH stimulation test (Fig. 18.26). However, these tests are nondiscriminatory in most cases and follow-up after a course of testosterone is the best strategy. Patients with hypogonadotropic hypogonadism should undergo evaluation of hypothalamic-pituitary axis and neuroimaging.

Management

Testosterone treatment should be deferred till the age of 14 years and bone age of 13.5 years. Boys with suspected constitutional delay in puberty should receive three-monthly injections of testosterone enanthate (100 mg). This should be repeated, if adequate response is not achieved. Serum testosterone levels should be estimated three months after the last dose of the drug. Low testosterone levels indicate hypogonadotropic hypogonadism and the need for continued treatment.

Turner Syndrome

Turner syndrome is the most important cause of hypergonadotropic hypogonadism in girls. The disorder affects 1 in 2500 newborn phenotypic females. These girls present with short stature, classical phenotype and delayed puberty. While most common karyotype is 45X,

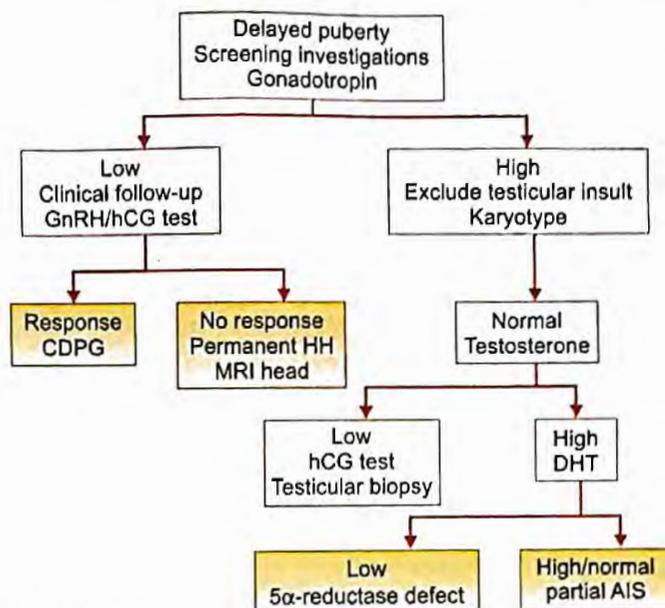


Fig. 18.26: Approach to delayed puberty in boys. AIS androgen insensitivity syndrome; CDPG constitutional delay in growth and puberty; DHT dihydrotestosterone; GnRH gonadotropin-releasing hormone; hCG human chorionic gonadotropin; HH hypogonadotropic hypogonadism; MRI magnetic resonance imaging

mosaic forms like 45X/46XX and 45X/46XY are also observed. Premature atresia of ovarian follicles and bilateral streak gonads may be present.

Clinical Features

Short stature is a frequent finding. Turner syndrome is identified at birth by presence of lymphedema, cystic hygroma and left-sided obstructive cardiac lesions. Features in childhood include cubitus valgus (wide carrying angle), shield chest with widely spaced nipples, web neck and short fourth metacarpal (Table 18.33). Cardiac associations such as coarctation of aorta, mitral valve prolapse and aortic stenosis are common. Renal malformations such as horseshoe kidney, duplication of renal pelvis and agenesis may be present. Endocrine associations include hypothyroidism and diabetes mellitus.

Table 18.33: Pointers to the diagnosis of Turner syndrome

Age group	Features
Intrauterine period	Increased neck translucency, cystic hygroma
Infancy	Cystic hygroma, lymphedema, coarctation of aorta, partial anomalous pulmonary venous return (PAPVR)
Childhood and adolescence	Growth failure, hearing defect, delayed puberty, skeletal abnormalities
Adulthood	Secondary amenorrhea, infertility

Table 18.34: Associations of Turner syndrome

System	Association	Intervention
Growth	Growth failure	GH, oxandrolone
Puberty	Delayed puberty, secondary amenorrhea, infertility	FSH estimation at 12 years, hormone replacement
Cardiovascular system	Coarctation of aorta, bicuspid aortic valve, partial anomalous pulmonary venous return (PAPVR), aortic dissection	Four limb blood pressure, ECG, ECHO at baseline, MRI at 18 years, imaging every 5 years
Ear	Otitis media, conductive and sensorineural hearing loss	Hearing assessment, otoscopic examination, hearing aid
Eye	Strabismus, ptosis, color blindness	Fundoscopy
Orthopedics	Scoliosis, lordosis, reduced cortical density, congenital dislocation of hip	Orthopedic review
Renal system	Collecting duct abnormality, horseshoe kidney, positional abnormality	Ultrasound kidney
Autoimmune disorders	Hypothyroidism, celiac disease	Thyroid function, tissue transglutaminase antibodies
Skin	Pigmented nevi	Monitoring for size

Assessment

Ultrasound pelvis reveals hypoplastic uterus and poorly developed ovaries. FSH levels are elevated. Karyotype is advised in all patients to exclude the presence of a Y chromosome, which is associated with gonadoblastoma in 25–30% cases. Echocardiography and ultrasound for kidneys should be done in all patients for screening cardiac and renal malformations. Thyroid profile and blood sugar estimations are recommended at baseline and yearly. Periodic hearing evaluation for deafness is advised (Table 18.34).

Management

GH therapy (0.35–0.5 mg/kg/week) is indicated in Turner syndrome for improving stature. Estrogen treatment should be deferred till the age of 12 years to ensure adequate growth. Gonadectomy is recommended in patients with a Y chromosome in view of high risk of gonadoblastoma.

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DISORDERS OF SEX DEVELOPMENT

Disorders of sex development (DSD) previously termed as intersex disorders, are rare but constitute a medical, social and psychological emergency.

Physiology

Sexual differentiation is a complex process involving a close interaction of genetic, phenotypic and psychological factors. Usually genetic sex guides gonadal sex, which is responsible for the determination of phenotypic manifestations and gender identity (Fig. 18.27). Any deviation from this pattern results in DSD.

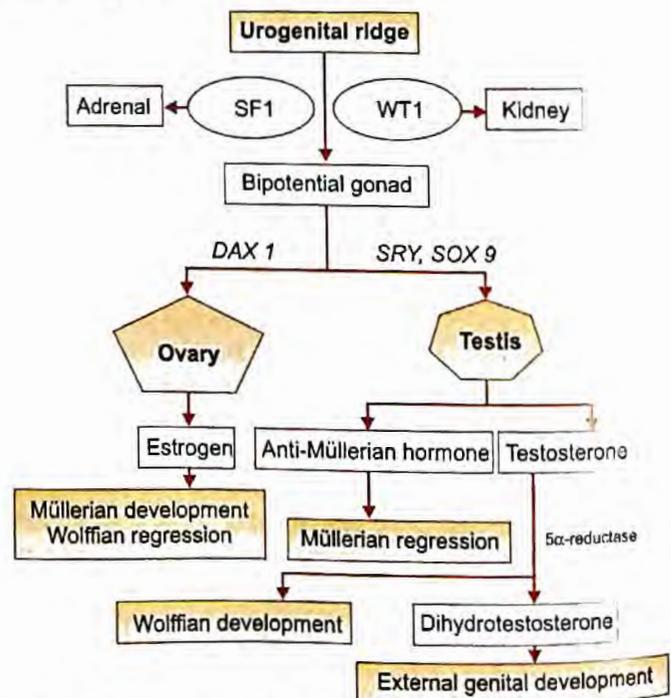


Fig. 18.27: The process of sex development (DSD) and its disorders. DAX1 dosage sensitive sex reversal gene; SF1 steroidogenic factor 1; SOX9 transcription factor related to SRY; SRY sex-determining region on the Y chromosome; WT1 Wilms tumor 1 gene

Gonadal differentiation: Germ cells arise from the coelomic epithelium of hindgut and migrate to the gonadal ridge at 4–6 weeks of gestation. These cells combine with somatic cells to give rise to the bipotential gonad. A transcriptional factor present on the Y chromosome called the sex-determining region of the Y chromosome (SRY) is one of the most important regulators of sexual differentiation. SRY acts in conjunction with other genes like Wilms tumor gene 1 (*WT1*), *SOX9* (a transcription factor on X chromosome) and dosage-sensitive sex reversal (*DAX1*) gene to induce testicular development. In the absence of SRY, the bipotential gonad develops into ovary.

Genital differentiation: Following development of testis, antimüllerian hormone secreted by Sertoli cells induces regression of Müllerian ducts. Testosterone produced by Leydig cells is responsible for sustenance of Wolffian ducts. Dihydrotestosterone (DHT), produced by action of 5 α -reductase on testosterone, is responsible for male external genital development (scrotal fusion and development of corpus spongiosum and penile corpus cavernosa).

Feminization is the default process of sexual development. In the absence of antimüllerian hormone and testosterone, Müllerian ducts differentiate into fallopian tubes, uterus and the upper two-thirds of the vagina. Labioscrotal swellings and urethral folds do not fuse and give rise to labia majora and minora, respectively. The genital tubercles form the clitoris while canalization of the vaginal plate creates the lower portion of the vagina. Prenatal exposure to androgens may lead to labioscrotal fusion, while exposure thereafter usually causes clitoromegaly alone and no labial fusion.

Classification

DSD may be caused by defects in gonadal differentiation (gonadal dysgenesis), androgen production (increased in females and reduced in males) or action (androgen insensitivity syndrome) (Table 18.35).

Increased androgen production in girls: Excess androgen production during the critical period of fetal development may result in masculinization of a female. These disorders are the commonest form of DSD. Congenital adrenal hyperplasia should be excluded in all children with DSD. 21-hydroxylase deficiency is characterized by deficiency of glucocorticoids and mineralocorticoids with elevated androgen levels. Delay in diagnosis could be fatal, underscoring the importance of early diagnosis. 11 β -hydroxylase deficiency, 3 β -hydroxysteroid dehydrogenase deficiency and P450 oxidoreductase deficiency are the other forms of CAH that present with virilization. Transplacental androgen exposure due to maternal medications or hyperandrogenism may lead to virilization in newborns. These disorders are readily identifiable by history of virilization in mother. Rarely aromatase deficiency may be associated with virilization of mother during pregnancy and DSD in the newborn.

Table 18.35: Karyotype based classification of disorders of sex differentiation (DSD)

46,XX DSD

- Androgen excesss
 - Congenital adrenal hyperplasia
 - 21-hydroxylase deficiency
 - 11 β -hydroxylase deficiency
 - 3 β -HSD deficiency
 - POR deficiency
 - Placental aromatase deficiency
 - Maternal virilizing tumors
 - Maternal ingestion of androgenic drugs
- Abnormal gonadal developments
 - Ovotesticular DSDs
 - 46,XX testicular DSD (*SRY+*, *SOX9* duplication)

46,XY DSD

- Disorders of androgen synthesis or actions
 - LH receptor mutations
 - Congenital adrenal hyperplasia
 - StAR deficiency
 - 3 β -HSD deficiency
 - 17-hydroxylase/17,20-lyase deficiency
 - POR deficiency
 - 17 β -HSD deficiency
 - 5 α -reductase deficiency: Types I and II
 - Androgen insensitivity syndrome (AIS): Complete or partial
 - Smith-Lemli-Opitz syndrome
- Abnormal gonadal development
 - Gonadal dysgenesis: Complete or partial
 - Gonadal regression
 - Ovotesticular DSD
- Other conditions
 - Persistent Müllerian duct syndrome

Sex chromosome DSD

- 45,X (Turner syndrome and variants)
- 47,XXY (Klinefelter syndrome and variants)
- 45,X/46,XY (mixed gonadal dysgenesis, ovotesticular DSD)
- 46,XX/46,XY (chimeric, ovotesticular DSD)

HSD: Hydroxysteroid dehydrogenase; POR: P450 oxidoreductase; StAR: Steroidogenic acute regulatory protein

Inefficient androgen action in boys: These disorders result from decreased production, activation or action of androgens. Androgen insensitivity syndrome (AIS) previously referred to as testicular feminization syndrome, an X-linked disorder of androgen action, is the commonest cause and is characterized by resistance to androgens. AIS forms a spectrum ranging from a normal female to a boy with hypospadias, to a male with infertility. Complete androgen insensitivity presents in the neonatal period as a girl with inguinal mass and primary amenorrhea in older girls. Pubic and axillary hair is sparse or absent. Müllerian structures are absent. High DHT levels are diagnostic. 5 α -

reductase deficiency is associated with reduced DHT production. These children virilize during puberty due to increased testosterone levels. High testosterone and low DHT levels are diagnostic. Testosterone biosynthetic defects include deficiency of StAR, 3β -hydroxysteroid dehydrogenase, 17α -hydroxylase and 17β -hydroxysteroid dehydrogenase enzymes. Diagnosis requires estimation of testosterone precursors and basal and hCG-stimulated testosterone and androstenedione levels.

Disorders of gonadal differentiation: These disorders are associated with abnormal gonadal development. The gonad is usually streak (no functional gonadal tissue). Combinations of partially functional testis or ovary or ovotestis may be observed. *SRY* gene deletion results in normal female phenotype with 46,XY karyotype. Mutations in genes involved in the testicular differentiation (*WT1*, *SOX9*, steroidogenic factor 1 and *DAX1*) are other causes of 46,XY gonadal dysgenesis. These disorders are associated with renal (*WT1* mutation), skeletal (*SOX9*) and adrenal abnormalities (*DAX1*). 46,XY gonadal dysgenesis is associated with risk of development of gonadoblastoma. Asymmetric gonadal location may result in asymmetric genital appearance. 46,XX gonadal dysgenesis is usually caused by *SRY* translocation and presents as normal appearing male. Ovotesticular DSD, the new term for true hermaphroditism, is characterized by the presence of both ovarian and testicular tissue in the same individual.

Evaluation

Detailed workup for DSD is indicated in the infants with genital ambiguity, girls with inguinal masses (probable AIS), boys with cryptorchidism (probable 21-hydroxylase deficiency) and penoscrotal hypospadias (probable undervirilization disorder) and adolescent girls with amenorrhea (probable AIS). 21-hydroxylase deficiency should be excluded by estimating blood electrolytes and levels of 17-OHP.

Clinical: Family history of genital ambiguity is suggestive of genetic disorders such as 21-hydroxylase deficiency or androgen insensitivity syndrome. CAH is likely, if there is a history of fetal losses and sibling deaths and family history of consanguinity. On the other hand, history of similar disorder in healthy male relatives (brothers and maternal uncles) is suggestive of AIS. Gonads in complete AIS may be mistaken for inguinal hernia and operated. Intake of progestational drugs during first trimester and features of virilization in mother should be searched. Failure to thrive, polyuria and lethargy indicate 21-hydroxylase deficiency (Table 18.36). Virilization during puberty is suggestive of 5α -reductase deficiency, while feminization indicates AIS. General examination should include assessment for facial dysmorphism and hyperpigmentation. Maternal examination for features of hyperandrogenism like hirsutism, acne and change in voice should be done.

Table 18.36: Clinical pointers to etiology of disorders of sexual differentiation (DSD)

Pointer	Likely diagnosis
Pigmentation	Congenital adrenal hyperplasia, <i>SF1</i> defect, StAR defect
Polydactyly	Smith-Lemeli-Optiz syndrome
Skeletal dysplasia	<i>SOX9</i> defect
Genital asymmetry	Mixed gonadal dysgenesis, ovotesticular DSD
Hypertension	11β - or 17α -hydroxylase defect
Hemihypertrophy	<i>WT1</i> mutation
Renal failure	Denys-Drash syndrome

Genital examination: The most important step is identification of gonads. Bilaterally rounded structures below the inguinal canal are most likely testis. Unilateral gonads are suggestive of mixed gonadal dysgenesis. The labioscrotal region should be evaluated for the extent of fusion (Fig. 18.28). Müllerian structures may be confirmed by rectal examination. The length of phallus and number of openings in the urogenital region should be recorded. Asymmetrical labioscrotal region is suggestive of gonadal dysgenesis or ovotesticular DSD. The genitalia should be staged according to the classification proposed by Prader from grades I to V, with grade I representing female with clitoromegaly and V male with cryptorchidism.

Investigations: Initial investigations should include karyotyping, estimation of blood levels of electrolytes and 17-OHP and pelvic ultrasound. Fluorescent in situ hybridization (FISH) can be used to confirm the presence of Y chromosome. Identification of Müllerian structures is an important part of evaluation of ambiguous genitalia.



Fig. 18.28 46,XY DSD due to partial androgen insensitivity syndrome. Note the nearly female appearance of the external genitalia with an underdeveloped buried penis and poorly developed scrotum and testes

Genitogram is helpful in determination of level of fusion, which is of surgical importance. Further investigations are guided by clinical and laboratory evaluation.

Presence of Müllerian structures with clitoromegaly and no palpable gonads in a child with 46,XX karyotype indicate androgen excess state and need for estimation of serum 17-OHP to rule out CAH. Similarly absence of Müllerian structures in a child with 46,XY karyotype is suggestive of inefficient testosterone action and should be evaluated with estimation of testosterone and DHT. The presence of both Müllerian structures and palpable gonads indicates gonadal dysgenesis or ovotesticular DSD. Absent gonads and Müllerian structures may be caused by vanishing testis syndrome or dysfunctional intra-abdominal testis. Estimation of levels of anti-Müllerian hormone (AMH) and hCG stimulation test are helpful in differentiating the two conditions. Children with vanishing testis will have low levels of AMH and inappropriate response to hCG stimulation.

Management

Management involves parental counseling, decision about sex of rearing, timing of surgical correction and gonadectomy.

Parental counseling: Birth of a child with DSD generates significant parental anxiety and stress. The most important aspect of counseling is reassurance of parents that the child is healthy and the condition is amenable to surgical and/or medical treatment. Gender specific connotation (his or her, testis, ovary) should be avoided and neutral terms like gonads and phallus be used. Future implications regarding sexual and fertility prospects should be discussed.

Decision about gender of rearing: Gender assignment should depend on the potential for future sexual and reproductive function, anatomical status, feasibility of reconstructive surgery and social acceptance and norms. Girls with virilization disorders usually have potential for fertility and should be reared as females. Individuals with

complete AIS should also be reared as females. Decision of gender of rearing is difficult in disorders of inefficient androgen action. This should depend on genital appearance, surgical feasibility and psychological evaluation.

Surgery: There has been a trend of performing early surgeries before gender identity is established. Most centers perform clitoroplasty at the age of 1 year with vaginoplasty reserved during puberty for girls with vaginal stenosis. Gonadectomy should be done in gonadal dysgenesis or ovotesticular DSD, if a Y cell line is present.

Cryptorchidism (Undescended Testes)

Cryptorchidism is present in about 3% of full-term infants and 20% of premature infants. In most of these cases testes descend spontaneously by the age of one year with a decrease in the prevalence to 1%. Spontaneous testicular descent is unlikely after the age of one year and the prevalence in adult population is 0.8%.

Etiology

Most children with undescended testis do not have an identifiable underlying cause. Endocrine causes, account for only a small proportion of boys with undescended testis. The possibility of salt-wasting 21-hydroxylase deficiency presenting with sex reversal should be considered in newborns with bilateral cryptorchidism. Undescended testis may be associated with hypopituitarism, dysmorphic syndromes and disorders of androgen production and action.

Evaluation

It is important to differentiate true undescended testis from retractile or ectopic testis due to therapeutic and prognostic implications (Fig. 18.29). Poorly developed scrotum and inability to bring down the testis to the scrotal sack suggests true undescended testis. Retractable testis is an otherwise fully descended testis that has an active cremasteric reflex, which retracts it into the groin.

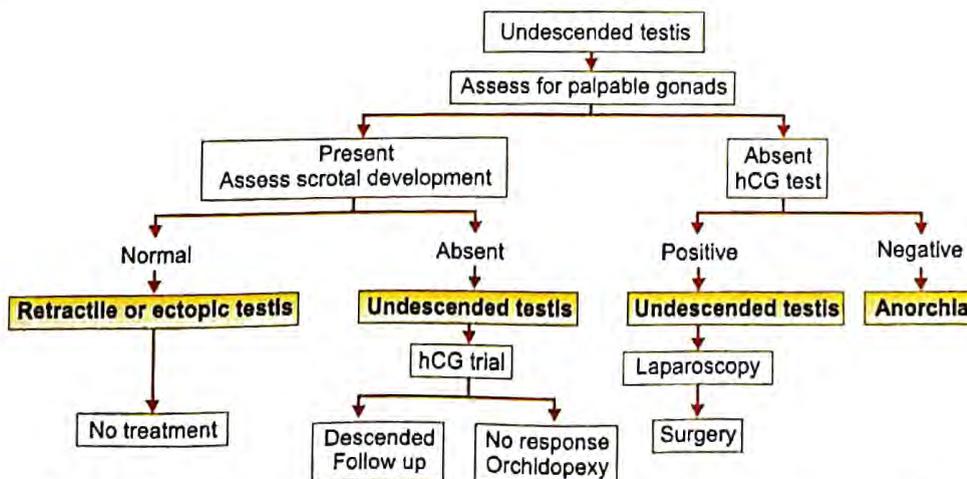


Fig. 18.29: Approach to cryptorchidism. hCG human chorionic gonadotropin

Penoscrotal hypospadias and genital ambiguity are suggestive of disorders of androgen production or action. The hCG stimulation test should be done in boys with bilateral nonpalpable testis to differentiate abdominal testis from anorchia.

Management

Undescended testis is associated with significant complications like torsion, trauma, inguinal hernia, testicular dysfunction and development of malignancy. These children should be treated early because of the increased risk for malignancy and infertility in later life. The optimal time of therapy is before the age of one year. The commonly used medical treatment is human chorionic gonadotropin (hCG) 250 units below 1 year, 500 units between 1 and 5 years and 1,000 units above 5 years administered twice a week for 5–6 weeks. Good response occurs within a month. Retraction rate of testes after cessation of therapy is high. If the response to hCG is poor, patient should be treated early with orchiopexy.

Micropenis

A penis whose length in stretched position is less than 2 SD below the mean for the age is termed micropenis. Most often it is the result of primary or secondary testicular failure.

Etiology

Micropenis results from decreased androgen action during fetal life. It may be due to hypogonadotropic hypogonadism as in Kallmann syndrome, Prader-Willi syndrome, septo-optic dysplasia, or Klinefelter syndrome. It may also be a manifestation of partial androgen insensitivity syndrome or testosterone biosynthetic defects.

Evaluation

Penile length should be measured in a fully stretched state by grasping the glans between thumb and forefinger. A firm ruler or caliper should be pressed against the pubic ramus to depress the suprapubic fat pad. The measurement should be made along the dorsum to the tip of the glans penis excluding the length of foreskin. Penile size is often underestimated in boys with obesity (due to the suprapubic fat) and hypospadias (due to chordee). Investigations should include estimation of gonadotropin and testosterone levels. Low gonadotropin and testosterone levels indicate hypogonadotropic hypogonadism. Elevated gonadotropin levels (hypergonadotropic hypogonadism) should prompt evaluation for testicular dysgenesis, steroidogenic defects or AIS.

Management

All boys with micropenis are treated with a course of low dose testosterone (25 mg testosterone enanthate or cypionate monthly for three doses). The aim of this short course of testosterone treatment is to increase penile length

and not to induce puberty. Boys with micropenis should be reared as males as normal sexual function is usually attainable with early intervention.

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DIABETES MELLITUS

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia and glycosuria. The factors that contribute to hyperglycemia include decreased insulin secretion and its action and increased glucose production. Hyperglycemia resulting from diabetes mellitus causes damage to several organs and body systems, including the kidneys, eyes and cardiovascular system. There is substantial change in the epidemiology of diabetes in children in recent years. While type 1 diabetes caused by insulin deficiency remains the predominant form in children, type 2 diabetes is emerging as an important entity in obese adolescents.

Diagnostic Criteria

The definition of diabetes in children is similar to adults. Fasting blood glucose more than 126 mg/dL (7 mmol/L), postprandial blood glucose two hours after an oral glucose load of 75 g of more than 200 mg/dL (11.1 mmol/L) or random blood glucose greater than 200 mg/dL with classical symptoms is diagnostic of diabetes mellitus (Table 18.37).

Glycated hemoglobin or hemoglobin A1c (HbA1c) is now accepted as a diagnostic criterion for diabetes in

Table 18.37: Diagnostic criteria of diabetes mellitus (American Diabetes Association, 2016)

Parameter	Levels
Fasting plasma glucose	≥126 mg/dL (7.0 mmol/L)
2 hours after 1.75 g/kg glucose	≥200 mg/dL (11.1 mmol/L)
Random blood glucose with symptoms	≥200 mg/dL (11.1 mmol/L)
HbA1c	≥6.5% (48 mmol/mol)

adults with levels greater than 6.5% indicating diabetes. The validity of HbA1c as diagnostic criteria in children is still disputed. Most children with type 1 diabetes have blood glucose level substantially higher than 200 mg/dL and do not need a glucose tolerance test. Tolerance testing is restricted to children with obesity and suspected type 2 diabetes. The test is performed after adequate carbohydrate intake for three days (150 g/m²/day) and overnight fast. The child is given glucose (1.75 g/kg, maximum 75 g) as a chilled liquid with blood glucose measurements done at 0 and 120 minutes.

Classification

Reduced levels of action of insulin cause diabetes. Most children with diabetes have type 1 diabetes caused by damage to beta cells of pancreas (Table 18.38). Type 2 diabetes is an important cause in obese adolescents. Other forms of childhood diabetes include genetic forms of diabetes (monogenic diabetes of young, MODY) and neonatal diabetes.

In most situations, the type of diabetes is evident on clinical presentation and extensive diagnostic workup is not required. Investigations for classification of diabetes are reserved for children with onset after puberty (likely to be type 2 diabetes or MODY), no ketoacidosis at diagnosis (likely to be type 2 diabetes or MODY), those with obesity and acanthosis nigricans (likely to be type 2 diabetes) or in the presence of abdominal pain and steatorrhea (exocrine pancreatic disorder).

Investigations for classification for diabetes include ultrasound abdomen (for pancreatic calcification), levels of C-peptide (a marker of beta cell function), GAD and insulin autoantibodies (indicators of autoimmune nature of type 1 diabetes) and genetic analysis for MODY (Table 18.39). The disease classification is often challenging as C-peptide levels may be low due to glucotoxicity in

Table 18.38: Classification of diabetes mellitus (American Diabetes Association 2014)

I. Type 1 diabetes

Absolute insulin deficiency due to beta cell destruction:
Up to 95% of all pediatric diabetes

1. IA (autoimmune)
2. IB (non-autoimmune)

II. Type 2 diabetes

Insulin resistance with relative insulin deficiency: 10–50% of diabetes in adolescents depending on ethnicity served.

III. Other specific types of diabetes

1. *Genetic defects of beta cell function*: Maturity onset diabetes of the young (MODY), neonatal diabetes, mitochondrial disorders
2. *Genetic defects in insulin action*: Insulin receptor defects, lipodystrophy, type A insulin resistance, Rabson-Mendenhall syndrome
3. *Diseases of exocrine pancreas*: Pancreatitis, trauma/pancreatectomy, cystic fibrosis, fibrocalcific pancreatic disease, hemochromatosis
4. *Genetic syndromes*: Turner, Klinefelter, Down, Prader-Willi, Wolfram, Laurence-Moon-Bardet-Biedl syndromes
5. *Endocrinopathies*: Growth hormone excess, Cushing syndrome, hyperthyroidism
6. *Drug or chemical induced*: Steroids, L-asparaginase, cyclosporine, tacrolimus, interferon, pentamidine, thiazides, diazoxide, phenytoin
7. *Infections*: Congenital rubella, cytomegalovirus
8. *Uncommon forms*: Stiff-man syndrome, anti-insulin receptor antibodies

IV. Gestational diabetes

Diabetes diagnosed in the second and third trimesters of pregnancy that is clearly not overt diabetes

Table 18.39: Differentiating features of common causes of diabetes in children

Feature	Type 1 diabetes mellitus	Type 2 diabetes mellitus	Maturity onset diabetes of the young (MODY)
Age at onset	Any age; most common in children	Post-pubertal; adults and adolescents	Post-pubertal; adults and adolescents
Onset of disease	Acute	Insidious	Insidious
Diabetic ketoacidosis at onset	30–60%	5–25%	Less than 5%
Family history of diabetes	5–10%	75–90%	100%
Obesity	Around 20%	More than 90%	Unusual
Acanthosis nigricans	Absent	Usually present	Absent
Insulin requirement	Universal	Variable	Variable
C-peptide levels	Low	High, normal	Low-normal
Insulin sensitivity	Normal	Low	Normal
Islet cell antibodies	40–70%	Unusual	Negative
Management	Insulin	Diet, metformin	Diet, sulfonylurea

the initial stage of type 2 diabetes and autoantibodies are positive in only 60% of Indian children with type 1 diabetes.

Type 1 Diabetes Mellitus

Type 1 diabetes is the commonest form of childhood diabetes characterized by insulin deficiency due to damage to beta cells of pancreas. The disorder requires lifelong insulin replacement.

Epidemiology

There is a significant geographic variation in the incidence of type 1 diabetes. Scandinavia has the highest incidence, with Finland having the incidence of 35/100,000/year. Indian data suggest an incidence of 10.5/100,000/year. Type 1 diabetes can occur at any age but has two discernible age peaks of higher incidence. The first peak occurs around 5 to 7 years is related to exposure to viral infections, while the second peak around puberty is linked to increase in GH and sex steroids.

Pathogenesis

Children born to parents with type 1 diabetes have a higher risk of developing the disease. The risk is higher, if the affected parent is father (7% compared to 4%, if mother is affected). If a sibling is affected, the risk is 6% when the onset is before 10 years of age and 3% thereafter. The role of heredity is less significant in type 1 diabetes compared to type 2. In studies on identical twins, concordance rates of only 30–40% have been reported for type 1 diabetes suggesting that factors other than heredity play an important role in the pathogenesis of the disease.

The most important genetic focus for type 1 diabetes lies in chromosome 6 and is linked with expression of HLA antigens. HLA-DR3 and DR4 have emerged as important determinants of developing type 1 diabetes. Other genes implicated in pathogenesis include insulin gene and cytotoxic T lymphocyte antigen 4 (CTLA4). Together these genes can explain around 60% heritability of type 1 diabetes. Protection against the disease is provided by the HLA-DR2 haplotype.

Infections predisposing to type 1 diabetes include mumps, coxsackievirus, cytomegalovirus and rubella (congenital rubella syndrome). Rodenticides have been implicated in the development of diabetic ketoacidosis in Korea. There is increasing evidence that early introduction of cow's milk protein may be an important factor in the subsequent development of diabetes in genetically susceptible infants. This has led to delayed introduction of cow's milk in infants.

There is substantial evidence for autoimmunity in type 1 diabetes. Lymphocytic infiltration around the beta cells is found on autopsy of individuals of type 1 diabetes who die due to incidental causes. At diagnosis, 70–80% of white children with type 1 diabetes have islet cell antibodies

(ICA). These antibodies usually predate the clinical presentation of insulin-dependent diabetes mellitus by a few months or years. This suggests that they play a major role during the initial pathogenesis of the disease. The prevalence of antibodies in newly diagnosed Indian children with type 1 diabetes is substantially lower.

Clinical Features

Children and adolescents usually present with symptoms of diabetes that are ongoing for a month or two prior to seeking physician's contact, with an acute increase in symptoms over the previous week. Symptoms of type 1 diabetes include polyuria, nocturia, enuresis, polydipsia, recent weight loss, polyphagia and fatigue. Recent acute infection is often noted at presentation. Unfortunately, these symptoms are often ignored resulting in delayed diagnosis.

Course of Illness

Most children respond to insulin therapy. Once insulin is initiated, blood sugars gradually decline. Often, after around a week of insulin therapy, the need for exogenous insulin declines, due to a transient recovery of insulin secretion. This phase is called the "honeymoon phase of diabetes". Some children may be completely insulin-free during this time. This phase lasts from a few days to a month, and rarely to one year. The need for insulin gradually increases till such time when the pancreas can no longer secrete insulin. At this point, the daily insulin requirement plateaus at around 0.8–1 unit/kg/day.

Ambulatory Care

Day-to-day management of type 1 diabetes involves medical management of glycemic control, and avoidance of acute complications and prevention of chronic complications on one hand and achieving social, scholastic and psychological goals of the child on the other. Comprehensive education and ongoing involvement with the family is mandatory. Teamwork approach with pediatrician/endocrinologists, diabetic nurse educator, social worker and nutritionist is essential.

Insulin

Insulin is the cornerstone of type 1 diabetes management. The body secretes insulin at a basal rate with intermittent secretion with meals. The aim of management is to mimic this pattern as best as possible.

Dose: Insulin dose is guided by pubertal status with lower dose for prepubertal children (0.6 unit/kg/day) compared to pubertal (1.0–1.2 unit/kg/day) and post-pubertal children (1.0 unit/kg/day). In the post-ketoacidosis phase, the dose may be as high as 2–2.5 unit/kg/day.

Preparations: Chemical modifications of insulin alter their action profile providing flexibility in tailor made insulin

Table 18.40: Pharmacokinetic profile of insulin preparations

Preparation	Onset	Peak	Duration	Indications
Rapid-acting				
Lispro	5–10 min	1–3 hours	3–4 hours	Small child on mixed split regimen, insulin pump, Multiple daily injections (MDI)
Aspart	5–10 min	1–3 hours	3–5 hours	
Short-acting				
Regular	30–60 min	2–4 hours	5–8 hours	Diabetic ketoacidosis (DKA), mixed split regimen
Intermediate-acting				
NPH	1–2 hours	2–8 hours	16–24 hours	Mixed split regimen, basal bolus regimen
Long-acting				
Glargine	2–4 hours	Peakless	20–24 hours	Basal insulin
Detemir	1–2 hours	6–12 hours	20–24 hours	Basal insulin, mixed split regimen
Degludec	0.5–1 hours	Peakless	>24 hours	Basal insulin

regimen. Currently all available forms of insulin are derived by recombinant DNA technology (Table 18.40).

Short-acting (regular) insulin: Regular insulin that is structurally the same as natural insulin, is the agent of choice for IV infusion while managing diabetic ketoacidosis (DKA). On subcutaneous administration, the medication forms hexamers in the skin, delaying onset of action by 30–60 minutes. Regular insulin should hence be given 30 minutes before a meal, which may be a problem in young children and toddlers with unpredictable eating patterns. The longer duration of action is helpful, if there is a substantial gap between meals especially in school-going children who have early breakfast and late lunch.

Rapid-acting insulins (lispro, aspart and glulisine): These insulins do not form hexamers after injection and have immediate onset of action. They are ideal for toddlers with irregular eating patterns and can be given even after a meal. They provide better post-meal glycemic control compared to regular insulin and reduce the risk of hypoglycemia. Insulin analogs are, however, expensive and provide inadequate lunchtime cover on a two-injection regime.

Intermediate-acting insulin (NPH): NPH is a chemically modified insulin (protamine) with prolonged duration of action of 12–18 hours. It is traditionally used with short-acting insulin for mixed split regime, but has significant intra-individual variability in absorption resulting in fluctuating glycemic control.

Long-acting insulin (glargine, detemir and degludec): These long-acting forms provide peakless cover for 18–36 hours. They are useful as basal insulin in basal bolus regimen.

Insulin Regimen

The decision about the choice of insulin regimen is dependent on age, socioeconomic status and level of glucose control of a child. A physiological regimen with

multiple daily injections is preferred in most children with the exception in a resource-poor setting where a conventional regimen is more practical.

Basal bolus regimen: Basal bolus regimen mimics physiological insulin secretion with the use of a long-acting basal insulin (detemir or glargine, 40–50% of total daily dose) and mealtime rapid-acting analog (aspart, glulisine or lispro, 50–60% of total daily dose, Fig. 18.30). The mealtime dose is distributed over 3–5 times a day depending on the diet pattern of the child. This regimen offers flexibility, as changes in mealtimes do not cause significant fluctuations in glycemic control. The risk of hypoglycemia is also lower compared to mixed split regimen.

Mixed split regimen (two or three injections per day, Fig. 18.31): This involves the combination of short- and intermediate-acting insulin mixed at the time of injection. The injections are given before breakfast (two-thirds of daily dose) and before dinner (one-third of daily dose). The ratio of short- to intermediate-acting insulin is 1 to 2. This regimen has the advantage of less frequent injections

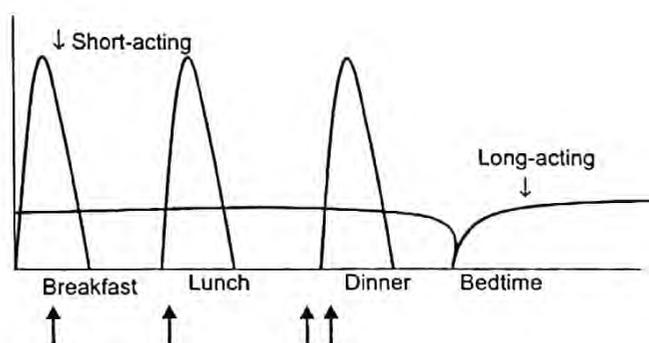


Fig. 18.30: Basal bolus regimen. Intermediate- (NPH) or long-acting insulin (glargine or detemir) is given before dinner or at bedtime (40–50% of total daily dose; black arrow). Rapid- or short-acting insulin (aspart or lispro) is given before each meal (50–60% of total daily dose; blue arrows)

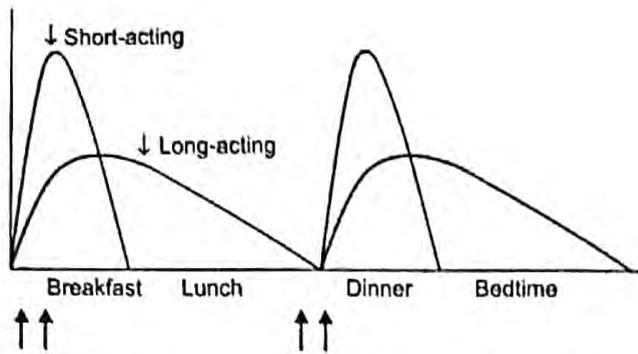


Fig. 18.31: Mixed split regimen. Insulin is given before breakfast (two-thirds of daily dose) and dinner (one-third of daily dose). Each injection is a combination of intermediate- or long-acting (NPH or detemir; two-thirds of the total dose; black arrows) and short- (regular) or rapid-acting insulin (lispro or aspart, one-third of the total dose; blue arrows). Regular meal pattern is required to prevent hypoglycemia

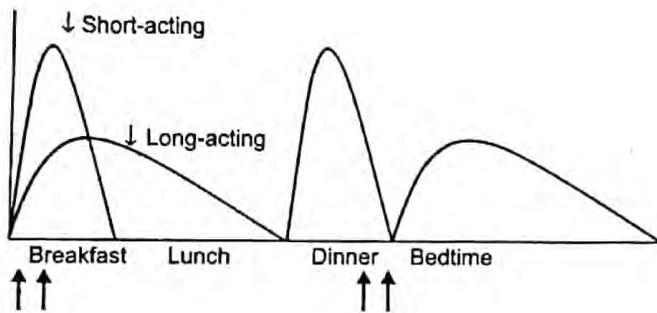


Fig. 18.32: Modified mixed split regimen. The night-time intermediate-acting insulin has been shifted from before dinner to bedtime. This is indicated in the presence of nocturnal hypoglycemia and high pre-breakfast blood glucose levels. Delayed peak of intermediate-acting insulin reduces the risk of nocturnal hypoglycemia on one hand while providing reasonable cover for morning hyperglycemia

and lower cost. The regimen requires rigid dietary control and strict lifestyle with regular mealtimes and snacks. In a variation of the regimen, the intermediate-acting insulin is shifted to bedtime to prevent nocturnal hypoglycemia and morning hyperglycemia (Fig. 18.32).

Continuous subcutaneous insulin infusion (insulin pump): Insulin pump is an external device that infuses insulin at a predetermined rate with additional boluses given at mealtime. The basal dose can be adjusted for different times of the day and boluses tailored to different amount and types of meals to provide good glycemic control with limited glycemic variability. Insulin pump is superior to basal bolus regimen in terms of insulin requirement, glycemic variability and weight gain. Closed loop systems and insulin pumps with capability to detect blood sugar levels and infusing desired amount of insulin, are expected to be available soon and provide physiological glycemic control.

Diabetes Education

Structured diabetes education is mandatory for the management of diabetes in children. Key areas to be covered in the program include pathophysiology of diabetes, insulin use, sick day management, hypoglycemia, nutrition, physical activity and social issues (Table 18.41).

Nutritional Management

The key to successful nutritional management in type 1 diabetes is flexibility. Overzealous control is associated with rebellious behavior and dietary indiscretion. There is no 'diabetic diet' for children and they should be encouraged to have a normal healthy diet. Importance should be given to consistency of mealtimes. Dietary exchanges and a 'nutritional pyramid approach' are useful in providing variety for children. Occasional treats during special occasions and eating out are allowed, if covered appropriately with insulin (Table 18.42).

Monitoring

Self-monitoring of blood glucose (SMBG): SMBG is critical for management of type 1 diabetes. It should ideally be done before each meal and at bedtime. Post-meal and midnight blood sugars are measured as required, adjusted according to the patient age (Table 18.43). In children with significant glycemic variability, continuous glucose monitoring system (CGMS) provides information about glycemic control every 5 minutes over a 72-hour period to help decide about insulin adjustment.

Hemoglobin A1c: HbA1c is a marker of glycemic control over previous 3 months and is the best predictor of long-term complications. Target levels for HbA1c are less than 7.5% in children and adolescents. These levels may be falsely low in children with sickle cell disease, iron deficiency and increased red cell turnover as in hemolytic anemia. Falsely elevated HbA1c levels are seen with uremia and high dose aspirin treatment.

Follow-Up

Children with diabetes should be followed every three months or more frequently as needed. Clinical assessment should include assessment of growth, puberty, blood glucose levels, and examination of injection sites and care of feet. Children with persistent hypoglycemia should be evaluated for adrenal insufficiency, hypothyroidism, celiac disease and diabetic nephropathy with decreased insulin excretion. Puberty is associated with an increase in insulin requirement due to the effect of sex hormones and GH. The requirement further increases in adolescents with obesity.

Sick Day Care

Key aspects of sick day management include frequent blood glucose monitoring, regular fluid intake and treatment of the intercurrent illnesses. Insulin requirement

Table 18.41: Diabetic education

Category	Should know	May know	Optional
Disease	Diabetes is a lifelong disease Normal outcome is possible with appropriate therapy	Role of insulin as life-saving therapy Differences of type 1 vs. 2 diabetes Pathophysiology of diabetes Complications	Glucose homeostasis Disease classification Role of autoimmunity Disease associations
Treatment	Insulin is the only mode of treatment Daily injections are a must Physical activities No alternative medicine	Insulin preparations Time course of injections Injection devices Exercise and sports	Insulin regimens Insulin pumps Newer Insulins Competitive sports Hope for the future
Skills	Insulin storage Drawing up and mixing of insulin Insulin injection techniques Self blood glucose testing Diabetes diary and log	Glycemic targets Insulin changes Ketone monitoring	Ketone monitoring Glucagon injection
Nutrition	Healthy eating Avoid simple sugars Mid-meal snacks	RDA for age Food exchanges High fiber intake	Carbohydrate counting Insulin to carb ratio Glycemic index
Follow-up	Honeymoon phase Hypoglycemia Sick day guidelines	Role of HbA1c Complication Physical activity DKA prevention	CBGM Transplantation Career counseling

CBGM: Continuous blood glucose monitoring; DKA: Diabetic ketoacidosis; RDA: Recommended dietary allowances

Table 18.42: Nutritional guidelines for type 1 diabetes

Component	Recommendation	Implication
Energy	100% of RDA	No restriction
Carbohydrate	50–55% of calories Low GI carbohydrate	No restriction Moderate sugar intake
Fat	25–40% of energy	Less saturated fat
Saturated	<10% of total energy	Less red meat, whole milk
Polyunsaturated	<10% of total energy	
Monounsaturated	>10% of total energy	
Cholesterol	<300 mg/day	
Protein	10–15% of calories	No restriction
Fiber	More than 10 g/day	More fruits, vegetables

Table 18.43: Age-related glycemic targets

Target	<6 years	6–12 years	>12 years
Blood glucose			
Premeal	100–180 mg/dL	70–180 mg/dL	70–130 mg/dL
Bedtime	110–200 mg/dL	100–180 mg/dL	90–140 mg/dL
HbA1c	Less than 8%	Less than 7.5%	Less than 7.5%

usually increases during a febrile illness but may decrease with vomiting and diarrhea. Basal insulin should never be omitted in sick children with type 1 diabetes. In children with blood glucose less than 80 mg/dL, rapid-acting insulin should be withheld and the dose of intermediate-acting insulin is reduced by 20–30%. No extra insulin is required in children with febrile illness and blood glucose

between 80 and 270 mg/dL. Blood ketones should be measured, if blood glucose is more than 270 mg/dL. Children with moderate ketosis (blood ketones between 1 and 1.5 mmol/L) should be given extra regular insulin (10% of total daily dose). Impending DKA (blood ketone >1.5 mmol/L) is managed with extra doses of regular insulin (15–20% of total daily) and hourly blood glucose

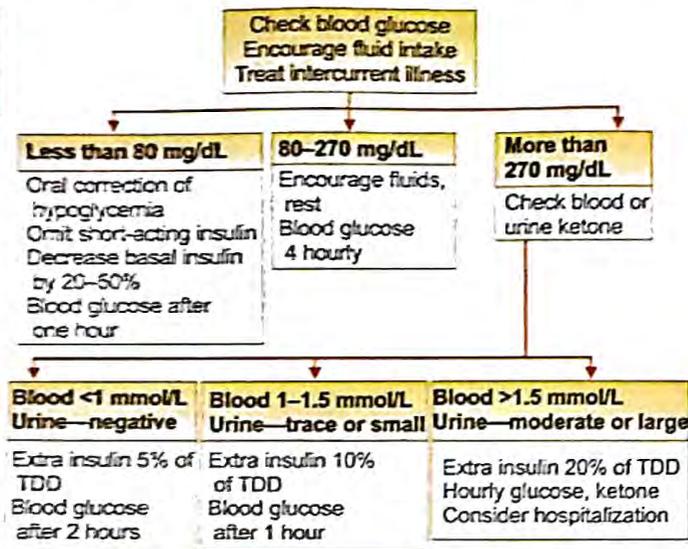


Fig. 18.33: Guidelines for sick day management in children with type 1 diabetes mellitus. TDD total daily dose

monitoring (Fig. 18.33). The child should be hospitalized, if recurrent vomiting, poor oral intake and persistent hyper- or hypoglycemia are present.

Hypoglycemia

Hypoglycemia is common in children with diabetes and is an impediment to glycaemic control. It should be considered in presence of autonomic (e.g. sweating, palpitations, tremor, hunger) or neuroglycopenic symptoms (e.g. headache, confusion, drowsiness, seizures). Children with hypoglycemia should immediately receive 15–20 g of rapidly absorbed glucose, followed by long-acting carbohydrate. Severe hypoglycemia is a medical emergency and should be treated with injectable glucagon (150 g/kg) or intravenous dextrose.

Diabetic Ketoacidosis

DKA is the most severe acute complication of diabetes mellitus. Previously believed to be limited to subjects with type 1 diabetes, DKA is increasingly observed in type 2 diabetes and MODY. Early identification and management are essential to limit the extent of mortality and morbidity associated with DKA. Thirty to forty percent of freshly diagnosed children with type 1 diabetes present with DKA. Although epidemiological data from India is lacking, the figure is higher than the developed countries.

Pathophysiology

DKA is the end result of absolute or relative insulin deficiency combined with excess of counter-regulatory hormones such as glucagon, catecholamines, cortisol and GH (Fig. 18.34). DKA is usually precipitated by infection, stress and trauma, and conditions associated with increased insulin requirement and higher level of counter-regulatory hormones. These hormonal alterations result in hyperglycemia and lipolysis resulting in increased free

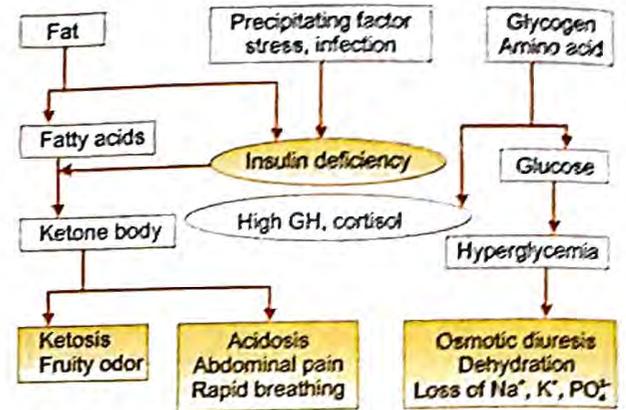


Fig. 18.34: Pathophysiology of diabetic ketoacidosis. GH growth hormone; K⁺ potassium; Na⁺ sodium; PO₄⁻ phosphate

fatty acid production. Oxidation of fatty acids in liver generates β-hydroxybutyrate and acetoacetic acid (ketones). Accumulation of ketoacids produces acidosis resulting in Kussmaul breathing (acidosis), abdominal pain (acidosis) and fruity odor of breath (acetone). Hyperglycemia results in increased urinary water losses due to osmotic diuresis and dehydration. Acidosis causes shift of intracellular ions, most importantly potassium and phosphate, to the extracellular compartment. However, serum levels of potassium are variable, depending on the stage of DKA. Initially, serum potassium levels are high; as therapy with insulin is initiated, the patient becomes hypokalemic. Hyperglycemia also falsely lowers serum sodium resulting in pseudohyponatremia; each 100 mg/dL elevation in blood sugar lowers sodium by 1.6 mEq/dL.

When to Suspect

There is need for high index of suspicion for DKA and it should be considered in the differential diagnosis of the following:

- *Encephalopathy*: CNS infections, severe malaria, poisoning
- *Acute abdomen*: Pancreatitis, appendicitis
- *Dehydration*: Gastroenteritis
- *Tachypnea*: Bronchial asthma, pneumonia
- *Hyperglycemia with acidosis without ketosis*: Renal failure, septicemia
- *Ketoacidosis without hyperglycemia*: Starvation, salicylate poisoning, organic acidemia

Criteria for Diagnosis

DKA should be diagnosed in presence of all of the following: (i) hyperglycemia (glucose >200 mg/dL); (ii) metabolic acidosis (pH <7.3, bicarbonate <15 mEq/L); and (iii) ketosis (blood ketone >1.5 mmol/L, or urine ketone >2+).

Management

DKA is a life-threatening condition and should be managed in a hospital equipped with facilities for

intravenous infusion and measurement of blood gas and electrolytes. Children younger than 2 years of age and those with severe DKA should be managed in an ICU.

Evaluation

Clinical: Initial evaluation should be guided towards assessment of adequacy of airway, breathing and circulation. Level of dehydration is ascertained along with hemodynamic status. Careful neurological evaluation including assessment of level of consciousness, pupils (dilated fixed in presence of cerebral herniation), cranial nerves (sixth nerve palsy suggests cerebral edema) and deep tendon reflexes (brisk if raised intracranial tension) is mandatory.

Investigations

Serum sodium: There is usually a significant sodium deficit (4–6 mEq/kg). The sodium levels are falsely reduced in hyperglycemia mandating the need to use corrected sodium. Rapid decline in serum sodium is a risk factor for cerebral edema.

Serum potassium: There is substantial intracellular potassium deficit (3–6 mEq/kg). Serum levels are, however, normal or high due to extrusion of intracellular potassium due to acidosis and insulin deficiency. Treatment of DKA is associated with the risk of hypokalemia due to its intracellular shift following reversal of metabolic acidosis and correction of insulin deficiency.

Serum phosphate: Usually there is significant phosphate deficit.

Infection screening: Transient leukocytosis is common; infection should be considered in presence of persistent leukocytosis and fever.

Renal function tests: High blood urea usually indicates severe DKA.

Electrocardiography: This is often done to screen for hypokalemia or hyperkalemia.

Management

Initial stabilization: The child should be assessed for adequacy of airway, breathing and circulation. Initial fluid bolus of 10 mL/kg normal saline over 1-hour should be given in children with dehydration (Fig. 18.35). Oxygen and respiratory support should be provided if required. The child should be kept nil by mouth with insertion of nasogastric tube and urinary catheter, if unconscious.

Fluid therapy: Fluid therapy is the mainstay of treatment for DKA. However, rapid and excessive fluid intake is a risk factor for developing cerebral edema. The aim is to provide maintenance requirement and deficit evenly over 48 hours (72 hours for children with high plasma

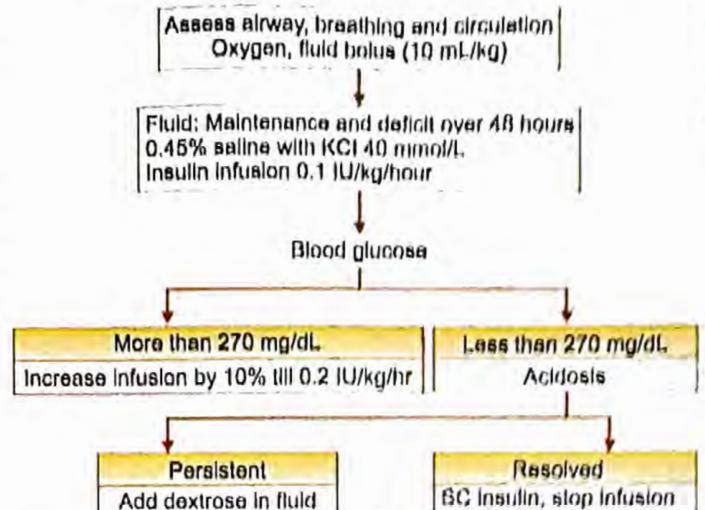


Fig. 18.35: Management of diabetic ketoacidosis, KCl potassium chloride; SC subcutaneous

osmolality). In most children the fluid deficit is 5–10%. Fluid requirement is usually around 3–3.5 L/m²/day (Table 18.44). Care is taken to avoid fluid administration of more than 4 L/m²/day due to risk of cerebral edema. The amount of fluids given at other centers prior to referral should also be considered while calculating fluid requirements.

Insulin: Insulin should be administered after initial hydration as blood glucose levels fall rapidly even without insulin. Early insulin treatment is associated with drastic fall in plasma osmolality, hypokalemia and increased risk of cerebral edema.

Continuous intravenous infusion is the preferred route. The intravenous tubing should be flushed with insulin as insulin binds to plastic tube. There is no role of initial insulin bolus. Insulin infusion should be started at 0.1 unit/kg/hr. In infants and mild DKA, the infusion rate should be kept at 0.05 unit/kg/hr. The dose should be increased if fall in glucose is less than 50 mg/dL/hr. The dose is increased in quantum of 0.02 IU/kg/hr. The insulin infusion rate should be reduced only after resolution of acidosis.

If facility for intravenous insulin is not available, intramuscular regular insulin may be used. The first dose is 0.3 unit/kg followed by 0.1 unit/kg hourly. Recurrent intravenous boluses of insulin should be avoided due to the risk for cerebral edema. Subcutaneous insulin is not recommended due to decreased absorption in the setting of poor perfusion.

Serum sodium: Most patients have significant sodium deficits (4–6 mEq/kg). Slow rise in sodium in patients with rapid fall in glucose is a risk factor for cerebral edema. Normal saline (154 mEq/L) should be used in the first 6 hours of therapy; thereafter the sodium content should be between 77 and 154 mEq/L.

Table 18.44: Guidelines for fluid infusion rate (mL/hour) in DKA

Weight	Level of dehydration			Weight	Level of dehydration		
	Mild/nil	Moderate	Severe		Mild/nil	Moderate	Severe
5 kg	24	27	31	38 kg	101	125	156
7 kg	33	38	43	40 kg	104	129	162
8 kg	38	43	50	42 kg	107	133	168
10 kg	48	54	62	44 kg	110	137	174
12 kg	53	60	70	46 kg	113	141	180
14 kg	58	67	79	48 kg	116	146	186
16 kg	64	74	87	50 kg	119	150	191
18 kg	70	80	95	52 kg	122	154	197
20 kg	75	87	104	54 kg	124	158	203
22 kg	78	91	110	56 kg	127	162	208
24 kg	80	95	115	58 kg	130	167	214
26 kg	83	100	121	60 kg	133	171	220
28 kg	86	104	127	62 kg	136	175	226
30 kg	89	108	133	64 kg	139	179	232
32 kg	92	112	139	66 kg	142	183	238
34 kg	95	116	145	68 kg	145	187	244
36 kg	98	120	151	70 kg	148	191	250

Serum potassium: Although there is deficit in total body potassium, extracellular potassium levels may initially be high due to acidosis and insulin deficiency. There is a risk of life-threatening hypokalemia following correction of insulin deficiency and resolution of metabolic acidosis. In patients with initial potassium levels less than 3.5 mEq/L, potassium replacement should precede administration of insulin. In other situations potassium replacement is begun, at a concentration of 40 mEq/L, after initial hydration at the time of initiation of insulin infusion. Potassium should not be administered if the level is >6 mEq/L, the patient is anuric or ECG changes of hyperkalemia are present.

Dextrose: Hyperglycemia resolves prior to correction of acidosis. Decreasing insulin infusion rate with lowering of blood glucose is not recommended since that would prolong the duration of acidosis. Dextrose (5%) is therefore added to intravenous fluids once blood glucose levels fall below <270 mg/dL.

Acid-base management: Alkali treatment should be avoided as it poses risks for cerebral edema, lactic acidosis and hypokalemia. It is considered only if pH is less than 6.9 with hemodynamic compromise or if there is severe hyperkalemia (serum potassium >6.5 mEq/L with ECG changes).

Monitoring

Careful clinical and laboratory monitoring is necessary. This should include hourly monitoring of neurological status, heart rate, blood pressure and fluid input/output. Laboratory monitoring includes hourly blood glucose and

four-hourly blood ketone, pH, bicarbonate and electrolytes (Table 18.45).

Discontinuation of acute treatment: Subcutaneous insulin should be considered once the patient is conscious, ready to accept orally and has resolution of acidosis. Regular or rapid acting insulin (0.25 unit/kg) should be given 30 minutes before eating. Alternatively the child may be started on a basal bolus or mixed split regime. Insulin infusion should be stopped only 30 minutes after insulin to provide overlap, and avoid recurrence of hyperglycemia.

Complications of DKA

DKA is a life-threatening condition with potential for significant long-term morbidity. Timely identification and treatment of these complications are essential (Table 18.46).

Cerebral edema: Cerebral edema is the most serious complication of DKA and the most common cause of death. The incidence of clinical cerebral edema is 0.5–1.0% in developed countries, but is higher in India. Risk factors include age less than 5 years, severe acidosis, insulin bolus, excessive hydration and alkali treatment. Cerebral edema usually presents at 4–12 hours following treatment, but may be present at diagnosis. The condition is suspected in presence of persistent hemodynamic instability or worsening in clinical condition after initial improvement. Early pointers include headache, vomiting, drowsiness, irritability, and hypertension with bradycardia. Severe cerebral edema is indicated by unconsciousness, focal neurological deficits, papilledema and fixed dilated pupils. The diagnosis is clinical and there is no need for confirmation by imaging. Children with suspected

Table 18.45: Laboratory parameters and response to treatment in DKA

Parameter	Expected	Concern	Action
Blood sugar	Decrease by 50–100 mg/dL/hour	Decline >100 mg/dL/hour Decline <50 mg/dL/hour	Add dextrose to IV hydration fluid Prepare fresh infusion, flush tubing with insulin
Blood pH	Resolution by 12 hours	Persistent at 12 hours	Exclude infection, shock, lactic acidosis
Serum sodium	Increase	Increase <2 mmol/L/hour	Increase sodium concentration in IV fluid
Serum potassium	Gradual decrease	Hypokalemia	Increase potassium concentration in IV fluid
Anion gap	Resolution by 12 hours	Elevated at 12 hours	Exclude lactic acidosis, consider infection
Plasma osmolality	Stable	Decrease by >2 mOsm/kg/hour	Increase sodium concentration, decrease fluid rate
Blood urea	Decrease	Persistently elevated	Exclude renal failure

Table 18.46: Complications of DKA

Acute	Chronic
Cerebral edema	Growth hormone deficiency
Infections: Bacterial, fungal	Mental retardation
Hypoglycemia	Diabetes insipidus
Hypokalemia	
Acute respiratory distress syndrome	
Venous thrombosis	

cerebral edema should be immediately treated with intravenous mannitol (5 mL/kg) followed by fluid restriction and head end elevation.

Infections: Bacterial and fungal infections are common. Indicators include persistent fever, leukocytosis, black nasal discharge (rhinocerebral mucormycosis) and hemoptysis (pulmonary aspergillosis).

Hyperosmolar Non-Ketotic State

This condition is characterized by severe hyperglycemia (usually >600 mg/dL), hyperosmolality (>350 mOsm/kg), low plasma ketones (negative or positive at <1:2 dilution) and severe dehydration. Although chiefly a complication of type 2 mellitus, it can occur in type 1 diabetes if insulin is present to prevent ketoacidosis, but is insufficient to control the blood sugar. Management is similar to DKA with a need for slower dehydration correction, more fluids and lower insulin requirement.

Long-term Complications of Type 1 Diabetes

Regular screening for long-term complications is essential for their early identification, prevention and appropriate treatment (Table 18.47). Screening for complications should be started after 5 years of diagnosis if the onset of diabetes is before puberty, and 2 years if diagnosed in puberty.

Lipoatrophy is fat atrophy at the injection site. This can be prevented by rotation of injection sites.

Limited joint mobility, due to flexion contractures of metacarpophalangeal and proximal interphalangeal joints, is typically noted in the hands.

Growth failure occurs in children whose diabetes is not well controlled. Mauriac syndrome occurs with poor control of diabetes and is characterized by hepatomegaly, pale skin and extreme short stature.

Delayed puberty is associated with inadequate control of diabetes and delayed bone age.

Hypoglycemic unawareness is caused by frequent hypoglycemia associated with tight metabolic control of diabetes. It is due to impaired counter-regulatory response to hypoglycemia. Raising blood sugar targets and prevention of hypoglycemia usually causes reversal of hypoglycemic unawareness.

Retinopathy is characterized by microaneurysms and proliferative disease. Earlier 80–90% individuals developed eye disease by 15 years of diabetes. With intensive management of diabetes this complication is delayed to beyond childhood. Ophthalmologic examination should be conducted once the child is more than 10-year-old and has had diabetes for 3–5 years. Annual follow-up is suggested.

Peripheral neuropathy is unusual in children and adolescents. This results in decreased nerve conduction velocity and sensory changes. An abnormality in vibration perception may be the first finding.

Nephropathy is defined by presence of albumin in the urine. Annual screening for microalbuminuria is initiated once the child is 10 years of age or has had diabetes for 5 years. If screening shows elevated ratio of spot urine microalbumin to creatinine, 24 hours urine microalbumin is estimated. Patients with significant microalbuminuria should receive ACE inhibitors to delay the progression of nephropathy.

Dyslipidemia: Fasting lipid profile is performed on all children more than 2-year-old at time of diagnosis (after glucose control is achieved), or if there is family history of high cholesterol (>240 mg/dL) and/or a cardiovascular event before 55 years. If there are no concerns of hyper-

Table 18.47: Screening for complications in children with type 1 diabetes mellitus

Complications	Indications	Procedures	Management
Retinopathy	First eye examination after 3 months of diagnosis; screening after 11 years	Initial examination of dilated fundus	Improvement in diabetes control Laser treatment for visual loss
Prepubertal	Duration of diabetes >5 years from onset		
Pubertal	Duration of diabetes >2 years from diagnosis		
Nephropathy	Annual screening after 11 years	Annual screening for micro albuminuria: Albumin excretion rate (AER) 20–200 µg/min or AER 30–300 mg/day	Improvement in diabetes control Control of blood pressure ACE inhibitors to reduce proteinuria
Prepubertal	Duration of diabetes >5 years from onset		
Pubertal	Duration of diabetes >2 years from diagnosis		
Hypothyroidism	At diagnosis; thereafter every 2 years	Serum TSH and FT ₄ estimation Thyroid autoantibodies	Thyroxine therapy
Hyperlipidemia	Annual screening after 12 years	Serum lipid profile	Strict diet control Statins
Prepubertal	At diagnosis; thereafter every 5 years		
Pubertal	At diagnosis; thereafter every 2 years		

lipidemia in the family, screening is performed after onset of puberty (>12 years). For pubertal children (>12-year-old), a fasting lipid profile is performed at diagnosis after glucose control is achieved. If LDL is <100 mg/dL, lipid profile is repeated every 5 years. If lipids are abnormal, annual monitoring is recommended in both age groups. Intervention is needed if fasting LDL >100 mg/dL, initially by dietary modification with decrease in saturated fat in diet. A pharmacologic agent is added for LDL >160 mg/dL, and in patients at risk of cardiovascular disease and LDL values 130–159 mg/dL after initiation of dietary changes and lifestyle intervention. The goal of therapy is LDL level <100 mg/dL.

Hope for Future

Given the need for lifelong treatment in type 1 diabetes, it is only expected that most patients seek permanent cure from the malady. Unfortunately no such cure is available at the moment. The efforts at developing cure for type 1 diabetes are directed towards reversing the autoimmune process or restoration of β-cell mass. Immunosuppressive agents (steroids, cyclosporine A, azathioprine, anti-thymocyte globulin and anti-CD3 antibody) have resulted in only partial and transient response. These strategies are limited by the fact that over 95% of β-cell mass is destroyed by the time of diagnosis of the disease. The other, more appealing approach for cure for type 1 diabetes mellitus, involves restoration of β-cell mass using pancreatic, islet cell or stem cell transplantation. Pancreatic transplant is a major endeavor requiring long-term immunosuppression and is not recommended in adolescents with type 1 diabetes. Studies have failed to show long-term remission with islet cell or stem cell transplantation.

Type 2 Diabetes Mellitus

Type 2 diabetes in children and adolescents is increasing rapidly with the advent of childhood obesity epidemic. The disorder presents with milder symptoms than type 1 diabetes though DKA can develop occasionally. Diagnosis is established based on presence of obesity, acanthosis nigricans, elevated insulin levels, normal C-peptide, and lack of glutamic acid decarboxylase (GAD) antibodies. Lifestyle measures and metformin are the mainstay of treatment. Adolescent type 2 diabetes, however, has an aggressive course compared to adult type 2 diabetes, with faster loss of cell function. Children who present with ketosis are treated with insulin initially and transitioned to oral hypoglycemic agents once endogenous glucose secretion recovers. These children and adolescents should be evaluated for hyperlipidemia, diabetic retinopathy and nephropathy at diagnosis. It is recommended that children at risk of type 2 diabetes be regularly screened for diabetes.

Monogenic Diabetes of Young (MODY)

MODY represents a group of inherited conditions characterized by impaired cell function. The disorder presents with relatively mild, non-ketotic diabetes in a lean individual with strong family history of diabetes affecting three generations. The condition responds to lifestyle measures and low doses of sulfonylurea.

Neonatal Diabetes Mellitus

Onset of diabetes before three months of life suggests neonatal diabetes. It is a challenging condition requiring meticulous monitoring and treatment. The disease represents transient cell dysfunction (transient neonatal diabetes), permanent insulin secretion defect (permanent neonatal diabetes) or congenital insulin resistance

syndrome. The most common cause of permanent neonatal diabetes is activating KATP channel, the on-off button for insulin secretion. These disorders are amenable to treatment with sulfonylurea.

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Diseases of Central Nervous System

Rashmi Kumar

NEUROLOGICAL DIAGNOSIS

History

An accurate history gives insight into the disease process. Vascular events often have the most acute onset, symptoms being worst at the onset with improvement soon after. Acute inflammatory processes like infections and acute disseminated encephalomyelitis (ADEM) are not as sudden in onset as vascular events. Subacute onset is typical of infections like tuberculous meningitis, brain abscess and some brain tumors. A relapsing remitting course is seen in multiple sclerosis and metabolic diseases. A subacute or chronic progressive downhill course is seen in degenerative disorders and neoplasms. A history of consanguineous marriage or family history of neurological disorders suggests a hereditary disorder.

Development History

Neurological disorders are often associated with abnormal development. A careful history of development milestones should be elicited. Age of onset of developmental deviation may suggest the onset of disease. Development may be abnormal in all or some domains or may regress after a period of normal development. Acute insults lead to sudden regression of development.

Clinical Examination

Methods of examination are modified according to the age of the child from adult scheme in older cooperative children to play method in younger children.

Localization of Neurological Lesion

Neurological lesions are broadly divided into upper and lower motor neuron lesions (Table 19.1). The distribution of weakness suggests the level of lesion. A spinal lesion results in paraplegia or quadriplegia below the level. A lesion at or above the brainstem usually causes hemiplegia. Lesions in the brainstem usually cause crossed paralysis, i.e. ipsilateral cranial nerve palsy with contralateral limb weakness. Lesions in the internal

Table 19.1: Localization of neurological disorder

Upper motor neuron (UMN)

Cortex	Contralateral UMN hemiplegia or monoplegia with UMN facial palsy; with/without seizures; spasticity; brisk deep tendon reflexes
Internal capsule	Contralateral dense UMN hemiplegia with UMN facial palsy; spasticity; brisk reflexes
Brain stem	Contralateral UMN hemiplegia with ipsilateral LMN cranial nerve palsy; spasticity; brisk reflexes
Spinal cord	Quadriplegia or paraplegia

Lower motor neuron (LMN)

Anterior horn cells	LMN type weakness in spinal segment; loss of reflexes; fasciculation
Neuropathy	LMN type weakness in nerve distribution; early and complete loss of reflexes
Neuromuscular junction	Weakness and fatigue of ocular and pharyngeal muscles
Muscle	Weakness, especially proximal; Gower sign; depressed deep tendon reflexes

capsule cause dense contralateral hemiplegia affecting the arm more than the leg along with contralateral upper motor neuron facial palsy. Lesions in the cortex often cause seizures and more localized weakness, such as monoplegia. Acute destructive upper motor neuron lesions, as occurs with stroke, may cause flaccidity.

In lesions of the spinal cord, reflexes are usually lost at the level of the lesion. Sudden acute transverse lesions of the cord may cause complete loss of all function below that level which may last for a few weeks (spinal shock). Chronic lesions of the anterior horn cells give rise to fasciculations. Peripheral neuropathy causes weakness with early and complete loss of reflexes. Neuromuscular junction disorders like myasthenia cause weakness of extraocular and pharyngeal muscles towards the later part of the day. Muscle weakness may cause depressed but elicitable reflexes and positive Gower sign, if proximal muscles are involved.

Investigations

Lumbar Puncture

Examination of cerebrospinal fluid (CSF) is required for the diagnosis of CNS infections. The normal CSF is clear, colorless and sterile with less than 5 cells (lymphocytes) per mm³, protein 20–40 mg/dL and sugar level approximately two-thirds of concomitant blood sugar. CSF may be examined for antibody levels, culture and sensitivity, microbial DNA by polymerase chain reaction (PCR), myelin basic protein (in demyelinating disorders), and specific metabolites like lactate (in neurometabolic disorders). Lumbar puncture should be deferred in presence of raised intracranial tension (risk of brain herniation), circulatory failure, overlying local infection or severe bleeding disorder.

Ultrasonography

This bedside procedure is especially useful for newborn and infants with open fontanelle. The ventricles, periventricular tissues and parts of the cortex are well-visualized, whereas the peripheral cortex, subdural spaces and posterior fossa are poorly seen.

Computerized Tomography (CT)

This is relatively quick and inexpensive compared to magnetic resonance imaging. Calcification and bleeding are well visualized. Posterior fossa and temporal lobes are not visualized well, nor are myelination, migration disorders and small cortical dysplasias.

Magnetic Resonance Imaging (MRI)

This offers better anatomic detail than CT especially for myelination and migration disorders, and vascular and congenital abnormalities. Sagittal and coronal views provide important information on midline, posterior fossa and temporal lobe structures. There is no risk of exposing the brain to harmful ionizing radiations.

Genetic Tests

Genomic imbalances or copy number variations are increasingly recognized as a cause of intellectual disability. Techniques used include fluorescent *in situ* hybridization, multiplex ligation-dependent probe amplification (MLPA) and chromosomal microarray. While MLPA has a yield of 5–10%, microarray, which examines the whole genome, yields diagnosis in up to 20% patients with intellectual disability with or without dysmorphism. Next generation sequencing is an emerging technique that allows detection of single nucleotide changes through the whole genome.

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SEIZURES AND EPILEPSY

A seizure is an abnormal paroxysmal electrical activity in the brain resulting in motor, sensory behavioral or autonomic manifestations. About 5% children experience a seizure in the first 5 years of life. A detailed account of the sequence of events should be taken. Table 19.2 lists the chief causes of seizures.

Table 19.2: Etiology of seizures

Neonatal seizures

Birth asphyxia or trauma

Intracranial hemorrhage

Hypoglycemia

Hypocalcemia or hypomagnesemia

Infections: Meningitis, septicemia, tetanus neonatorum, intrauterine infections

Developmental malformations

Inborn errors of metabolism

Pyridoxine dependent seizures

Maternal withdrawal of medications

Accidental injection of local anesthetic into fetal scalp

Beyond newborn period

Simple febrile convulsions

Epilepsy syndromes

Infections: Bacterial meningitis, intrauterine infections, tuberculous meningitis, aseptic meningitis, encephalitis, cerebral malaria, Reye syndrome

Metabolic causes: Dyselectrolytemia, hypocalcemia, hypomagnesemia, inborn errors of metabolism

Space occupying lesions: Neoplasm, brain abscess, tuberculoma, cysticercosis

Vascular: AV malformations, intracranial thrombosis, hemorrhage

Miscellaneous: Hypertensive encephalopathy, sequelae of birth trauma and birth asphyxia, gray matter degeneration, storage disorders

Drugs, poisons: Phenothiazines, salicylates, phenytoin, strychnine, carbon monoxide, lead

Status Epilepticus

Any seizure persisting for more than 30 minutes or multiple seizures, irrespective of duration, with no regaining of consciousness in between, is termed status epilepticus. A single convulsion usually lasts for less than 5 minutes. There is a growing opinion that if a convulsion lasts beyond that time it should be treated as status epilepticus. As a corollary, if any child is brought convulsing to the emergency, he should be treated as status. In over 50% of cases, status epilepticus occurs as the patient's first seizure. Status epilepticus is caused by the same entities that cause isolated

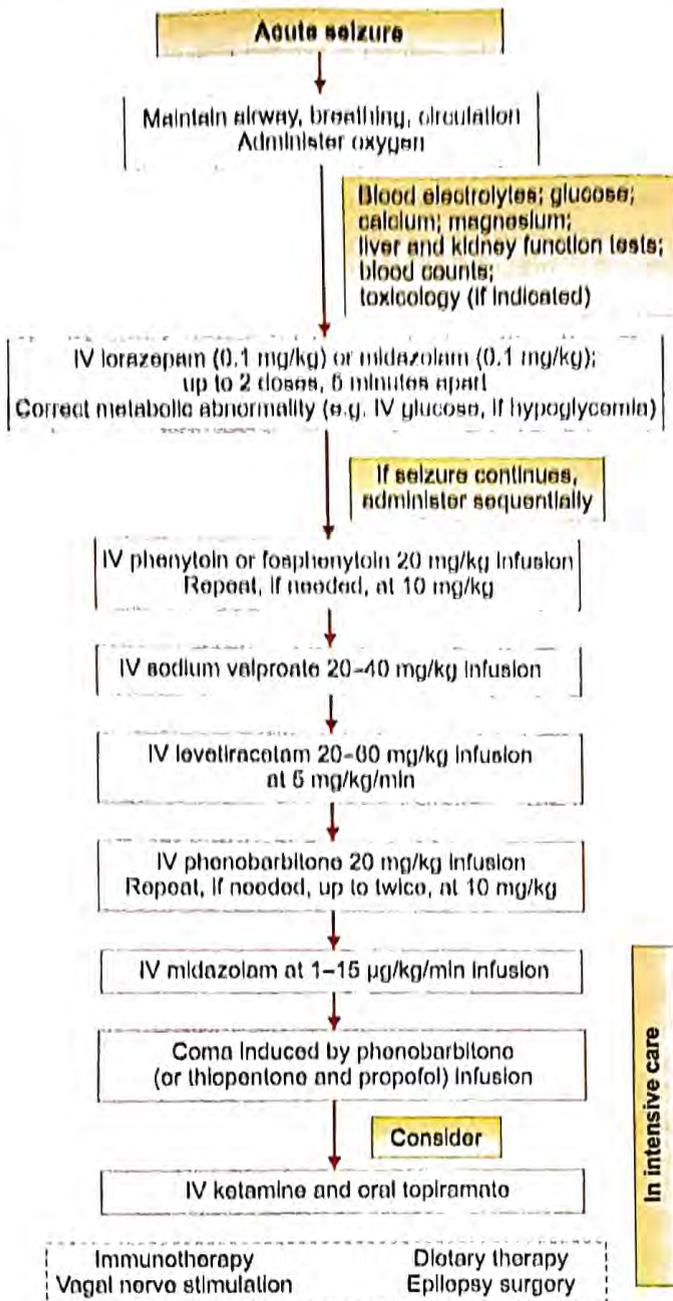


Fig. 19.1: Sequential drug therapy in the management of status epilepticus

seizures. The condition can cause multiorgan dysfunction, neurodevelopmental sequelae, and, in 10% cases, death. Figure 19.1 summarizes the management of status epilepticus. The term *refractory status epilepticus* is used for seizures that persist despite the use of benzodiazepine and one anticonvulsant in appropriate doses. Seizures that do not respond despite 24 hours of anesthesia are termed *super-refractory*.

Febrile Seizures

Febrile seizures refer to seizures associated with high-grade fever ($>38^{\circ}\text{C}$) occurring in neurologically healthy children between 6 months and 5 years of age, without underlying intracranial infection and without history of

prior unprovoked seizures. Febrile seizures affect 3–8% of children up to 7 years of age. About 25–40% have a positive family history. Fever may be caused by minor upper respiratory tract infection, gastroenteritis, viral exanthem, bacterial infection, malaria or immunization. Febrile seizures must be differentiated from acute symptomatic seizures due to intracranial infection and those triggered by fever in children with underlying epilepsy.

Types

A simple febrile seizure is a generalized seizure (without focal features) that lasts less than 15 minutes and occurs only once within a 24 hours period of fever in a neurologically normal child. About 15–20% cases are complex febrile seizure, diagnosed in presence of any of the following: (i) focal signs or symptoms; (ii) duration >15 minutes; or (iii) recurrent seizures within the same febrile illness. Recurrent febrile seizures may be noted in children with: (i) age <18 months; (ii) family history; (iii) multiple seizures; (iv) first seizure at low temperature ($<40^{\circ}\text{C}$).

Outcome

After an initial febrile seizure, 3–12% children develop epilepsy by adolescence. The risk of epilepsy is 1.5–2.4% for simple febrile seizures and increases in children with: (i) pre-existing neurodevelopmental abnormality; (ii) complex febrile seizure; and (iii) family history of epilepsy. It was suggested that a prolonged febrile seizure in infancy can cause hippocampal injury and mesial temporal sclerosis, leading to temporal lobe epilepsy. Subsequent studies demonstrate that a hippocampus that has already been damaged either by a perinatal insult or genetic predisposition may cause prolonged febrile seizure in infancy.

Management

An acute episode of seizure is terminated by intravenous lorazepam or midazolam. In case the patient presents in status, standard protocol for management of status epilepticus is followed.

In first episode of febrile seizure, lumbar puncture is indicated in clinically suspected meningitis or if Hib/pneumococcal immunization status is not known.

Prophylaxis

In children with risk factors for recurrence or those with frequent recurrences (≥ 3 in 6 months or ≥ 4 in one year), intermittent prophylaxis reduces recurrences by 80%. Oral benzodiazepines (diazepam 0.6–0.8 mg/kg/day in 3 divided doses or clobazam 0.8–1 mg/kg/day in 2 divided doses) should be started at the first sign of any febrile illness and continued for first 3 days of febrile illness.

Acute Symptomatic Seizures

A seizure occurring within a week of acute neurological injury, such as stroke, trauma, anoxia, active inflammation

and infection, and within 24 hours of acute metabolic derangements, requires evaluation with serum electrolytes, lumbar puncture and neuroimaging if indicated clinically. Antiepileptic therapy is initiated and discontinued after 3–6 months if awake and sleep EEG records are normal.

EPILEPSY

Epilepsy is defined as occurrence of two unprovoked seizures over a day apart beyond the neonatal period. Patients with one unprovoked seizure and a high probability of further seizures in the next decade, similar to the recurrence risk (over 60%) following two unprovoked seizures, are also termed having epilepsy. The International League Against Epilepsy (ILAE) 2017 classification categorizes epilepsy using semiological phenomena at onset, as follows.

Generalized Onset Epilepsy

Tonic-clonic

A tonic phase lasting at least 30 seconds and associated with uprolling of eyeballs, frothing from mouth, tongue bite, perioral cyanosis and/or incontinence of stool and urine, is followed by clonic movement of all limbs.

Myoclonic

Sudden, jerky shock-like violent contractions involve axial and appendicular muscles.

Atonic

Sudden loss of tone involving axial and appendicular muscles.

Spasm

Well-sustained, sudden inward and/or outward movements of head, neck, trunk and extremities occur in cluster or in isolation.

Absence

Brief periods of behavioral arrest, lasting 30–60 seconds, occur without associated motor phenomenon.

Tonic

Only tonic phase, as described in tonic-clonic seizure, occurring without the clonic component.

Focal Onset Epilepsy

These may be motor, sensory or autonomic. They account for 60% of epilepsies in childhood. They more often have a structural cause. Important causes are atrophic lesions, a structural cause. Important causes are atrophic lesions, scars, inflammatory granulomas, strokes and vascular insults, head trauma, abscess and neoplasms. In our country, neurocysticercus granulomas are a common cause, which classically produce a ring or disc like enhancing lesions on neuroimaging. A simple focal or partial seizure is not associated with loss of consciousness. A transient paralysis

of the affected limb of up to 24 hours may result, and is known as Todd's palsy. Focal or partial seizures may spread to involve the whole body (secondary generalization).

Complex partial seizures are associated with automatisms or loss of consciousness. Complex partial seizures arising from the temporal lobe are also called psychomotor epilepsy. Patients may have a 'déjà vu' feeling, visual, olfactory or visceral aura and peculiar posturing or automatisms which are usually repetitive. There is no memory for the event.

Etiology

Epilepsy may have genetic, structural, metabolic and unknown etiology.

Differential Diagnosis

Various paroxysmal events mimic epilepsy. Entities seen commonly in children are discussed.

Benign neonatal sleep myoclonus: A well infant presents with bursts of myoclonic or clonic movements only during sleep in the first week of life. The movements abort as soon as the child awakens. The conditions lasts for a few weeks to months. Only reassurance is required.

Breath holding spells: This behavioral problem usually affects boys between 6 months and 3 years of age. The sequence of events is typical. The child first has a long cry, usually after being denied some demand. Then the child holds his breath and turns blue and limp. This may be followed by tonic and a few clonic movements. Parents must be reassured and advised about consistent parenting practices. They should refrain from giving into the child's demand or giving him undue attention just after the episode. Iron deficiency should be treated.

Syncope: This usually occurs in the upright position. Patient may have been standing immobile for sometime or have suffered sudden fear or emotion. The fall to the ground is usually not as sudden as in a convulsion. The patient is pale and pulse is slow. The attack is aborted by lying flat or with legs elevated as this improves the cerebral blood flow.

Psychogenic seizures: These occur more commonly in older girls. The patient subconsciously tends to gain something. There are bizarre body movements with eyes tightly shut and pelvic thrusts. Very often the child does it when there is an audience around.

Epileptic Encephalopathies

Conditions in which epileptiform abnormalities themselves contribute to progressive cognitive decline form a part of one of two common syndromes.

West Syndrome

This is the most common epileptic encephalopathy in infancy, and is characterized by the triad of epileptic spasms, hypsarrhythmic EEG and psychomotor

retardation or regression. Etiology is diverse. Almost any type of brain insult in early life can lead to this syndrome. About two-thirds patients are symptomatic and one-third cryptogenic; the outcome is usually better in the latter category. The treatment of choice is either ACTH or corticosteroids; alternatively, vigabatrin may be used. Prognosis for neurodevelopment is variable and depends on seizure control and underlying etiology.

Lennor-Gastaut Syndrome

This is one of the most difficult epilepsies to treat. Onset occurs in late infancy or early childhood. Mixed seizures, including tonic, atonic, myoclonic, atypical absence and/or generalised tonic-clonic seizures, are characteristic. Etiology is diverse. Intellectual regression invariably occurs. EEG shows generalised slow spike and sharp wave activity of 1.5–2.5 Hz. Drugs used include valproate, lamotrigine, benzodiazepines, topiramate, levetiracetam and zonisamide. Therapeutic options in refractory cases include dietary therapy and epilepsy surgery.

Investigations

A video EEG is indicated in all cases of unprovoked seizure. While a normal EEG does not rule out seizure, it is useful in diagnosing epilepsy syndromes and pseudo-seizures and in enabling decisions regarding antiepileptic drug withdrawal. Some salient EEG findings are summarized in Table 19.3. In tropical countries, neuroimaging (preferably MRI brain with contrast) should be done in all cases with unprovoked seizure as neurocysticercosis and tuberculomas are the most common causes of seizures.

Principles of Drug Therapy

Table 19.4 shows agents used for various seizure types. All parents and caregivers should be advised for domiciliary management of seizures, which includes putting the child in recovery position and administering intranasal or buccal midazolam or lorazepam.

AEDs are started after two unprovoked episodes of generalized tonic clonic seizures. However, it is indicated after a single episode if the neuroimaging or EEG is abnormal or the child has presented in status epilepticus.

Initial therapy is monotherapy, initially in low dose that is gradually increased to maximum pharmacologically tolerated dose. Polytherapy is indicated if there are multiple seizure types or failure to respond to monotherapy. Rational combination should be used; drugs with the same mechanism of action and similar adverse effect profile should be avoided.

Up to one-third of epilepsies are drug refractory or medically intractable. Refractory epilepsy is usually defined as failure of 2–3 appropriately chosen AEDs with a minimum number of disabling seizures, or the lack of remission over a certain period of time. Various factors like quality of life, natural history of the disease and available treatment options determine intractability. Therapeutic options include dietary therapy, vagal nerve stimulation, immunotherapy and epilepsy surgery.

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Table 19.3: Diagnostic utility of electroencephalography in epilepsy

Finding	Likely diagnosis
Spike followed by slow waves	Interictal pattern of epilepsy
3 Hz spike and wave discharges; provoked by hyperventilation	Absence epilepsy
Chaotic high voltage record with multifocal spikes (hypsarrhythmia)	West syndrome
Brief bursts of polyspikes with photosensitivity	Juvenile myoclonic epilepsy
Spike wave complexes in Rolandic areas	Benign epilepsy with centrotemporal spikes
Generalised periodic epileptiform discharges	Subacute sclerosing panencephalitis
Lateralized periodic epileptiform discharges	Herpes simplex encephalitis

Table 19.4: Choice of therapies for epilepsy

Seizure	First choice	Second choice
Focal seizure	Oxcarbamazepine; carbamazepine	Valproate; phenytoin
Generalized tonic-clonic	Valproate; phenytoin	Levetiracetam; lamotrigine
Absence	Valproate; lamotrigine	Levetiracetam; topiramate; zonisamide
Epileptic spasms	ACTH or steroids	Vigabatrine
Myoclonic	Valproate	Levetiracetam; topiramate; zonisamide
Tonic	Valproate; lamotrigine	Levetiracetam; topiramate; zonisamide
Atonic	Valproate; lamotrigine	Levetiracetam; topiramate; zonisamide

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CONGENITAL MALFORMATIONS

Hydrocephalus or excessive accumulation of CSF in the brain can be congenital or acquired. Etiology, clinical features and evaluation are discussed in a later section.

Microcephaly

This is defined as occipitofrontal circumference more than 3 standard deviations below the mean for age, gender and sex. Primary or genetic microcephaly may be inherited in autosomal dominant or autosomal recessive manner, or be associated with Down, Edward, cri du chat, Cornelia de Lange, Rubinstein-Taybi and Smith-Lemli-Opitz syndrome. Secondary or nongenetic microcephaly follows insults and is caused by congenital infections (rubella, cytomegalovirus, toxoplasmosis, syphilis), fetal alcohol syndromes, radiation, fetal hydantoin syndrome, maternal diabetes, malnutrition and hypoxic ischemic encephalopathy. Postnatal causes include severe hypoglycemia, Rett syndrome and human immunodeficiency virus infection. A receding forehead, overriding cranial sutures and intellectual disability are usually noted.

Neural Tube Defects

Disorders affecting the closure of the neural tube are among the commonest congenital anomalies, affecting 1.5 per 1000 live births. The risk in subsequent pregnancies is increased to 3–4 per 1000 live births.

Spina bifida occulta refers to failure of bony fusion of the vertebral column that is covered by skin with or without an overlying tuft of hair (Fig. 19.2a), lipoma or a sinus. A sinus carries the risk of recurrent meningitis and should be excised. *Meningocele* refers to bulging out of meninges through the bony defect. A soft mass is present in the lumbar or sacral region through which CSF may exude. The open meninges may get infected. Early repair is

essential. *Meningomyelocele* refers to herniation of meninges and neural tissue through a spinal defect (Fig. 19.2b). The extent of neurological deficit depends on the level of the lesion. Usually, there is lower motor neuron type of paraplegia with bladder and bowel dysfunction and perineal anesthesia. Most patients have type II Arnold-Chiari malformation, and half are associated with aqueductal stenosis, leading to hydrocephalus. Club feet and dislocated hips may be present. *Encephalocele* is a midline bony defect in the calvaria with herniation of brain and meninges (Fig. 19.2c).

Management of severe defects is difficult and multidisciplinary. Many patients develop hydronephrosis and chronic kidney disease due to neurogenic bladder. Severely affected children require several reparative surgeries. Ambulatory potential depends on the level and degree of neurological deficit.

Neural tube defects can be diagnosed based on antenatal ultrasound, raised amniotic fluid α -fetoprotein and maternal serum and amniotic fluid acetylcholinesterase. The risk of defects is lowered by about 72% by daily intake of 0.4 mg folic acid in periconceptual period.

Agenesis of Corpus Callosum

This anomaly affects about 2% of children, may be partial or complete and occurs in isolation or with other brain malformations. Secondary destruction of the corpus callosum can occur with hypoxic ischemic encephalopathy or infarcts. Patients may be asymptomatic or present with epilepsy, cognitive defects or learning disability. Aicardi syndrome is characterized by agenesis of corpus callosum, retinal colobomas, intellectual disability and infantile spasms in girls. Neuroimaging shows parallel lateral ventricles with or without interhemispheric cysts, intracranial lipomas and disorders of neuronal migration, such as neuronal heterotopia, lissencephaly, pachygyria and schizencephaly.

Arnold-Chiari Malformation

Type I malformation is characterized by downward displacement of the cerebellar tonsils by 3–5 mm through the foramen magnum into the upper cervical canal.



Fig. 19.2: Neural tube defects. (a) Tuft of hair overlying spina bifida occulta; (b) Dorsolumbar meningocele; (c) Occipital encephalocele

Patients may be asymptomatic or present with headache, dizziness, vertigo, torticollis, downgaze nystagmus and drop attacks. MRI reveals the diagnosis. In type II malformation, the pons, medulla, vermis and elongated fourth ventricle are displaced into the upper cervical canal. Neural tube defects occur in almost all cases. Cerebellar, brain stem and cortical abnormalities may be present.

Dandy-Walker Malformation

Failure of the foramen of Magendie to open results in ballooning of the posterior wall of the fourth ventricle to form a cyst in the posterior fossa. It is associated with other cerebellar and cerebral anomalies. Infants present with hydrocephalus with occipital prominence. Delayed development, cerebellar ataxia and spasticity are usually present.

Syringomyelia and Hydromyelia

A fluid filled cavity or syrinx within the spinal cord may occur as an isolated anomaly or associated with Chiari malformation, tumor, infarction or trauma. Manifestations include dissociated sensory loss in a cape-like distribution, atrophy of hand muscles and spasticity in lower limbs. Decompression requires laminectomy and syringotomy.

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NEUROCUTANEOUS SYNDROMES

These are disorders which affect both the nervous system and skin. There are 5 major syndromes. All are inherited except Sturge-Weber syndrome. One of the common manifestations is a tendency to form benign and sometimes malignant tumors in various parts of the body.

Neurofibromatosis (NF)

This is the most common neurocutaneous syndrome. Inheritance is autosomal dominant with highly variable penetration. NF1 or von Recklinghausen disease is caused by defects in *NF1* gene on chromosome 17 while the gene for NF2 is located on chromosome 22. NF1 is diagnosed in presence of two or more of the following: (i) Six café au lait spots more than 5 mm size in prepubertal and more than 15 mm in postpubertal children; (ii) Two or more neurofibromas or one plexiform neurofibroma; (iii) Axillary freckling; (iv) Optic glioma; (v) Two or more iris hamartomas (Lisch nodules); (vi) Osseous lesions such as sphenoid dysplasia or thinning of long bones; (vii) A first degree relative with NF1. Nervous system abnormalities include optic glioma, intraspinal neurofibroma, aqueductal stenosis, dural ectasia and MRI findings of increased signal intensity in basal ganglia, cerebellum, brain stem and subcortical white matter.

Tuberous Sclerosis Complex

Two types are recognized based on underlying defect in *TSC1* (locus 9q34) and *TSC2* (locus 16p13.3). Inheritance is autosomal dominant. CNS manifestations include developmental delay, intellectual disability, seizures (often epileptic spasms) and autism. Subependymal nodules (Fig. 19.3a) and cortical tubers (Fig. 19.3b) are seen on neuroimaging. The former may undergo malignant transformation to glial tumors. Skin manifestations include ash leaf macules (Fig. 19.3c), adenoma sebaceum (Fig. 19.3d), café au lait spots and shagreen patches. Other organs involved include kidneys (angiomyolipomas), lungs (lymphangiomyomatosis), heart (rhabdomyoma) and retina (hamartomas). Treatment is symptomatic with anticonvulsants and surgery for tumors. Periodic monitoring is essential for renal, lung, heart and retinal tumors.

Sturge-Weber Syndrome

A facial nevus or port wine stain (Fig. 19.4a) in the distribution of the first branch of the trigeminal nerve is



Fig. 19.3: Findings in tuberous sclerosis include: (a) Subependymal nodule on non-contrast CT of brain; (b) Cortical tubers on axial FLAIR magnetic resonance imaging; (c) Hypopigmented ash leaf macule; and (d) Hyperpigmented maculopapular facial rash (adenoma sebaceum)



Fig. 19.4: Features of Sturge-Weber syndrome include (a) Hemifacial angioma or port-wine stain; and (b) Intracranial calcifications in left hemisphere on computed tomography

associated with an 'ipsilateral rail road pattern' of intracranial calcification (Fig. 19.4b) and glaucoma. Presentation is with contralateral hemiparesis, focal seizures and/or intellectual disability. Control of seizures may require surgery. Monitoring for glaucoma is essential.

Ataxia Telangiectasia

This autosomal recessive disorder (locus 11q) presents with progressive cerebellar ataxia with onset at 1–2 years of age. Choreoathetosis may occur. After 2–3 years of age, telangiectasias are noted in skin flexures and/or bulbar conjunctiva (Fig. 19.5). An immune deficiency co-exists with recurrent sinopulmonary infections and later malignancies—lymphoma and lymphocytic leukemia. Deficiency of IgA and IgE and increased α fetoprotein is found in 80–90% patients. Intellect is normal at first but may lag with time. Death usually occurs by 20 years.

von Hippel-Lindau Disease

This disorder is characterized by cerebellar and retinal hemangioblastomas, spinal cord angiomas and cystic tumors of kidneys and pancreas. Children present with cerebellar signs and raised intracranial tension.



Fig. 19.5: Bulbar conjunctival telangiectasia in a child with ataxia telangiectasia

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INFECTIONS AND ACUTE ENCEPHALITIS SYNDROME

Meningoencephalitis is the most common CNS infection. The term acute encephalitis syndrome, was coined by the World Health Organization in 2006 for the purpose of surveillance for Japanese encephalitis. It is defined as an illness characterised by acute onset of fever and a change in mental status manifesting as confusion, disorientation, coma, inability to talk and/or new onset seizures, except simple febrile seizures. Causes of acute encephalitis and encephalopathies are listed in Table 19.5.

Viral Meningoencephalitis

CNS infections may be caused by primary neurotropic viruses (arboviruses, herpesviruses and rabies) and, less often, by 'incidental' CNS pathogens (enteroviruses, orthomyxoviruses, paramyxoviruses and adenoviruses). Sudden onset of fever with or without nonspecific symptoms is followed within hours to days by convulsions, coma, focal deficits and signs of raised intracranial tension. Presentation and outcomes vary between individuals, particularly if the host is immunocompromised. The patient may die in the acute phase or recover completely or partially.

Lumbar puncture shows up to 1000 cells/mm³ in the CSF that are chiefly lymphocytes with or without

Table 19.5: Etiology of acute encephalitis syndrome

Encephalitis

- RNA viruses (mumps, measles, rubella, enteroviruses)
- DNA viruses (herpes simplex, cytomegalovirus, Epstein-Barr)
- Arthropod borne viruses (Japanese B, West Nile, Russian spring summer, equine viruses)
- HIV, rabies, lymphocytic choriomeningitis, dengue virus, slow virus infections, prion infections
- Rickettsia; fungi (cryptococcus); protozoa (*T. gondii*)
- Bacteria (tuberculous meningitis, listeria)

Encephalopathies

- Acute disseminated encephalomyelitis
- Postinfectious: Typhoid, shigella, Reye syndrome
- Hypoxic encephalopathy, heat hyperpyrexia
- Metabolic: Diabetic acidosis, uræmic coma, hepatic coma, neonatal hyperbilirubinemia, lactic acidosis, mitochondrial disorders, inborn errors of metabolism
- Fluid and electrolyte disturbances.
- Hyponatremia, hyponatremia, alkalosis, acidosis
- Toxic: Heavy metals (lead, mercury, arsenic), insecticides, Cannabis indica, carbon monoxide
- Post-vaccination

polymorphonuclear cells. Protein is mildly increased and sugar is normal. Etiology is determined in only a small proportion. Viral detection by CSF polymerase chain reaction (PCR) or specific antibodies are necessary but have low diagnostic yield.

Sick patients require careful monitoring in an intensive care unit, targeting maintenance of vital functions and ensuring asepsis, adequate nutrition, good nursing care and appropriate physiotherapy. Symptomatic management includes administering antipyretics and anticonvulsants and measures to reduce intracranial tension.

Japanese Encephalitis (JE)

JE virus is the leading cause of viral encephalitis in India and worldwide, with the majority of cases occurring in Asia. In India, most cases are reported from southern and eastern states with outbreaks during and after monsoons.

Etiology and Transmission

JE virus is a single stranded neurotropic RNA virus belonging to family *Flaviviridae*. The chief vector across Asia is *Culex tritaenirhynchus*, a zoophilic mosquito that breeds in rice fields. The infection is zoonotic, with pigs and Ardeid birds as the chief hosts that harbor, amplify and transmit the infection without developing illness, despite significant viremia. Man is an incidental dead-end host in whom the brief viremia deters further transmission.

Clinical Features

JE tends to occur in epidemics and outbreaks, chiefly affecting children between 5 and 15 years of age or young adults. A prodrome of fever, headache, vomiting and diarrhea, lasting a few hours to days, is followed by an acute encephalitic stage with persistent fever, seizures, coma, focal deficits and signs of raised intracranial tension

lasting 7–10 days. In severe cases, signs of raised intracranial tension and hyperventilation are followed by shock and rapid death. Others recover gradually over weeks to months, but majority of survivors have prominent extrapyramidal sequelae.

Diagnosis

CSF shows nil to moderate pleocytosis with elevated protein and normal sugar. MRI shows characteristic changes in bilateral thalami, basal ganglia and midbrain (Fig. 19.6a). JE virus specific IgM can be detected by ELISA in CSF and serum and has 95% sensitivity and specificity when performed in CSF by 10 days of illness; earlier samples may be negative. Viral isolation and detection by PCR in CSF or brain during early illness has low yield.

Management

Management is essentially supportive, as outlined above.

Prevention

JE can be controlled by reducing contact with mosquitoes (using insecticide spray, larvicides, bed nets and repellants), vaccination of pigs and location of pigsties away from human dwelling, and, most usefully, by vaccinating susceptible humans. However, human vaccination does not interrupt the natural cycle of JE virus and does not provide herd immunity. JE vaccination is now part of the National Immunization Program in endemic states (see Chapter 10).

Mouse brain killed vaccine: This was the earliest vaccine to be manufactured against JE but is no longer in use.

Live-attenuated SA-14-14-2 strain vaccine: This is the only live-attenuated JE vaccine currently available. It is produced by Chengdu Biologicals and is being used in the public sector in China since 1998, Nepal (since 1999)

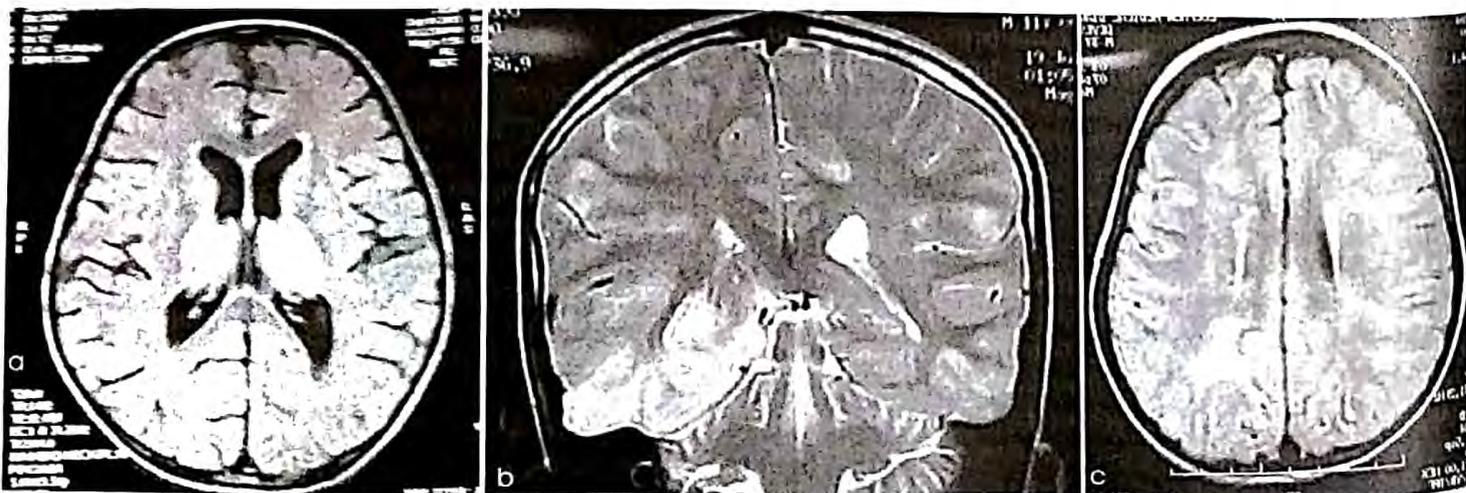


Fig. 19.6: Magnetic resonance imaging in acute encephalitis. (a) Axial FLAIR images showing bilateral thalamic involvement in Japanese B encephalitis; (b) Coronal T2-weighted images showing right temporal involvement in herpes encephalitis; and (c) Axial FLAIR Images showing bilateral subcortical and periventricular patchy asymmetrical white matter signal changes in acute disseminated encephalomyelitis

and India (since 2006). Studies conducted in Nepal reported efficacy of 99.3% in the same year, 98.5% after one year and 96.2% after 5 years. An Indian study found vaccine efficacy to be 94.5% after 6 months. Dose is 0.5 ml given subcutaneous.

IC51 Vaccine–Ixiaro: This is a new generation formalin inactivated vaccine manufactured by Intercell (Austria) and distributed by Novartis Vaccines. It is prepared from the SA-14-14-2 strain grown in Vero cells. This is the only JE vaccine to have received US Food and Drug Administration (FDA) approval for use in adults and children beyond 2 months of age. This vaccine produced with Austrian collaboration is available in India as JEEV (Biological E Ltd). Schedule is 2 doses 28 days apart followed by a booster after one year. Dose is 0.25 ml below 3 years and 0.5 ml beyond.

Indian Strain vaccine: Another Vero cell-derived purified inactivated JE vaccine is developed from an Indian strain of the virus (821564 XZ) isolated in Kolar, Karnataka, during the early 1980s and characterised by the National Institute of Virology, Pune. This vaccine was developed through public–private partnership between the Indian Council of Medical Research and Bharat Biotech Ltd. It has received manufacturing and marketing approval from the Drug Controller General of India and is being marketed by the name, JENVAC.

Chimeric vaccine: Another JE vaccine under development is the live attenuated YFV-17D/ JEV vaccine (Acambis, UK). The premembrane and envelop (prME) genes of an attenuated human vaccine strain (SA-14-14-2) of JE virus are inserted between core and nonstructural genes of a yellow fever 17D infectious clone, resulting in a live chimeric vaccine. Recruitment for phase 3 studies is ongoing in Thailand.

Herpes Simplex Virus (HSV) Encephalitis

This is the leading cause of sporadic encephalitis and has a severe fulminant presentation with high rates of mortality and disabling sequelae. A non-specific prodrome of headache, malaise, fever and vomiting is followed by altered consciousness, focal or generalised seizures and focal neurologic deficits. Presence of focal signs is considered characteristic of HSV encephalitis. Presentations include movement disorders, stroke, behavioral disturbances, hallucinations and memory loss.

Examination of the CSF reveals pleocytosis, mild protein elevation and occasionally, red blood cells. EEG may show a characteristic picture of periodic lateralised epileptiform discharges. Neuroimaging shows characteristic temporal lobe signal changes, with MRI being more sensitive than CT (Fig 19.6b). PCR for HSV1 in the CSF has 75% sensitivity and 100% specificity and is considered the gold standard for diagnosis.

Management includes supportive care and specific antiviral treatment with intravenous acyclovir at 20 mg/

kg every 8 hour for 14–21 days. However, despite early therapy, less than 40% patients survive without disability and 5% may relapse.

Acute Bacterial Meningitis

This is a relatively common and potentially fatal condition. A high index of suspicion is essential to enable timely diagnosis and treatment.

Risk Factors and Pathogenesis

Infections are most common in the first 5 years of life. Risk factors include bacterial colonization of nasopharynx, overcrowding, poverty and male sex. Anatomic defects such as fracture base of skull, pilonidal sinus and immunodeficiencies predispose to meningitis. Bacteremia is followed by lodging of bacteria in choroid plexus and the meninges. An intense inflammation leads to meningeal exudates, ventriculitis, perivascular inflammatory exudates, venous occlusion, infarction, necrosis and/or raised intracranial pressure.

Etiology

The causative organisms vary with age. In the first 2 months of life, the most common pathogens include Gram negative bacteria, followed by *Staphylococcus aureus*, group B streptococci and *Listeria monocytogenes*. Between 2–24 months, *Hemophilus influenzae* type b infections are most common, followed by *Streptococcus pneumoniae* and meningococcus. Beyond 2 years of age, pneumococcus and meningococcus are the most common organisms, followed by *Hemophilus influenzae* type b.

Clinical Features

Clinical features vary with age. Newborn and young infants present with lethargy, poor feeding, shrill cry and seizures. Older infants present with fever, poor feeding, irritability and photophobia. A tense bulging anterior fontanelle in a febrile infant suggests meningitis. Older children present with abrupt onset of high fever, severe unrelenting headache, anorexia, myalgia, photophobia and meningeal signs, and may develop convulsions and coma.

Meningeal signs are lacking till 2 years of age. Signs of raised intracranial pressure include hypertension, bradycardia, bulging fontanelle, third or sixth cranial nerve palsy, posturing or breathing abnormalities. Papilledema is unusual, especially in infants. A search should be made for septic foci elsewhere. Purpuric rash suggests meningococemia.

Differential Diagnosis

Viral and tuberculous meningoencephalitis are the chief differential diagnoses. The latter is particularly considered when faced with partially treated bacterial meningitis.

Diagnosis

Diagnosis is confirmed by CSF examination. However, lumbar puncture must be deferred, if there are signs suggesting raised intracranial pressure due to the risk of herniation and death. CSF examination reveals raised pressure, turbid fluid, markedly increased cell count (often in thousands per mm^3) chiefly comprised of polymorphonuclear cells, increased protein and low sugar (less than 40% of the concomitant blood sugar). Gram stain and bacterial culture may enable diagnosis. However, PCR to detect bacterial DNA is more sensitive. Other useful tests are latex agglutination test, countercurrent immunoelectrophoresis and blood culture. In very early cases, CSF examination may be normal for cell count, protein and sugar but culture may be positive. In cases partially treated with antibiotics, CSF cell count is lower and has a predominance of lymphocytes and culture is sterile.

Imaging in bacterial meningitis may be normal or show intense meningeal enhancement or intracranial complications such as subdural effusion (Fig 19.7a) or empyema, ventriculitis, brain abscess, hydrocephalus or infarcts. Other complications include syndrome of inappropriate secretion of antidiuretic hormone and sequelae of injury such as deafness, epilepsy, intellectual disability, neurological deficits and hydrocephalus.

Treatment

Empirical intravenous therapy with third generation cephalosporin should be initiated without delay. Vancomycin is added if there is lack of clinical response by 48–72 hours. Antibiotics are revised based on results of investigations. Therapy is usually administered for 3 weeks in neonates and for 7–10 days in older children. Dexamethasone, administered intravenously at 0.15 mg/kg/dose every 6 hours for two days, beginning with the first dose of antibiotic is considered useful in preventing hearing loss and short-term neurological sequelae.

Prevention

The risk of bacterial meningitis is reduced considerably by mass vaccination against *hemophilus*, pneumococci and

meningococci. Close contacts of patients with meningococcal meningitis should receive chemoprophylaxis with rifampicin at 10 mg/kg/dose twice daily for two days.

Tuberculous Meningitis

This is the most severe form of tuberculosis. Predisposing factors are young age, presence of a household contact, recent measles and protein energy malnutrition.

Pathophysiology

Primary infection is followed by intermittent bacillemia and seeding of meninges, termed Rich's foci. During stress and lowered immunity, these foci rupture to cause tuberculous meningitis, with characteristic thick exudates in the basal cisterns and endarteritis.

Clinical Features

The first or prodromal phase of the illness is characterized by nonspecific irregular fever, anorexia, irritability and occasional vomiting and lasts 1–4 weeks. The second stage has neurological manifestations like seizures, focal deficits and meningeal signs. The third stage is one of coma and sequelae. Hydrocephalus (communicating or obstructive), decerebrate posturing, cranial nerve palsies, optic atrophy, extrapyramidal signs and focal deficits are more common in tuberculous than other CNS infections. Chief differential diagnosis are partially treated bacterial meningitis and viral meningoencephalitis.

Diagnosis

Diagnosis is based on clinical features and investigations. CSF typically shows raised pressure, up to 500 cells per mm^3 with lymphocytic predominance, increased protein and low sugar (level about half the concomitant blood sugar level). However, CSF may mimic bacterial meningitis or be normal in about 10–15% cases each.

Neuroimaging often shows hydrocephalus and basal exudates (Fig. 19.7b). The diagnosis is supported by prolonged history of symptoms, family history of tuberculosis, positive Mantoux (tuberculin) test, chest

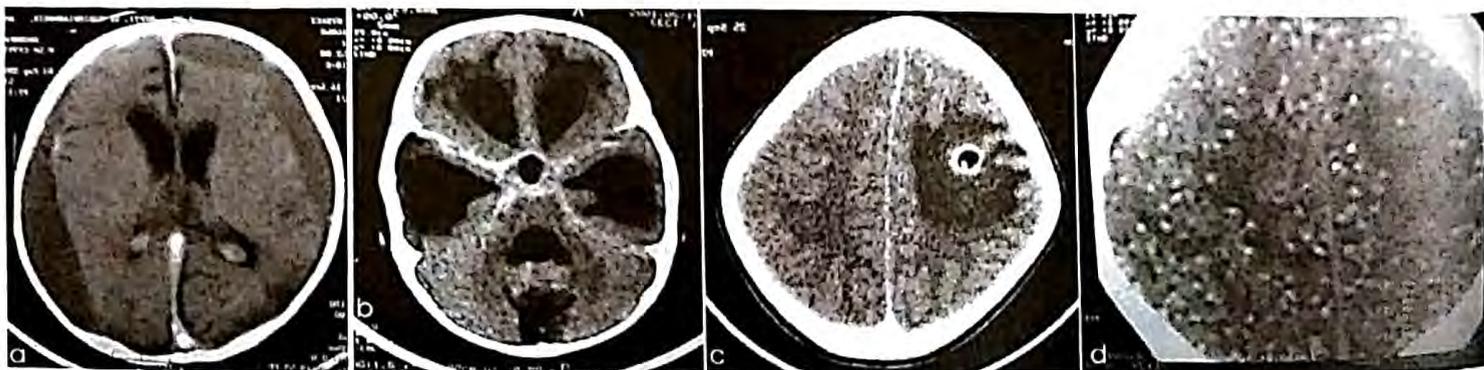


Fig. 19.7: Computed tomography in acute encephalitis. Contrast enhanced images showing: (a) Bilateral subdural effusion in a child with acute bacterial meningitis; (b) Communicating hydrocephalus with basal meningeal enhancement in a child with tubercular meningitis; (c) Ring enhancing lesion with eccentric dot in left parietal lobe suggestive of neurocysticercosis; and (d) Non-contrast image shows multiple calcified neurocysticercal lesions, described as 'starry sky'

radiographic evidence of tuberculosis and findings on CSF examination and neuroimaging. The diagnosis is confirmed if CSF culture or PCR is positive for *Mycobacterium tuberculosis* or acid-fast bacilli are present. Gene Xpert is a quick cartridge based test for *M. tuberculosis* genome and drug resistance to rifampicin.

Treatment

Antitubercular treatment includes two months of four drug (intensive) therapy and 10 months of two drug (maintenance) therapy (Chapter 11). Intravenous is dexamethasone is followed by oral administered for 8–12 weeks to prevent sequelae. Patients with obstructive hydrocephalus require CSF diversion by shunt or third ventriculostomy.

Prognosis

Prognosis is related to patient age and stage of disease at diagnosis. Early treatment (stage 1) results in complete cure. While 80% of patients treated in stage 2 of disease survive, 50% show sequelae. Only 50% of patients treated in stage 3 survive and 80% show sequelae. Complications include hydrocephalus, optic neuritis, infarction and spinal block due to arachnoiditis. Sequelae include focal neurological deficits, epilepsy, intellectual disability, blindness and occasionally, endocrinopathies.

Neurocysticercosis

Parasitic infestation of the brain by the encysted larvae of pork tapeworm *Taenia solium* is a public health problem in many developing regions including Southeast Asia, Latin America and sub-Saharan Africa. The condition affects 9% people across ages and 13% of children. Neurocysticerci account for up to 35% patients presenting with seizures in rural regions, with active or degenerating neurocysticerci being more common than calcified granulomas. Humans acquire the infection by consuming undercooked pork containing cysticerci or by eating food contaminated with feces containing tapeworm eggs. The eggs form larvae that cross into the bloodstream to seed the brain.

Pathogenesis

Parenchymal or cerebral infection is more common than extraparenchymal neurocysticercosis, manifesting as intraventricular, spinal or ocular cysts or arachnoiditis. Cysts may be single or multiple, and usually form at the gray-white matter interface. Four stages are recognised, namely the vesicular, colloidal, granular-nodular and nodular-calcified lesions. The first two or active stages carry low risk of seizures and do not enhance on neuroimaging. Cysticerci usually cause seizures in the degenerating or granular-nodular stage, and are detected as enhancing lesions on MRI.

Clinical Features and Diagnosis

Patients are usually older than 3 years and present with recent onset of focal or generalised epilepsy. Neuroimaging reveals one or multiple ring-enhancing lesions with perifocal edema (Fig. 19.7c) with or without an asymmetric scolex within the ring. Patients may occasionally present with encephalitis and raised intracranial pressure with or without seizures. Neuroimaging in these cases reveals cerebral edema in a brain studded with cysts in various stages, including enhancing and nonenhancing cysticerci, termed a 'starry sky' appearance (Fig. 19.7d).

The combination of clinical and radiological findings is usually diagnostic. Radiological differential diagnoses include tubercular and *Toxoplasma* granulomas. Serology by enzyme linked immunoelectrotransfer blot assay has high sensitivity (100%) and specificity (83–100%) for multiple and extraparenchymal neurocysticercosis, but has poor diagnostic utility for one to few cysticerci and calcified lesions.

Management

Symptomatic treatment of seizures is essential. Anti-epileptic therapy is continued for at least 6 months and until the lesions disappear. Definitive antihelminthic therapy is recommended for up to 5 lesions. Albendazole is the preferred agent and is administered at 15–20 mg/kg/day in two divided doses for a week. Cysticidal therapy is contraindicated in ocular neurocysticercosis and cysticercal encephalitis since degenerating cysts may evoke intense inflammatory response. All patients should first receive oral prednisolone at 1–2 mg/kg/day for 5–7 days, beginning prior 2–3 days to antihelminthic therapy.

Acute Disseminated Encephalomyelitis

Immune-mediated cerebral inflammation may follow viral exanthem or vaccination. While measles is the most common cause, causative infections include rubella, mumps, varicella zoster, influenza A and B, *Rickettsia* and *Mycoplasma pneumoniae*. Vaccines that may precipitate the syndrome are rabies, vaccinia, measles and yellow fever. Patients present with altered consciousness, convulsions and multifocal neurological signs affecting cerebellum, optic nerves, long tracts and spinal cord. Fever may be absent at onset. CSF may reveal mild pleocytosis. MRI shows characteristic scattered lesions in the white matter, at times affecting the deep grey matter and other areas (Fig. 19.6c). Treatment options include pulse corticosteroids, intravenous immunoglobulin and plasmapheresis.

Autoimmune Encephalitis

Neurological syndromes presenting with neuropsychiatric features, mutism, movement disorders, seizures and cognitive decline may be caused by serum and/or CSF antibodies against ion channels, receptors and associated

proteins. Anti-NMDA receptor antibody encephalitis, voltage-gated potassium channel antibody-associated encephalitis and limbic encephalitis are well described in adults, often occurring as paraneoplastic syndrome. However, 23–40% of patients present in childhood. Treatment options include pulse methylpredisolone, intravenous immunoglobulin, plasma exchanges and intravenous rituximab.

Encephalopathies

The term encephalopathy is used for diffuse cerebral dysfunction due to a non-inflammatory pathology, as against encephalitis which is characterized by inflammation. However, the two are often difficult to distinguish clinically. Fever cannot discriminate between the two entities as encephalopathy may be precipitated by systemic infection, and fever may have an alternative cause.

Dengue Encephalopathy

Neurological manifestations, including encephalopathy, are common with dengue infections and may be caused by vasculitis, cerebral edema, hypoperfusion or hyponatremia. However, virus invasion of the brain producing encephalitis has also been documented.

Reye Syndrome

This acute encephalopathy may follow a viral upper respiratory tract infection (90% cases) or varicella (5–7%). History of salicylate ingestion is common. The onset is abrupt with protracted vomiting followed by delirium, combative behavior and stupor. While most children have a mild course, there may be rapid worsening with seizures, coma and death. Common findings include mild hepatomegaly, hypoglycemia and elevated serum transaminases (>3-fold) and ammonia and coagulopathy with normal levels of serum bilirubin. Liver biopsy reveals diffuse microvesicular fatty infiltration without any inflammation or necrosis.

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CEREBRAL PALSY

Cerebral palsy refers to permanent, nonprogressive and occasionally evolving, disorders of tone, movement or posture, caused by an insult to the developing brain. It is the most common chronic motor disability in childhood,

Table 19.6: Etiology of cerebral palsy

Genetic or prenatal

Structural malformations of nervous system
Congenital or intrauterine infections
Maternal or obstetric complications
Teratogens

Perinatal

Birth asphyxia
Prematurity; low birth weight
Birth trauma; intracranial hemorrhage
Hyperbilirubinemia; hypoglycemia
Central nervous system (CNS) infection

Postnatal

CNS infection
Hypoxia
Trauma; toxins

affecting 2–3 infants per 1000 live births. While perinatal asphyxia was considered the most common cause, it accounts for less than 10% of cases. Various causes are listed in Table 19.6.

Clinical Features

The most common presentation is with developmental delay. Physical findings are persistence of neonatal reflexes, increased tone, fisting with cortical thumb, scissoring of legs, toe-walking, abnormal posture and gait, abnormal movements and/or hyperreflexia. Common comorbidities include intellectual disability, microcephaly, seizures, behavioral problems, difficulty in speech, language, swallowing or feeding, blindness, deafness, squint, malnutrition, sleep disturbances and excessive drooling. Contractures may develop that are initially dynamic and later fixed.

Classification

Cerebral palsy is classified topographically as quadriplegic, hemiplegic, monoplegic or diplegic, and physiologically as spastic, dyskinetic, ataxic or mixed. Spastic palsy may be quadriplegic, diplegic or hemiplegic, while dyskinetic palsy may be choreoathetoid or dystonic.

Spastic quadriplegia is the most common type of cerebral palsy in India. It is often caused by perinatal asphyxia or neonatal illness. Common comorbidities are intellectual disability, seizures, pseudobulbar palsy, microcephaly, squint or visual disturbances, speech abnormalities and deformities. Neuroimaging may show cystic encephalomalacia.

Spastic diplegia is the second most common type, and is linked to prematurity. Intellect is often preserved. Neuroimaging shows periventricular leucomalacia.

Spastic hemiplegic palsy usually results from a vascular insult or perinatal stroke. Early hand preference is a clue.

Neuroimaging usually reveals focal changes or a porencephalic cyst. These children are usually mobile. They may have preserved or impaired intellect.

Dyskinetic or extrapyramidal palsy may result from asphyxia or kernicterus. Rigidity, dystonia, dyskinesia and drooling are prominent while intellect is relatively preserved. Radiology may indicate abnormalities in basal ganglia or thalamus.

Ataxic palsy is caused by cerebellar malformations and is associated with other cerebellar signs.

Mixed CP refers to a presentation including both spastic and extrapyramidal features.

Evaluation

A detailed history is taken to detect various manifestations and antecedent events. Physical and neurologic examination should include detailed assessment of development and evaluation for dysmorphism and neurocutaneous markers. Spasticity is classified using tools such as Gross Motor Function Classification System and Modified Ashworth Scale.

Management

Management requires multidisciplinary inputs from the pediatrician, occupational therapist, physiotherapist, clinical psychologist, orthopedic surgeon, speech therapist, ophthalmologist, ENT specialist, social worker and special educator. Generalised spasticity is managed by physiotherapy and drugs such as diazepam, baclofen, tinazidine or dantrolene. Localized spasticity can be effectively treated with injection of botulinum A toxin. Some patients may require tendon release or tendon lengthening. Dystonia is managed with trihexiphenidyl, botulinum or levodopa.

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NEUROLOGICAL REGRESSION

Various disorders present with progressive deterioration in mental and motor functions, causing loss of acquired milestones. Inherited metabolic storage disorders are the most common etiology; other causes include sequelae of infections (e.g. HIV encephalopathy, subacute sclerosing panencephalitis and progressive rubella panencephalitis), hydrocephalus, hypothyroidism and vitamin B₁₂

deficiency. Static disorders such as cerebral palsy may appear to regress due to formation of contractures, epilepsy, movement disorders or emotional problems.

Epileptic encephalopathies also cause neuroregression. Acute deterioration following illness, trauma or brain infections after which the child remains static or improves need to be differentiated. The neurocutaneous disorders also have progressive neurologic deterioration. Diseases like lupus erythematosus and multiple sclerosis can also appear like a progressive degeneration.

Evaluation

A detailed history should elicit the age at onset, course and evolution of illness, history of consanguinity and family history. Progressive deterioration may be difficult to detect in patients with infantile onset. Other features include feeding difficulties, vomiting, failure to thrive, lethargy, irritability and lack of visual fixation and social interaction. Small molecule disorders (aminoacidopathies; urea cycle disorders; organic acidemias and fatty acid oxidation defects) typically have a relapsing and remitting course with progressive deterioration, while large molecule storage diseases (lysosomal storage disorders; glycogen storage disorders and mucopolysaccharidoses) have chronic progressive course. Physical examination should focus on appearance (Fig. 19.8), detailed neurological examination including fundoscopy, hepatosplenomegaly, and specific findings in eye, skin and



Fig. 19.8: Coarse facial features with psychomotor retardation in a child with (a) Mucopolysaccharidosis type 2; and (b) Cretinism (congenital endemic hypothyroidism)

Table 19.7: Inherited causes of psychomotor regression

Onset In early Infancy*With hepatosplenomegaly*

Gaucher type 2
 Niemann-Pick type A
 Sandhoff disease

Without hepatosplenomegaly

Maple syrup urine disease
 Classic phenylketonuria
 Leigh disease
 Menkes kinky hair disease
 Biotinidase deficiency
 Glutaric aciduria
 Zellweger syndrome

Onset at 1–2 years

Homocystinuria
 Late infantile neuronal ceroid lipofuscinosis
 Rett syndrome

Onset after 2 years*With hepatosplenomegaly*

Gaucher type 3

With vision loss

Adrenoleukodystrophy
 Myoclonic epilepsy with ragged red fibres
 Wilson disease

GM1 gangliosidosis
 Mucopolysaccharidosis types 1 and 2
 Sialidosis type 1

Pelizaeus-Merzbacher disease
 Krabbe disease
 Canavan disease
 GM2 Tay-Sachs disease
 Alexander disease
 Early infantile neuronal ceroid lipofuscinoses
 Lesch-Nyhan disease

Megalencephalic leukoencephalopathy with subcortical cysts
 Metachromatic leukodystrophy

Niemann-Pick type C

Subacute sclerosing panencephalitis
 Pantothenate kinase associated neurodegeneration

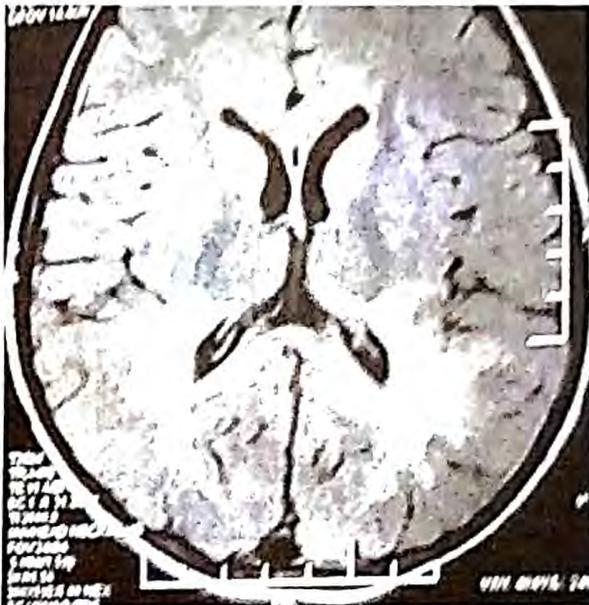


Fig. 19.9: Characteristic predominantly posterior white matter involvement in a patient with adrenoleukodystrophy

skeleton that may indicate the underlying etiology. Table 19.7 lists disorders based on age of onset; specific clinical and diagnostic features are discussed in Chapter 24.

Biochemical tests are targeted towards detecting the suspected defect and include serum ammonia, arterial

and CSF lactate, blood sugar, blood tandem mass spectrometry, and urinary aminoacidogram, glyco-saminoglycans, gas chromatography and mass spectrophotometry. The MRI of brain may suggest the diagnosis (Fig. 19.9). Specific diagnosis relies on enzyme analysis in leukocytes or fibroblasts and specific genetic testing.

Treatment

The first priority is to evaluate for and manage conditions for which specific therapy is available, such as hypothyroidism, hydrocephalus, vitamin B₁₂ deficiency, lead poisoning, Wilson disease, adrenoleukodystrophy, and biotinidase deficiency. Specific diets are useful in conditions such as galactosemia, fructose intolerance and phenylketonuria. Enzyme replacement therapy is available for Gaucher disease, milder variant of mucopolysaccharidosis type 1, glycogen storage disease type 2 (Pompe disease) and Fabry disease. Transplantation of the bone marrow and liver may be useful in patients with Hurler disease and glycogen storage disease, respectively. Several disorders are already screened for as part of newborn screening programs in many countries. While most conditions have a poor outcome, specific diagnosis enables prenatal counseling and antenatal diagnosis in subsequent pregnancies.

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ATAXIA

The term ataxia refers to disturbance of fine control of posture and movement, usually caused by abnormalities of the cerebellum or its afferent and efferent connections, posterior column of the spinal cord or the vestibular system. Ataxia may be acute and/or recurrent or chronic and progressive (Tables 19.8 and 19.9).

Acute or Recurrent Ataxia

The most common causes in children are acute post-infectious cerebellitis and drug toxicity, followed by migraine, brainstem encephalitis and underlying neuroblastoma. Some of these are being described below:

Brainstem Encephalitis

Ataxia and cranial nerve palsies may be the presenting feature of encephalitis. CSF pleocytosis and abnormal brainstem auditory evoked potentials may be found.

Migraine

Basilar migraine may present as recurrent episodes of cerebellar or brainstem dysfunction. Peak occurrence is in adolescent girls. Gait ataxia, visual loss, vertigo, parasthesias, tinnitus and occasionally loss of consciousness may occur, followed by throbbing occipital headache.

Benign paroxysmal vertigo is a migraine seen in infants and preschool children. The predominant symptom is recurrent attacks of vertigo with pallor, nystagmus and

fright lasting a few minutes. Consciousness is maintained. With time these attacks decrease and stop altogether and typical migraine may develop.

Conversion Reaction

Hysterical ataxia is relatively common in older children and adolescents. Although the hysteria is involuntary, there is some secondary gain. The child does not have difficulty sitting but when made to stand there is severe swaying from the waist, so that she lurches and staggers from one object to the other. Diagnosis is by observation only.

Episodic Ataxias (EA)

These are due to ion channel mutations. EA type 1 results from a mutation of potassium channel gene *KCNA1*. Attacks of ataxia and myokymia of the face and limbs lasting 10 minutes to 6 hours in duration usually start after 5–7 years of age. EA type 2 is due to mutation in voltage dependent calcium channel gene. Episodes of ataxia, vertigo, jerk nystagmus with vomiting lasting one hour to a day occur 1–3 times per month. Onset is in school age. Most patients are normal between attacks but some may have slowly progressive truncal ataxia and nystagmus.

Postinfectious/Immune-Mediated Disorders

Acute Postinfectious Cerebellitis

This most commonly affects children between 2 and 7 years of age after an attack of varicella. Ataxia starts suddenly and is worst at the onset. It varies from mild unsteadiness to complete inability to stand. Recovery occurs spontaneously over 3 to 20 weeks. No treatment is required.

Miller-Fisher Syndrome

This is a variant of Guillain-Barré syndrome. A previously well child develops ataxia, ophthalmoplegia and areflexia. Cerebrospinal fluid shows findings similar to Guillain-Barré syndrome. The course is self-limited and complete recovery occurs within 6 months.

Table 19.8: Anatomical localization of ataxia

Feature	Cerebellar	Sensory	Vestibular
Ataxia	Limb or truncal	Limb	Truncal
Dysarthria	Present	Absent	Absent
Nystagmus	Present	Absent	Present
Vertigo	Absent	Absent	Present
Hypotonia	Present	Absent	Absent
Deep tendon reflexes	Pendular	Absent	Normal
Romberg sign	Absent	Present	Absent
Vibration and position sense	Normal	Decreased	Normal

Table 19.9: Causes of ataxia**Acute or recurrent**

Postinfectious and autoimmune: Acute postinfectious cerebellitis, Miller-Fisher syndrome, opsoclonus myoclonus ataxia (occult neuroblastoma)

Drugs: Phenytoin, psychotropic drugs, antihistaminics

Brainstem encephalitis

Migraine: Basilar migraine, benign paroxysmal vertigo

Inherited disorders: Hartnup disease, maple syrup urine disease, pyruvate dehydrogenase deficiency, episodic ataxia types 1 and 2

Trauma: Concussion; hematoma

Chronic*Static*

Malformations and inherited defects: Arnold Chiari, Dandy Walker and Joubert syndrome

Stroke

Post-traumatic

Progressive

Inherited degenerative disorders: Spinocerebellar ataxia, abetalipoproteinemia, ataxia telangiectasia, Friedreich ataxia, Refsum disease, Hartnup disease

Brain tumors: Cerebellar astrocytoma, medulloblastoma, ependymoma

Acquired: Multiple sclerosis, vitamin B₁₂ deficiency

Multiple Sclerosis

About 3–5% of patients of multiple sclerosis present before 6 years of age. Ataxia is the most common initial feature, followed by seizures, encephalopathy and hemiparesis. A polyphasic course is characteristic. Repeated episodes of demyelination occur in noncontiguous areas of the nervous system. Cerebrospinal fluid during episodes show mild pleocytosis with raised protein and oligoclonal bands. MRI brain shows scattered demyelinating plaques with predilection towards juxtacortical and periventricular white matter, infratentorial area and spinal cord.

Opsoclonus Myoclonus Ataxia (OMA)

This syndrome is characterized by chaotic eye movements (opsoclonus), myoclonus, ataxia and encephalopathy. Occurrence is between 6 months and 4 years. Encephalopathy manifests as personality change or irritability. Opsoclonus persists even during sleep. Around half of the cases are associated with neuroblastoma. A relapsing and remitting course is seen.

Chronic Progressive Ataxia

The term chronic ataxia is used for entities which have an insidious onset and progress beyond months to years. Some of the important causes are being described below. The salient causes have been tabulated in Table 19.9.

Abetalipoproteinemia

This is an autosomal recessive disorder caused by defect in the gene for microsomal triglyceride transfer protein. Manifestations are fat malabsorption, failure to thrive, acanthocytosis, severe anemia, ataxia and retinitis pigmentosa with night blindness. Ataxia results from severe vitamin E deficiency. Plasma cholesterol and triglycerides are low and apolipoprotein B is absent in the plasma. Treatment includes dietary fat restriction and large doses of vitamin E.

Ataxia Telangiectasia

Described on page 561.

Friedreich Ataxia

This is the most common autosomal recessive ataxia. It is caused by an unstable triplet repeat of the frataxin gene at chromosome 9q13. Onset of symptoms usually occurs between 2 and 15 years with a slowly progressive ataxia. Dysarthria, absent tendon reflexes, extensor plantar responses, pes cavus, scoliosis, loss of position and vibration sense, hypertrophic cardiomyopathy and diabetes are other associated features.

Refsum Disease

This rare autosomal recessive disorder is characterized by peripheral polyneuropathy, cerebellar ataxia, retinitis pigmentosa and ichthyosis. The symptoms evolve slowly and insidiously from childhood through adolescence and early adulthood. Blood levels of phytanic acid are increased in patients with Refsum disease.

Joubert Syndrome

This is a rare brain malformation characterized by hypoplasia of the cerebellar vermis as well as a malformed brainstem. The most common features of Joubert syndrome in infants include ataxia, hyperpnea, hypotonia, abnormal eye movements, seizures and impaired intellectual development. Physical deformities such as polydactyly, cleft lip or palate, kidney and liver abnormalities may also occur. Most cases are autosomal recessive in inheritance but some appear to be sporadic. A characteristic sign on MRI is the inverted 'molar tooth' sign seen in the brainstem and cerebellum.

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MOVEMENT DISORDERS

Disorders of movement that impact the smoothness and accuracy of movement are seen with many neurological

illnesses like hypo- or hypertonia, weakness and ataxia. This chapter will focus on involuntary abnormal movements, i.e. excessive movements that are not under the patient's control. They usually occur as a result of disorders of the basal ganglia.

Abnormal movements have been classified into 5–6 types but there is such a rich variety of movements that all cannot be classified or even described. They require visualization.

Abnormal movements need to be differentiated from convulsions. Unlike convulsions that are usually paroxysmal, occur during sleep or wakefulness and are associated with altered consciousness and abnormal EEG, abnormal movements are usually non-paroxysmal, tend to occur in awake state and disappear during sleep, and are unlikely to be associated with loss of consciousness or EEG abnormality. Important types are discussed below.

Chorea

This is a rapid, random, non-rhythmic, non-stereotyped and quasipurposive movement, often superimposed on a voluntary movement. Chorea may move from limb to limb or one side of body to another, giving the impression of restlessness. Describing chorea is tough as the movement is not stereotyped. 'Jack in the box' movements may be seen. The movements are often elicitable by asking the patient to raise both arms above the head or stretched out in front. The examiner may feel alternating 'milkmaid' movements upon holding the patient's hand. The most common conditions presenting with chorea in India are Sydenham chorea, Wilson disease and sequelae of meningoencephalitis (Table 19.10).

Sydenham Chorea (*rheumatic chorea*)

This is an immune-mediated late manifestation of rheumatic fever. Onset is insidious, often with unilateral chorea. Hypotonia, dysarthria and emotional lability may be present. The condition improves gradually over 3–4

Table 19.10: Causes of chorea

Chorea as predominant symptom

Inherited defects: Glutaric aciduria, benign familial chorea, Wilson disease, Fahr disease, abetalipoproteinemia, Huntington chorea, ataxia telangiectasia, Lesch-Nyhan syndrome

Systemic disorders: Sydenham chorea, hyperthyroidism, systemic lupus erythematosus

CNS infections

Tumors

Drugs: Anticonvulsants, oral contraceptives, antiemetics, theophylline

Chorea as one of the symptoms

Perinatal brain insult

Postinfectious

Vascular disease: Stroke, Moyamoya disease

months. Patients should receive prophylaxis against group A streptococcal infection. Pimozide, valproate, haloperidol, benzodiazepines or phenothiazines may be used to control abnormal movements.

Chorea and other abnormal movements may be seen during recovery from tubercular or *viral (especially JE)* meningoencephalitis. Movements usually last several weeks to months and may be incapacitating.

Athetosis

These are slow, writhing, distal movements of the limbs. It may occur alone, usually after perinatal brain injury (perinatal asphyxia, kernicterus), or along with chorea, as choreoathetosis.

Dystonia

This refers to abnormal posture due to sustained muscle contraction. Focal dystonias, such as blepharospasm, orofacial or hemifacial spasm and writer's cramp are rare in childhood. However, generalized dystonias in children may begin as focal dystonia.

Torticollis

Sustained turning of the head to one side may be caused by dystonia, benign paroxysmal torticollis, cervicomedullary malformations or syringomyelia, diplopia, juvenile rheumatoid arthritis, posterior fossa or cervical cord tumors and sternocleidomastoid injury or tumor.

Benign Paroxysmal Torticollis

Benign paroxysmal torticollis is believed to be a migraine variant. Episodes of head tilting and rotation to one or other side begin in the first year. Pallor, irritability, malaise and vomiting may be associated. Attacks last 1–3 days, remit spontaneously and recur 3–6 times per year.

Dopa Responsive Dystonia

Dopa responsive dystonia or Segawa disease is inherited in an autosomal dominant or recessive manner. Children present between 4 and 8 years of age with gait disturbance, toe walking and/or posturing of arms. A diurnal pattern is observed in more than half, with symptoms worsening by the evening. Small doses of levodopa provide immediate and complete relief. Untreated patients may progress to parkinsonism with cogwheel rigidity and bradykinesia.

Idiopathic Torsion Dystonia

Idiopathic torsion dystonia is an autosomal dominant condition with variable penetrance, occurring most commonly in Ashkenazi Jews. Presentation peaks bimodally at 9 years and 45 years. Dystonia begins in the legs to become generalized. Dysarthria, dysphagia, orofacial movements, postural tremor and blepharospasm may be present. Botulinum toxin helps in focal problems.

Trihexiphenidyl, baclofen, carbamazepine, benzodiazepines or levodopa may be useful. Outcomes vary from complete disability to functional independence.

Wilson Disease

Wilson disease, an autosomal recessive disorder characterized by copper accumulation in liver, brain and cornea, presents variably at 3–50 years. Children usually present with acute or chronic hepatitis or hepatic failure. Neurological symptoms predominate in the second decade, and include disturbance of speech or gait, often unchanged for years, followed by dysarthria, dystonia, rigidity, abnormalities of gait and posture, tremor and drooling. Dementia and psychiatric symptoms may also occur. Almost all cases with neurological involvement show golden-brown pericorneal discoloration, termed Kayser-Fleischer rings. Diagnosis is suggested by reduced serum ceruloplasmin levels (<20 mg/dl), increased urinary copper excretion and increased hepatic copper content on biopsy. Patients require lifelong chelation with oral D-penicillamine or trientine, titrated to maintain urinary copper excretion at 5–10 times normal. Pyridoxine, zinc and vitamin E is given. Patients slowly recover over months. However, some patients progress to liver failure despite therapy, necessitating liver transplantation.

Pantothenate Kinase associated Neurodegeneration

Pantothenate kinase associated neurodegeneration is an autosomal recessive disorder associated with iron deposition in basal ganglia. Patients present with progressive dystonia, initially affecting feet, leading to equinovarus deformity, followed by rigidity in hands. Two-thirds patients have retinitis pigmentosa while one-fourth develop seizures. MRI is characterized by 'eye of tiger' appearance of the basal ganglia on T2-weighted images. Management is symptomatic.

Symptomatic Generalized Dystonia

Symptomatic generalized dystonia may follow various types of brain injury. Progressively severe dystonia is observed beginning 2–3 years after kernicterus or perinatal asphyxia. Patients with stroke, head trauma, tumor of basal ganglia, antiphospholipid syndrome and neuronal storage disease may show hemidystonia.

Myoclonus

These are sudden, brief, jerky, involuntary movements that are focal, multifocal or generalized. Generalized myoclonus is not stereotyped. Myoclonus is more common when awake but may not disappear completely during sleep. It may occur in isolation, as part of myoclonic epilepsy, where EEG shows epileptiform discharges, or as part of systemic or CNS disorders. Myoclonus cannot be voluntarily suppressed. A very wide variety of systemic and central nervous system disorders can cause myoclonus. *Essential myoclonus* refers to focal or

generalized myoclonus that occurs chiefly during action or stress, involves the face, trunk or proximal muscles, has onset in first or second decade of life, and is associated with normal EEG and neuroimaging. Therapy with nitrazepam or clonazepam may be useful.

Tics

These are sudden, brief, purposeless, complex stereotyped movements or utterances, which are exacerbated by stress, are suppressible and disappear during sleep. Examples include clearing the throat, eye blinking, grimacing, lip smacking and shrugging of shoulders.

Tourette syndrome is characterized by motor and verbal tics and attention deficit. Verbal tics include snorting, sniffing, grunting or hissing. Disease course waxes and wanes over prolonged period. The condition is perhaps caused by streptococcal infection in genetically predisposed individuals. Pimozide, haloperidol or fluphenazine may be used if the tics are bothersome.

Tremor

These are involuntary oscillating, rhythmic and usually distal movements of low amplitude on both sides of an axis. Tremors may be physiological, precipitated by anxiety, fatigue, stress or drugs such as xanthines, adrenergic agonists, nicotine, thyroid hormone and amphetamines. Tremors may be secondary to injury to basal ganglia following meningoencephalitis and neurodegenerative diseases.

Infantile Tremor Syndrome

Infantile tremor syndrome was described in exclusively breastfed Indian infants, presenting at 8–18 months of age with listlessness, developmental delay and regression, pallor, depigmented sparse hair and hyperpigmented knuckles. Subsequent symptoms include progressive limb tremors, bleating cry, and arms positioned like a 'bird about to take flight'. The condition is linked to cobalamin deficiency and responds to therapy with cobalamin and propranolol.

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STROKE

Neurological weakness of one-half of the body (upper and lower limb), termed hemiplegia, is caused most commonly by a stroke, defined as rapidly developing focal or global

disturbance of brain function lasting more than 24 hours with no obvious nonvascular cause. Other causes of hemiplegia include transient ischemic attack, Todd palsy, granuloma, tumor, abscess, encephalitis, demyelinating disorders, congenital brain malformation, neurocutaneous disorders and migraine.

Stroke may be broadly classified as ischemic or hemorrhagic variants that account for 55% and 45% of all cases in childhood, respectively. Ischemic stroke may be caused by arterial thrombi or embolism or due to cerebral venous sinus thrombosis. Weakness due to stroke is typically sudden, worst at the onset and improves gradually over days to months. Almost 20% of childhood stroke is recurrent.

Acute Ischemic Stroke

One or more risk factors for acute ischemic stroke, listed in Table 19.11, are present in two-thirds of patients. In the others, no cause for stroke can be found despite extensive evaluation. Patients with arterial thrombi may have prodromal symptoms, stuttering course and history of transient ischemic attacks, while those with embolism usually present with sudden loss of function. The precise neurological deficit depends on the site of infarction. The

most common (90%) presentation is with hemiparesis, hemisensory signs, aphasia and/or visual field defects. Cortical strokes may cause convulsions, contralateral hemiparesis, cortical sensory loss and aphasia. Internal capsule infarction may cause contralateral dense hemiplegia, upper motor neuron type of facial palsy, hemianesthesia and homonymous hemianopia. Altered sensorium may occur with posterior fossa stroke. Brainstem infarction causes crossed paralyses of cranial nerve ipsilaterally and contralateral limb palsy.

Initial stabilisation includes attention to airway, breathing and circulation, supportive treatment for hypoxemia, hypoglycemia, dehydration, seizures and fever. Thrombolysis with tissue plasminogen activator (tPA), administered intravenously within 3 hours and intra-arterial within 6 hours of the event, are recommended in adults; however, no clear guidelines are available for children. Pending investigations for cause, ultrafractionated or low molecular weight heparin may be administered.

Suggested evaluation is listed in Table 19.12. Neuroimaging should be done as soon as possible. Ultrasound is useful if fontanelle is open. Transcranial Doppler shows changes in cerebral blood flow velocity in moderate to

Table 19.11: Risk factors for acute ischemic stroke

Cardiac disease

Complex cyanotic heart disease
Infective endocarditis
Cardiomyopathy
Atrial myxoma; rhabdomyoma

Hematological

Iron deficiency anemia
Sickle cell disease
Polycythemia
Leukemias

Prothrombotic disorders

Protein C or S deficiency
Antithrombin III deficiency
Activated protein C resistance
Factor V Leiden mutation

Vascular conditions

Cervicocephalic arterial dissection
Moyamoya disease
Fibromuscular dysplasia
Diabetes

Metabolic conditions

Homocystinuria
Mitochondrial encephalomyopathy lactic acidosis and stroke
Fabry disease

Drugs and toxins

Cocaine
Sympathomimetics; amphetamines
Oral contraceptives

Fibrillation; sick sinus syndrome; heart block
Valvular heart disease
Prosthetic valves
Patent foramen ovale

Disseminated intravascular coagulation
Hemolytic uremic syndrome
Thrombotic thrombocytopenic purpura

Prothrombin gene mutation *G20210A*
Hyperhomocysteinemia
Antiphospholipid antibody syndrome

Neurofibromatosis
Vasculitis: Primary; secondary to lupus
Infections: Tuberculosis; varicella

Organic acidemias
Ornithine transcarbamylase deficiency
Pyruvate dehydrogenase deficiency

L-asparaginase
Anabolic steroids

Table 19.12: Investigation for stroke

Complete blood count with erythrocyte sedimentation rate
 Hemoglobin electrophoresis
 Complete lipid profile
 Imaging: Carotid Doppler; computed tomography if hemorrhage suspected; MR imaging, arteriography and venography; carotid angiography, if indicated
 Echocardiography and electrocardiography
 Evaluation for procoagulant state

- *During acute phase:* Serum homocysteine levels; genetic testing for mutations (factor V Leiden, prothrombin gene); activated protein C resistance; lupus anticoagulant, anticardiolipin and β_2 glycoprotein-1 antibody
- *After 8–12 weeks:* Levels of protein C, S and antithrombin III

Antinuclear and anti-neutrophil cytoplasmic antibody; rheumatoid factor



Fig. 19.10: Contrast enhanced computed tomography showing diffuse hypodensity with midline shift in a patient with acute middle cerebral artery infarct

severe ischemia. CT is preferred in unstable patients or when intracranial hemorrhage is suspected. It may be normal in early ischemic stroke for up to 72 hours after onset, after which there is edema in the affected area (Fig. 19.10). MRI can identify ischemia within hours and diffusion weighted imaging within 45 minutes. While four vessel carotid angiogram is most accurate for distal arteries, lesions of internal carotid artery, moyamoya disease, arteriovenous malformations and aneurysms, MR angiography is a satisfactory alternative.

Appropriate rehabilitation should be planned. Long-term low dose aspirin is administered to prevent recurrence. Treatment of the underlying cause is important to prevent recurrence. Conditions with a high risk of recurrence (e.g. cardiac or prothrombotic disorders) require long-term oral anticoagulants.

Table 19.13: Causes of intracranial hemorrhage

Arteriovenous malformation: Sporadic; hereditary hemorrhagic telangiectasia
 Capillary telangiectasia
 Cavemous malformations
 Aneurysms
 Bleeding and clotting diathesis
 Vasculitis
 Hypertension
 Trauma

Intracranial Hemorrhage

Clinical presentation is more dramatic than with ischemic stroke, with severe headache and vomiting due to raised intracranial pressure, and meningeal signs due to leaking of blood into the CSF. Causes of intracranial hemorrhage are listed in Table 19.13. A thorough evaluation is warranted as a potential cause is found in about 90% cases. It must be noted that cerebral venous sinus thrombosis also can result in ICH because of back pressure.

CT scan is preferred to MRI in diagnosis of hemorrhage. MR, CT or 4-vessel carotid angiography is required to delineate arteriovenous malformations and aneurysms. Complete blood counts, including platelet count, clotting factor assays like von Willebrand factor antigen, factor VIII and factor XII and liver function tests are required.

Management consists of resuscitation and supportive care. Identification of the cause may be followed by definitive treatment, in addition to rehabilitative measures.

Cerebral Venous Sinus Thrombosis (CVST)

Risk factors for CVST are listed in Table 19.14. Thrombosis of cerebral veins presents with dilated scalp veins, features of raised intracranial pressure and altered sensorium in addition to focal neurologic signs. Unenhanced CT scan may show linear densities (dense cord) in the sinuses. Later, enhanced CT scan may reveal a filling defect or

Table 19.14: Risk factors for cerebral venous sinus thrombosis

Dehydration, hypoxia
 Cardiac disease: Congenital, postoperative, post-catheterization
 Anemias: Sickle cell disease, iron deficiency anemia, thalassemia
 Head and neck infections
 Metabolic: Homocystinuria; prothrombotic disorders
 Nephrotic syndrome
 Malignancy: Leukemia, lymphoma
 Systemic diseases: Systemic lupus erythematosus, Behçet disease, inflammatory bowel disease
 Drugs: L-asparaginase, oral contraceptives, steroids
 Other structural conditions: Head injury, brain tumor, hydrocephalus, Sturge-Weber syndrome

empty delta sign. CT or MR venography is more definitive. Diffusion and perfusion MRI and digital subtraction angiography are needed in equivocal cases. A detailed evaluation for prothrombotic states is essential.

Initial treatment is supportive. Antibiotics are given if bacterial infection is suspected. Ultrafractionated heparin or low molecular weight heparin followed by warfarin for 3–6 months is the treatment of choice. Thrombolytic treatment is recommended only in selected cases.

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PARAPLEGIA AND QUADRIPLEGIA

Paraplegia refers to weakness of trunk and both lower limbs, while quadriplegia denotes weakness of all four limbs. Paraplegia or quadriplegia may occur due to disorders of cerebrum, spinal cord, peripheral nerves, neuromuscular junction or muscles (Table 19.15). While cerebral disorders are upper motor neuron type, spinal cord lesions may cause either upper or lower motor neuron involvement and the other three types of lesions show lower motor neuron involvement.

Cerebral Disorders

Lesions involving parasagittal and periventricular areas, in particular, cause paraplegia or quadriplegia. Common causes include perinatal asphyxia, structural malformations and sequelae of CNS infections.

Spinal Cord Disorders

These may cause acute or chronic progressive paraplegia or quadriplegia. Cervical cord lesions present as quadriplegia, whereas lower lesions present as paraplegia. Lower motor neuron signs are present at the level of the cord lesion and upper motor neuron signs are noted below the lesion. Acute transverse lesions of the cord may cause spinal shock with loss of all motor, sensory, autonomic and reflex functions below the level of lesion. Patients with chronic spinal cord lesions present with clumsy gait, foot deformity and/or stunted limb growth. Malformations like meningocele and meningomyelocele are obvious at birth. The skin overlying spinal dysraphism may show abnormalities like pigmentation, tuft of hair, lipoma or sinus. Congenital atlanto-axial dislocation may cause acute or slowly progressive quadriplegia at any age, and is usually caused by odontoid hypoplasia, occurring either

Table 19.15: Causes of paraplegia or quadriplegia

Spastic

Compressive

Tuberculosis of spine with or without paraspinal abscess

Extradural: Metastasis from neuroblastoma, leukemia, lymphoma; inflammatory process, such as epidural abscess (usually posterior to the spinal cord), bony abnormalities such as achondroplasia, Morquio disease, hemivertebrae and occipitalization of atlas vertebra, atlantoaxial dislocation

Intradural: Neurofibroma, dermoid cyst

Intramedullary: Glioma, ependymoma, hemato- or hydro-myelia

Noncompressive myelopathies

Vascular anomalies of the spinal cord: Arteriovenous malformations, hemangiomas and telangiectasia

Trauma or transection of cord

Transverse myelitis/myelopathy: Viral, neuromyelitis optica, segmental necrosis due to vascular occlusion, e.g. of anterior spinal artery

Familial spastic paraplegia

Lathyrism

Degenerative spinal cord disease

Supra-cord lesions

Cerebral palsy

Hydrocephalus

Bilateral cortical disease

Bilateral white matter disease

Flaccid weakness

Spinal shock in the initial stages of spinal cord damage, e.g. after trauma, vascular, inflammatory, neoplastic lesions, or transverse myelopathy

Guillain-Barré syndrome

Acute poliomyelitis

Spinal muscular atrophies

Peripheral neuropathies

Botulism, Riley-Day syndrome

Pseudoparalysis

Surgery, osteomyelitis, fractures, myositis, metabolic myopathy

in isolation or as part of Down syndrome, mucopolysaccharidosis (e.g. Morquio syndrome) or Klippel-Feil syndrome (decreased number and abnormal fusion of cervical vertebrae). These are later replaced by upper motor neurone signs within a few days to weeks.

Transverse Myelitis

Transverse myelitis is an acute demyelinating condition of the cord characterized by sudden onset of often symmetrical leg weakness with loss of reflexes, movements and sensation below a certain level with bladder and bowel dysfunction over 1–2 days. Longitudinally extensive transverse myelitis may occur with optic neuritis sequentially or together, termed Devic disease (neuromyelitis optica). Diagnosis is enabled by contrast enhanced

magnetic resonance imaging of the cord. High dose intravenous steroids are the treatment of choice.

Spinal Muscular Atrophy

Spinal muscular atrophy is a hereditary disorder characterized by degeneration of the anterior horn cells of the spinal cord. There are 3 types with different age of presentation. Type 1 presents soon after birth with flaccid quadriplegia. Tongue fasciculations are seen. Extraocular muscles are spared and the baby appears alert. Type 2 presents between 6 and 18 months of age and type 3 presents after 18 months of age with motor delay. Diagnosis is by molecular testing.

Spinal Cord Compression

Spinal cord compression may be caused by congenital lesions, tumors, Pott's spine, and disc prolapse. Root pains may be an initial symptom. It is important to remember that early symptoms of a compressive cord lesion may be missed especially in a young child and they may present suddenly like an acute noncompressive cord lesion.

Polyneuropathy

The most common polyneuropathy presenting as quadriplegia is acute inflammatory demyelinating polyneuropathy or Guillain-Barré syndrome. This postinfectious immune-mediated disorder presents acutely with symmetrical ascending paralysis, early and complete loss of deep tendon reflexes with or without sensory changes like pain, paresthesias and loss of position and vibration sense. Autonomic disturbances may occur. Involvement of thoracic muscles may cause respiratory insufficiency, which is important to recognize. Treatment options include intravenous immunoglobulin and plasmapheresis.

Neuromuscular Junction Disorders

Myasthenia gravis usually presents with ptosis and weakness of extraocular muscles worsening in the later part of the day. It may occasionally cause generalized weakness. Repetitive nerve stimulation test shows a decremental response. Antibodies against acetylcholine receptors are found in up to 85% of generalized immune mediated myasthenia.

Muscle Disorders

These cause proximal weakness, usually with preserved deep tendon reflexes.

Suggested Reading

- Fenichel GM. Paraplegia and quadriplegia. In: *Clinical Pediatric Neurology*. 7th edn. Saunders, Philadelphia. 2013; pp. 253–269.
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HEADACHE

Headache is a common reason for neurological consultation in children. Headaches may be acute, recurrent or chronic and primary (e.g. migraine) or secondary to an intracranial or systemic cause.

Pathophysiology

The brain and most of the dura and ependyma are pain insensitive. Pain sensitive intracranial structures are vascular sinuses, large arteries and dura mater at the base of the brain, and extracranial structures are skin, subcutaneous tissue, cranial nerves, arteries, muscles, periosteum, sinuses and teeth. Inflammation, injury, displacement or traction of these structures may cause headache. The trigeminal and upper cervical nerves mediate the pain sensations.

Evaluation of a Child with Headache

Evaluation is primarily clinical and investigations to rule out serious underlying disorders are required infrequently. A detailed history about the pattern of headache should include description of episodes, frequency, duration, location and associated symptoms. Severe progressive recent onset headache may suggest intracranial pathology. Neurologic examination should include fundus examination.

Migraine

Migraine presents as acute recurrent headache occurring in episodes lasting 2–72 hours. Migraine accounts for 75% of consultations for headache, affecting about 10% children aged 5–15 years. Below the age of 7 years, both sexes are equally affected. At older age, girls are affected more often. Typical features include unilateral localization (in two-thirds of patients), throbbing character, moderate to severe intensity, triggering by stress, exercise, trauma and menstruation and association with nausea, vomiting, photophobia and phonophobia.

Migraine is classified as migraine with aura (classic migraine), migraine without aura (common migraine) and migraine equivalents. Migraine without aura is twice as common among school age children as migraine with aura, but both may occur in the same person. Usual features of aura are visual aberrations, flashing lights, coloured lines, blind spots, blurred vision, hemianopia or visual hallucinations. Dysesthesias of limbs and perioral region, focal motor deficits like hemiplegia, ophthalmoplegia and aphasia may also occur. Aura is transient and usually lasts less than a day. Migraine equivalents are transitory disturbance in neurologic function, including benign paroxysmal vertigo, cyclic vomiting, paroxysmal torticollis, acute confusional migraine, hemiplegic migraine and ophthalmoplegic migraine.

Family history is present in 90% cases, especially in classic migraine. Inheritance is believed to be multi-

factorial rather than Mendelian, and familial hemiplegic migraine is the only well-established monogenic migraine syndrome.

Known triggers of migraine should be avoided. During the attack, the child should be given an analgesic and asked to rest. Nonsteroidal anti-inflammatory drugs like ibuprofen are usually effective. Sleep is also effective; the attack is usually over by the time the child awakens. Selective serotonin agonists like sumatriptan, available as oral, sublingual preparations and nasal sprays, are effective and non-sedative. Severe migraine may benefit from intravenous prochlorperazine maleate, dihydroergotamine or sodium valproate. Prophylactic therapy is indicated, if there is significant school absenteeism. Flunarizine, amitriptyline, propranolol, topiramate and valproate may be used.

Tension Type Headache

This is a common type of headache, affecting 10–25% of children, with a lifetime prevalence of 70%. Headache could be episodic or chronic, persisting for weeks or months. Episodic tension type headache affects all ages and both sexes and is related to fatigue and stress. The pain is a constant ache usually localized to the back of head and neck. It is probably mediated by sustained contraction of muscles attached to the skull. While nausea and vomiting are absent, photophobia and phonophobia may occur.

Suggested Reading

- Fenichel GM. Headache In: Clinical Pediatric Neurology. A signs and symptoms approach. 6th edn. Saunders, Philadelphia 2009; pp. 76–89.
- Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edn. Cephalgia. 2013; 33:629–808.

RAISED INTRACRANIAL PRESSURE, SPACE OCCUPYING LESIONS AND HYDROCEPHALUS

Intracranial pressure refers to the pressure of CSF within the cranium. It is normally pulsatile and less than 5 mm Hg in newborns, 6–15 mm Hg in infants and 10–15 mm Hg in older children. Intracranial pressure is considered severely elevated, if raised above 40 mm Hg.

Pathophysiology

Raised intracranial pressure results in decreased cerebral blood flow and/or herniation of brain tissue. Cerebral blood flow is normally about 50 mL per 100 g of brain tissue per minute and depends on cerebral perfusion pressure, the difference between mean arterial pressure and intracranial pressure. Various myogenic, metabolic and neurogenic autoregulatory mechanisms help maintain cerebral blood flow. Decrease in cerebral blood flow to below 40% leads to progressive ischemia, neuronal death, cerebral edema and further increase in intracranial pressure, leading to diffuse bilateral cortical dysfunction and coma. Causes of raised intracranial pressure are listed in Table 19.16 and common causes are discussed below.

Table 19.16: Causes of raised intracranial pressure

Hydrocephalus (For details, see Table 19.19)
Central nervous system infections
Intracranial hemorrhage
Space occupying lesions: Tumors, granulomas, abscesses
Metabolic causes: Reye syndrome; inborn errors of metabolism, acute hepatic failure
Arterial, venous stroke
Hypertensive encephalopathy
Idiopathic

Clinical Features

Symptoms of raised intracranial pressure are headache, vomiting and visual disturbances, progressing to focal neurological deficits and coma. Chronically raised intracranial pressure before closure of sutures results in increased head size and hydrocephalus, presenting as bilateral sunseting, tense bulging anterior fontanelle, hypertension and bradycardia. Sixth cranial nerve palsy due to raised intracranial pressure, termed a false localizing sign, presents as squint and diplopia. In older patients with closed sutures, percussion of the skull produces a sound like a cracked pot, termed a positive Macewen sign. Herniation of brain tissue causes various clinical syndromes (Table 19.17), compression of the brainstem, coma and death.

Management

Invasive methods to monitor intracranial pressure with intracranial catheters and transducers should be used only in intensive care setting with strict aseptic precautions and are contraindicated in presence of coagulopathy. Measures to manage raised intracranial pressure are listed in Table 19.18.

Space Occupying Lesions

Brain Tumors

Primary brain tumors are the second most common malignancy in childhood after leukemia, and may be malignant or benign. Their incidence is increased in neurocutaneous syndromes like tuberous sclerosis and neurofibromatosis. Tumors present chiefly with focal neurological deficits and symptoms of raised intracranial pressure. Two-thirds of pediatric brain tumors are infratentorial. Of these, medulloblastoma and cerebellar astrocytomas account for a third each while brainstem gliomas and ependymomas constitute the majority of the rest. Since the posterior fossa is tightly encased with narrow CSF pathways, infratentorial tumors present with raised intracranial pressure and hydrocephalus. Common supratentorial tumors include astrocytomas, cranio-pharyngioma, ependymomas, choroid plexus papillomas and pineal body tumors. Neuroimaging by MRI helps define the nature and extent of tumor.

Table 19.17: Herniation syndromes

Location/type	Abnormality	Clinical features
Subfalcine	Medial displacement of the cingulate gyrus	Impaired consciousness; monoparesis of the contralateral lower limb
Lateral transtentorial	Downward and medial displacement of uncus and parahippocampal gyrus	Unilateral dilated pupil with ptosis (third nerve palsy); impaired consciousness; abnormal respiration; hemiparesis
Central transtentorial	Downward displacement of diencephalic structures	Impaired consciousness; abnormal respiration; symmetrical small reactive or midposition fixed reactive pupils; decorticate followed by decerebrate posturing
Upward transtentorial	Upward displacement of cerebellar vermis and midbrain	Prominent brainstem signs; downward gaze deviation; decerebrate posturing
Transforaminal	Downward displacement of cerebellar tonsils and medulla	Neck rigidity; impaired consciousness; ophisthotonus; decerebrate rigidity; vomiting; irregular respiration; apnea; bradycardia

Table 19.18: Management of raised intracranial pressure

Raise head end by 30 degrees; keep head in midline

Hyperventilate to maintain PCO₂ at 30–35 mm Hg

Administer mannitol at 0.25–1 g/kg (1.25–5 mL/kg of 20% solution) as intravenous (IV) bolus; repeat every 8 hours for 48–72 hours

Administer hypertonic (3%) saline at 0.1–1 mL/kg/hr to maintain serum sodium at 145–155 mEq/L

Administer IV furosemide at 1–2 mg/kg/dose

Switch to oral acetazolamide or glycerol when stable

Consider corticosteroids (oral or IV) for vasogenic edema

Consider decompressive craniectomy

Medulloblastoma: These midline cerebellar tumors usually affect young children, accounting for 30–40% of

pediatric posterior fossa tumors. Boys are affected 2–4 times as often than girls. These rapidly growing, malignant tumors present with cerebellar signs and features of raised intracranial pressure. Neuroimaging reveals a midline mass arising from the vermis, effacing the fourth ventricle and basal cisterns, causing obstructive hydrocephalus (Fig. 19.11a). The tumors are usually hyperdense with prominent enhancement (90%) and associated with cysts or necrosis (40–50%) or calcification (10–20%). Forty percent of patients have evidence of CSF seeding at diagnosis. The prognosis is poor.

Cerebellar astrocytoma: These arise from either cerebellar hemispheres, and present with ataxia, incoordination and nystagmus. Most tumors are low-grade and slow-growing and carry a satisfactory prognosis as they can usually be excised completely.

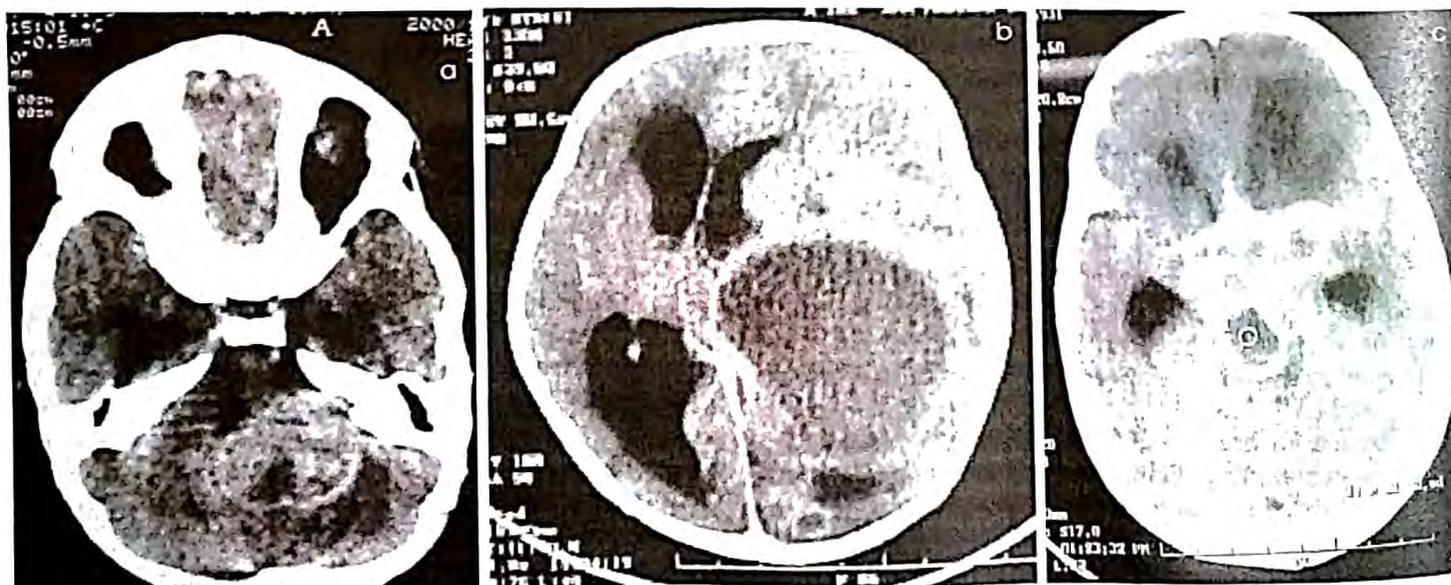


Fig. 19.11: Contrast enhanced tomography in the setting of raised intracranial tension showing (a) Enhancing heterogenous mass arising from vermis suggesting medulloblastoma; (b) Left parietal enhancing lesion with midline shift in a case of brain abscess; and (c) Multiple basal ring enhancing lesions and meningeal enhancement in a patient with tubercular meningitis

Brainstem glioma: These usually present between 5 and 10 years of age with lower cranial nerve palsies, long tract signs, cerebellar signs and signs of raised intracranial pressure. While both focal brainstem gliomas and diffuse intrinsic pontine glioma carry grave prognosis, the latter have worse outcomes.

Ependymoma of the fourth ventricle: These arise from cells lining the ventricle. Tumors arising from the floor of the fourth ventricle present with torticollis and ataxia, while those arising from the side of the ventricle affect cranial nerves, presenting with impaired hearing, dysphagia and clumsiness.

Craniopharyngioma: These are cystic benign supratentorial tumors arising from the squamous epithelial rest cells of the Rathke pouch. Clinical features include growth failure, visual field defects (bitemporal hemianopsia or unilateral or asymmetric field defects), signs of raised intracranial pressure and endocrine abnormalities like diabetes insipidus and delayed puberty. X-ray skull may reveal calcifications. Treatment includes cyst aspiration and radiotherapy.

Glioma of cerebral hemispheres: These usually present with seizures and hemiparesis; features of raised intracranial pressure are usually delayed. Histologically, these may be astrocytoma, oligodendroglioma or glioblastoma.

Glioma of optic nerve: These relatively uncommon tumors usually occur in a setting of NF1 and present with decreased vision, and later with proptosis, symptoms of raised intracranial pressure, focal neurological deficits and hydrocephalus. Hypothalamic involvement may result in polyuria and polydipsia. Imaging indicates an enlarged optic nerve.

Brain Abscess

Infection within the brain parenchyma leads to brain abscess formation, usually in the setting of a predisposing condition. Congenital cyanotic heart disease account for 25–45% of brain abscess in children. Infected sinuses, middle ear or tooth infection, bacterial meningitis, compound skull fractures, penetrating skull injury, neurosurgery and immunodeficiencies are other predisposing conditions. Microorganisms implicated include streptococci (both aerobic and anaerobic), gram-negative anaerobic bacilli, *Enterobacteriaceae* and *Staphylococcus aureus*. Fungi and mycobacterial infection may occur in immunocompromised patients.

Classically, the presentation is subacute with a triad of fever, focal neurological deficits and signs of raised intracranial pressure. However, fever may be lacking in 20–50% patients or may be low grade. Intense inflammation and edema produce severe mass effect, leading to herniation and death. MRI helps identify early cerebritis, microabscesses and posterior fossa collection. The abscess appears as a ring-enhancing lesion with

surrounding edema. Large lesions show mass effect, distortion of surrounding structures and midline shift (Fig. 19.11b). CSF may show mild pleocytosis due to meningeal reaction; however, lumbar puncture is usually contraindicated because of risk of herniation. Management includes administration of intravenous antibiotics with good penetration into the CSF for 4–8 weeks. Anaerobic coverage must be ensured. A third-generation cephalosporin with vancomycin and metronidazole provides satisfactory empiric coverage. Drainage of the abscess must be done through burr hole, craniectomy, craniotomy or by stereotactic aspiration.

Subdural Collections

Subdural collections usually occur as a complication of bacterial meningitis, chiefly in infancy. **Subdural effusions** are usually sterile and resolves spontaneously; drainage is only necessary if associated with pressure effect. They may, however, be associated with prolonged fever. **Subdural empyemas** are collections of pus in subdural spaces and are detected on imaging by an enhancing capsule. They usually require drainage but may refill. **Subdural hematomas** are usually traumatic and present with features of chronically raised intracranial pressure. A vascular membrane forms around the hematoma. As blood cells get absorbed, the fluid's protein content increases, thus increasing oncotic pressure that draws fluid into the hematoma. The collection grows, tearing small bridging veins within the hematoma, further increasing bleeding. The sequence of bleeding, increased pressure and growth repeats itself. The skull may show positive transillumination. Imaging reveals a biconvex collection, as compared to the crescent shape seen with epidural collections.

Granulomas

These lesions are more common in developing countries, and include tubercular, parasitic, and less commonly, fungal granulomas.

Tuberculoma

Tuberculoma is a common space occupying lesion, occurring alone or with tuberculous meningitis. Symptoms include seizures, focal neurological deficits and raised intracranial pressure. Imaging shows large (>20 mm) conglomerate ring-enhancing lesions in the supratentorial compartment (Fig. 19.11c). Tuberculomas are more irregular in outline than cysticercal lesions and may cause mass effect and midline shift. There may be intense perifocal edema. A hypodense centre suggests a tubercular abscess. Tuberculomas may appear or increase in size even while the patient is on antitubercular treatment, probably due to immune reconstitution. Treatment involves antitubercular treatment, including two months of intensive (four drug) therapy and 10 months of maintenance (isoniazid and rifampicin) therapy.

Hydrocephalus

This term refers to abnormal accumulation of CSF in the brain, leading to increased pressure and increased ventricular size, and if occurring before sutural fusion, in increased head size.

Pathophysiology

CSF is produced by the ventricular choroid plexus by ultrafiltration and active secretion at a rate of 20 mL/hr and passes through the ventricular system to be absorbed by arachnoid granulations into venous sinuses. Hydrocephalus is termed obstructive when there is obstruction to flow of CSF in the ventricular system and communicating when there is increased production or defective absorption of CSF due to non-obstructive causes. Chief causes are listed in Table 19.19.

Clinical Features

A large head may cause difficulty in delivery, making Cesarean section necessary. Infants present with large tense anterior fontanelle or an abnormally rapid growth in head size, manifest as increase in head circumference by more than 1 cm every fortnight, separation of sutures by more than 0.5 cm after the first 2 weeks and persistent widening of the squamoparietal sutures. After sutural fusion, children usually present with symptoms of raised intracranial pressure. A positive Macewen or crack pot sound on skull percussion suggests sutural separation. The setting sun sign indicates upward gaze palsy due to pressure on the quadrigeminal plate.

Differential diagnosis of a large head include rickets, hemolytic anemia, achondroplasia, familial macrocephaly, megalencephaly and neurometabolic disorders (mucopolysaccharidoses, Tay-Sachs, Canavan and Alexander diseases). Where fontanelle is open, cranial ultrasound reveals increased ventricular size. CT scan and MRI provide details on severity and etiology. Mildly enlarged ventricles may be seen in cerebral atrophy and should not be confused with hydrocephalus.

Table 19.19: Causes of hydrocephalus

Congenital

- Aqueductal stenosis (X-linked)
- Dandy-Walker malformation
- Arnold-Chiari malformation
- Vein of Galen malformation
- Intrauterine infections (toxoplasmosis, rubella, cytomegalovirus)
- Arteriovenous malformation

Acquired

- Intraventricular hemorrhage
- CNS Infections
- Tumors and space occupying lesions, especially of posterior fossa

Management

Untreated hydrocephalus before sutural fusion results in grossly increased head size and cortical thinning. After sutural fusion, untreated cases usually succumb to raised intracranial pressure. While medical measures may temporarily reduce intracranial pressure, CSF diversion, most commonly by a shunt, is more useful. Usually valved tubing is placed between the ventricle and peritoneal cavity. The ventriculoperitoneal shunt usually requires multiple revisions as the child grows older. Shunt surgery may be complicated by infection leading to meningitis, shunt displacement, block or kinking leading to chronic shunt dysfunction, and abdominal complications such as peritonitis or abscess. Another option for obstructive hydrocephalus is endoscopic third ventriculostomy that allows CSF to pass directly into the basal cisterns.

Prognosis

Outcomes of hydrocephalus are guarded. Almost two-thirds of children have variable mental and motor disabilities, even with appropriate treatment.

Idiopathic Intracranial Hypertension

Previously termed *benign intracranial hypertension* or *pseudotumor cerebri*, the condition is characterised by normal or reduced ventricular size and normal CSF chemistry. Idiopathic intracranial hypertension usually affects adults or adolescents, chiefly female, and is associated with obesity. Its pathophysiology remains unclear. Suggested mechanisms include increased CSF production, decreased CSF absorption or increased cerebral venous pressure, in a setting of endocrinopathy, anemia or use of vitamin A derivatives, tetracyclines, steroids or hormonal contraceptives.

Patients present with symptoms of increased intracranial pressure, such as headache, diplopia or blurred vision. Sixth cranial nerve palsy may occur as a false localizing sign. If present, papilledema and visual deficits require prompt evaluation and treatment. Options in management include oral acetazolamide, glycerol or corticosteroids, repeated lumbar puncture and surgical decompression (optic nerve sheath decompression and shunt surgery).

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- Fenichel GM. Management of increased intracranial pressure. In: *Clinical Pediatric Neurology*. 7th edn. Saunders, Philadelphia. 2013. pp 89–112.
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COMA

Definition and Pathophysiology

The word coma, derived from the Greek word 'koma' or deep sleep, represents a state of sustained severe alteration

of consciousness. Normal consciousness is maintained by integrity of cerebral cortex, thalamus and brainstem and regulated by the ascending reticular activating system, located in upper pons, midbrain and diencephalon. Altered consciousness or coma results from diffuse lesions of bilateral cerebral cortex or focal lesions of the ascending reticular activating system (Table 19.20). The most common causes of coma are trauma and CNS infections. Raised intracranial pressure causes herniation of brain structures, compressing the brainstem (Table 19.17).

Evaluation

General Physical Examination

Patients with raised intracranial pressure show bradycardia and hypertension. The respiratory pattern may indicate the level of the lesion. Cheyne Stokes breathing is observed in diencephalic involvement, while

Table 19.20: Causes of coma

Causes without focal neurological signs

Cerebrospinal fluid is normal

Poisonings, narcotic agents, toxins

Metabolic disorders, e.g. hypoglycemia, diabetic acidosis, uremia, inborn metabolic errors, Reye syndrome, hepatic encephalopathy

Head injury, concussion

Septicemia, cerebral malaria, dengue

Postictal

Hyperpyrexia, febrile encephalopathy

Water intoxication

Cerebrospinal fluid is abnormal

Meningitis

Encephalitis

Subarachnoid hemorrhage

Cerebral vein thrombosis

Midline cerebral tumors

Causes associated with focal neurological signs

Demyelinating disorders

Postictal coma

Intracerebral bleed, vascular malformation

Tumors, infarcts, strokes

Infections: Brain abscess, subdural empyema, encephalitis

Head injury, intracranial hemorrhage

Miscellaneous

Systemic illnesses, hypertension, shock

apneustic and ataxic breathing patterns suggest progressive brainstem compression. Clues to etiology on examination include evidence of injury and tongue bite (trauma); jaundice and fetor hepaticus (liver disease); petechiae (coagulopathy); ketotic breath odor (metabolic disease); dry flushed skin (belladonna poisoning) and moist skin with increased salivation (organophosphorus poisoning).

Neurological Examination

The severity of coma is assessed by Glasgow Coma Scale modified for use in children (Table 19.21). Alternatively, the alert, response to verbal, response to pain, unresponsive (AVPU) scale is administered, using a deep painful stimulus by a strong pinch or pressure on the nailbed or supraorbital area. Meningeal signs, tone and posturing are looked for. Decerebrate posturing suggests injury to upper pons, while decorticate posturing indicates bilateral cortical lesion with preserved brainstem function. Flaccid areflexia indicates loss of all cortical and brainstem functions up to the pontomedullary junction.

Funduscopy may indicate papilledema, hemorrhage or signs of hypertension. Pupils are pinpoint in pontine lesions and morphine poisoning and small, equal and reactive in coma due to metabolic or toxic causes. Bilateral fixed dilated pupils are seen preterminally, in severe ischemia or with atropine or belladonna poisoning. Unilateral unreactive pupil indicates impending transtentorial herniation. Sixth cranial nerve palsy is often a false localizing sign.

Focal neurological deficits suggest a structural lesion. Papilledema, hypertension, bradycardia, abnormal breathing pattern, posturing and third and sixth cranial nerve palsies suggest raised intracranial pressure. Brainstem reflexes including doll's eye, oculovestibular and corneal reflexes provide information on the integrity of the brainstem.

Investigations

Complete blood counts, blood glucose, electrolytes, kidney and liver function tests, venous blood gas, serum ammonia and lactate should be ordered. Where indicated, screening for toxins should be performed. Blood and CSF cultures should be obtained if suspecting an infection. Neuroimaging helps assess for structural brain injury.

Table 19.21: Glasgow Coma Scale modified for children below 2 years of age

Score	Best motor response	Best verbal response	Eye opening
1	None	None	None
2	Extension to pain	Moaning to pain	To pain
3	Flexion to pain	Crying to pain	To call
4	Withdrawal to pain	Irritable cry	Spontaneous
5	Localises	Cooing and babbling	
6	Moves on command		

Management

The first priority in managing coma is ensuring that airway, breathing and circulation are maintained. Specific therapy is administered where available. Supportive treatment includes antipyretics for fever, anticonvulsants for seizures, and measures to manage raised intracranial pressure (Table 19.18). Sedative anticonvulsants are avoided to prevent interference with evaluation of depth of coma. Appropriate nursing is essential in improving outcomes during prolonged coma, and includes chest physiotherapy to prevent hypostatic pneumonia, adequate nutrition, care of the skin and eyes to prevent bedsores, corneal ulceration and exposure keratitis, care of the bowel and bladder to prevent constipation, fecal impaction and urinary tract infection, and physiotherapy to prevent deep vein thrombosis and contractures.

The patient should be placed in lateral head down position with frequent changes from side to side. This position—also called the 'recovery' (from anesthesia) position—reduces obstruction to breathing from tongue falling back, protects against hypostatic pneumonia by facilitating drainage from lungs and guards somewhat against aspiration.

Persistent Vegetative State

This term refers to a state after recovery from coma when the patient returns to a wakeful state with preserved sleep wake cycle but without any awareness.

Brain Death

This term refers to complete cessation of all brain function including the brainstem. Criteria for brain death are listed in Table 19.22. The proximate cause of brain death should be known and the condition should be irreversible, with potentially reversible causes excluded, including use of CNS depressants, hypothermia, shock, and metabolic and endocrine disturbances. All brainstem reflexes should be absent with apnea. Since brains of young infants have increased resistance to damage, longer observation periods and ancillary tests are recommended in this group. Two independent physicians must conduct a full examination twice at the recommended time interval. The apnea test should be performed by disconnecting the patient from the ventilator after achieving normal blood gas, allowing arterial carbon dioxide to rise to 60 mm Hg or 20 mm Hg above baseline; absence of respiratory effort (positive apnea test) is consistent with brain death.

It is possible to sustain life on life support systems sometimes indefinitely even after brain death but the individual can never return to a functional state. The diagnosis of brain death is important in deciding to discontinue the life support systems and also for organ transplantation.

Different countries have their own laws and criteria for diagnosis of brain death.

Table 19.22: Guidelines to determine brain death*

Clinical criteria: Complete loss of consciousness, vocalization and volitional activity

Absent brainstem reflexes: Absence of all of the following:
Pupillary responses to light (with pupils midposition, 4–6 mm)
Oculocephalic reflex

Oculovestibular (caloric) responses

Corneal reflex

Jaw reflex

Facial grimacing to deep pressure on supraorbital ridge or temporomandibular joint

Pharyngeal gag reflex

Coughing in response to tracheal suctioning

Sucking and rooting reflexes

Apnea: Absence of respiratory drive at PaCO₂ of 60 mm Hg or 20 mm Hg above baseline

Prerequisites

Clinical and/or neuroimaging evidence of acute CNS catastrophe severe enough to explain the condition

Core temperature more than 32°C[^]

No drug (sedatives, narcotics) or alcohol intoxication, poisoning or neuromuscular blockade

Normal blood pressure

No confounding conditions such as severe electrolyte, acid-base, metabolic or endocrine disturbances

Two evaluations, separated by a time interval of 48 hours, if <2 months old; 24 hours, if 2–12 months old; 12 hours, if 1–18 years old; and at any interval, if >18 years old

Ancillary tests: Two tests required if <2-month-old; one test if 2–12-month-old; tests optional if >1 year old^{^^}

Cerebral angiography

Electroencephalography

Transcranial Doppler ultrasonography

Cerebral scintigraphy

*Adapted from American Academy of Pediatrics, Task Force on Brain Death in Children 2011, and the American Academy of Neurology, Practice Parameters for the Clinical Diagnosis of Brain Death; and consistent with the Indian Transplant of Human Organs (THO) Act, 2014
[^]35°C according to the THO act

^{^^}Two tests 6 hours apart at all ages according to the THO Act

Suggested Reading

- Act and Rules under Transplant of Human Organs Act (THOA) Transplantation of Human Organs and Tissues Rules, 2014; available at notto.nic.in/act-end-rules-of-thoa.htm.
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Neuromuscular Disorders

Sheffali Gulati

A motor unit comprises one anterior horn cell and all the muscle fibers that it innervates. Neuromuscular disorders may be due to lesions anywhere along the motor unit. These include neuronopathies (disorders of anterior horn cell), neuropathies (disorders of axon or its myelin), neuromuscular junction disorders and myopathies (disorders of muscle).

APPROACH TO EVALUATION

The predominant presenting complaint of a patient with a neuromuscular disorder is weakness. Weakness may also result from disorders of the upper motor neuron, e.g. cerebral palsy. Weakness due to an upper motor neuron lesion is associated with increased tone, brisk reflexes and extensor plantar responses. Additional features that suggest central nervous system involvement include decrease in level of consciousness, seizures and cognitive impairment.

Lower motor neuron lesions are associated with significant weakness, hypotonia, depressed reflexes and flexor plantar responses. Anterior horn cell involvement (e.g. spinal muscular atrophy) is associated with generalized weakness and wasting, fasciculations and hyporeflexia. Peripheral nerve involvement (e.g. hereditary sensory and motor neuropathies) is associated with predominantly distal weakness and wasting, hyporeflexia and sensory involvement. Neuromuscular junction involvement (e.g. myasthenia gravis) leads to fatigable and fluctuating weakness. Muscle diseases (e.g. muscular dystrophies) present with proximal weakness and relatively preserved bulk and reflexes. The mode of inheritance is variable, e.g. X-linked recessive in Duchenne muscular dystrophy and Becker muscular dystrophy; autosomal dominant in facioscapulohumeral dystrophy; and autosomal recessive in sarcoglycanopathies and congenital muscular dystrophies.

The presentation and pattern of disease over time allows definition of possible conditions. Muscular dystrophy is associated with inexorable weakness. Metabolic disease and ion channelopathies (periodic paralysis) are associated with episodic course.

Inflammatory disorders such as dermatomyositis are associated with waxing and waning course and pain. Cardiac disease often accompanies Duchenne muscular dystrophy, Pompe disease and myotonic dystrophy. Skin rash is seen in dermatomyositis; eyes are involved in myotonic dystrophy, congenital muscle dystrophies and mitochondrial diseases. Liver involvement may be seen with mitochondrial disorders, acid maltase deficiency and carnitine deficiency.

Laboratory Evaluation

Creatine phosphokinase (CPK), a muscle enzyme, is elevated in most muscular dystrophies. Muscle biopsy enables diagnosis based on specific morphological features, immunohistochemistry (absent or reduced staining for specific protein) and enzyme histochemistry (absent or reduced enzyme function). Electrophysiological tests, including nerve conduction studies and electromyography, help localize the lesion and assess its severity. Muscle imaging (ultrasound and MRI) is useful in certain cases. Molecular genetic testing is available for many disorders, including spinal muscular atrophy and Duchenne muscular dystrophy.

Hypotonia

Hypotonia is a common sign of neuromuscular disorders. Any lesion along the motor unit can result in *peripheral hypotonia*, characterized by depressed muscle stretch reflexes and loss of muscle power. The common causes of floppiness in infants are shown in Fig. 20.1. Hypotonia *in utero* may result in hip dislocation or multiple contractures (*arthrogryposis*). The mother may give a history of reduced fetal movements or polyhydramnios.

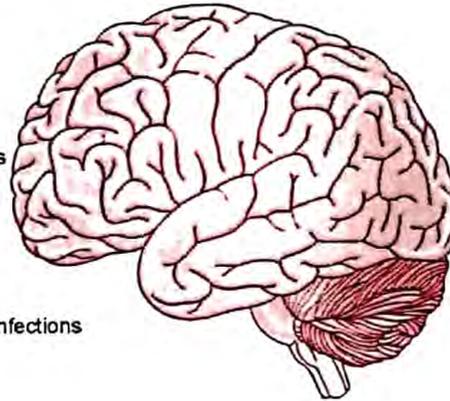
An alert hypotonic infant with absent deep tendon reflexes, predominantly distal movements and fasciculations is the typical phenotype of spinal muscular atrophy. Neuropathies usually present later in childhood. Atrophy out of proportion to weakness, depressed or absent reflexes and predominantly distal weakness suggests a nerve disorder. Fatigability, ptosis, proximal muscle weakness and history of myasthenia gravis in the

Central Hypotonia

Chromosomal disorders
Prader-Willi syndrome; trisomies

Static insult
Cerebral malformations
Perinatal insult

Infections
Sepsis/Meningitis; intrauterine infections



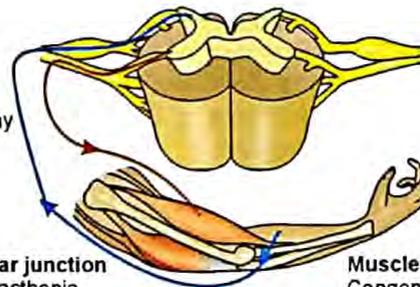
Neurometabolic conditions

Acid maltase deficiency
Biotinidase deficiency
GM1/GM2 gangliosidosis
Lowe syndrome
Peroxisomal disorders
Familial dysautonomia

Benign congenital hypotonia

Peripheral Hypotonia

Nerve
Charcot-Marie-Tooth disease
Congenital hypomyelinating neuropathy
Giant axonal neuropathy



Anterior horn cell
Spinal muscular atrophy

Neuromuscular junction
Congenital myasthenia
Transitory myasthenia
Botulism

Muscle
Congenital myopathies
Congenital muscular dystrophy

Fig. 20.1: Common causes of 'floppy infant'. Maintenance of normal tone requires an intact central and peripheral nervous system

mother suggest a neuromuscular junction disorder. Predominantly proximal muscle weakness, normal or depressed tendon reflexes and static or improving course indicate a muscle disease. Deep tendon reflexes are preserved in muscle disease or, if reduced, are in proportion to the degree of muscle wasting and weakness. Atrophy is less prominent in muscle disorders.

Central hypotonia is characterized by preserved muscle power and normal or brisk deep tendon reflexes. Sometimes patients may display features of both central and peripheral hypotonias; common causes of *mixed hypotonia* include hypothyroidism, motor unit disorders with superimposed hypoxia, acid maltase deficiency, mitochondrial disorders and infantile neuronal degeneration.

Mixed hypotonia: Features of both central and peripheral hypotonias as in lysosomal storage disorders, mitochondrial disorders and peroxisomal disorders.

Suggested Reading

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Muscle Weakness in Older Children

Distal weakness is predominantly seen in neuropathies and some muscle disorders like myotonic dystrophy. Proximal weakness has broad differential diagnosis (Fig. 20.2). The child may complain of difficulty in rising from the chair, going up and down the stairs or reaching with their arms. Some disorders such as chronic inflammatory demyelinating polyneuropathy (CIDP) and certain muscle dystrophies show both proximal and distal weaknesses.

DISORDERS AFFECTING ANTERIOR HORN CELLS

Spinal muscular atrophy and poliomyelitis are the two most common anterior horn cell disorders in children. Besides these, other enteroviruses (e.g. coxsackievirus and echovirus), juvenile form of amyotrophic lateral sclerosis, and neurometabolic disorders like Tay-Sach disease, neuronal ceroid lipofuscinosis and Pompe disease, may also involve anterior horn cells.

Spinal Muscular Atrophy

This is an autosomal recessive disease caused by a mutation in the *SMN1* gene at chromosome 5q13.2 region.

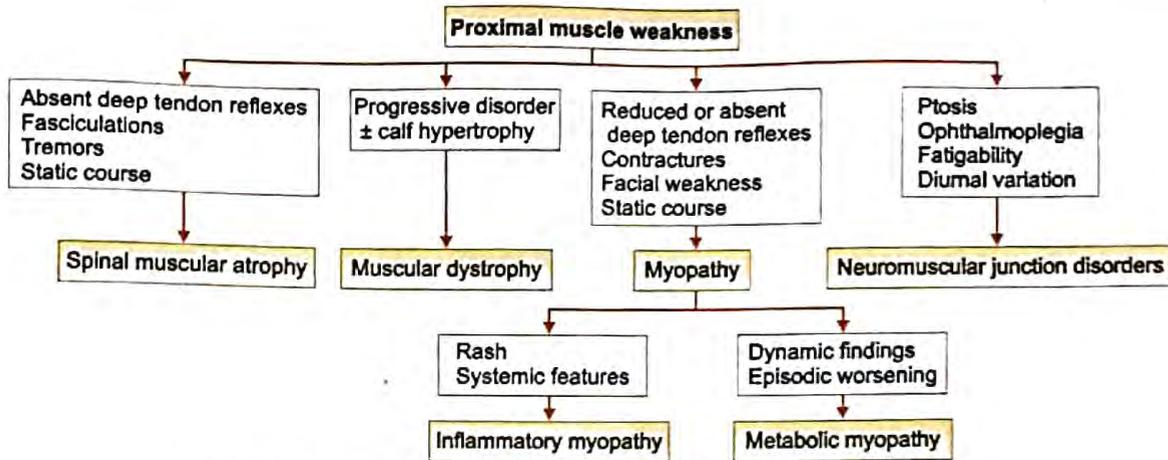


Fig. 20.2: Clinical approach to a child with proximal muscle weakness

This region also carries *SMN2* gene, the copy number of which acts as a main modifier of the various clinical phenotypes encoding the SMN protein of anterior motor horn cells. Four clinical types are recognized. Type 0: It is the most severe form and presents in the fetal life. Most children do not survive. Patients with type 1 disease (Werdnig-Hoffmann disease) present with profound hypotonia, flaccid weakness and global areflexia (Fig. 20.3). Respiratory weakness, poor swallowing and tongue fasciculations are common. These children usually never learn to sit. Aspiration pneumonia is an important cause of morbidity and mortality. Patients with type 2 disease (Dubowitz disease) have onset of illness at 6–18 months of age and are usually able to sit unaided. They may develop kyphoscoliosis, tremors (polyminimyo-clonus), poor swallowing and respiratory insufficiency. Patients with type 3 disease (Kugelberg Welander disease)



Fig. 20.3: A 5-month-old boy with motor delay and repeated chest infections, shows generalized hypotonia, absent deep tendon reflexes, poor muscle power and tongue fasciculations. Note the 'frog-like' posture and subcostal retractions due to respiratory muscle weakness. A diagnosis of spinal muscular atrophy type 1 was made

present later in childhood (>18 months) and are usually able to walk. These children are often misdiagnosed as limb girdle muscular dystrophy or myopathy. Global areflexia, fasciculations, polyminimyo-clonus and tremors give a clue towards underlying anterior horn cell pathology.

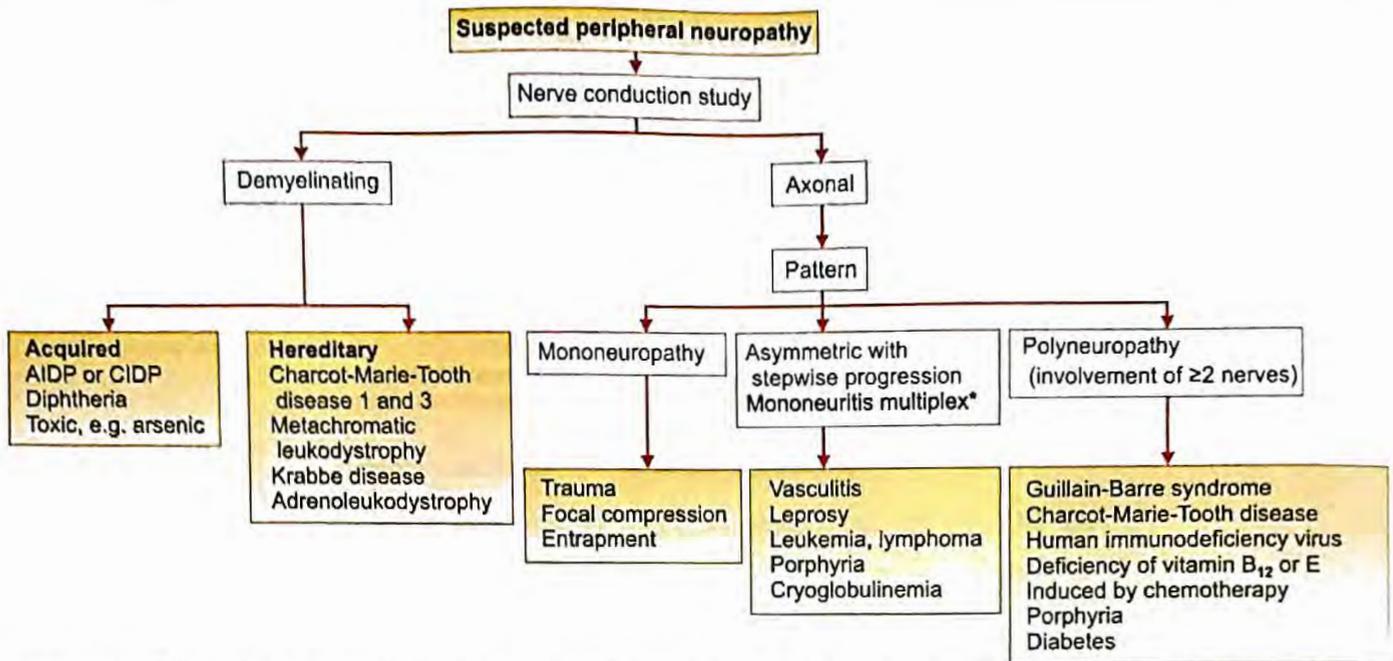
Treatment is supportive and includes respiratory care, management of problems in feeding and swallowing, ensuring adequate nutrition, treatment for gastroesophageal reflux, orthopedic care and rehabilitation, appropriate immunization and family education and counseling. Newer genetic based therapies have been developed for SMA like *SMN1* gene replacement therapy and *SMN2* upregulation/modification. Spinraza (Nusinersen) is an antisense oligonucleotide and is the first disease modifying therapy approved for SMA. It has shown significant benefits in these patients, but needs repeated intrathecal administrations.

Suggested Reading

- Darras BT, Markowitz JA, Monani UR, et al. Spinal muscular atrophy: A clinical approach, second ed. Academic Press, San Diego 2015: 117–145.
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PERIPHERAL NEUROPATHIES

Most neuropathies are chronic. Guillain-Barré syndrome is the most common cause of acute neuropathy. Clinical features, presentation, electrophysiological characteristics and laboratory studies help in evaluating the diagnosis (Fig. 20.4).



*Mononeuritis multiplex refers to the involvement of multiple separate non-contiguous peripheral nerves, either simultaneously or serially.

Fig. 20.4: Approach to peripheral neuropathies in childhood. AIDP acute inflammatory demyelinating polyneuropathy; CIDP chronic inflammatory demyelinating polyneuropathy.

Type of neuropathy: Most neuropathies are primarily axonal. Detection of a demyelinating pattern narrows the differential diagnosis. Clinical pointers to a demyelinating process include: (i) global areflexia; (ii) moderate to severe muscle weakness with relative preservation of bulk; (iii) predominantly motor symptoms; and (iv) hypertrophy of nerves. The differentiation between axonal and demyelinating neuropathy is mainly electrophysiological. Demyelination is suggested by: (i) decreased conduction velocity; (ii) prolonged distal latencies and late responses; (iii) asymmetry; (iv) presence of conduction block; and (v) abnormal conduction block and temporal dispersion (suggesting an acquired process). Axonal disorders show decreased compound muscle action potentials with preserved conduction velocity and distal latencies.

Pattern of neuropathy: Most polyneuropathies show distal-to-proximal gradient of symptoms and signs ('length dependent' or 'dying back' pattern). More proximal nerves may be involved rarely, e.g. inflammatory demyelinating polyneuropathy and porphyria. The presence of asymmetry and a stepwise progression is seen in mononeuritis multiplex. Mononeuropathies are rare in children.

Type of nerve fiber involved: Neuropathies that affect large fibers result in sensory deficits (impaired touch or vibration), weakness and loss of deep tendon reflexes. Small fiber neuropathies present with distal sensory deficit, burning dysesthesias and autonomic dysfunction. Pure sensory neuropathies are unusual.

Hereditary Neuropathy

A slowly progressive course, prominent sensory signs in absence of sensory symptoms, foot deformities and a family history point towards an inherited neuropathy (Table 20.1). Charcot-Marie-Tooth disease is the most common hereditary neuropathy, and the most common peripheral neuropathy in children.

Patients with Charcot-Marie-Tooth disease show distal weakness and wasting, especially of the peroneal compartment (stork leg appearance; Fig. 20.5), distal sensory impairment, skeletal deformities, contractures and diminished or absent deep tendon reflexes.

Table 20.1: Hereditary neuropathies

Primary disease

Charcot-Marie-Tooth disease
Hereditary neuropathy with liability to pressure palsies
Hereditary sensory and autonomic neuropathies
Distal hereditary motor neuropathies
Hereditary neuralgic amyotrophy
Familial amyloid polyneuropathy

Multisystem disorder

Lipid metabolism
Leukodystrophies
Phytanic acid storage disorder
Sphingomyelin lipidoses
Porphyria

Defective DNA repair: Ataxia-telangiectasia, xeroderma pigmentosa

Hereditary ataxias: Friedrich ataxia, spinocerebellar ataxia

Miscellaneous: Neuroacanthocytosis, mitochondrial disorders

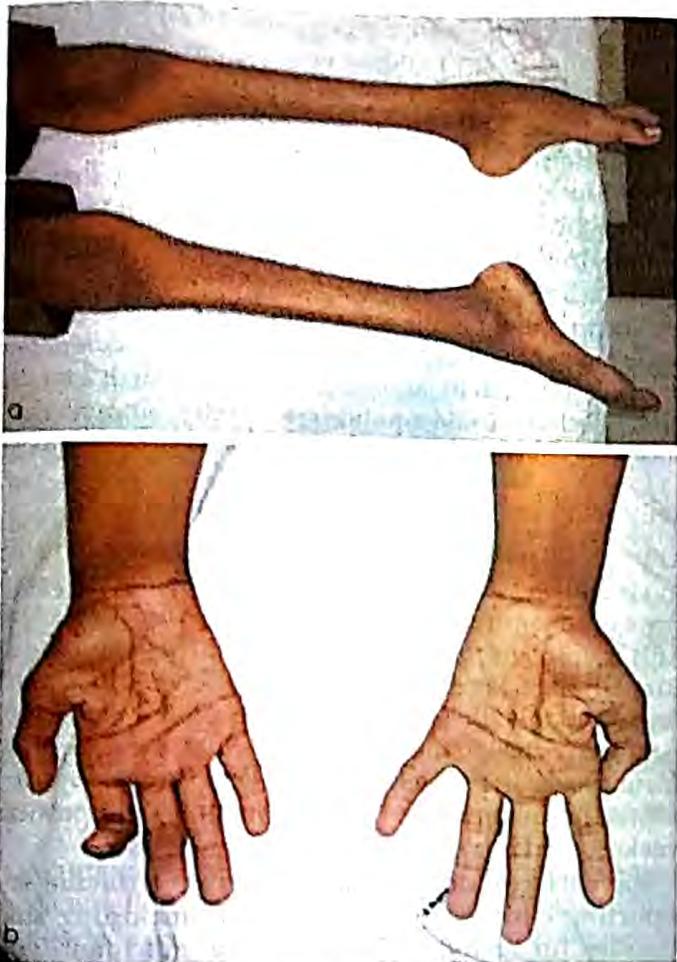


Fig. 20.5: Charcot-Marie-Tooth disease in a 7-year-old boy with progressive gait difficulties, frequent twisting of ankles, foot deformities and thinning of legs. Examination revealed distal weakness and wasting, absent ankle reflexes and enlarged common peroneal nerves. (a) Note the 'stork leg' appearance of legs with foot deformities; and (b) Hand deformities

Guillain-Barré Syndrome

This is a common cause of acute flaccid paralysis (AFP) in children. It is a rapidly progressive, predominantly motor, symmetric polyradiculoneuropathy that leads to bulbar and respiratory compromise. Four subtypes are described:

Subtypes

- Acute inflammatory demyelinating polyneuropathy (AIDP)
- Acute motor axonal polyneuropathy (AMAN)
- Acute motor and sensory axonal neuropathy (AMSN)
- Miller-Fisher syndrome (MFS)

Variants

- Acute pandysautonomia
- Acute sensory neuropathy
- Bickerstaff brainstem encephalitis
- Acute paraplegic variant
- Acute ophthalmoparesis
- Pharyngeal-cervical-brachial variant
- Polyneuritis cranialis

The condition can occur at any age. About two-thirds patients have an antecedent upper respiratory or gastrointestinal infection 1–6 weeks prior to onset of symptoms. The clinical features include acute onset of symmetrical ascending weakness that is both proximal and distal. Facial weakness is frequent, and involvement of respiratory muscles occurs in one-fourth cases. Dysautonomia is common and is suggested by tachycardia, arrhythmia, ileus, bladder dysfunction, labile blood pressure and impaired thermoregulation. The weakness usually reaches its nadir 2–4 weeks after onset and is followed by recovery over weeks to months. The illness is usually monophasic but 7–16% patients may suffer from recurrent episodes of worsening after an initial improvement. As compared to demyelinating forms, the axonal form of Guillain-Barré syndrome exhibits a more rapid and severe course, with frequent involvement of respiratory muscles and cranial nerves and mild involvement of the autonomic nervous system. The Miller Fisher syndrome is characterized by the triad of ophthalmological abnormalities, ataxia and areflexia. Diagnostic criteria of Guillain-Barré syndrome are summarized in Table 20.2.

Immunotherapy is the mainstay of treatment. Intravenous immunoglobulin (IVIG, 2 g/kg over 2–5 days) should be administered or plasma exchanges performed, if the child presents within 2–4 weeks of onset of symptoms. Such treatment is indicated in non-ambulatory patients, but their role in mobile, mildly affected patients is unclear. Plasma exchanges may hasten recovery compared to supportive treatment alone in adult patients. The use of IVIG after plasma exchange does not confer extra benefit. Patients who do not respond to initial treatment with IVIG may benefit from a second course of therapy which is usually given after 2–4 weeks. Supportive care includes cardiorespiratory care, physical therapy, nutritional management, management of neuropathic pain, care of bladder and bowel and prevention of deep vein thrombosis.

Chronic Inflammatory Demyelinating Polyradiculoneuropathy

This uncommon condition is slowly progressive (>4 weeks) or relapsing and has symmetric proximal and distal weakness in the upper and lower extremities with concomitant sensory loss. Asymmetric forms, distal predominant forms and sensory predominant forms also occur. The minimum duration of symptoms to reach the trough in patients with the condition is 2 months. This helps to distinguish this condition from Guillain-Barré syndrome, which usually evolves in less than 4 weeks. Electrophysiology and nerve biopsy help in diagnosis. Treatment modalities for chronic inflammatory demyelinating polyradiculoneuropathy include IVIG, plasma exchange and prednisolone. Spontaneous remissions are uncommon, and most patients require long term immunomodulating therapy.

Table 20.2: Diagnostic criteria for Guillain-Barré syndrome**Features required for diagnosis**

Progressive weakness in more than 1 limb (usually starts in legs)

Areflexia (or decreased tendon reflexes) in weak limbs

Features that strongly support diagnosis

Progression of symptoms over days to 4 weeks

Relative symmetry of symptoms

Mild sensory symptoms or signs

Autonomic dysfunction

Cranial nerve involvement, most common bilateral weakness of facial muscles.

Absence of fever at the onset of neurological symptom

Typical electrophysiological findings

Abnormal or absent F wave and H reflex

Reduced motor with or without sensory nerve action potentials (axonal variant: AMAN)

Prolonged distal latencies, reduced conduction velocities, presence of conduction block or increased temporal dispersion (demyelinating variant: AIDP)

Albuminocytologic dissociation: High concentration of protein in CSF; mononuclear cell counts $<50/\text{mm}^3$

Features that raise doubt about the diagnosis

Bladder or bowel dysfunction at onset and/or persistent bladder or bowel dysfunction

Fever at onset

Sharp sensory level

Marked persistent asymmetry of weakness

Severe pulmonary dysfunction with limited limb weakness at onset

Severe sensory signs with limited weakness at onset

CSF showing increased number of mononuclear cells (>50 cells/ mm^3) or polymorphonuclear cells

AMAN: Acute motor axonal polyneuropathy, AIDP: Acute inflammatory demyelinating polyneuropathy

Suggested Reading

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- Joint Task Force of the EFNS and the PNS. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy. *Eur J Neurol* 2010; 17: 356–363.
- Yuki N, Hartung HP. Guillain-Barre syndrome. *N Eng J Med* 2012; 366:2294–2304.
- Wilmshurst JM, Ouvrier R. Hereditary peripheral neuropathies of childhood: a brief overview for clinicians. *Neuromuscul Disord* 2011; 21:763–7.

ACUTE FLACCID PARALYSIS

Acute flaccid paralysis (AFP) is a clinical syndrome characterized by rapid onset of weakness, progressing to maximum severity within several days to weeks. The term 'flaccid' refers to the absence of spasticity or other upper motor neuron signs. In the Global Polio Eradication

Initiative, AFP is defined as any case of AFP in children <15 -year-old, or any paralytic illness at any age when polio is suspected. Common causes of AFP include Guillain-Barré syndrome, poliomyelitis, transverse myelitis, traumatic neuritis, postdiphtheric neuropathy and nonpolio enteroviral illnesses. The differential diagnosis varies with age (Table 20.3); distinguishing features are summarized in Table 20.4.

Major immunization initiatives have resulted in sharp decline in poliomyelitis across the world. The last case of confirmed wild poliovirus (P1 type) in India was reported from West Bengal in January 2011. On 27 March 2014, the WHO declared India a polio-free country, since no cases of wild polio were reported in three years.

Acute Flaccid Paralysis (AFP) Surveillance

AFP surveillance underpins the polio eradication initiative and is the chief strategy to screen for circulating wild polio virus in the post-polio eradication era. All patients with AFP within the last 6 months should be reported to Surveillance Medical Officer of the World Health Organization. Other conditions that require notification include: (i) isolated facial palsy; (ii) isolated bulbar palsy; (iii) unproven hypokalemia; (iv) neck flop; (v) floppy baby; (vi) flaccid hemiplegia; (vii) encephalitis; (viii) postictal weakness; and (ix) post-diphtheric polyneuritis.

Surveillance is done in major four steps: (i) finding and reporting children with AFP, (ii) transporting stool samples for analysis, (iii) isolating and identifying poliovirus in laboratory, and (iv) mapping the virus to determine its origin.

These cases are immediately investigated, within 48 hours of notification, by a trained medical officer. After confirming the case as AFP, the investigator takes medical history and conducts examination, and proceeds with other aspects of case investigation including collection and

Table 20.3: Differential diagnoses of acute flaccid paralysis

Muscle disorders	Inflammatory myopathy Periodic paralysis Hypokalemia Infections
Neuromuscular junction disorders	Myasthenia gravis Botulism Eaton-Lambert syndrome
Neuropathies	Guillain-Barré syndrome Traumatic neuritis Postdiphtheric neuropathy Porphyria Vasculitis
Anterior horn cell disorders	Poliomyelitis Nonpolio enteroviruses
Spinal cord disease	Transverse myelitis Spinal cord compression Trauma

Table 20.4: Differentiating among common causes of acute flaccid paralysis

	<i>Poliomyelitis</i>	<i>Guillain-Barré syndrome</i>	<i>Transverse myelitis</i>	<i>Traumatic neuritis</i>
Fever	Present; may be biphasic	May have a prodromal illness	May have a prodromal illness	Absent
Symmetry	Asymmetric	Symmetrical	Symmetrical	Asymmetric
Sensations	Intact; may have diffuse myalgias	Variable	Impaired below the level of the lesion	May be impaired in distribution of the affected nerve
Respiratory insufficiency	May be present	May be present	May be present	Absent
Cranial nerves	Affected in bulbar and bulbospinal variants	Usually affected	Absent	Absent
Radicular signs	May be present	Present	Absent	Absent
Bladder, bowel complaints	Absent	Transient; due to autonomic dysfunction	Present	Absent
Nerve conduction	May be abnormal	Abnormal	Normal	Abnormal
Cerebrospinal fluid	Lymphocytic pleocytosis; normal or increased protein	Albumino-cytologic dissociation	Variable	Normal
MRI spine	Usually normal	Usually normal	Characteristic*	Normal

* Local enlargement of the spinal cord and increased signal intensity over several spinal segments

transportation of stool specimens for laboratory testing, search for additional cases and outbreak investigation in the affected community, 60 days follow-up examination, analysis of laboratory results and case classification.

Collection of stool specimens from every patient is an important aspect of the eradication strategy. From every case of AFP, two stool specimens are collected, ideally within 14 days of onset of paralysis and at least 24 hours apart. While the optimal period for detection of poliovirus in the stool is within 14 days of onset of paralysis, specimens may be collected from any late-reported case up to 60 days from the onset of paralysis. Beyond 60 days after paralysis, the likelihood of detecting poliovirus is very low. Voided stool sample, is preferred. In cases where it is not possible, other methods include digital extraction (when child is constipated or dies), postmortem stool collection (contents of large intestine) and use of rectal tube. Enema or purgatives are not recommended. Each specimen should be 8 g each (about the size of one adult thumb), collected in a clean, dry, screw-capped container. The specimens are collected, labeled and then transported in the 'cold chain'.

Two types of cell lines are used for poliovirus isolation. The human rhabdomyosarcoma (RD) cell lines favor growth of all enteroviruses, and L20B cell lines favor the growth of only polioviruses. If cytopathic effects appear in L20B cell line, the isolate then goes for neutralization test to determine the serotype (type 1, 2 or 3) using appropriate antisera. Intratypic differentiation is done to determine, if the isolate is wild or vaccine poliovirus; the former isolates undergo genetic sequencing.

A case is classified as *polio*, if wild poliovirus is isolated from the stool specimen. Cases with inadequate stool specimens and having residual weakness who have died or are lost to follow up undergo additional investigation and are presented for review by the National Expert Review Committee. This committee classifies the case as *compatible with polio* or *discarded as non-polio AFP*. Experience indicates that at least 1 case of non-polio AFP occurs for every 100 000 children aged <15 years per year (background AFP rate). As per National Polio Surveillance Project, the non polio AFP rate, which is an indicator of surveillance sensitivity should be equal or to more than 1:100, 000.

Suggested Reading

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- Surveillance of acute flaccid paralysis, 3rd edn. New Delhi: Ministry of Health & Family Welfare, Government of India; 2005

NEUROMUSCULAR JUNCTION DISORDERS

Disorders affecting the neuromuscular junction can be acquired or inherited (Table 20.5). They are usually pure motor syndromes affecting proximal, bulbar or extraocular muscles.

Myasthenia Gravis

About 20% patients with myasthenia have onset in childhood or adolescence. Fatigable weakness is the hallmark. Most patients have ptosis or ophthalmoplegia

which may be asymmetric and variable over time. Pupillary reactions are normal. Children may develop diplopia on sustained gaze or continuous activity like reading. On attempting to tightly close the eyes, after a few minutes, the cornea may get exposed due to inability to sustain contraction of orbicularis oculi (peep sign).

About half of the children with ocular findings may develop bulbar or limb girdle weakness within 2 years. Bulbar weakness may manifest in form of difficulty in swallowing and chewing and nasal and slurred speech. Limb weakness is usually symmetric and proximal. Deep tendon reflexes are either normal or reduced in proportion to the degree of muscle weakness. Respiratory muscles may also get involved and may lead to *myasthenic crises*. Myasthenia gravis may be associated with thyroid disorders, systemic lupus erythematosus, diabetes mellitus and rheumatoid arthritis. Thymomas are found chiefly in adolescent onset myasthenia gravis and are rare (<5%) in early childhood.

Transitory neonatal myasthenia occurs in about 15% of babies born to myasthenic mothers. Symptoms start within a few hours after birth but may be delayed till the third day. These include difficulty in feeding, weak cry, hypotonia, lack of facial expression and respiratory insufficiency. Supportive care suffices in most cases. Oral or intramuscular pyridostigmine, usually for 4–6 weeks, may be warranted in severe cases.

Edrophonium testing is usually the first test performed in a suspected case of myasthenia gravis. The dose used is 0.1–0.2 mg/kg; may be repeated every minute to a total dose of 5 mg (weight <34 kg) or 10 mg (weight >34 kg). Effects are seen within 10 seconds and persist till 120 seconds. A positive result consists of transient resolution

of the clinical sign (ptosis, ophthalmoplegia, dysarthria) under observation. Edrophonium is not recommended for use in infants due to high risk of arrhythmias and short duration of action which precludes objective assessment. *Neostigmine* may also be used as a diagnostic test. The dose used is 0.125 mg/kg in an infant and 0.04 mg/kg IM in an older child. It is slower in action, with anticipated response in 10–15 min and maximum in 30 min (Fig. 20.6). If the result is equivocal or negative, the dose may be repeated in 4 hours.

Repetitive nerve stimulation studies are abnormal in 50–70% cases with generalized myasthenia gravis. A decrement of >10% is characteristic. Electromyography may be normal or may show unstable or myopathic muscle unit action potentials. Single fiber electromyography is more sensitive and may show increased jitter or blocking.

Acetylcholine receptor (AChR) antibodies may be positive in children with myasthenia gravis; the rates are lower in peri- and prepubertal children (50–60%). *Antibodies to muscle-specific kinase (Anti-MuSK)* are seen in 40% seronegative patients. X-ray chest or CT of anterior mediastinum may show thymoma or thymic hyperplasia.

Congenital Myasthenia Syndromes

The congenital myasthenia syndromes are exceptionally rare. They should be suspected in seronegative myasthenia gravis, floppy infant with underdeveloped muscles and in adults with childhood history of difficulties affecting cranial, respiratory, truncal or limb muscles. Common features include hypotonia, limb weakness, feeding and respiratory difficulties, arthrogryposis, ptosis, ophthalmoparesis, dysphagia and dysarthria. They do not respond to steroids and other immunosuppressants. Conditions like endplate acetylcholinesterase deficiency and slow channel congenital myasthenia may worsen with pyridostigmine.

Treatment

Cholinesterase inhibitors are the initial treatment for myasthenia gravis. Pyridostigmine is commonly used at doses of 1–7 mg/kg/day in 4 divided doses. Prednisolone, at low doses (0.5 mg/kg/d), may be used in a nonacute setting. Azathioprine, cyclosporine, cyclophosphamide and mycophenolate mofetil are used as steroid sparing drugs or for refractory cases. Drugs that interfere with neuromuscular transmission (Table 20.4) should be used with caution. Thymectomy is beneficial in seropositive patients.

A myasthenic crisis necessitates cardiorespiratory monitoring and support. It should be differentiated from cholinergic crises due to overdosage of acetylcholinesterase inhibitors. Antecedent events, predominance of cholinergic symptoms, ice pack test and edrophonium

Table 20.5: Neuromuscular junction disorders in children

Immune mediated	Metabolic causes
Myasthenia gravis	Botulism
Lambert-Eaton myasthenic syndrome	Organophosphate poisoning
Congenital myasthenic syndromes	Snake envenomation
Choline acetyltransferase deficiency	Tick paralysis
Paucity of synaptic vesicles	Hypermagnesemia
Endplate acetylcholinesterase deficiency	Drugs
Acetylcholine receptor defects	Aminoglycosides
Mutations in rapsyn or plectin	Erythromycin
Dok-7 deficiency	Tetracycline
	Fluoroquinolones
	Neuromuscular blocking agents
	Phenytoin
	D-penicillamine
	Lithium
	Interferon α



Fig. 20.6: Juvenile myasthenia gravis: A 9-year-old boy presented with drooping of eyelids, more in the evening than morning, and restricted eye movements. Examination revealed asymmetric ptosis, external ophthalmoplegia, normal pupils and normal motor examination. Note the improved ptosis (a) before and (b) after administration of neostigmine

challenge test help differentiate the two entities. IVIG or plasmapheresis may be required in patients with myasthenic crisis.

Suggested Reading

- Castro D, Derisavifard, S, Anderson, M, et al. Juvenile myasthenia gravis: a twenty year experience. *J Clin Neuromuscular Dis* 2013; 14, 95–102.
- Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidelines for management of myasthenia gravis. *Neurology* 2016; 87:419–25.

MUSCLE DISORDERS

Congenital Myopathies

The congenital myopathies are a diverse group of muscle disorders caused by genetic defects in the contractile apparatus of the muscle and defined by distinctive histochemical or ultrastructural changes on muscle biopsy. Majority of these disorders present as 'floppy infant' syndrome. The common presenting features include hypotonia, static or non-progressive muscle weakness and normal or decreased deep tendon reflexes. Respiratory insufficiency, feeding difficulties, contractures and skeletal deformities may be present. They may also present in late childhood or adulthood (Table 20.6).

Serum creatine kinase is either normal or mildly raised. Electromyography reveals a myopathic pattern. The disorders are clinically indistinguishable; distinction is possible by characteristic features on skeletal muscle biopsy incorporating new immunohistochemical techniques and electron microscopy. Advances in molecular genetics have improved our understanding of congenital myopathies.

Suggested Reading

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- Wang HC, Dowling JM, North K, et al. Consensus statement on standard of care for congenital myopathies. *J Child Neurol* 2012; 27:363.

Muscle Dystrophies

The muscular dystrophies are diseases of muscle membrane or supporting proteins characterized by pathological evidence of ongoing muscle degeneration and regeneration. Diagnosis of these disorders is based on clinical presentation, genetic testing, muscle biopsy and muscle imaging.

Dystrophinopathies

Dystrophinopathies are a group of disorders resulting from mutations in the dystrophin gene (located on short arm of X chromosome, Xp21). Duchenne muscular dystrophy is the most common dystrophinopathy with an incidence of 1 in 3500 live male births. Its allelic variant, Becker muscular dystrophy, differs by a later onset (usually >6 years old), and slower progression (wheelchair confinement >15 years), a higher incidence of myalgias, occasional rhabdomyolysis following exercise and early cardiomyopathy.

Over 4700 mutations are reported in the Leiden Duchenne dystrophy database. 65% of the pathogenic changes are large partial deletions. Mutations in the dystrophin gene can cause Duchenne muscular dystrophy or Becker muscular dystrophy. The phenotypic variation is explained by the reading frame hypothesis. In >90% of

Table 20.6: Classification of congenital myopathies

Subtype	Inheritance, genes	Histology	Clinical features
Core myopathies (central core disease; multimincore disease)	AD/RYR1, SEPNI, ACTA1, MYH7	Poorly defined fibers with short cores	RYR1 mutation is most common High risk of malignant hyperthermia
Nemaline myopathy	AD, AR, sporadic ACTA1, NEB, TPM2, TPM3, TNNT1	Nemaline bodies on Trichrome Gomori stain	Nebulin (NEB) mutation most common Onset congenital; muscles of face, ocular and neck, chest deformity, scoliosis
Centronuclear myopathies	AD, sporadic, X linked MTM1, DNM2, BIN1, RYR1, DM1	Central nuclei in all muscle fibers	Onset: Newborn to adult Facial weakness, ptosis, external ophthalmoplegia, weakness of neck flexors
Congenital fiber type disproportion	AD, AR, X-linked ACTA1, TPM3, TPM2, RYR1, SEPNI	Predominant type 1 fibers; small type 2 fibers	ACTA1 mutation most common Majority has less severe phenotype

cases, mutations that disrupt the reading frame (frame shift) lead to dystrophin deficiency and cause Duchenne dystrophy. In Becker dystrophy, mutations maintain the reading frame (inframe mutations) and result in abnormal but partly functional dystrophin.

Children with Duchenne dystrophy become symptomatic before age of 5 years and may have history of delayed walking. Gait disturbances become apparent at 3–4 years of age. Waddling gait, Gower sign and calf muscle pseudohypertrophy (Fig. 20.7) are classical findings. Weakness of neck flexors is early. Other muscles that show hypertrophy include vastus lateralis, infraspinatus, deltoid, gluteus maximus, triceps and masseter. The progression of weakness may plateau between 3 and 6 years of age, followed by increasing gait difficulty, development of contractures and lumbar lordosis. The age at loss of independent ambulation in untreated patients is between 8.8 and 10.5 years. After loss of ambulation, there is worsening kyphoscoliosis, increasing upper limb weakness and bulbar dysfunction.

Weakness of intercostal and diaphragmatic muscles with spinal deformity affects respiratory function. Dropping of vital capacity <20% of normal leads to nocturnal hypoventilation. Cardiomyopathy and arrhythmias are major cardiac manifestations. Children with deletion of exons 48 to 53 are especially prone to cardiac complications. The cause of death is a combination of respiratory insufficiency and cardiomyopathy. Other features include variable degree of intellectual disability and impaired gastric motility.

Around 10% of female carriers show variable degree of weakness with elevated levels of creatine kinase, calf hypertrophy, myalgias and cramps and increased risk of dilated cardiomyopathy. Rarely, the full Duchenne phenotype is present in girls with complete inactivation of normal X chromosome.

Serum creatine kinase levels are highly elevated (>10 times upper limit of normal), but do not correlate with severity of the disease or response to treatment. Multiplex PCR and the more sensitive multiplex ligation dependent

probe amplification (MLPA) are used for detection of mutations. Muscle biopsy may be required in mutation negative cases and to differentiate between Duchenne and Becker dystrophy. Biopsy shows necrosis and attempted regeneration of individual muscle fibers, variable muscle fiber diameter with both hypertrophic and small fibers, and central nuclei. Later, almost the entire muscle is replaced by fibrofatty tissue. On immunohistochemistry, absence of dystrophin (1, 2, 3) staining is seen in Duchenne dystrophy; dystrophin staining is reduced and patchy in Becker dystrophy.

Management: Patients with Duchenne dystrophy requires multidisciplinary management, aiming for maintenance of muscle strength and range of motion of joints by exercise, physiotherapy and avoidance of prolonged immobility. Corticosteroids (prednisone, deflazacort) are the only therapies proven to improve strength and prolong ambulation in children with the disease. Low dose prednisolone may be started with aim of preserving upper limb strength, reducing progression of scoliosis and delaying decline in respiratory and cardiac functions. Supportive management also includes pulmonary and cardiac care, nutrition, calcium homeostasis, appropriate immunization and orthopedic care (Table 20.7). Newer therapies include exon skipping using antisense oligonucleotides. Phase 3 trials have shown significant clinical benefits and Eteplirsen has been FDA approved, although more clinical data is required to prove its efficacy.

Myotonic Dystrophy Type 1

It is the most common muscular dystrophy seen in adults. This disorder transmitted in an autosomal dominant manner, is caused by an abnormal expansion (>80) of trinucleotide [CTG] repeats in the DMPK gene on chromosome 19. The classic form presents in childhood with myotonia, facial weakness, distal limb weakness, cataracts (iridescent spoke-like posterior capsular cataract), frontal baldness, endocrinopathies (testicular atrophy, hyperinsulinism, adrenal atrophy and growth hormone disturbances), cardiac arrhythmias and disturbed



Fig. 20.7: (a) Duchenne muscular dystrophy. The child presented with progressive gait difficulties and lurching. Examination shows proximal muscle weakness, more in the lower limbs, calf hypertrophy and positive Gower sign. (b) Examination in another child shows hypertrophy of deltoid and infraspinatus with wasting of posterior axillary fold muscles (Valley sign)

Table 20.7: Management of Duchenne muscular dystrophy
Corticosteroids

Indication: Children >2 years with static or declining function
Dose: Prednisolone 0.3–0.75 mg/kg/day

(initially 0.3–0.5 mg/kg/day, if non-ambulatory)
 Deflazacort, 0.9 mg/kg/day (preferred in children with excessive weight gain or behavioral problems)

Ensure immunization against pneumococcus, influenza and varicella before starting steroids

Monitoring

Pulmonary function tests: Every 6 months if non-ambulatory; annually in ambulatory patients

Echocardiography: Once in 2 yr for <10 yr of age; annually if >10 years

Serum calcium, phosphate, 25(OH) vitamin D₃ (biannually)
 DEXA scan annually

Physical therapy

Effective stretching and appropriate positioning at various joints, assistive devices to prevent contractures, avoid high resistance strength training

Surgery: For fixed contractures and spinal deformities

Other components

Respiratory and cardiac care
 Management of gastrointestinal problems
 Psychosocial management
 Family education and genetic counseling

Newer therapies

Exon skipping, gene therapy, cell therapy, pharmacological approaches (utrophin upregulation, read through compounds, myostatin inhibitors)

Gastrointestinal motility. The *congenital form* may present with respiratory failure, poor feeding, hypotonia, facial

diplegia, clubfoot and gastroparesis. Myotonia is absent in neonates and infants. There may be a history of decreased fetal movements and polyhydramnios in the mother. EMG shows a myopathic pattern and myotonia ('revving engine' sound). Genetic testing is confirmatory.

Medications that block sodium channels (procainamide, disopyramide, phenytoin, quinine, mexiletine); tricyclic antidepressants (clomipramine, imipramine); diuretics (acetazolamide, thiazides) and other agents (taurine, nifedipine, diazepam, carbamazepine, prednisone and albuterol) have been used for treatment, with variable results.

Facioscapulohumeral Muscular Dystrophy

The clinical spectrum of this autosomal dominant disorder ranges from asymptomatic children to wheelchair bound patients. The age at onset is variable. The disease may start with asymmetric facial weakness followed, sequentially, by scapular fixator, humeral, truncal and lower limb weakness. Biceps and triceps are typically involved with sparing of deltoid and forearm muscles resulting in the "Popeye" arm appearance. Lower abdominal muscles are weaker than upper abdominal muscles resulting in Beevor sign. Side-to-side asymmetry of muscle weakness is typical (Fig. 20.8). Other features include high frequency hearing loss, Coats disease (retinal telangiectasia, exudation and detachment), atrial arrhythmias and restrictive respiratory disease. The diagnosis is confirmed by demonstrating the shortening of the macrosatellite repeat D4Z4 which is normally in one allele of 4q35. Treatment is supportive.

Limb Girdle Muscular Dystrophy

Limb girdle muscular dystrophy is a group of clinically heterogeneous syndromes with autosomal dominant or recessive inheritance. Most childhood onset limb girdle dystrophies are associated with predominant lower extremity weakness. Cardiac or other systemic involvement



Fig. 20.8: Facioscapulohumeral dystrophy; (a) Note the facial weakness and inability to completely close the eyes; (b) Asymmetric scapular winging

is variable. Serum creatine kinase is modestly elevated but can be high in the sarcoglycanopathies, dysferlinopathy and caveolinopathy. Autosomal recessive limb girdle dystrophies have early onset, rapid progression and higher creatine kinase values. Treatment is symptomatic.

Congenital Muscular Dystrophy

These patients usually present at birth or in first year of life. Infants show hypotonia, weakness, arthrogryposis, bulbar dysfunction or respiratory insufficiency. Weakness is static or slowly progressive. Diagnosis is supported by dystrophic myopathic features on muscle biopsy, elevated creatine kinase levels and exclusion of common myopathies of newborn.

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- Patient education leaflets is available at http://aifms.edu/aifms/departments/pediatrics/ped_neuro/patientedu.htm
- Thornton CA. Myotonic dystrophy. *Neurol. Clin.* 2014;32(3):705–719.

Inflammatory Myopathies

The inflammatory myopathies are a diverse group of disorders in which muscle appears to be injured by the

immune system. Dermatomyositis is the most common pediatric inflammatory myopathy, which typically affects skin and muscle but may involve joints, gut, lung, heart and other internal organs (see Chapter 22).

Metabolic Myopathies

The metabolic myopathies are a group of muscle disorders resulting from failed energy production related to defects in glycogen, lipid or mitochondrial metabolism. The symptoms arise due to a mismatch between the rate of ATP utilization and the capacity of muscle metabolic pathways to regenerate ATP. Affected children and adults present with exercise intolerance, weakness and myoglobinuria; newborns and infants present with severe multisystem disorders. Most metabolic myopathies have intermittent rather than static findings. Some children present with progressive proximal muscle weakness mimicking a dystrophy or an inflammatory myopathy.

In patients with glycolytic or glycogenolytic defects, symptoms are induced by either brief isometric exercise, such as lifting heavy weights, or by less intense but sustained dynamic exercise. In disorders of lipid metabolism, the abnormalities are induced by prolonged exercise and fasting. Investigations include serum creatine kinase and ammonia, urine myoglobin, tandem mass spectroscopy, gas chromatography mass spectrometry, electrophysiological studies, forearm ischemia exercise test, muscle biopsy and molecular studies.

Suggested Reading

- Berardo A, DiMauro S, Hirano M. A diagnostic algorithm for metabolic myopathies. *Curr Neural neuroscience Rep.* 2010 Mar;10(2):118–26.
- Lilleker JB, Keh YS, Roncaroli F, Sharma R, Roberts M. Metabolic myopathies: a practical approach. *Practical Neurology.* 2017 Dec 8; [practneurol-2017-001708](https://doi.org/10.1093/pm/pnx008).

Childhood Malignancies

Rachna Seth

Advances in management have greatly improved the survival of children with malignancies. Malignancies in children are difficult to detect because their clinical features are often non-specific and may mimic common disorders of childhood (Table 21.1). Cancers in children are considered clinicobiologically distinct compared to adults; they are more aggressive but respond satisfactorily to chemotherapy. Common childhood malignancies include leukemia (30–40%), brain tumors (21%) and lymphoma (11%) followed by neuroblastoma, retinoblastoma and tumors arising from soft tissues, bones and gonads (Fig. 21.1). Some malignancies are typical to a site and have predilection for a particular age group (Table 21.2). Regional variations are known; there is higher proportion of T-cell lineage acute lymphoblastic leukemia (ALL) in India compared to the western countries. The burden of brain tumors is lower and that of retinoblastoma is also higher in India.

LEUKEMIAS

Leukemias, the most common cancer in children, are malignant neoplasms arising from clonal proliferation of abnormal hematopoietic cells, disruption of normal marrow

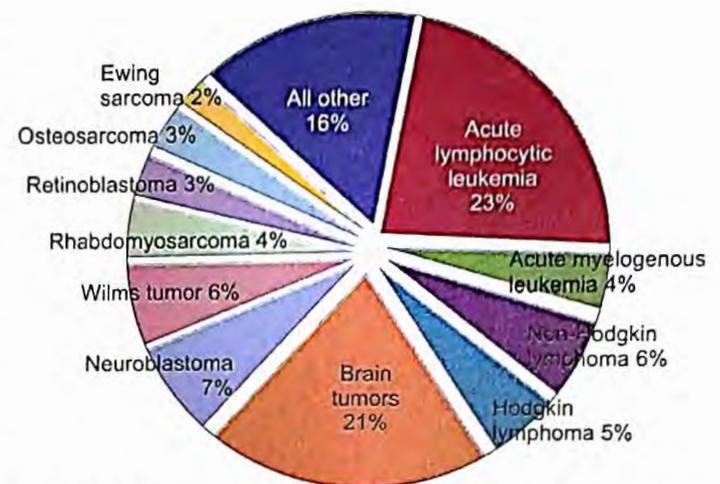


Fig. 21.1: Spectrum of childhood cancers. One-third of childhood cancers comprise acute lymphocytic leukemia, acute myelogenous leukemia, non-Hodgkin lymphoma and Hodgkin lymphoma. Brain tumors account for approximately 20% of all tumors.

function and marrow failure. They are classified as lymphoid or myeloid depending on the lineage of the progenitor stem cell involved and as acute or chronic

Table 21.1: Clinical features of cancers mimicking common illnesses

Features	Possible malignancy
Fever, enlarged lymph nodes, malaise	Leukemia, lymphoma, Ewing sarcoma, neuroblastoma, PNET, LCH
Pallor, anemia	Leukemia, lymphoma, neuroblastoma
Headache, nausea, vomiting, fever seizures	Brain tumors, leukemia
Earache, rhinitis, pharyngitis	Soft tissue sarcoma
Epistaxis	Leukemia
Diarrhea, vomiting, hepatosplenomegaly	Neuroblastoma, lymphoma, hepatic tumors, leukemia
Hematuria	Wilms tumor
Jaundice	Lymphoma, liver tumors, LCH
Failure to thrive	Common to many cancers, LCH
Bony pains, mass(es)	Any tumors; osteosarcoma, LCH
Squint, epiphora, red eye	Retinoblastoma

PNET: Primitive neuroectodermal tumor; LCH: Langerhans cell histiocytosis

Table 21.2: Predominant pediatric malignant tumors by age and site

Tumor	Less than 1 year	1–12 years	12–21 years
Leukemia	Congenital leukemia	Acute lymphoblastic leukemia (ALL) Acute myeloid leukemia (AML)	Acute lymphoblastic leukemia Acute myeloid leukemia
CNS	Juvenile myelomonocytic leukemia (JMML) Medulloblastoma Ependymoma Astrocytoma, glioma Choroid plexus papilloma	JMML (<3 years) Chronic myeloid leukemia (age >3 years) Medulloblastoma Ependymoma Astrocytoma, glioma Choroid plexus papilloma (<3 years) Craniopharyngioma (older child) Cerebellar astrocytoma (older child)	Cerebellar astrocytoma Astrocytoma Cranio-pharyngioma Medulloblastoma
Lymphoma	Rare	Non-Hodgkin lymphoma Hodgkin lymphoma	Hodgkin lymphoma Non-Hodgkin lymphoma
Chest	Neuroblastoma Teratoma	Neuroblastoma (common up to 4 years) Lymphoma (commoner in >4 years) Teratoma Rhabdomyosarcoma	Lymphoma Ewing sarcoma
Head and Neck	Retinoblastoma Neuroblastoma Rhabdomyosarcoma	Retinoblastoma (<5 years) Neuroblastoma (younger child) Lymphoma (>4 years) Rhabdomyosarcoma	Lymphoma Soft tissue sarcoma
Abdomen	Neuroblastoma Hepatoblastoma Wilms tumor (>6 months)	Neuroblastoma (younger child) Wilms tumor (younger child) Lymphoma (older child) Hepatoblastoma Rhabdomyosarcoma	Lymphoma Liver carcinoma Soft tissue sarcoma Dysgerminoma
Genitourinary	Yolk sac tumor Teratoma	Rhabdomyosarcoma Yolk sac tumor	Teratocarcinoma Teratoma Embryonal carcinoma
Extremity	Fibrosarcoma	Fibrosarcoma Rhabdomyosarcoma Ewing sarcoma	Osteosarcoma Ewing sarcoma Soft tissue sarcoma
Multisystem	Langerhans cell histiocytosis	Langerhans cell histiocytosis	

depending on their natural history. Acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) are common; a small proportion has chronic myeloid leukemia (CML) and juvenile myelomonocytic leukemia (JMML).

Acute Lymphoblastic Leukemia (ALL)

ALL is the most common childhood malignancy accounting for one-fourth of all childhood cancers and three-fourths of all newly diagnosed patients with acute leukemia. Its incidence is approximately 3–4 cases per 100,000 children below 15 years of age. Boys have higher rates than girls, especially in adolescents with T-cell ALL. There is a peak in incidence of childhood ALL between 2 and 5 years due to ALL associated with a pre-B lineage (common ALL). Significant progress in treatment of ALL in last two decades has led to cure rates of over 80% in most developed countries.

Acute Myeloid Leukemia (AML)

Acute myeloid leukemia (AML) also termed as acute non-lymphoblastic leukemia, the second most common type of leukemia in children, accounts for 15–20% of leukemia in children. AML is much more complex and resistant disease than ALL and results from clonal proliferation of hematopoietic precursors of myeloid, erythroid and megakaryocytic lineage. Intensive myelosuppressive induction and post-remission therapy result in long-term survival in 40–50% patients.

Etiopathogenesis

The etiology of acute leukemia is unknown in the majority. Several genetic syndromes are associated with an increased risk of leukemia (Table 21.3).

Table 21.3: Genetic and environmental risk factors for childhood leukemia

Genetic	Environmental
Down syndrome	Ionizing radiation
Fanconi anemia	Alkylating agents: Cyclophosphamide, ifosfamide, carboplatin, procarbazine
Shwachman-Diamond syndrome	Epipodophyllotoxins: Etoposide, teniposide
Bloom syndrome	Nitrosourea: Nitrogen mustard
Ataxia telangiectasia	Benzene
Diamond-Blackfan anemia	
Kostmann syndrome	
Li-Fraumeni syndrome	
Severe combined immune deficiency	
Paroxysmal nocturnal hemoglobinuria	
Neurofibromatosis type I	

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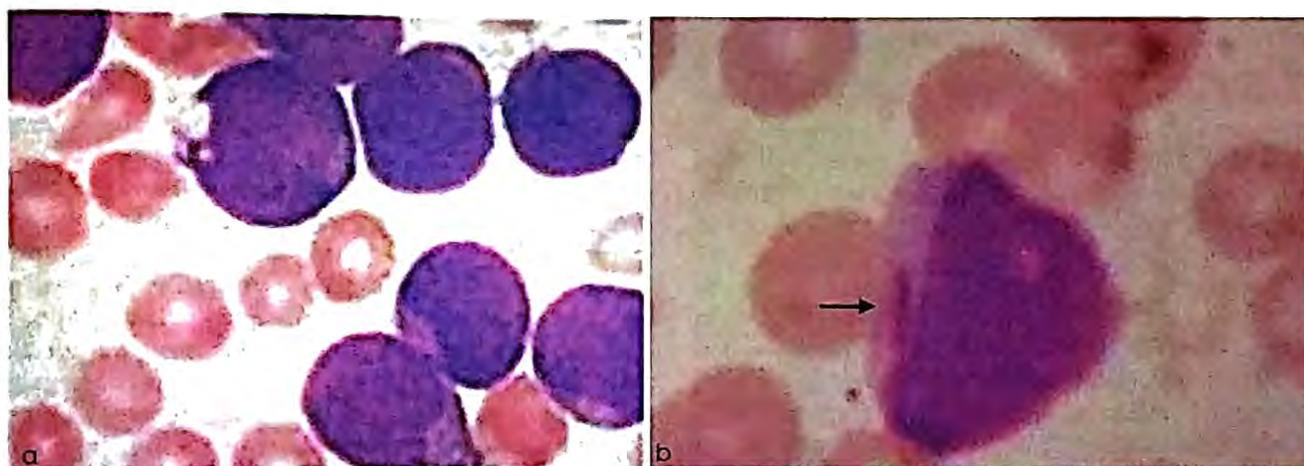


Fig. 21.2: (a) Bone marrow from a child with acute lymphoblastic leukemia shows reduced normal marrow elements which are replaced by lymphoblasts. The neoplastic lymphoblasts are slightly larger than lymphocytes and have round or convoluted nuclei, fine chromatin, often with a smudged appearance, inconspicuous nucleoli and scant basophilic cytoplasm. (b) Peripheral smear of a 6-year-old child diagnosed with acute myeloid leukemia (AML-M₂) showing a myeloblast containing an Auer rod (pink-colored aggregated lysosome)

Table 21.4: French-American-British (FAB) classification of acute lymphoblastic leukemia

Cytologic features	L1 (80–85%)	L2 (15%)	L3 (1–2%)
Cell size	Small cells predominate; homogenous	Large; heterogeneous	Large; homogenous
Amount of cytoplasm	Scanty	Moderately abundant	Moderately abundant
Nucleoli	Small, inconspicuous	One or more, often large	One or more, prominent
Nuclear chromatin	Homogenous	Variable, heterogeneous	Stippled, homogenous
Nuclear shape	Regular, occasional clefts	Irregular clefts, indentation	Regular, oval to round
Cytoplasmic basophilia	Variable	Variable	Intensely basophilic
Cytoplasmic vacuolation	Variable	Variable	Prominent

Classification

Acute Lymphoblastic Leukemia

Morphology: The classification of acute leukemia has evolved from one that was primarily morphology based to one based on immunophenotyping, karyotyping and molecular biology (Fig. 21.2a). ALL is classified using the French-American-British (FAB) criteria into morphologic subtypes (Table 21.4).

Immunophenotype: Immune phenotype classification describes ALL as B cell or T cell derived. Progenitor B cell derived ALL constitute 80–85% ALL; 15% are derived from T cells and 1–2% from mature B cells.

Cytogenetics: Genetic abnormalities in the leukemic clone greatly impact therapy and prognosis. Conventional cytogenetics and fluorescence *in situ* hybridization should be performed on the bone marrow specimen to look for common genetic alterations (Table 21.5).

Table 21.5: Genetic abnormalities in acute lymphoblastic leukemia (ALL)

Chromosomal abnormality, translocation, affected gene	Subtype	Frequency(%)	Implication
Hypertdiploidy (>50 chromosomes)	Pre-B	20–30	Excellent prognosis
t(12;21)(p13;q22) <i>ETV6/RUNX1</i>	Pre-B	15–25	Excellent prognosis, needs minimal therapy
Trisomy 4 and 10	Pre-B	20–25	Excellent prognosis
t(1;19)(q23;p13) <i>TCF3/PBX1</i>	Pre-B	2–6	High risk, probable CNS relapse
t(4;11)(q21;q23) <i>MLL/AF4</i>	Pre-B	1–2	Infant ALL, poor prognosis High tumor burden, drug resistant
t(9;22)(q34;q11.2) <i>BCR/ABL1</i> (Philadelphia chromosome)	Pre-B	2–4	Very high risk; improved outcome with imatinib and chemotherapy
t(8;14)(q23;q32.3) <i>MYC IgL</i>	Mature B cell	2	Burkitt leukemia, need intensive therapy, favorable outcome
Hypodiploidy (<44 chromosomes)	Pre-B	1–2	Unsatisfactory outcome
<i>HOX 11</i> rearrangement by t(5;14)(q35;q32)	T	7–8	Good prognosis
Early T cell precursor	T	12	Poor prognosis

Table 21.6: Classification of acute myeloid leukemia (AML)

French-American-British (FAB) classification	
M0	Minimal differentiation
M1	Myeloblastic leukemia without maturation
M2	Myeloblastic leukemia with maturation
M3	Promyelocytic leukemia
M4	Myelomonocytic leukemia
M5	Monocytic leukemia
M6	Erythroleukemia
M7	Megakaryocytic leukemia

Acute Myeloid Leukemia

The classification is summarized in Tables 21.6 and 21.7. Myeloblast containing an Auer rod is shown in Fig. 21.2b.

Clinical Features

The duration of symptoms in a patient with ALL varies from days to weeks and in some cases few months. The clinical features are attributed to bone marrow infiltration with leukemic cells (bone marrow failure) and extramedullary involvement, and include pallor and fatigue, petechiae, purpura or bleeding, and infections. Lymphadenopathy, hepatomegaly and splenomegaly are present in more than 60% (Fig. 21.3a). Bone or joint pain and tenderness may occur due to involvement of periosteum of bones or joints; skin rash/eruption may also occur. Infants and young children may present with a limp or refusal to walk. Tachypnea and respiratory distress may be present secondary to severe anemia leading to congestive heart failure or secondary to the presence of mediastinal mass leading to tracheal compression

Table 21.7: Genetic abnormalities in AML

Rearrangements (genes)	Frequency, %	Clinical features	Survival, %
t(8;21)(q22;q22) (<i>ETO/AML1</i>)	12	Chloromas common	75–85
inv(16)(p13;q22) (<i>MYH 11/CBF</i>)	8	Eosinophilia	75–85
t(15;17)(q22;q12) (<i>PML/RAR</i>)	12	FAB M3, Auer rods, ATRA sensitive	90
Normal karyotype, gene mutations			
<i>NPM</i> (nucleophosmin)	8–10		75–85
<i>CEBPA</i> (CCAAT-enhancer binding protein alpha)	4–6	FAB M1, M2	80
<i>FLT 3/ITD</i> (Fms-related tyrosine kinase 3-internal tandem duplication)	10–15		<35
<i>WT1</i>	8–10		35–55
No known mutations	24		
Poor risk cytogenetics			
Deletion 5q	1		<35
Monosomy 7	2		<35



Fig. 21.3: (a) An 8-year-old child presented with acute lymphoblastic leukemia, prolonged fever and generalized lymphadenopathy; (b) A 6-year-old child with acute myeloid leukemia showing bilateral subconjunctival bleeds. (c) A 9-year-old child with acute myeloid leukemia showing gum hypertrophy; (d) A 10-year-old girl with acute myeloid leukemia presenting with proptosis (chloroma orbit)

(superior mediastinal syndrome). A large mediastinal mass may cause superior vena cava syndrome with facial edema and plethora, throbbing headache, conjunctiva congestion and dilated neck veins.

Patients with high tumor burden may present with very high total white cell (TLC) count (hyperleukocytosis, TLC $>100\,000/\text{mm}^3$) or tumor lysis syndrome.

A few patients (5–10%) have central nervous system involvement at diagnosis; they present with cranial nerve palsies, seizures and occasionally raised intracranial pressure (headache, vomiting, irritability, papilledema). The diagnosis of CNS leukemia is made on examination of the cerebrospinal fluid. Overt testicular leukemia is seen in ~1% boys, when it presents with firm, painless, unilateral or bilateral swelling of the testes; the diagnosis is confirmed on biopsy. Rare sites of extramedullary involvement include heart, lungs, kidneys, ovaries, skin, eye or the gastrointestinal tract.

The clinical presentation of AML is similar to ALL but more likely to have high TLC and incidence of infections (Fig. 21.3b). Unlike ALL, lymphadenopathy and massive hepatosplenomegaly is not very common. However, infants and toddlers with M4 and M5 AML subtypes have more organomegaly, high leukocyte counts and CNS disease at diagnosis. Gum hypertrophy a common feature of the M4 subtype (Fig. 21.3c). Disseminated intravascular coagulation may occur with any subgroup, but is common in acute promyelocytic leukemia (M3). Chloromas are localized collections of leukemic cells that which may occur at any site including CNS, neck, bones (typically orbit) and skin (Fig. 21.3d). Patients with high TLC may present with signs of leukostasis such as pulmonary infiltrates causing respiratory distress or stroke. Central nervous system involvement may occur in up to 15% patients.

Differential Diagnosis

The clinical profile of ALL may mimic infectious mononucleosis, acute infectious lymphocytosis, idiopathic

thrombocytopenic purpura (ITP), aplastic anemia and viral infections (e.g., cytomegalovirus) that might result in leukemoid reactions and pancytopenia. ITP is the most common cause of acute onset petechiae and purpura in children. There is no evidence of anemia and have normal TLC and differential count. Bone marrow smear reveals normal hematopoiesis and normal or increased number of megakaryocytes. Aplastic anemia may present with pancytopenia, or juvenile rheumatoid arthritis with fever, joint symptoms (limp, arthralgia or arthritis), pallor, splenomegaly and leukocytosis. ALL should be distinguished from other malignancies (neuroblastoma, non-Hodgkin lymphoma, rhabdomyosarcoma, Ewing sarcoma and retinoblastoma) that present with bone marrow involvement.

Laboratory Features and Diagnosis

Clinical presentation, peripheral blood counts and morphology are indicative of the diagnosis of ALL (Table 21.8). Children may present with pancytopenia or

Table 21.8: Evaluation of a child with suspected leukemia

- History and physical examination
- Complete blood count and differential count
- Peripheral smear examination (cell morphology), leukocyte platelet count, immune phenotype
- Chest X-ray (include lateral view, if mediastinal mass is present)
- Blood electrolytes, urea, creatinine, uric acid, lactate dehydrogenase, calcium, phosphate, bilirubin, and oxaloacetate and pyruvate transaminases
- Prothrombin time, coagulation profile
- Bone marrow aspirate: Morphology, immunophenotype, cytogenetics, FISH/PCR for specific translocations
- Bone marrow biopsy
- *Serology:* HIV antibody, hepatitis B surface antigen and antibody, hepatitis C antibody
- CSF cytology (give first dose of methotrexate with diagnostic tap)

hyperleukocytosis. The diagnosis is confirmed by peripheral smear examination and bone marrow aspirate and biopsy. It is necessary to perform an aspirate as well as biopsy at time of initial diagnosis. Higher leukocyte (TLC) counts are more common with T cell ALL. The bone marrow where >25% of bone marrow cells are leukemic lymphoblasts is diagnostic for ALL (20% in case of AML). While morphology of the leukemic blasts can give important clues to the diagnosis, it needs to be confirmed by immunophenotyping of the bone marrow. Immunophenotype differentiates the cellular lineages of ALL into pre-B, T cell and mature B cell. This distinction is important as there are therapeutic implications of the cellular origin of ALL. The diagnosis for AML is also ascertained by peripheral smear and bone marrow examination, with determination of morphologic, cytochemical, immunophenotypic and genetic characteristics of blast cells (Table 21.7).

Evaluation of CSF for blasts to determine CNS involvement is important for staging. The spinal tap is performed ideally with platelet count $\sim 100000/\text{mm}^3$. Children with CNS leukemia require more intensive therapy. Occasionally, the diagnosis of AML is preceded by a prolonged preleukemic phase lasting several weeks or months, characterized by lack of one of the normal blood cell lineages, with refractory anemia, moderate neutropenia or thrombocytopenia. The condition is referred to as a myelodysplastic syndrome; some patients show hypoplastic bone marrow that develops later into acute leukemia.

Management

Improved supportive care and use of combination chemotherapy has led to a survival in >80% overall and >95% children with low risk ALL. Treatment is determined by the risk of relapse in each patient. The risk based approach allows use of modest therapy for children with likely satisfactory outcome, and intense treatment for those with severe disease.

Successful treatment of ALL requires the control of bone marrow or systemic disease, and treatment (or prevention) of extramedullary disease in sanctuary sites, particularly the central nervous system.

Therapy for ALL is divided into 4 stages: (i) Induction therapy to attain remission; (ii) CNS prophylaxis or CNS preventive therapy; (iii) intensification or consolidation phase; and (iv) maintenance or continuation therapy. The intensification phase, following induction of remission, may not be required in low risk patients, though recent studies suggest benefits in long-term survival with intensification therapy in both low risk and high risk patients. The average duration of treatment in ALL is 24–30 months, with no advantage of extending treatment beyond 3 years.

Induction Therapy

The goal of this phase is to eradicate leukemia such that at end of this phase there are <5% leukemic blasts in the bone marrow. Induction therapy with a regimen combining vincristine and prednisone administered for 4 weeks induces remission in 80–95% patients. Current induction regimens that combine vincristine, prednisolone, L-asparaginase and an anthracycline result in remission in 95–98% by 4–6 weeks. Patients who achieve rapid early remission (<5% blasts in marrow) by day 7 or 14 of induction have a better prognosis than slow responders. Failure to achieve this at end of induction is associated with high-risk of relapse.

CNS Preventive Therapy

Most children with leukemia have subclinical CNS involvement at diagnosis, which might act as a sanctuary where blasts are protected because of the blood-brain barrier. CNS prophylaxis has enabled increased survival rates in leukemia. Given the concern of long-term neurotoxicity and risk of brain tumors following standard cranial irradiation, experts recommend lower dose irradiation combined with intrathecal administration of methotrexate. Alternative regimens include the use of triple intrathecal therapy consisting of methotrexate, hydrocortisone and cytarabine without cranial irradiation or high dose systemic chemotherapy. Others propose that irradiation be limited to patients with high risk features at diagnosis, including T cell ALL with leukocyte counts $>100000/\text{mm}^3$, Philadelphia chromosome positive and presence of CNS leukemia.

Intensification (Consolidation) Therapy

Consolidation with high dose methotrexate, L-asparaginase, epipodophyllotoxin, cyclophosphamide and cytarabine has improved survival of patients with ALL, especially those with high-risk disease. Use of these medications may result in significant granulocytopenia and need for supportive care.

Maintenance (Continuing) Therapy

Approximately 2–3 logs of leukemic blasts are killed during the induction therapy, leaving a cell burden in the range of 10^9 – 10^{10} . Additional therapy is necessary to prevent a relapse. Once remission is achieved, maintenance therapy is continued for an additional 2–2.5 years. Multiple drug combinations and schedules are used, some based on periodic reinduction, others on continued delivery of effective drugs. The main agents used are 6-mercaptopurine daily and methotrexate once a week, with or without vincristine and prednisolone or other cytostatic drugs.

Infant ALL

The outcome of ALL remains poor in infants, even with intense therapy including stem cell transplant. Only 30–

40% of children with MLL t(4;11) gene rearrangement are cured. Therapy usually includes high dose cytarabine and methotrexate in addition to standard ALL therapy.

Philadelphia Chromosome Positive ALL

ALL with t(9;22), known as Philadelphia chromosome positive, was conventionally considered high risk due to chemoresistance and need for bone marrow transplantation. Long-term combination therapy with imatinib has improved the 3 years survival to 80%.

Other High-Risk Groups

Hypodiploidy (<44 chromosomes), t(17;19), remission induction failure and minimal residual disease >1% at end of induction is associated with poor outcome. Most patients need allogeneic stem cell transplantation, although there is no strong evidence to support benefit of this approach.

Compared to ALL, cure rates in AML are hampered by lower remission and increased relapse rates due to resistance to multiple medications, and higher risk of death in remission due to infections and hemorrhage. Intensification of therapy and improved supportive care has resulted in improved long-term survival for AML from <10 to ~50%.

A risk-based approach is used for therapy. Patients with favorable features or normal cytogenetics are treated with chemotherapy alone. Patients with unfavorable genetic alterations undergo stem cell transplantation in the first remission. The induction regimen used commonly is cytosine arabinoside (100 mg/m²/day given as continuous infusion for 7 days) and daunorubicin (45 mg/m²/day for 3 days) with or without additional agents (etoposide, thioguanine). While remission is induced in about 70–80%, most children relapse within 1 year. Consolidation therapy includes high dose chemotherapy with cytosine arabinoside and etoposide. Allogeneic bone

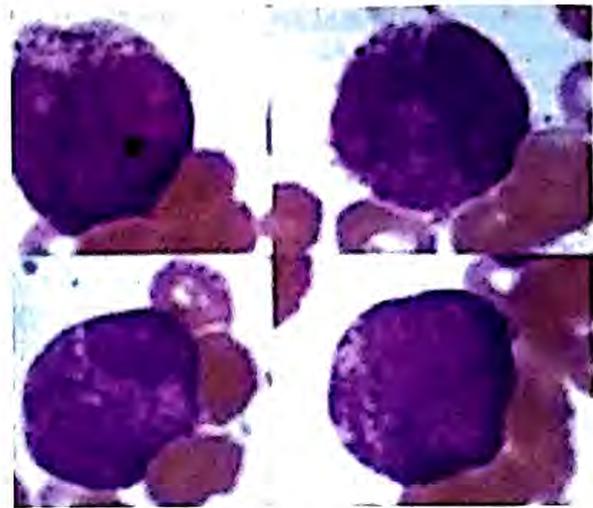


Fig. 21.4: Acute promyelocytic leukemia. Peripheral blood smear showing abnormal promyelocytes

marrow transplantation during early remission is associated with a better long-term survival.

Acute promyelocytic leukemia (APML): Patients with acute promyelocytic leukemia, M3 (Fig. 21.4), which accounts for 10–15% patients of AML, are treated with all transretinoic acid (ATRA), arsenic trioxide and chemotherapy with anthracyclines and high dose cytarabine.

Prognosis

Early response to treatment in childhood ALL as judged by clearance of blasts from peripheral blood by day 7 and bone marrow by day 14 of therapy is one of the best predictors for outcomes. Unsatisfactory prognostic factors include hypodiploidy, Philadelphia chromosome positivity, mixed lineage leukemia, IKZF-1 gene deletion, age <1 year or >10 years, leukocyte count >50,000/mm³

Table 21.9: Prognostic features in acute lymphoblastic leukemia (ALL)

Feature	Standard risk	High risk
Age	2–10 years	<1 year; >10 years
Sex	Female	Male
Initial leukocyte count	<50000/cu mm	>50000/cu mm
Hepatosplenomegaly	Absent	Massive
Lymphadenopathy	Absent	Massive
Mediastinal mass	Absent	present
Central nervous system leukemia	Absent	Present
Phenotype	Pre B (T-cell intermediate)	Mature B cell
Ploidy	Hyperdiploidy	Hypodiploidy
Cytogenetics	t(12;21), trisomy 4 and 10	t(9;22), t(4;11), t(8;14)
Response to treatment	Good early response	Poor early response
Minimal residual disease after 1st induction	Negative	Positive

and presence of minimal residual disease at end of induction by PCR assay or by flow cytometry (Table 21.9).

~15–20% patients with ALL relapse, most commonly in the bone marrow followed by CNS and testis. The prognosis for patients who relapse depends on the site and time of relapse. Early bone marrow relapse before completing maintenance therapy has the worst prognosis; late relapses after cessation of maintenance therapy show better (30–40%) survival. Relapse at extramedullary sites, particularly testis, is more favorable in terms of survival. Late isolated CNS relapse (>18 months) can be effectively cured with cranial irradiation and systemic chemotherapy. Therapy for relapse is more aggressive than first line therapy.

Adverse prognostic factors in AML include: Older age, obesity, M0 and M7 subtype, and CNS disease at diagnosis. Lack of minimal residual disease, M3 subtype, AML associated with Down syndrome and presence of favorable cytogenetics [Inv16, t(8;21), t(15;17)] are associated with favorable outcome.

Late Effects of Treatment

Long-term effects of treatment are of concern. Patients who have received cranial irradiation at a young age are at risk for cognitive and intellectual impairment and development of CNS neoplasms. There is a risk of secondary AML after intensive use of epipodophyllotoxins (etoposide, teniposide). Endocrine dysfunction leads to short stature, obesity, precocious puberty, osteoporosis, thyroid dysfunction and growth hormone deficiency. Patients with prior therapy with an anthracycline are at risk of cardiac toxicity.

Down Syndrome and Acute Leukemia

Children with Down syndrome (trisomy 21) have a 15–20 fold higher risk of acute leukemia, compared to the general population with a cumulative risk of ~2.1%. The ratio of ALL to AML in Down syndrome is similar to that in other children. One-half to two-thirds patients of acute leukemia in children with Down syndrome are ALL, the exception being the first 3 years of life when AML predominates and exhibits a distinctive biology. Approximately 10% children with Down syndrome develop a preleukemic clone, transient myeloproliferative disorder with somatic mutations in hematopoietic transcription factor GATA1. These children present with high leukocyte count, circulating blasts in peripheral blood, hepatosplenomegaly, effusions, anemia and thrombocytopenia in the neonatal period, which resolves by 3 months. About 20% patients with the transient myeloproliferative disorder develop AML. AML in children with Down syndrome generally develops before 5 years of age, has low leukocyte count and does not have CNS involvement; two-thirds show acute megakaryocytic leukemia (FAB M7). Since blast cells in these patients have high sensitivity to medications, they require less intense chemotherapy and

show better outcomes than AML in those without trisomy 21. Children with trisomy 21 are also at higher risk for ALL. However, these patients do not show a preleukemic phase and their outcome is inferior to those without Down syndrome and ALL.

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CHRONIC MYELOID LEUKEMIA

Chronic leukemias constitute 3% of leukemias in childhood. Chronic myeloid leukemia (CML) is a clonal disorder that originates in a pluripotent hematopoietic stem cell and is characterized by myeloid hyperplasia of the bone marrow, extramedullary hematopoiesis, elevation of white blood cell count (with appearance of the complete range of granulocyte precursors in the peripheral blood). CML bears a specific cytogenetic marker that is known as the Philadelphia (Ph) chromosome. Ionizing radiation is implicated in the pathogenesis of CML. Two main forms of well differentiated myelogenous leukemia are recognized.

Adult CML: The condition is clinically and hematologically comparable to the adult form of chronic myelogenous leukemia and occurs in children above the age of 4 years (Fig. 21.5a).

Juvenile CML: This form presents in infancy and early childhood, usually below the age of 4 years, and has a more rapid course (Fig. 21.5b).

Adult Variety of CML

Though the adult variety of CML is a common leukemia in adults, it is rare in children accounting for 3–5% cases. CML patients show a triphasic course: The usual phase at diagnosis (~85% patients) is the chronic phase, which may progress to the accelerated phase and blast crisis resembling acute leukemia in which myeloid or lymphoid blasts proliferate in an uncontrolled manner.

Children present in the chronic phase with fatigue, malaise, weight loss, excessive sweating, abdominal fullness, and bleeding due to platelet dysfunction; splenomegaly is usually massive. Symptoms of leukostasis such as headache, dizziness and visual disturbances may occur rarely. Symptoms in the accelerated phase or blast



Fig. 21.5: (a) A 6-year-old boy with chronic myeloid leukemia presenting with fever, anemia, significant splenomegaly and hepatomegaly of 6 months duration. (b) A 1-year-old boy presented with fever, rashes, anemia, significant splenomegaly and hepatomegaly. He was diagnosed as juvenile myelomonocytic leukemia

crisis include fever, night sweats, rapid weight loss, splenic pain, lymphadenopathy, cutaneous infiltration, bleeding or infection.

Leukocytosis is present in all cases and 80% patients have leukocyte counts >100,000/cu mm. The differential

count shows all forms of myeloid cells from promyelocytes, myelocytes and metamyelocytes to polymorphonuclear leukocytes; basophilia is common. Genetic testing for the Philadelphia (Ph) chromosome in conjunction with marrow morphology allows confirmation of the diagnosis.

Treatment

The aim of treatment is to control increasing white cell counts. First and second-generation oral tyrosine kinase inhibitors (TKI) are the treatment of choice. Majority of patients achieve complete hematologic and cytogenetic response following imatinib therapy and the rate of progression to accelerated or blast crisis is reduced. The starting dose of imatinib is 340 mg/m²/day. Bone marrow cytogenetics is monitored every 6 months until a complete cytogenetic response is obtained. Survival after development of accelerated phase is usually less than a year and after blast transformation only a few months. Allogeneic stem cell transplantation is recommended for patients who do not respond to TKI.

Juvenile Chronic Myeloid Leukemia

JCML, also termed as juvenile myelomonocytic leukemia (JMML), is an uncommon hematological malignancy accounting for less than 2% leukemias in children. Patients with neurofibromatosis are at high risk for development of JCML. Compared to ACML, JCML is a disease of infancy and early childhood below the age of 5 years, has more acute and severe course with relatively more frequent lymphadenopathy, anemia, hepatosplenomegaly, skin involvement (eczema, xanthoma and café au lait spots), infection and thrombocytopenia.

Peripheral smear shows leukocytosis (usually less than 1000 000/cu mm) with the full spectrum of granulocyte precursors and increased normoblasts; monocytosis is striking (Table 21.10). Thrombocytopenia and anemia are common. The leukocyte alkaline phosphatase score is normal or low and fetal hemoglobin levels are elevated. Bone marrow aspirates show increased cellularity with predominance of granulocytic cells in all stages of maturation; megakaryocytes are normal or decreased. Most patients have normal

Table 21.10: Diagnostic criteria for juvenile myelomonocytic leukemia (JMML)

Category 1 (all must be present)	Age <13 years Splenomegaly Absolute monocyte count >1000/cu mm Blasts in peripheral blood/marrow <20% Absent philadelphia chromosome and <i>BCR/ABL</i> fusion gene
Category 2 (at least 1 of the following)	Somatic mutation in <i>RAS/PTPN11</i> Clinical diagnosis of NF1 or monosomy 7
Category 3 (at least 2 of the following)	Circulating myeloid precursors Leukocytes >10,000/cu mm Elevated fetal hemoglobin, HbF (corrected for age) Clonal cytogenetic abnormalities (excluding monosomy 7)

karyotype or nonspecific chromosomal abnormalities. Philadelphia chromosome is negative; monosomy 7 is found in 30% patients.

JCMML has a fulminant and rapidly fatal course. Management involves supportive care including packed red cell and platelet transfusions, treatment of infections and allogeneic stem cell transplant, if a matched sibling donor is present.

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LYMPHOMA

Lymphomas are the third most common malignancy, comprising 10–15% of childhood cancers. About 60% are non-Hodgkin lymphoma and 40% are Hodgkin lymphoma (Table 21.11).

HODGKIN LYMPHOMA

Hodgkin lymphoma is a lymphoreticular neoplasm primarily of B cell lineage that involves lymph nodes and the lymphatic system. The incidence ranges from 5–7/100,000 population; the condition is uncommon below the age of 5 years and exhibits three distinct forms in developing countries: The childhood form (younger than 14 years), a young adult form (15–44 years) and older adult form (55–74 years). There is a male preponderance (10:1) in children affected below 7 years of age, with equal sex distribution beyond 12 years of age. The vast majority (80–90%) achieve disease remission with multiagent chemotherapy with or without radiotherapy.

Epidemiology

The etiology of Hodgkin lymphoma is multifactorial with a role for infectious agents, genetic susceptibility, socioeconomic factors, environment and immune dysregulation. Siblings have a 7-fold increase in risk and multiple studies confirm a gender concordance of sibling pairs. A strong evidence of genetic susceptibility further comes from a 100-fold increased risk in monozygotic twins compared with dizygotic twins. Epidemiologic studies have suggested links between Hodgkin lymphoma and viral illnesses like Epstein-Barr virus (EBV). EBV viral DNA can be found in Hodgkin-Reed-Sternberg cells, suggesting monoclonal proliferation of the neoplastic clone following infection. EBV infection is commonly seen in young children with mixed cellularity disease. Immune deficiency (congenital/acquired) and autoimmune conditions (rheumatoid arthritis, SLE, sarcoidosis, ITP) are associated with increased risk of Hodgkin lymphoma.

Pathology

Lymph nodes are the most common tissue on which the diagnosis of Hodgkin lymphoma is made. However, liver, spleen, bone marrow or lung may provide the material for histological examination. It is necessary to obtain the entire node by excision biopsy for proper examination. Fine needle aspiration biopsy and frozen section material are not optimal for histology.

The WHO classification of Hodgkin lymphoma recognizes two subtypes: Nodular lymphocytic predominant Hodgkin lymphoma (NLPHL) and classical Hodgkin lymphoma. NLPHL subtype is characterized by large cells with multilobed nuclei referred to as popcorn cells. These patients are generally asymptomatic and present with localized nonbulky mediastinal disease. The hallmark of classic Hodgkin lymphoma is the Reed-Sternberg (RS) cell, a binucleated or multinucleated giant cell with bilobed nucleus and two large nucleoli, giving an owl eye appearance to the cells. There are four varieties of Hodgkin disease, characterized by the number of RS cells, characteristics of inflammatory milieu and presence or absence of fibrosis (Table 21.12). Nodular sclerosing is the

Table 21.11: Clinical features of Hodgkin and non-Hodgkin lymphoma

Clinical feature	Hodgkin lymphoma	Non-Hodgkin lymphoma
Nodal spread	Continuous	Discontinuous
Localized	Yes	Rare
Extranodal disease	Rare	Common
Central nervous system disease	Rare	Common
Bone marrow involved	Rare	Common
Class B symptoms	Common	Uncommon
Abdominal disease	Uncommon	Common
Subtype based therapy	Not important	Crucial
Cure rates	85–90%	70–80%

Table 21.12: Histological subtypes of Hodgkin lymphoma

Histology	Frequency	Prognosis
Nodular lymphocyte predominant	10%	Excellent
Classical Hodgkin lymphoma		
Nodular sclerosis	20–50%	Very good
Mixed cellularity	20–40%; most common in developing countries and in children	Good
Lymphocyte rich	10–15%	Excellent
Lymphocyte depletion	5–15%	Poor

most common type in developed countries, whereas in developing countries including India, the mixed cellularity type accounts for ~60% cases. On immunophenotyping, the classic subtypes are positive for CD15 and CD30 and may be positive for CD20, whereas NLPHL is negative for CD15 and CD30 but positive for CD20 and CD45.

Clinical Features

Children with Hodgkin lymphoma present with painless cervical or supraclavicular lymphadenopathy; the nodes are firm and rubbery in consistency (Fig. 21.6a). Cervical lymph nodes are the most frequent (80%) site of primary involvement; 50% patients also have mediastinal adenopathy and superior mediastinal syndrome. Less commonly, axillary or inguinal lymphadenopathy is the presenting feature. About 20–30% of children present with systemic “B” symptoms, with fever over 38°C, night sweats and unexplained loss of >10% body weight at presentation. The frequency of these symptoms increases with advanced disease and indicate an unfavorable prognosis.

Other prognostic factors include stage of disease, histopathological subtype (risk increases from lymphocyte predominant to nodular sclerosis to mixed cellularity to

lymphocyte depletion), bulky mediastinal disease, extensive splenic involvement and more than 5 nodal sites in stage III. Bone involvement by classical HL may cause pain. Bone marrow involvement rarely results in cytopenias and has been associated with a variety of paraneoplastic syndromes.

Diagnostic Work-up and Staging

Evaluation includes careful assessment of all lymph node bearing areas and relevant investigations (Tables 21.13 and 21.14).

Management

Treatment modalities, including total nodal radiation therapy to chemotherapy to combination of chemotherapy and radiotherapy have led to significant improvement in survival rates.

Most children are treated with combination chemotherapy alone or in combination with radiotherapy. Superior efficacy and absence of significant toxicity have made ABVD the preferred regimen for Hodgkin lymphoma; concerns of this protocol include cardiomyopathy and pulmonary fibrosis. The dose of radiation



Fig. 21.6: (a) This 10-year-old boy presented with fever and significant bilateral cervical lymphadenopathy. Lymph node biopsy showed features of Hodgkin lymphoma; (b) A 10-year-old boy with fever, significant right cervical lymphadenopathy was diagnosed as Burkitt lymphoma; (c) Chest X-ray of a 7-year-old boy with mediastinal mass and left-sided pleural effusion. He was diagnosed as T lymphoblastic lymphoma on lymph node biopsy

Table 21.13: Diagnostic evaluation for children with Hodgkin lymphoma

Physical examination; measure size and number of lymph nodes
Complete blood counts, ESR, CRP, liver and renal functions, alkaline phosphatase, LDH
Bopsy of lymph node or involved extranodal site
Chest X-ray posteroanterior and lateral views; measure mediastinal mass thoracic cavity ratio
CT scan: Neck, chest and abdomen
Bone marrow biopsy (all children except stages IA, IIA)
Bone scan (recommended in children with bone pains or raised alkaline phosphatase)
CT scan brain, cerebrospinal fluid examination (if indicated clinically)
Gallium scan, positron emission tomography (PET) (identifies more sites than conventional imaging; accurate for residual mass)
PET-CT identifies more sites of initial disease than conventional imaging and is accurate in detecting tumor tissue in post-therapy masses. <i>Rapid early response</i> (significant reduction in disease volume and PET negativity within 1–2 chemotherapy cycles) has favorable outcome. PET-CT is advised ≥ 3 weeks following completion of chemotherapy, and 8–12 weeks postradiation
Surgical staging with lymph node sampling and lymph-angiography (in selected cases)

therapy ranges between 15 and 25 Gy with modifications based on patient age, response to chemotherapy and presence of bulky/residual tumor. Several studies have demonstrated that chemotherapy alone is effective therapy for pediatric Hodgkin lymphoma. The advantage of this

approach is elimination of radiation-associated adverse effects like myocardial dysfunction, musculoskeletal growth deficits and second malignancy.

Treatment for patients with favorable clinical presentation (localized node involvement: Stage I, II, IIIA; absence of B symptoms; no evidence of bulky disease) consists of 2–4 cycles of chemotherapy (ABVD/others) and low dose involved field radiation. Unfavorable clinical presentation (B symptoms; bulky mediastinal/peripheral lymphadenopathy; extranodal extension of disease; advanced disease: Stage IIIB-IV) are treated with 4–6 cycles of ABVD with/without radiotherapy. The role of additional radiotherapy in stage III and IV lymphoma is controversial. Hematopoietic stem cell transplantation (HSCT) is offered to patients who relapse or for those who are refractory to primary therapy.

Prognostic Factors

Factors affecting outcome include pretreatment factors (advanced stage, presence of 'B' symptoms, bulky disease, extranodal extension, male sex and elevated ESR) and treatment related factors (rapidity of response to initial cycles of chemotherapy). Hodgkin lymphoma is one of the most curable cancers of childhood, especially if detected in early stages. Appropriate staging, availability of advanced techniques of investigation and use of risk adapted treatment protocols have resulted in excellent overall survival.

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Table 21.14: Modified Ann Arbor staging for Hodgkin lymphoma

Stage	Involvement
I	Single lymph node region (I) or one extra lymphatic site/organ (I _E) by direct extension
II	Two or more lymph node regions on the same side of diaphragm (II), or one or more lymph node regions on same side of diaphragm plus local extralymphatic extension (II _E)
III	Lymph node regions on both sides of the diaphragm (III), which may be accompanied by local extralymphatic extension (III _E)
	III1 Abdomen disease is limited to the upper abdomen: Spleen or its hilar nodes, celiac nodes, porta hepatis nodes
	III2 Abdomen disease includes paraortic, mesenteric and iliac nodes, with or without disease in upper abdomen
IV	Diffuse involvement of one/more extralymphatic organ/sites with or without associated lymph node involvement
A	No B symptoms
B	Presence of at least one of the following: Unexplained weight loss >10% baseline during 6 months before staging Recurrent unexplained fever >38°C Recurrent night sweats
X	Bulky tumor

X Bulky tumor is either a single mass of tumor tissue exceeding 10 cm in largest diameter, or a mediastinal mass extending one-third of the maximum transverse intrathoracic diameter measured to the inside of the ribs on a standard posteroanterior chest radiograph

E lesion Localized extranodal extension of Hodgkin lymphoma from a contiguous/nearby nodal site

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NON-HODGKIN LYMPHOMA

Non-Hodgkin lymphoma (NHL) comprises a heterogeneous group of neoplasms that most commonly occur during the second decade. Together with Hodgkin disease, NHL comprises the third most common childhood malignancy.

Epidemiology

The relative frequency and incidence of NHL show geographic variations. There is male preponderance, with male to female ratio of 3:1 in children <15-year-old. NHL is uncommon before 3 years of age. Age-specific trends of incidence of NHL may correlate with histologic subtype. Burkitt and Burkitt-like lymphomas occur in children between 5 and 15 years, while the incidence of lymphoblastic lymphoma is constant across all age groups. Diffuse large B cell lymphoma (DLBCL) is a disease of older adolescents. In equatorial Africa, 50% of all cancers are lymphomas (chiefly Burkitt lymphoma). In United States and Europe, one-third of childhood NHL is lymphoblastic, one-half are small noncleaved cell lymphomas (Burkitt, non-Burkitt or Burkitt-like) and the rest are large cell lymphomas. In India, lymphoblastic lymphoma is more common.

Lymphoblastic lymphomas are T cell derived, while undifferentiated lymphomas (Burkitt, non-Burkitt) are B cell derived. NHL may follow previous chemotherapy for Hodgkin disease, or be associated with immuno-

deficiency and DNA repair deficiency syndromes (Wiskott-Aldrich syndrome, X-linked lymphoproliferative disorders and ataxia telangiectasia), acquired immunodeficiency syndrome and organ transplantation (post-transplant lymphoproliferative disease). Infection with malaria and EB virus are considered risk factors for Burkitt lymphoma.

Pathology

The major histological types of NHL are Burkitt/Burkitt-like lymphoma (BL), lymphoblastic lymphoma (LL), diffuse large B cell lymphoma (DLBL) and anaplastic large cell lymphoma (ALCL) (Table 21.15).

Clinical Features

NHL in children has distinct clinical and behavior properties when compared to adults. Lymphomas in adults are commonly low or intermediate grade and are dominantly nodal, have variable growth fraction with poor long-term outcome. NHL in children is high grade, extranodal with high growth fraction and good outcome. Children usually present with extranodal disease involving the mediastinum, abdomen, or head and neck region (Fig. 21.6b). Intrathoracic NHL, most often T-cell, may have features of superior mediastinal or superior vena caval syndrome. There may be associated pleural or pericardial effusion (Fig. 21.6c). Cervical adenopathy, abdominal pain, ascites, palpable abdominal mass, intestinal obstruction or intussusception, cranial nerve palsy, bone or jaw swelling, and cytopenias due to marrow involvement are other features.

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Table 21.15: Types of non-Hodgkin lymphoma (NHL)

Type	Immune type	Features	Translocation	Remarks
Burkitt, Burkitt-like lymphoma 50% of NHL	Mature B cell (surface IgG ±IgM) CD10, 19, 20; kappa and lambda	Intra-abdominal, head, neck; jaw (Waldeyer ring) Less common: CNS, testes, marrow	t(8:14)(q24;q32) t(2;8)(p11;q24) t(8;22)(q23;q23)	<i>India:</i> sporadic form is common and with abdominal presentation <i>Africa:</i> Endemic form common with jaw mass
Diffuse large B cell lymphoma (DLBCL) 10–20% of NHL	Mature B cell CD 19, 20, 22, 38, 79a	Nodal, abdomen, bone Less common: CNS, marrow, mediastinum	t(8:14)(q24;q32) t(2;17)(p11;q24)	10–20% of NHL; often localized 20% present as primary mediastinal disease; poor prognosis
Lymphomatous lymphoma Precursor T & B cells 20% of NHL	Pre T cell (~70%) Pre B cell (~30%)	Mediastinal, bone marrow, skin, bone	t(1;14)(p32;q11) t(11;14)(p13;q11) t(11;14)(p15;q11) t(10;14)(q24;q11) t(7;19;)(q35;p13)	Majority 70% are T lineage with mediastinal mass >25% blasts: Managed as leukemia
Anaplastic large cell lymphoma 10% of NHL	CD30; anaplastic lymphoma kinase (ALK, CD246), epithelial membrane antigen positive	Lymph node, skin, bones, visceral, soft tissues	t(2;5)(p23;q35) t(1;2)(q21;q23) t(2;3)(p23;q21) t(2;17)(p23;q23) t(X;2)(q11-12;p23) Inv 2(p23;q35)	Varied presentation; extranodal nodal involvement Systemic symptoms present Prolonged waxing/waning course Diagnosis delayed and difficult

Table 21.16: St. Jude staging system for childhood non-Hodgkin lymphoma

<i>Low risk (localized)</i>	
I	Single tumor (extranodal), single anatomic area (nodal) excluding mediastinum or abdomen
II	Single tumor (extranodal) with regional node involvement Primary gastrointestinal tumor (completely resected with or without involvement of mesenteric nodes) Two/more tumors/nodal areas on one side of the diaphragm
<i>High risk (advanced)</i>	
III	All primary intrathoracic (mediastinal, pleural and thymic) tumors All extensive primary intra-abdominal disease All paraspinal or epidural tumors regardless of other tumor sites Two/more nodal or extranodal areas on both sides of diaphragm
IV	Any of the above with central nervous system and/or bone marrow involvement

Diagnosis

NHL are rapidly growing tumors and require prompt diagnosis. Selection of the appropriate lymph node or mass for histological diagnosis is necessary. Histology is supplemented, where possible, with immunophenotypic and cytogenetic studies. If the clinical condition is not suitable for biopsy, due to a large mediastinal mass causing superior vena cava syndrome, the diagnosis may be made with less invasive procedures including percutaneous needle aspiration, examination of body fluids (e.g. pleural fluid) or bone marrow. All newly diagnosed patients should be carefully staged (Table 21.16) and worked up (Table 21.17).

Management

Improvement in survival has been possible due to use of highly effective chemotherapy and strong supportive care. Surgery has limited role in treatment, other than for diagnosis. Radiotherapy is restricted to emergencies, e.g., spinal cord compression due to paraspinal disease. Multiagent chemotherapy, directed to the histologic subtype and stage of the disease, is recommended for NHL.

Table 21.17: Evaluation of a patient with non-Hodgkin lymphoma

History and physical examination
Complete blood count; peripheral smear examination
Liver and renal function tests, electrolytes, LDH, uric acid
Biopsy for histology; cytochemical, immunologic, cytogenetics and molecular studies
Pleural, pericardial or peritoneal fluid: Cytomorphology, immunophenotype characterization
Bone marrow aspiration and biopsy: Cytomorphology, immunophenotype characterization
Chest radiograph (include lateral view if mediastinal widening)
Ultrasonography chest and abdomen
CT scan/MRI of neck, chest and abdomen
Positron emission tomography-CT (optional)
Echocardiography

Emergency Management

Life-threatening complications in NHL include:

- Superior vena cava obstruction and esophageal compression from mediastinal masses with lymphoblastic lymphoma
- Airway obstruction from pharyngeal or intrathoracic mass
- Tumor lysis syndrome seen with lymphoblastic lymphoma and Burkitt lymphoma
- Respiratory/cardiac compromise due to massive pleural/pericardial fluid
- Paraplegia from epidural tumor or raised intracranial pressure, and neurological deficit from intracranial lymphoma or CNS involvement
- Obstructive jaundice and pancreatitis from compression of bile or pancreatic ducts
- Gastrointestinal bleeding, obstruction, intussusception and rarely perforation

These complications need to be recognized early and treated appropriately. Patients with superior mediastinal or vena caval syndrome require therapy with high dose IV dexamethasone. Tumor lysis syndrome must be anticipated and prevented by ensuring hydration, and use of rasburicase or allopurinol; those with acute kidney injury or metabolic aberrations require hemodialysis.

The cornerstone for treatment of pediatric NHL is multiagent chemotherapy. Different chemotherapeutic regimens are used for treatment of B and T cell lymphomas. Most successful protocols are the German BFM (Berlin, Frankfurt, Munster) protocols and a modified version of LSA2L2 protocol. These are intensive protocols that use combinations of 8 to 10 drugs. Cranial irradiation or prophylactic intrathecal chemotherapy is given in stages III and IV disease. Chemotherapy is given for a period of 1 to 2 years depending on the stage and extent of the disease. Radiation is recommended for specific indications, like CNS involvement. Long-term survival in patients with lymphoblastic lymphoma with limited disease is 80–90% and for advanced disease 70–80%.

Therapy for B cell (Burkitt, non-Burkitt) lymphomas is different. Most protocols consist of short duration (6 months) intensive alkylating high dose methotrexate,

vincristine, anthracyclines, etoposide and cytarabine. CNS prophylaxis is provided with intrathecal chemotherapy. Long-term survival is highly satisfactory with survival in more than 90% patients with limited disease and 75–85% in patients with extensive disease. Survival rates in patients with bone marrow disease have also improved dramatically. The use of anti-CD20 monoclonal antibodies (rituximab) directed against B-cell antigens has been combined with standard chemotherapy to improve survival. Anaplastic large cell lymphoma may be treated either as Burkitt or as lymphoblastic lymphoma. The management of relapses is a challenge that requires intensive protocols and stem cell transplantation.

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RETINOBLASTOMA

Epidemiology

Retinoblastoma is the most common primary intraocular tumor of infancy and childhood with an incidence of 1 in every 20,000 live births. About 90% cases are diagnosed by the age 3–4 years and 98% by 5 years. One-third patients have bilateral disease, which is often multifocal and diagnosed at a younger age. The tumor is highly sensitive to chemotherapy and survival rates in developed countries are greater than 90%.

Genetics

The retinoblastoma gene (*RB1*), encoded on chromosome 13q14, was the first described tumor suppressor gene. Loss

of one *RB1* allele predisposes to cancer, while loss of the second allele, in developing retinal cells, leads to retinoblastoma.

Retinoblastoma, a tumor of the embryonic neural retina, can be sporadic or inherited. Sporadic tumors are unilateral, unifocal and occur at an older age, while inherited tumors occur earlier and are often bilateral and multifocal (Fig. 21.7a). The "two hit" model of oncogenesis proposes that two mutational events are required for development of retinoblastoma, the first hit being an inherited mutation in *RB1* and the second is acquired in the somatic retinal cell. In sporadic retinoblastoma both mutations occur in the somatic retinal cell. Most cases of hereditary retinoblastoma have a spontaneous new germline mutation while their parents have wild type *RB1* alleles. The risk of an offspring inheriting an *RB1* mutation from a parent with germline mutation is 50%; 97% children with inherited mutation is at risk of retinoblastoma. Germline mutations of *RB1* also cause an increased risk of a second malignancy of the lung, soft tissue, bladder, skin, bone and brain; the risk is higher when these patients receive radiation therapy for the retinoblastoma. A small proportion (5–10%) of unilateral tumors is hereditary.

Clinical Features

The tumor arises from retina and grows towards the vitreous. Its progression results in involvement of ocular coats and optic nerve leading to scleral, orbit and central nervous system involvement. Hematogenous dissemination may lead to distant metastasis. Leukocoria (white pupillary reflex) is the most common presentation (Fig. 21.7b). Strabismus, poor visual tracking and glaucoma are other presenting features. Orbital inflammation, hyphema and irregular pupil, phthisis bulbi (Fig. 21.7c) and a fungating ocular mass suggest advanced disease is often detected late, in developing countries, retinoblastoma either with an orbital mass (proptosis) or with distant metastasis to the bones, bone marrow, lymph nodes and central nervous system.



Fig. 21.7: Retinoblastoma: (a) Familial retinoblastoma in two siblings; (b) A 3-year-old boy showing leukocoria; (c) A 3-year-old boy with phthisis bulbi

Table 21.18: International classification of intraocular retinoblastoma

Group A	Very low risk	No tumor greater than 3 mm in dimension; away from fovea and optic nerve
Group B	Low risk	Any eye with tumor not in group A with no vitreous seeding, subretinal fluid <5 mm from base of tumor
Group C	Moderate risk, focal seeds	Tumors with focal fine vitreous seeding or subretinal fluid (<1 quadrant)
Group D	High risk	Massive/diffuse vitreous seeding, extensive subretinal masses
Group E	Very high risk, extensive retinoblastoma	Unsalvageable eyes Tumor involving >50% globe, touching the lens, involves anterior segment Diffuse infiltrating retinoblastoma, neovascular glaucoma Opaque media from hemorrhage Tumor necrosis, aseptic orbital cellulitis, phthisis bulbi

Table 21.19: International retinoblastoma staging

Stage	Description
Stage 0	Eye has not been enucleated and no dissemination of disease Conservative treatment
Stage I	Eye enucleated, completely resected histologically
Stage II	Eye enucleated, microscopic residual tumor in form of tumor invasion into extrascleral space or optic nerve
Stage III	<i>Regional extension</i> Overt orbital disease Preauricular or cervical lymph node extension
Stage IV	<i>Metastatic disease</i> Hematogenous metastasis (without central nervous system involvement): Single or multiple lesions Central nervous system extension (with/without regional or metastatic disease) Prechiasmatic lesion, CNS mass, leptomeningeal and cerebrospinal fluid disease

Diagnosis

The diagnosis is based on history, clinical examination and imaging. Ocular examination of both eyes should be done under anesthesia. Imaging studies such as ultrasound, CT/MRI (preferred) scans are used to assess the orbital, optic nerve and for intracranial extension. Rarely children with hereditary retinoblastoma show a pineal tumor (trilateral retinoblastoma) that is detected on imaging. CSF and bone marrow examination are done only if indicated on clinical examination or imaging. Biopsy or aspiration cytology is not routinely required unless the diagnosis is in doubt. Occasionally an adjacent lymph node needs to be aspirated for metastasis. Screening for *RB1* mutations on peripheral blood or tumor tissue, helps differentiate somatic from germline mutations.

Staging

Retinoblastoma may be intraocular or extraocular. Intraocular retinoblastoma denotes that the disease is limited to the eye, and is confined to the retina or extends to the choroid, ciliary body, anterior chamber and optic nerve head (Tables 21.18 and 21.19). Extraocular retinoblastoma refers to extension of the illness beyond the eye, including tissues around the eye (orbital retinoblastoma) or spread to the central nervous system, bone marrow or lymph nodes (metastatic retinoblastoma).

Treatment

The aim of treatment is survival with eradication of disease; maintenance of vision and preservation of globe and vision are secondary goals. Treatment depends on size, location, extent of the tumor and whether it is hereditary or sporadic. Retinoblastoma is curable when the disease is intraocular.

Laser therapy: Argon or diode laser is the primary treatment for smaller tumors, but is also sometimes used after chemoreduction.

Cryotherapy: A special probe applied through the sclera to produce low temperatures (−60 to −80°C) is suitable for tumors smaller than 4 disc diameters close to the retina.

Chemotherapy: Chemotherapy enables salvaging the affected eye, avoiding enucleation or external beam radiotherapy and risk of second malignancies. Systemic chemotherapy most often comprises a combination of vincristine, carboplatin and etoposide. Chemotherapy may also be used for chemoreduction, as an adjunct modality or for therapy of metastasis. Newer routes of drug (melphalan, carboplatin) administration by periocular, intravitreal and intraophthalmic artery injection have improved outcomes in intraocular retinoblastoma.

Enucleation: In cases of unilateral disease with large tumors where no useful vision can be preserved, enucleation is performed early. In children with bilateral

disease systemic chemotherapy is used initially, followed by local treatment with laser photocoagulation or cryotherapy in order to preserve vision. The eye with the no useful vision should be enucleated in these cases.

Radiotherapy: External beam radiotherapy is considered, if chemotherapy and focal therapy fail. Radiotherapy may lead to orbital deformity, sicca syndrome, cataracts, radiation retinopathy, neovascular glaucoma and risk of a second malignancy.

Hematopoietic stem cell transplantation: Patients with extraocular disease have poor prognosis with respect to survival. Those with regional extraocular disease (involving orbit, optic nerve or preauricular region) may be treated with a combination of conventional chemotherapy and external beam radiotherapy. Patients with distant metastasis require high dose chemotherapy, external beam radiotherapy and hematopoietic stem cell transplantation.

Prognosis

Most tumors that are confined to the eye are cured. Focal therapy or enucleation is curative in more than 95% of patients with unilateral disease. Cures are infrequent when extensive orbital or optic nerve extension has occurred or the patient has distant metastasis.

Genetic counseling is an important component of management. All first degree relatives of children with known or suspected hereditary retinoblastoma should have regular examination for evidence of malignancy until 7 years of age.

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WILMS TUMOR

Wilms tumor or nephroblastoma is the commonest malignant neoplasm of the kidney and second most common abdominal malignancy in children. Approximately 6% of all childhood cancer is Wilms tumor with a peak incidence at 2-3 years of age. Individuals with horseshoe kidney have a higher risk of Wilms tumor.

Genetics

While a vast majority of Wilms tumors are sporadic, 1-2% may be familial. Familial tumors occur at an earlier age and have a high propensity for being bilateral. The tumor is thought to develop in the foci of embryonal

kidney tissue called nephrogenic rests. *WT1* is the best characterized Wilms tumor gene, with mutations of this gene observed in approximately 20% of Wilms tumors, occasionally in association with mutations in *CTNNB1* (catenin beta 1; 3p22.1) and *WTX* (gene on X-chromosome). The *WT1* gene is located on chromosome 11p13 and encodes for a transcription factor that is critical for normal development of kidneys and gonads. *WT2* is localized to a cluster of genes at 11p15. Patients with *WT1* mutations have higher risk of recurrence and bilateral disease.

Children with some genetic syndromes are predisposed to Wilms tumor. These include WAGR (Wilms tumor, aniridia, genitourinary abnormalities and mental retardation, *WT1* del11p13), Denys-Drash syndrome (renal failure, mesangial sclerosis, male hermaphroditism, *WT1* missense mutation) and Beckwith-Wiedemann syndrome (hemihypertrophy, macroglossia, omphalocele, organomegaly, *WT2* del11p15.5). Loss of heterozygosity of 1p and/or 16q and high expression of telomerase are associated with poorer outcome in Wilms tumor.

Pathology

The histopathology may be favorable (differentiated blastemal, stromal and epithelial cells) or unfavorable (diffuse or focal anaplasia, clear cell sarcoma, rhabdoid tumor). Most tumors are unicentric; 11% are multicentric.

Diagnosis

Most patients present with an asymptomatic abdominal mass detected by their parents or physician during routine examination. Features at diagnosis include: hematuria (10-25%), hypertension (25%), abdominal pain (30%), fever (20%), anorexia and vomiting. Wilms tumor should be considered in any child with abdominal mass. Tumor thrombus extending into the inferior vena cava is found in 4-10%. Other features at presentation include anemia, thrombocytosis, acquired deficiency of von Willebrand factor and factor VII, and polycythemia. Differential

Table 21.20: Evaluation of Wilms tumor

Investigation	Purpose
Abdominal ultrasound	Organ of origin, identify contralateral kidney Location of tumor thrombus in vena cava
CT scan	Localization of tumor and extent of spread
Chest X-ray	Pulmonary metastasis
Bone scan, skeletal survey	Bone metastasis, especially in clear cell sarcoma
Brain imaging (MRI, CT scan)	Brain metastasis in rhabdoid tumor and clear cell sarcoma
Fine needle aspiration cytology	Cytological confirmation of tumor prior to chemotherapy

Table 21.21: Staging for Wilms tumor (National Wilms Tumor Study Group)

Stage I	Tumor confined to the kidney and completely resected Renal capsule and sinus vessels not involved beyond 2 mm Regional lymph nodes dissected and negative
Stage II	Tumor extends beyond the kidney but is completely resected with negative margins and lymph nodes At least one of the following: (i) Penetration of renal capsule; (ii) Invasion of renal sinus vessels
Stage III	Residual tumor abdomen following surgery confined to abdomen Lymph nodes (renal hilum, para-aortic chain, beyond) show tumor Diffuse peritoneal contamination by tumor Implants on peritoneal surface
Stage IV	Tumor extends beyond surgical margins (microscopy, gross examination) Tumor not completely resected because of infiltration of vital structures
Stage V	Hematogenous metastasis, metastasis to distant lymph nodes Bilateral renal involvement at time of initial diagnosis

diagnosis includes neuroblastoma and other flank masses including hydronephrosis, multicystic kidney, and rarely abdominal lymphoma and retroperitoneal rhabdomyosarcoma. Features of associated syndromes may be present in 10–20%. Evaluation and staging of Wilms' tumor are discussed in Tables 21.20 and 21.21.

Treatment

The approach to treatment differs across the world. While the Childrens Oncology Group recommends upfront resection of the tumor, the International Society of Pediatric Oncology (SIOP) recommends preoperative chemotherapy without biopsy. The outcome with both approaches is similar. Upfront surgery provides accurate diagnosis prior to starting chemotherapy while preoperative chemotherapy shrinks the tumors making surgery easier and decreasing the risk of spillage and rupture. Radiation has limited role in the management.

Patients <2-year-old with tumors <550 g with favorable histology are at low risk and may be treated with nephrectomy alone followed by close observation. Chemotherapy for other stages I or II patients includes vincristine and actinomycin for 18 weeks. Doxorubicin and abdominal radiation are additional therapies for stage III illness. Cyclophosphamide, carboplatin and etoposide are used for anaplasia and metastatic disease. Pulmonary radiation is used for pulmonary metastasis.

Overall ~90% of children with Wilms' tumor are long term survivors. Young age, low stage and low weight (<550 g) are favorable prognostic factors. Presence of anaplasia and loss of heterozygosity of 1p or 16q increase the risk of recurrence. Survivors of Wilms' tumor have relatively few late effects. Cardiotoxicity, renal failure, second malignancy and pulmonary toxicity is reported in survivors of advanced stage disease who receive intensive chemotherapy and radiation.

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NEUROBLASTOMA

Neuroblastoma, derived from the neural crest, is the most common intra-abdominal and extracranial solid tumor in children, accounting for 7–8% of all cancers. This is a disease of early childhood with approximately 90% patients presenting before 5 years of age and almost 50% within the first 2 years of life. The etiology is not known but familial cases occur, and there is association with neurofibromatosis, Hirschsprung disease, heterochromia, fetal hydantoin and fetal alcohol syndromes and Friedreich ataxia. Rearrangement or deletion of the short arm of chromosome 1 is present in 80% patients. Neuroblastoma is one of the few cancers that may undergo spontaneous regression.

The pathology varies from extremely undifferentiated small round blue cell tumor (neuroblastoma) to tumors with mature Schwannian stroma with ganglion cells (ganglioneuroblastoma and ganglioneuroma). The characteristic histopathologic feature is the Homer-Wright pseudorosettes which are circular groupings of dark tumor cells surrounding pale neurofibrils. Neuroblastomas can resemble other small round blue cell tumors such as rhabdomyosarcoma, Ewing sarcoma and non-Hodgkin lymphoma, but are differentiated by characteristic immune histochemistry. The pathology is closely correlated with prognosis, and tumors that show better differentiation, more Schwannian stroma and low mitosis-karyorrhexis index have favorable outcome.



Fig. 21.8: Neuroblastoma. (a) 'Raccoon's eye' (loft eyelid) in a child with metastatic disease; (b) CT abdomen showing a suprarenal mass suggestive of neuroblastoma

Genetics

The *Myc-N* oncogene, encoding the N-myc proto-oncogene protein, is used as a biomarker for risk stratification. *Myc-N* amplification, defined as greater than or equal to 10 copies of *Myc-N* per nucleus, occurs in 20% of cases, and is associated with more aggressive disease. Hyperdiploidy in the tumor tissue is associated with a favorable prognosis in children <2-year-old. Loss of heterozygosity of 1p, 11q, 14 q and gain of 17q are associated with worse prognosis.

Clinical Features

The tumor may occur at any site where sympathetic tissue is found: Abdomen 65% (adrenal medulla 46%, rest 19%), posterior mediastinum (25%), pelvis (4%), head and neck (3%) and others (3%). Chief systemic symptoms include pallor, fatigue, weight loss, abdominal distension and pain, fever, irritability and bone pains. Local symptoms include periorbital edema and ecchymosis (raccoon eyes, Fig. 21.8a), proptosis, exophthalmos, squint, retinal hemorrhage and optic atrophy; cervical lymphadenopathy, Horner syndrome; supraclavicular mass; superior mediastinal syndrome; vertebral nerve compression causing gait

disturbances, bowel and bladder dysfunction; abdominal mass, hepatomegaly; skin nodules and features of bone marrow involvement. Secretion of catecholamines might result in paroxysmal episodes of sweating, pallor, flushing, headache, palpitations and hypertension. The opsoclonus myoclonus syndrome is uncommon and characterized by rapid eye movements, ataxia and irregular muscle movements. Secretion of the vasoactive intestinal peptide may result in watery diarrhea and hypokalemia. Metastatic spread occurs via lymphatics and blood.

Diagnosis

The gold standard for diagnosis is by histopathology and immunohistochemistry. Other investigations include blood counts, urinary catecholamine excretion, bone marrow aspiration and biopsy, liver function tests, abdominal ultrasound, and X-ray and bone scan for metastasis. Nuclear scanning with I-123 or I-131 MIBG detects tumors and metastasis accurately. CT scan of chest, abdomen and pelvis is indicated to assess extent of disease (Fig. 21.8b). MRI is preferred for paraspinal tumors to assess spinal cord compression.

Table 21.22: International neuroblastoma staging

Stage I	Localized tumor confined to the area of origin; complete excision, with or without microscopic residual disease; identifiable ipsilateral and contralateral lymph nodes negative microscopically
Stage II	Localized tumor with incomplete gross excision; identifiable ipsilateral and contralateral lymph nodes negative microscopically
Stage IIB	Localized tumor with complete or incomplete gross excision, with positive ipsilateral regional lymph nodes; identifiable contralateral lymph nodes negative microscopically
Stage III	Tumor infiltrating across the midline with or without regional lymph node involvement; or unilateral tumor with contralateral regional lymph node involvement; or midline tumor with bilateral regional lymph node involvement
Stage IV	Tumor disseminated to distant lymph nodes, bone, bone marrow, liver or other organs (except stage IV-S).
Stage IV-S	Localized primary tumor as defined for stage 1 or 2 with dissemination limited to liver, skin, and/or bone marrow (limited to infants less than 1-year-old)

Table 21.23: Management of neuroblastoma

Risk category	Stage	Age, months	MYCN amplification	Therapy	Survival
Low	I	Any	No	Surgery	>90%
	IIA, IIB	Any	No	Surgery; low dose chemotherapy	>80%
	IV-S	<12	No	Observation/chemotherapy/radiation	
Intermediate	III	Any	No	Chemotherapy	>75%
	IV	<18	No	Radiotherapy to tumor bed if residual disease present + second look surgery	
	IV-S	Any	No		
High	II, III, IV	Any	Yes	Multiagent chemotherapy + autologous bone marrow transplant + maintenance therapy with 13- <i>cis</i> retinoic acid	50%
	IV-S	<12	Yes		
	IV	>18	No		

Quantitation of serum neuron-specific enolase and ferritin, amplification of *Myc-N* gene, tumor cell ploidy and age-based histologic classification are of prognostic value. Patients with neuroblastoma can be divided into those with favorable and unfavorable features. The former, characterized by young age (<1.5 years), favorable stage (I, II and IV-S) (Table 21.22), normal levels of ferritin and favorable histology, has a survival expectancy of 90% or more. Older patients with stage III or IV disease, serum ferritin >150 ng/mL and tumors of unfavorable histology have survival rates of 20% or less.

Treatment

Treatment modalities include chemotherapy, surgery and radiation therapy. Localized neuroblastoma can be treated by surgery alone and does not require chemotherapy (Table 21.23). Patients with stage IV-S just require careful observation. Chemotherapy is the chief of treatment for advanced neuroblastoma. The regimens used include OPEC (vincristine, cyclophosphamide, cisplatin, teniposide (VM-26), CADO (vincristine, cyclophosphamide, doxorubicin) and PECADO (vincristine, cyclophosphamide, doxorubicin, cisplatin, teniposide). Other modalities include surgery, radiotherapy and autologous bone marrow transplantation. Addition of *cis*-retinoic acid to autologous stem cell transplantation has been shown to improve survival in patients with high risk neuroblastoma. In all treatments good remissions are often reached, but the recurrence rate is high.

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MALIGNANT TUMORS OF THE LIVER

Primary tumors of the liver are rare; over two-thirds of these tumors are malignant. Over 80% of malignant liver tumors in children are hepatoblastomas. The disease usually affects

children from infancy to 5 years of age. These may present as an asymptomatic abdominal mass; as disease progresses patients have abdominal pain, weight loss, vomiting and anorexia. Serum α fetoprotein (AFP) is a useful diagnostic marker for disease assessment during and after completion of therapy. Tumor thrombi may extend into hepatic veins and inferior vena cava. Liver may become involved due to metastasis from cancers which include lymphoma (Hodgkin and non-Hodgkin lymphoma) neuroblastoma, Wilms tumor and desmoplastic small cell tumor. Benign neoplasms of liver include mesenchymal hamartoma, hemangioma, hemangioendothelioma, adenoma and teratoma.

Diagnostic imaging includes CT or MRI of the abdomen along with the CT of the chest for evaluation of metastatic disease. Complete resection of the tumor either by partial hepatectomy or by liver transplantation is critical for successful treatment.

Hepatocellular carcinoma is an aggressive hepatic neoplasm affecting older children or adolescents. Children with biliary atresia, infantile cholestasis, glycogen storage disease and wide array of cirrhotic diseases are predisposed to developing hepatocellular carcinoma.

SOFT TISSUE SARCOMA

Pediatric soft tissue sarcomas are a group of malignant tumors that originate from primitive mesenchymal tissue and account for 6-7% of all childhood tumors. Rhabdomyosarcomas account for more than half of all cases of soft tissue sarcoma in children. Other soft tissue sarcomas include fibrosarcoma, synovial sarcoma and malignant peripheral nerve sheath tumors.

Soft tissue sarcomas may arise in any part of the body, most common by the trunk and the extremities. These neoplasms can present initially as an asymptomatic solid mass, or may be symptomatic because of local invasion to adjacent organs. Approximately 15-30% patients have metastatic disease at presentation, chiefly affecting the lung. Other sites for metastases include the skin, bone, liver, and lymph nodes. Treatment modalities include surgery, radiation and chemotherapy.

Rhabdomyosarcoma

Rhabdomyosarcoma, the commonest soft tissue sarcoma, is a malignant tumor of skeletal muscle. Almost half of these cases are diagnosed by 5 years of age and two-thirds by 10 years.

The chief sites are the head and neck (commonest), the genitourinary tract and the extremities. Orbital rhabdomyosarcoma presents in young children with proptosis or swelling of the eyelid. Genitourinary tumors may present as a pelvic mass, bladder and prostate enlargement or polypoid mass in the vagina. Almost one-fourth patients present with metastasis at diagnosis, commonly in lungs, bone marrow and bone. The major histologic types are: (i) Embryonal (60%), seen with tumors of head, neck and genitourinary tract, and has favorable prognosis; (ii) alveolar (20%) that is more common in older children, at the extremities and perineal region and has unfavorable outcome.

Rhabdomyosarcoma is curable in most children with localized disease who receive combined therapy with medications, radiotherapy and surgery, with more than 70% surviving 5 years after the diagnosis. Chemotherapeutic drugs include vincristine, actinomycin, cyclophosphamide and doxorubicin.

BONE TUMORS

Osteogenic sarcoma and Ewing sarcoma are two major bone tumors in children and adolescents. Both tumors occur commonly during the second decade of life and show male predominance.

Osteogenic Sarcoma

Its peak incidence is during adolescence, correlating with rapid bone growth. The distal femur and proximal tibia are the most frequent sites followed by proximal humerus and middle and proximal femur. Flat bones, e.g. vertebrae, pelvic bones and mandible are rarely affected. Patients present with a localized painful swelling that may be attributed to traumatic or infective conditions, delaying the diagnosis by months. Metastasis occurs early to the lungs and other bones. Germline mutations of tumor suppressor genes, including the retinoblastoma (*RB1*) gene are associated with increased incidence. Li-Fraumeni syndrome, associated with germline mutations of the tumor suppressor p53 gene, is characterized by increased incidence of breast cancer, soft tissue sarcoma, osteosarcoma, adrenocortical carcinoma and leukemia in first degree relatives. High dose radiation therapy, such as that for Ewing sarcoma or brain tumors, predisposes to development of osteosarcoma, either in or at sites distant from the radiation field. Benign bone lesions such as Paget disease, multiple hereditary exostoses, fibrous dysplasia and enchondromatosis may occasionally undergo malignant transformation to osteosarcoma.

Osteosarcoma is characterized by highly malignant pleomorphic spindle cells with malignant osteoid formation. Radiographic examination shows sclerotic or lytic bone lesions and periosteal new bone formation over the metaphyseal region. Biopsy is done to confirm the diagnosis. Imaging studies include CT chest and radionuclide bone scan to rule out metastasis; MRI provides an accurate assessment of tumor extent.

Successful treatment requires complete surgical resection followed by multiagent chemotherapy. Limb sparing surgery by wide resection of the primary tumor is followed by replacement of missing bone by prosthesis. Chemotherapeutic agents include doxorubicin, cisplatin, ifosfamide, cyclophosphamide and high dose methotrexate. The tumor is unresponsive to radiotherapy. With current regimens, more than two-thirds of patients without metastasis are cured.

Ewing Sarcoma

Ewing sarcoma occurs most often in the second decade, but can occur below the age of 10 years. They most often arise from flat bones such as pelvis, chest wall and vertebrae and the diaphyseal region of long bones. Common sites of metastasis are lungs and other bones; bone marrow metastasis is not uncommon. The typical presentation is with pain, swelling or a limp, often associated with fever and weight loss. Osteomyelitis and Langerhans cell histiocytosis particularly eosinophilic granuloma are the chief differential diagnosis (Fig. 21.9). Plain radiographs show destructive lesions of the



Fig. 21.9: Ewing sarcoma. Radiograph showing permeative lytic lesion with a prominent soft-tissue mass extending from the bone. Periosteal reaction is seen. The onion-skin (sunburst pattern) indicates an aggressive process suggesting Ewing sarcoma

diaphysis with multilayered or lamellated (onion skin) periosteal reaction.

Biopsy is necessary for confirmation, which shows monotonous population of small round blue cells that is differentiated from other round cell tumors by immunohistochemistry. Ewing sarcoma shows strong expression of surface glycoprotein CD99 and vimentin; reciprocal chromosomal translocation $t(11;22)(q24;q12)$ is pathognomonic and present in 85% cases. Chest CT, bone scan and bone marrow biopsy are performed to evaluate for metastasis.

These tumors are very well responsive to both chemotherapy and radiotherapy. Local surgery is an effective way to treat Ewing sarcoma, however surgical amputation is rarely indicated. Tumor control with radiotherapy requires moderately high doses ranging from 5500 to 6000 cGy. Multiagent combination chemotherapy includes vincristine, dactinomycin, cyclophosphamide and doxorubicin. In localized disease, without metastasis the cure rate is nearly 60% while in metastatic disease it is less than 30%.

BRAIN TUMORS

Tumors of the central nervous system (CNS) (brain, spinal cord) are the second most common neoplasms, accounting for 25% of all childhood cancers. Common brain tumors include low grade and high grade astrocytomas, medulloblastomas and ependymomas. Pediatric astrocytomas comprise a heterogeneous group of tumors including juvenile pilocytic astrocytomas (JPAs), low grade diffuse astrocytomas, gangliogliomas, oligodendrogliomas and mixed oligoastrocytomas. Medulloblastomas are malignant, tumors of cerebellum with over 70% of tumors occurring in children less than 16 years. Ependymomas are generally slow growing well circumscribed tumors that arise predominantly infratentorially in children with a peak incidence of 6 years of age.

The vast majority of pediatric CNS tumors is sporadic, with no known cause. Exposure of CNS to significant doses of radiation and presence of certain genetic syndromes (Table 21.24) increase the risk. Meningiomas



Fig. 21.10: Glioma of cerebellum with obstructive hydrocephalus in a 6-year-old boy with history of headache, vomiting and seizures for 6 months

and malignant gliomas arise within the radiation field several years or decades after radiation therapy. Children who have received cranial or craniospinal radiation for treatment of ALL are at risk. Approximately 15% patients with neurofibromatosis (NF1) develop optic gliomas during their lifetime; these usually have a benign course and may even regress spontaneously.

Clinical Features

Symptoms from Raised Intracranial Pressure (ICP)

Infratentorial tumors are more common than supratentorial tumors in children and hence more likely to develop acute or chronic hydrocephalus (Fig. 21.10). Recurrent headaches that are worse at night or early morning and worsen with lying down, early morning

Table 21.24: Genetic disorders associated with brain tumors

Disorder	Tumor	Other features
Neurofibromatosis type 1	Optic glioma	Autosomal dominant
Neurofibromatosis type 2	Acoustic neuromas, schwannoma	Peripheral nerve sheath tumors, cardiac sarcoma
Li-Fraumeni syndrome	Choroid plexus carcinoma	Sarcoma, adrenocortical cancer, breast cancer
Bilateral retinoblastoma	Pineal tumor: Trilateral retinoblastoma	Sarcoma
Tuberous sclerosis	Subependymal cell astrocytoma, malignant glioma	Autosomal dominant
Von Hippel-Lindau disease	Hemangioblastoma	Renal, adrenal and pancreatic tumors
Gorlin syndrome	Medulloblastoma	Very sensitive to radiation, basal cell carcinoma
Turcot syndrome	Medulloblastoma, malignant glioma	Adenomatous polyps in colon

vomiting, vision loss or features of VI nerve palsy and 'sunset sign' indicate raised ICP. Acute increase in ICP may present with Cushing triad of hypertension, bradycardia and altered pattern of respiration.

Symptoms from Compression or Infiltration

Headache can occur from direct compression of skull and meninges. Vomiting may be due to raised ICP but may occur due to direct infiltration of the vomiting centers at the base of fourth ventricle. Head tilt may occur as correction for diplopia arising from cranial nerve palsy. The diencephalic syndrome comprising of emaciation, euphoria and emesis is associated with tumors in the diencephalon. Parinaud syndrome of supranuclear vertical gaze palsy, with pupils that are reactive to accommodation but not to light is seen with tumors of the pineal region or upper brainstem.

Frontal lobe tumors may present with personality changes, seizures and headaches; tumors in the temporal lobe cause seizures and change in speech. Suprasellar tumors may be associated with endocrinopathies and visual changes. Multiple cranial nerve deficits are the classic presentation of brainstem gliomas, while nystagmus, ataxia and vomiting are present with cerebellar tumors. Spinal tumors may cause back pain, scoliosis, numbness, weakness and impaired bladder or bowel function.

Diagnosis

MRI, with and without contrast, is the imaging study of choice. CT scan is necessary in an acute presentation, where diagnosis is required urgently. While the distinction between benign and malignant tumors is critical, location of the tumor is an important determinant of prognosis. A benign tumor in an unresectable location may have as poor an outcome as a malignant tumor in a surgically accessible area of the brain. Patient age also determines the type of treatment and hence impacts the prognosis. Histological diagnosis is challenging and often requires use of special stains, immunohistochemistry and molecular testing.

Treatment

Treatment requires a multidisciplinary approach, with adequate use of surgery, chemotherapy and radiation. Complete surgical resection without damaging critical structures is the goal, but may be difficult to achieve depending on location of the tumor. Some patients need urgent surgical intervention to relieve raised intracranial pressure. With modern radiation therapy including intensity modulated radiation therapy and proton beam irradiation, exposure to normal tissue can be significantly reduced. Chemotherapy may be used concurrently with radiation therapy, including as a radiation sensitizer. Often high dose chemotherapy with autologous stem cell rescue is used for optimum treatment results. The efficacy of anti-

Table 21.25: Classification of histiocyte disorders

Dendritic cell disorders	Langerhans cell histiocytosis Secondary dendritic cell processes Juvenile xanthogranuloma Solitary histiocytoma with dendritic phenotype
Macrophage-related disorders	Hemophagocytosis syndromes (primary and secondary) Rosal-Dorfman disease Solitary histiocytoma with macrophage phenotype
Malignant histiocyte disorders	Monocyte related leukemias Extramedullary monocytic tumors Dendritic cell/macrophage-related histiocytic sarcoma

angiogenic therapy (bevacizumab), vascular endothelial growth factor (VEGF), in combination with chemotherapy is promising for management of high grade gliomas.

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HISTIOCYTOSIS

The childhood histiocytoses are a rare and diverse group of proliferative disorders characterized by infiltration and accumulation of histiocytes within various tissues (Table 21.25).

Table 21.26: Features of Langerhans cell histiocytosis

Non-specific symptoms	Fever, lethargy weight loss, diarrhea
Bone lytic lesions	Unifocal or multifocal Common sites: Skull, long bones, flat bones
Skin, soft tissue	Scaly erythematous lesions and red papules commonest on scalp
Lymph nodes	Enlargement in 50%
Endocrine (hypothalamopituitary axis)	Diabetes insipidus
Lungs	Asymptomatic; cough, respiratory distress, shortness of breath Radiologic features
Spleen	Enlarged in 30%
Liver	Enlarged in 20%; jaundice; sclerosing cholangitis
Bone marrow	Anemia, petechial rash, superadded infections, pancytopenia





Fig. 21.11: Langerhans cell histiocytosis. (a) Radiograph of skull showing lytic lesions; (b) Clinical photograph showing skin lesions and conjunctivitis.

Langerhans Cell Histiocytosis (LCH)

LCH is a rare non-malignant disease with unknown etiology characterized by a clonal proliferation of pathologic cells with the characteristics of Langerhans cells in single/multiple sites and an unpredictable course. The clinical presentation is heterogeneous ranging from single system involvement to a multisystem life threatening disease (Table 21.26). The hallmark of LCH is the presence of Birbeck granules (BG) on electron microscopy and positivity for S-100 protein and CD1a positivity. The number of Langerhans cells with BG can vary in different lesions. Langerin (CD207) is a type II transmembrane protein associated with BG and is presumed to be more sensitive and specific than CD1a.

The spectrum of LCH (eosinophilic granuloma, Hand-Schuller-Christain disease, Letterer-Siwe disease) reflects varying extents of the disease. The course of disease is unpredictable, varying from rapid progression and death, to repeated recurrence and recrudescence with chronic sequelae, to spontaneous regression and resolution. Patients with disease that is localized (skin or bone) have a good prognosis and are felt to need minimum or even no treatment. In contrast, multiple organ involvement, particularly in young children (under 2-year-old), carries relatively poor prognosis.

The most common involvement is of the skeleton (80%). Bone lesions can be single or multiple affecting skull bones, long bones, vertebrae, mastoid and mandible. The lesions may be painless or present with pain and local swelling; X-rays show sharp lytic lesions (Fig. 21.11a). Clinical manifestation includes vertebral collapse and spinal compression, pathological fractures in long bones, chronic draining ears and early eruption

of teeth. Other manifestations include seborrheic skin rash (Fig. 21.11b) in scalp area and back (60%), lymphadenopathy (33%), hepatosplenomegaly (20%), tachypnea, air leaks, parenchymal lung infiltrates (15%), jaundice, abdominal distension, neurodegenerative symptoms and features of malabsorption. Pituitary dysfunction may result in growth retardation and diabetes insipidus. Severe disease is characterized by fever, weight loss, malaise, failure to thrive and liver dysfunction. Liver involvement may result in sclerosing cholangitis and cirrhosis. Bone marrow involvement may lead to anemia and thrombocytopenia.

Diagnosis

The classical histopathologic feature of LCH is the presence of lesional histiocytes of LC phenotype, with varying proportion of macrophages, T lymphocytes, eosinophils and multinucleated giant cells. The cells show positivity to S-100, CD1a, and langerin (CD 207); BG are seen on electron microscopy. Diagnostic work up should include biopsy from most appropriate site, complete blood count, liver function tests, coagulation studies, skeletal survey, chest X-ray and urine specific gravity. These include ultrasound abdomen, CT chest and or abdomen and MRI brain. Bone marrow biopsies are required to exclude infiltration.

Treatment for localized disease or single bony lesion varies from observation, curettage, indomethacin, bisphosphonates, low dose radiation to systemic chemotherapy. Multisystem disease is treated with chemotherapy, combining vinblastine, prednisone and 6-mercaptopurine. Childhood LCH may have long-term sequelae some of which occur many years after completion of treatment.

Table 21.27: Diagnostic criteria for HLH

HLH diagnosis established, if one of the two is fulfilled
 A molecular diagnosis of HLH (e.g. *PERF, SAP, MUNC* mutations)
 OR

5 of the following 8 criteria are fulfilled

- Fever
- Splenomegaly
- Cytopenias in at least two cell lines
- Hemoglobin <90 g/L
- Platelets <100 × 10⁹/L
- Neutrophils <1 × 10⁹/L
- Hypertriglyceridemia and/or hypofibrinogenemia
- Fasting triglycerides >3 mmol/L (>265 mg/dL)
- Fibrinogen <1.5 g/L
- Hemophagocytosis in bone marrow, spleen or lymph nodes
- Low or absent activity of natural killer cells
- Ferritin >500 µg/L
- Soluble cD25 (soluble interleukin-2 receptor) >2400 units /mL

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSES (HLH)

HLH is an aggressive and potentially fatal syndrome which results from an inappropriate prolonged activation of lymphocytes and macrophages (Table 21.27). HLH is

attributed to defects in function of natural killer and cytotoxic cells, leading to pathological activation of T cells and macrophages and production of proinflammatory cytokines (interferon gamma, tumor necrosis factor alpha and interleukins). Young children with HLH and *kras* gene mutations, or a family history of HLH are described as having primary HLH. Older children with HLH or children without identifiable mutations are described to have secondary or acquired HLH, secondary HLH to infection or other stimuli (e.g. juvenile rheumatoid arthritis, SLE). Diagnostic criteria of HLH is shown in Table 21.27.

ONCOLOGIC EMERGENCIES

Oncologic emergencies may present at diagnosis of the malignancy, during course of the disease or as a consequence of therapy. A solid tumor may invade or compress vital organs like trachea, esophagus or superior vena cava. Effusions into the pleural space or pericardium may compromise functions of lung and heart. Metastasis into the brain may lead to cerebral edema and features of raised intracranial tension. Spinal cord tumor involvement may lead to cord compression. Bone marrow involvement results in anemia, bleeding due to thrombocytopenia or coagulation abnormalities (disease/chemotherapy), leukostasis, thrombosis, cerebrovascular episodes and infections.

Table 21.28: Common oncologic emergencies: Clinical features and treatment

Emergency	Manifestation	Illness	Treatment
Tumor lysis syndrome	Hyperkalemia (arrhythmia), hyperuricemia, hyperphosphatemia, hypocalcemic tetany, metastatic calcification, renal failure	ALL, AML, NHL Burkitt lymphoma	Hydration, allopurinol, rasburicase, hemodialysis
Hyperleukocytosis WBC >10 ⁵ /mm ³	Thrombosis, stroke, pulmonary infiltrate, hypoxia	Leukemia	Hydration, hydroxyurea Leukopheresis, chemotherapy
Superior vena cava/mediastinal syndrome	Swelling of face and neck; proptosis; difficulty in lying flat, breathing and swallowing; hoarse voice, Horner syndrome, wheezing, effusion (pleural/pericardial), features of CO ₂ retention (anxiety, confusion, lethargy, headache, syncope)	NHL, ALL, germ cell tumor	Prompt tissue diagnosis Steroids: first line of management Chemotherapy, radiation (rarely used in children) Intravenous lines in lower limb Monitor for tumor lysis
Spinal cord compression	Paraplegia, back pain, urinary retention, back pain, loss of deep tendon reflexes, hypotonia	Neuroblastoma Ewing sarcoma Lymphoma of vertebral body	Prompt therapy with dexamethasone Surgery occasionally required Definitive therapy of tumor
Increased intracranial pressure	Headache, emesis, hypertension, bradycardia, III and VI nerve palsy, seizures	Medulloblastoma Astrocytoma Brainstem glioma	Dexamethasone, surgical intervention, anticonvulsants
Febrile neutropenia	Oral or axillary temperature >38.3°C (101°F), or two consecutive temperature >38°C (100°F) in 12 hours period lasting at least 1 hour Neutropenia: Absolute neutrophil count <500/mm ³ or <1000/mm ³ with expected decline sepsis, shock, pneumonia, typhilitis (inflamed cecum), DIC	Child with malignancy on chemotherapy	Therapy with antibiotic(s) and antifungal medications after 3 days of fever
Typhilitis	Fever, neutropenia, acute abdominal pain, may progress to bowel infarction	Acute leukemia solid tumors	Supportive care, IV antibiotics consider G-CSF

Hormonal problems can occur because of paraneoplastic secretions (Table 21.28). Metabolic complications may occur prior to/at onset of chemotherapy following lysis of tumor cells. Therapy related complications include myocardial dysfunction (anthracyclines), extravasation of drugs (anthracyclines, vinca alkaloids), hemorrhagic cystitis (cyclophosphamide), cerebrovascular accidents (methotrexate, l-asparaginase) and pancreatitis (l-asparaginase, corticosteroids). Early diagnosis and urgent management of these conditions will save lives and allow for treatment of the underlying malignancy.

Suggested Reading

- Seth R, Bhat AS. Management of common oncologic emergencies. *Indian J Pediatr* 2011; 78(6):709–17.
- Seth R, Singh P, Puri K, Arora A, Rathore AS. Morbidity profile and outcome of hyperleukocytosis in childhood acute leukemia: experience from a tertiary center. *Int J Hematol Res.* 2015; 26:90–4.

LATE EFFECTS AND SURVIVORSHIP

With refinements in diagnostics and advances in therapeutics and supportive care the overall survival of childhood malignancy has increased significantly over the past few decades. Over 80% children and adolescents with cancer survive 5 or more years from diagnosis in many centers and are effectively cured of the disease. This is however at the cost of increased morbidity in the form of various late effects of cancer treatment. It is estimated that a third to half of childhood cancer survivors will experience a late term effect of cancer therapy; of which up to half may be life threatening.

The main goals of the Cancer Survivorship Program are to improve the health and well-being of childhood cancer survivors by promoting adherence to a schedule of follow-up appointments and routine screening tests, educate patients, parents and healthcare professionals about the

long-term effects of cancer treatment, integrate them appropriately into society, provide referrals to specialists as needed, offer psychological counseling and transition of patients to adult care when ready. The term long-term survivor refers to patients who are disease free for a minimum period of 5 years. 92% children who were disease free up to 5 years, were alive at 15 years after diagnosis.

Late Effects Associated with Childhood Cancer

The common late effects of pediatric cancer comprise deficits in growth and development, organ function, reproductive capacity and health of offspring and development of subsequent neoplasms.

- Growth and development:** The components affected include linear growth, sexual maturation, musculoskeletal development, skeletal maturation, intellectual function, emotional and social maturation (Table 21.29).
- Organ function:** Exposure to higher cumulative chemotherapy and radiation doses required for more biologically aggressive refractory disease increases the risk of both vital and nonvital organs toxicity. These include anthracycline related cardiotoxicity, pulmonary function abnormalities and, chronic liver disease.
- Reproductive capacity and pregnancy outcomes:** Reproductive functioning may be affected by various anticancer modalities (surgery, chemotherapy and radiation). Alkylating chemotherapy is toxic to the gonads. They produce a dose related gonadal germ cell injury. In boys, alkylators damage germ cells leading to infertility. Compared to boys, girls maintain an ovarian function at higher cumulative doses of alkylating agents and if dysfunction occurs it is often reversible.

Table 21.29: Late effects of pediatric cancer therapy on growth and development

Domain	Specific effect	Predisposing therapy	Modifying host factors
Linear growth	Delayed/accelerated growth Short stature; growth failure	Radiation of hypothalamic-pituitary axis	Younger age poses higher risk
Sexual maturation	Delayed puberty; hypogonadism Precocious puberty	Alkylating agents; radiation of hypothalamic-pituitary axis	Boys at higher risk for gonadal injury Girls at higher risk for precocious puberty
Musculoskeletal development	Hypoplasia, fibrosis Uneven/reduced skeletal growth	Radiation impacting bones and soft tissues	Younger age at irradiation
Skeletal maturation	Osteopenia Osteoporosis Osteonecrosis	Corticosteroids Methotrexate	Younger age at irradiation
Intellectual function	Neurocognitive deficits; reduced IQ; behavioral problems	Radiation >40 Gy; corticosteroids	Older age (>10 yr)
Emotional and social maturation	Mental health disorders Educational problems Vocational issues; unemployment Psychosocial issues	High dose methotrexate, cytarabine, cranial irradiation Any cancer experience	Younger age at irradiation Girls and CNS tumor survivors at increased risk

Sperm production is reduced in a dose dependent manner following radiation. Reversible azoospermia is seen at doses of 1–3 Gy but is irreversible at higher doses (>3 Gy). Prepubertal status does not protect from germ cell injury. Abdominal, pelvic or spinal radiation also contributes to germ cell depletion in girls. Ovaries of younger girls are more resistant to radiation damage as compared to ovaries of older women. Radiation doses >20 Gy cause irreversible ovarian failure and doses between 20 and 30 Gy delay pubertal development.

- iv. **Second malignant neoplasm (SMN):** Pediatric cancer survivors are at an increased risk for development of second cancers; host factors (genetics, immune function, and hormonal status), primary cancer therapy, environmental exposure and lifestyle factors play a role in the occurrence of secondary neoplasms. Common malignancies that occur as second neoplasms include acute myeloid leukemia (AML) including myelodysplastic syndrome and solid tumors. Secondary AML commonly develops in association with use of alkylating agents or topoisomerase II inhibitor therapy. Radiation therapy is also implicated in the occurrence of SMNs like acute leukemia and solid tumors involving the breast, thyroid, CNS, bones, and soft tissues. The latency for occurrence of SMN varies from 2–3 years to as long as 10 years. Breast cancer is the most frequently reported secondary solid tumor in childhood cancer survivors with incidence varying from 10 to 20% by 20 years from radiation.

BONE MARROW TRANSPLANTATION (BMT)

BMT is the established therapy for congenital or acquired disorders of the hematopoietic system and hematologic malignancies.

Allogenic hematopoietic stem cell transplantation (HSCT) occurs between a donor and a recipient who are immunologically identical. It can lead to graft vs host disease (GvHD), where immune cells from the donor react against antigens on host cells and graft rejection where immune competent host cells destroy donor stem cells before the graft is established. The risk of relapse of malignant disease is lower following allogenic HSCT because of immune effects of the graft on malignant cells.

Autologous HSCT involves the removal and storage of patient's own stem cells, which subsequent re-infusion following high dose myeloablative therapy. Higher doses of myeloablative chemotherapy can be administered than is otherwise possible. There is no risk of graft rejection or GvHD. This approach was initially restricted to solid tumors (neuroblastoma, germ cell tumors, retinoblastoma, medulloblastoma) where bone marrow was free of disease, but is now being used for hematological malignancies and lymphomas.

Peripheral HSCT: CD34 positive cells are mobilized from marrow into circulation in sufficient numbers for clinical use by use of recombinant human hematopoietic growth factors. These cells can establish durable marrow engraftment.

Umbilical cord transplantation: Cord blood banks are another source of stem cells. The graft composition and biological properties of umbilical cord stem cells are different from adults. Cord blood transplantation is associated with enhanced engraftment and reduced incidence of GvHD.

Uses of BMT

Allogenic BMT is indicated in all patients of acute myeloid leukemia after the first remission, except these with favorable cytogenetics and good risk group which includes acute promyelocytic leukemia with translocation t(15;17), t(8;21) and inversion (16) or low levels of minimal residual disease.

BMT is indicated in patients with acute lymphoblastic leukemia during their first remission and a risk factor including hypodiploidy, t(4;11) biophenotypic leukemia and high minimal residual disease after induction. Transplantation is also indicated after second and subsequent remissions.

BMT may also be considered for various non-malignant disorders, e.g. severe combined immunodeficiency, Wiskott-Aldrich syndrome, severe aplastic anemia and storage disorders.

Suggested Reading

- Guilcher GMT. Hematopoietic stem cell transplantation in children and adolescents. *Pediatr Rev* 2016;37:135–44.

Rheumatological Disorders

Surjit Singh

ARTHRITIS

Approach to Diagnosis

Arthritis is a common complaint in children. It is said to be present if there is swelling or effusion in a joint or if there are any two of the following 4 features: (i) Limitation of range of motion, (ii) pain, (iii) tenderness and (iv) increased heat. It can be secondary to an underlying illness (infectious or noninfectious), or may be a primary disease in itself. Clinical assessment based on a good history and physical examination provides more diagnostic clues than indiscriminate laboratory tests. A convenient way to classify arthritis is based on the duration of illness at presentation (Table 22.1).

Table 22.1: Classification of arthritis

Acute arthritis (usually <2 weeks)

Acute rheumatic fever
 Transient ('toxic') synovitis
 Kawasaki disease, Henoch-Schönlein purpura
 Septic arthritis (*S. aureus*, *H. influenzae*, *N. meningitidis*)

Subacute arthritis (2–6 weeks)

Reactive arthritis
 Systemic lupus erythematosus, dermatomyositis or polyarteritis nodosa
 Associated with leukemia or neuroblastoma
 Associated with Lyme disease or brucellosis
 Sickle cell disease
 Associated with hypogammaglobulinemia

Chronic arthritis (>6 weeks)

Juvenile idiopathic arthritis
 Ankylosing spondylitis
 Tubercular arthritis
 Legg-Calvé-Perthes disease
 Psoriasis

Transient Synovitis

This is a common condition in young children and is characterized by sudden onset of pain in hips, thighs or knees following an upper respiratory catarrh. It is a self-limiting disorder, lasts only 2–4 days and must not be confused with septic arthritis or acute osteomyelitis. Skin traction and judicious use of nonsteroidal anti-inflammatory drugs (NSAIDs) brings prompt relief.

Septic Arthritis

This is usually seen in neonates and infants. It presents almost always as a monoarthritis and is accompanied by fever, tenderness and limitation of joint movement. Causes include gram-negative bacilli, group B streptococci (in neonates), *Haemophilus influenzae* type B and *Streptococcus pneumoniae* in infants, and *Staphylococcus aureus* in older children. Ultrasonography, magnetic resonance imaging and radionuclide scans provide useful clues to the diagnosis. A diagnostic arthrocentesis is necessary to confirm the diagnosis (Table 22.2). Appropriate antimicrobials, aspiration and, in some cases (e.g. the hip joint), open drainage are required for treatment.

Tubercular Arthritis

This has become less common in our experience. It can result from actual infection with *Mycobacterium tuberculosis* or from an allergic phenomenon (Poncet disease). The former usually presents as mono-arthritis (e.g. hip or ankle joint) while the latter presents as polyarthritis with a strongly positive tuberculin reaction. Arthrocentesis may be diagnostic (Table 22.2).

Reactive Arthritis

This is not as common in children as in adults. It is diagnosed on the basis of Berlin criteria: (i) peripheral arthritis, usually lower limb, asymmetric oligoarthritis; (ii) evidence of preceding gastrointestinal or genitourinary infection (usually by *Shigella*, *Chlamydia* or *Yersinia*), in absence of clinical symptoms and (iii) exclusion of other arthritides.

Table 22.2: Synovial fluid characteristics in childhood arthritides

Type of arthritis	Physical characteristics	Cytology	Biochemistry	Comments
Septic arthritis	Turbid; serosanguineous	Polymorphonuclear cells present; Gram stain may be positive	Glucose reduced; protein elevated	Synovial fluid culture may be positive; synovial fluid, if inoculated in blood culture bottles, increases the yield
Tuberculous arthritis	Opaque	Lymphocytes present; stain for acid fast bacilli may be positive	Glucose may be normal; protein elevated	Polymerase chain reaction may be positive
Juvenile inflammatory arthritis	Cloudy	Polymorphonuclear cells present; Gram stain negative	Glucose low; protein elevated	Fluid characteristics often mimic those of septic arthritis
Systemic lupus erythematosus	Clear	Lymphocytes present; LE cell phenomenon may be positive	Protein normal or elevated; glucose may be normal	Synovial fluid complement C3 may be low

A small proportion of children with acute lymphocytic leukemia show bone and joint pains. Bone pain, that is more marked at night, is the predominant complaint in affected children. Hemogram shows lymphocytic predominance and thrombocytopenia, in contrast to a polymorphonuclear predominance and thrombocytosis characteristic of juvenile idiopathic arthritis. A bone marrow examination is required to confirm the diagnosis. X-linked agammaglobulinemia (Bruton disease) may sometimes present as an unusual 'aseptic' arthritis (due to *Mycoplasma* infection), but accompanying respiratory infection is usually present.

Arthritis can, at times, be the presenting complaint of hemophilia or human immunodeficiency virus infection.

Legg-Calvé-Perthes Disease

This is characterized by an avascular necrosis of the femoral head, occurring usually in boys 5–10 years of age. It may be a manifestation of an underlying hypercoagulable state (hypofibrinolysis or deficiency of protein C or S). Familial occurrence is common and the condition is bilateral in 10% patients. Affected children present with a painful limp. Initial X-rays may be normal. Isotope bone scans and magnetic resonance imaging are required to confirm the diagnosis. Subsequent X-rays show a characteristic sequential progression: (i) Widening of joint space, (ii) fragmentation of epiphysis with patchy areas of increased lucency or density, (iii) abnormalities of shape of femoral head and neck, and (iv) deformed head. Treatment options include femoral varus osteotomies or containment splints.

Juvenile Idiopathic Arthritis

The term juvenile idiopathic arthritis (JIA) was proposed by the Pediatric Standing Committee of the International League of Associations for Rheumatology (ILAR). It refers to a group of conditions characterized by chronic inflammatory changes of the joints. It is defined as arthritis

of one or more joints with onset below 16 years of age and persisting for at least 6 weeks. It has the following subtypes:

- i. Systemic
- ii. Oligoarthritis: (a) persistent (b) or extended
- iii. Polyarthritis: Rheumatoid factor negative
- iv. Polyarthritis: Rheumatoid factor positive
- v. Psoriatic arthritis
- vi. Enthesitis-related arthritis
- vii. Undifferentiated arthritis: that (a) fits no other category; or (b) fits more than one category

JIA is not rare; its estimated prevalence ranges from 0.4 to 1.3 per 1000 children below 16 years of age. It is the commonest rheumatological disorder of childhood and one of the most common causes of disability, chronic morbidity and school absenteeism. While Western studies suggest that JIA is more common in girls, in India, female predominance is not marked.

Systemic JIA (sJIA) is now considered to be a separate disease altogether. It is classified as an auto-inflammatory disorder in which the innate immune system is primarily affected unlike other types of JIA which represent defects of acquired immunity. The ILAR definition for sJIA requires that fever be present for at least 2 weeks and should be accompanied by one or more of the following: Evanescent rash, generalized lymphadenopathy, hepatosplenomegaly or serositis.

Etiology

The immune system is intimately involved in the evolution of JIA. HLA DR5 and DR8 are linked to early onset oligoarthritis (seen more often in girls), B27 to late onset oligoarthritis (seen more commonly in boys) and DR4, Dw4 and DR1 to rheumatoid factor positive polyarthritis. JIA is not a homogeneous disease and the different subtypes may represent separate clinical conditions.

The etiopathogenesis of JIA remains an enigma. Several environmental triggers (e.g. infection with rubella virus,

parvovirus B19, *M. tuberculosis*, *Mycoplasma pneumoniae* and enteric organisms, physical trauma or psychological stress) are linked to the onset of JIA, but their exact role is not clear. Cytokines like tumor necrosis factor- α (TNF- α), IL-6 and IL-1 have to have an important role to play in the pathogenesis of the disease. A number of auto-antibodies (for instance, antinuclear antibody) may be seen in the sera of children with JIA. The classical IgM rheumatoid factor is almost never detectable in preschool children with JIA. Older girls with polyarticular small joint disease of the hands (especially involving the metacarpophalangeal and proximal interphalangeal joints) may, however, be RF positive.

22

Clinical Subtypes

Three major types of onset are described according to the presentation during the first 6 months of disease, namely systemic JIA (with fever and rash), oligoarthritis (4 or fewer joints involved) and polyarthritis (more than 4 joints involved).

Systemic JIA (sJIA): About 5–15% of patients with JIA may have acute onset disease with prominent systemic features. These systemic features may sometimes precede joint manifestations by weeks or months. This condition should, therefore, be considered in differential diagnosis of any child with prolonged fever. The illness can occur at any age and is more common in boys.

It usually begins as an intermittent fever with a characteristic twice daily peak. Fever is generally more prominent in evening. It is accompanied by an evanescent maculopapular truncal rash. The rash may be difficult to recognize in individuals with dark skin. Affected children show marked irritability that decreases with subsidence of fever. Serosal involvement (in the form of pericarditis or pleuritis) may be prominent. Hepatosplenomegaly and lymphadenopathy are common at presentation and can lead to diagnostic confusion. There is moderate neutrophilic leukocytosis and an elevated erythrocyte sedimentation rate along with thrombocytosis. Rheumatoid factor is negative.

Oligoarthritis: Oligoarthritis is the most frequent type of JIA accounting for approximately 60–70% of patients. Four or fewer joints (usually large) are affected during the first 6 months of disease. Joint swelling, rather than joint pain, is the usual complaint. Two subtypes are described: The term persistent (if number of affected joints continues to be 4 or less) and extended (if number of affected joints exceeds 4 during the disease course).

Oligoarthritis is more common in young girls, typically 3–5 years of age. Asymmetric involvement of knee or ankle is characteristic. Small joints of hands and feet are not involved. Asymptomatic, and potentially blinding, iridocyclitis can be seen in 25% patients with early onset oligoarthritis, and is especially common in girls with antinuclear antibody (ANA) positivity.

Polyarthritis: Polyarthritis occurs in 25–30% of patients and is more common in girls. Joint pain, out of proportion to the degree of joint swelling, is the usual complaint. Fever and malaise can be significant. Two subtypes are known:

Rheumatoid factor negative: This subtype may occur at any age in childhood. Knees, wrists and hips are the joints usually affected. Small joints of hands and feet are less commonly involved and rheumatoid nodules are not seen. Joint disease in this subtype of JIA is far less severe than that seen in patients who are rheumatoid factor positive.

Rheumatoid factor positive: Age at onset is late childhood or early adolescence. The arthritis is symmetrical, additive, severe and deforming and typically involves small joints of hands, especially the metacarpophalangeal and the proximal interphalangeal. Cervical spine and temporomandibular joints can also be affected. This subtype is the only category of JIA which is somewhat similar phenotypically to adult onset rheumatoid arthritis. Rheumatoid nodules are present in some patients and they usually indicate severe disease.

Psoriatic arthritis: Psoriatic arthritis is said to be present when there is arthritis in association with psoriasis or any 2 of the following features—dactylitis, nail pitting and psoriasis in a first degree relative. Arthritis may precede, accompany or follow occurrence of psoriasis in children. Clinical features suggestive of psoriatic arthritis include simultaneous occurrence of small and large joint arthritis or involvement of distal interphalangeal joints.

Enthesitis-related arthritis: This condition is more common in boys, typically older than 8 years. Asymmetric large joint (e.g., knee, ankle, hip) involvement of lower extremity is characteristic. Many children are HLA B27 positive, and a proportion of these may go on to develop ankylosing spondylitis later as adults. However, sacroiliitis and spondylitis are usually not significant till late adolescence. Self-limiting acute symptomatic iritis may occur in some patients but it does not progress onto the chronic iridocyclitis seen in oligoarthritis of young girls. A family history of ankylosing spondylitis, psoriasis, Reiter disease and low back pain may be obtained in these children.

Laboratory Investigations

The clinician should recognize the differing patterns of joint involvement in various types of JIA. This 'pattern recognition' is often the most important diagnostic clue. Laboratory investigations may be of a little or no help in arriving at a diagnosis.

Synovial fluid aspiration for microscopy and culture is indicated in children with monoarthritis because septic arthritis may need to be excluded (Table 21.2). Complete blood counts should be requested along with an erythrocyte sedimentation rate. Acute lymphocytic leukemia can sometimes have an arthritic presentation,

and such children may be mistakenly diagnosed as having JIA. Bone marrow aspiration is therefore necessary if use of glucocorticoids is being contemplated for treatment of JIA.

C-reactive protein measurement is a surrogate marker of disease activity and is helpful on follow-up. Plain radiographs of affected joints are obtained at time of initial diagnosis and may be repeated for assessment of erosive disease. It should be noted that screening for rheumatoid factor is not a useful test for diagnosis of arthritis in young children, but it is an important prognostic factor in situations where it is positive.

Treatment

Management of JIA is multidisciplinary. Physiotherapy and occupational therapy should be tailored to specific needs of an individual child, in order to prevent deformities and facilitate 'mainstreaming' and rehabilitation. Physical therapy helps in relieving pain, maintenance of posture and joint mobility, improves muscle strength and prevents fixed flexion deformities. All patients with JIA need to be assessed by an ophthalmologist so that uveitis can be detected early and treated appropriately. Children with oligoarthritis need regular ophthalmological follow-up as uveitis can develop later.

Medical therapy: NSAIDs are the mainstay of symptomatic management. The conventional NSAIDs inhibit both isoforms of the enzyme cyclo-oxygenase, i.e. COX-1 (constitutive; mediates physiologic prostaglandin production necessary for gastrointestinal mucosal integrity and adequacy of renal blood flow) and COX-2 (inducible; mediates pathologic prostaglandin production, especially at sites of inflammation). NSAIDs commonly used in children are naproxen and ibuprofen. Indomethacin is believed to be of particular use in enthesitis related arthritis. Doses of commonly used NSAIDs are given in Table 22.3.

Development of Reye syndrome is a distinct possibility while a child is receiving NSAIDs, especially if there is an intercurrent viral illness. All children with NSAIDs must be monitored for gastrointestinal adverse effects. The recently introduced selective COX-2 inhibitors (e.g.

rofecoxib, valdecoxib) have lower gastrointestinal adverse effects, but are not recommended for use in children. Although the mechanism of action of all NSAIDs is the same, idiosyncratic responses are well known and a given patient may respond to one NSAID and not to the other. Response to therapy is usually slow and this fact must be explained to the parents. Treatment must continue for at least 4–6 weeks before a decision to switch over to another NSAID is made.

Disease modifying anti-rheumatic drugs (DMARDs) need to be started in almost all children with polyarthritis. Weekly methotrexate (15–25 mg/m²/week given subcutaneously or orally) has simplified management of severe forms of JIA. Children seem to tolerate methotrexate better than adults and have fewer adverse effects. Once the child is in stable remission (usually achieved after several months), the drug can be tapered to the minimum effective dose and then stopped. Methotrexate should always be given under close medical supervision. Periodic testing of liver functions is mandatory. Development of hepatic fibrosis, a dreaded adverse effect, is uncommon. Hydroxychloroquine is a useful adjunct and is often used along with methotrexate. Leflunomide, an inhibitor of pyrimidine synthesis, has been used in adults with rheumatoid arthritis.

Intra-articular injections of glucocorticoids (usually triamcinolone) are the preferred therapy for children with oligoarthritis who do not respond to an initial trial of NSAIDs. Systemic glucocorticoids (usually prednisolone 1–2 mg/kg/day; occasionally methylprednisolone 10–30 mg/kg) are necessary for severe unremitting arthritis, systemic manifestations (e.g. pericarditis, myocarditis, vasculitis) and rapidly progressive disease. Prednisolone, when used in this manner, is usually given as bridge therapy for a few weeks while awaiting the clinical response of methotrexate.

Iridocyclitis warrants therapy with local steroid instillation and mydriatic eye drops. Weekly methotrexate therapy is required for patients with severe uveitis.

Newer modalities of treatment include recently introduced biological agents like anakinra (IL-1 receptor antagonist); canakinumab (monoclonal antibody to IL-1); tocilizumab (monoclonal antibody to IL6 receptor); infliximab, golimumab and adalimumab (monoclonal antibodies to TNF- α); etanercept (recombinant soluble TNF receptor p75 fusion protein) and abatacept (inhibitor of T cell activation). Etanercept and infliximab are powerful biological agents against TNF- α . While etanercept has been used in children with polyarthritis not responding to methotrexate, infliximab has been more commonly used in adults with spondyloarthritis. Tocilizumab and anakinra have found favour in children with severe forms of sJIA. While these biologics are now being increasingly used as first line therapy in children with JIA, long-term safety of these products remains unclear.

Table 22.3: Doses of commonly used NSAIDs

	Dose, mg/kg/day	Maximum dose, mg/day	Frequency of administration
Naproxen	15–20	750	Twice daily
Ibuprofen	35–45	2400	Four times daily
Indomethacin	1–2	150	Three times daily
Diclofenac	2–3	150	Four times daily
Piroxicam	0.3–0.6	20	Once daily

The analgesic dose is usually half the anti-inflammatory dose

Course

Oligoarthritis usually has a good prognosis but localized deformities can develop due to asymmetric growth of limbs. Children with enthesitis related arthritis can develop spondylitis and sacroiliitis later, especially if they are HLA B27 positive.

Children with rheumatoid factor positive polyarthritis have a disease pattern similar to adults and show erosive and deforming arthritis. Prognosis is better for seronegative polyarthritis as remissions are obtained more often and residual joint lesions may be minimal.

The course of systemic onset disease can be extremely variable and response to therapy is not always satisfactory.

Inappropriately treated or untreated patients with JIA may develop flexion contractures of hips, knees and elbows, resulting in permanent disability. Neck stiffness is an especially debilitating problem and can result in torticollis. Temporomandibular joint involvement results in restricted opening of the mouth and may require surgical intervention.

Complications

Anemia, due to chronic ongoing inflammation, is almost always present in children with persistent active arthritis and serial hemoglobin levels mirror disease activity. Blood loss induced by NSAIDs can also be a contributory factor for the anemia. Chronic anterior uveitis may be clinically silent and potentially blinding. Girls below 6 years of age with oligoarthritis, and who have antinuclear antibodies, are at the highest risk of developing this complication.

Children with sJIA are especially prone to develop macrophage activation syndrome. This is a potentially fatal complication that presents with unremitting fever, sudden onset icterus, bleeding tendency, leukopenia, thrombocytopenia, hypofibrinogenemia, elevated triglycerides and raised ferritin levels. Prompt administration of intravenous methylprednisolone pulses can be life saving.

Growth disturbances, limb length discrepancies and joint contractures can be seen in children with long-standing disease. Growth failure may occur secondary to severe inflammation or treatment with glucocorticoids. Treatment with recombinant human growth hormone may be an option in children with growth disturbances. Secondary amyloidosis is a rare complication that presents with asymptomatic proteinuria and hypoalbuminemia, and is often irreversible.

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is an autoimmune disorder characterized by inflammation of connective tissues and blood vessels resulting in multisystem involvement. Clinical manifestations are variable and the course unpredictable. Childhood SLE is usually more

severe and has a poorer prognosis than adult SLE. The hallmark of SLE is the presence of antinuclear antibodies (ANA). Marked female predominance characteristic of adult SLE is usually not apparent in young children.

Diagnosis

Diagnosis of SLE is facilitated by Systemic Lupus International Collaborating Clinics (SLICC) criteria (Table 22.4). However, SLE is always a clinical diagnosis—the criteria merely provide helpful guidelines for reaching a diagnosis. In many patients, especially children, treatment may have to be initiated even when they do not fulfil the requisite criteria.

The malar rash, which is virtually pathognomonic of SLE, may not be apparent initially. It involves the cheek, bridge of nose and lower eyelids but characteristically spares the nasolabial folds (Fig. 22.1a). Discoid lesions are rare in childhood onset SLE. Oral ulcerations may involve the buccal mucosa or palate and are usually painless. Some children may have prominent frontal alopecia (Fig. 22.1b). Arthritis is generally mild and always non-erosive.

Renal involvement is a dreaded complication of SLE and one of the commonest causes of mortality in children. Lupus nephritis is conventionally classified as follows: *Class I*: Minimal mesangial; *Class II*: Mesangial proliferative; *Class III*: Focal proliferative; *Class IV*: Diffuse proliferative; *Class V*: Membranous; *Class VI*: Advanced sclerosing. Class III and Class IV lesions (i.e., proliferative glomerulonephritis) require the most aggressive forms of therapy.

Table 22.4: SLICC Classification Criteria for SLE

Requirements: ≥4 criteria (at least 1 clinical and 1 laboratory criteria) OR biopsy-proven lupus nephritis with positive ANA or anti-dsDNA

Clinical criteria

- Acute cutaneous lupus
- Chronic cutaneous lupus
- Oral or nasal ulcers
- Non-scarring alopecia
- Arthritis
- Serositis
- Renal involvement
- Neurologic involvement
- Hemolytic anemia
- Leukopenia
- Thrombocytopenia (<100,000/cu mm³)

Immunologic criteria

- Antinuclear antibody (ANA)
- Anti-dsDNA
- Anti-Smith
- Antiphospholipid antibody
- Low complement (C3, C4, CH50)
- Direct Coombs' test (do not count in presence of hemolytic anemia)



Fig. 22.1: Systemic lupus erythematosus. Note (a) Malar rash; and (b) Frontal alopecia

Neurological features include psychosis, seizures, alterations in sensorium, focal deficits and chorea. There may be no correlation between severity of clinical involvement and findings on neuroimaging. Hematologic abnormalities include Coombs' positive hemolytic anemia, leukopenia, lymphopenia and thrombocytopenia. In addition, there may be coagulation abnormalities due to presence of antiphospholipid antibodies. Cardiac manifestations include pericarditis, myocarditis, or verrucous (Libman-Sacks) endocarditis. A few autoimmune diseases may coexist with lupus including autoimmune thyroid disease, celiac disease and overlap syndromes.

Serology

Almost all patients with SLE have demonstrable ANA. Presence of anti-double stranded (anti-ds) DNA antibodies is highly specific of SLE and usually correlate with disease activity. Anti-histone antibodies are present in neonatal lupus especially those associated with characteristic of drug-induced lupus. Anti-Ro antibodies are present in neonatal lupus especially those associated with congenital heart block. Anti-Sm antibodies are a marker for CNS lupus.

Treatment

Glucocorticoids and hydroxychloroquine form the mainstay of therapy. Prednisolone is started at doses of 1–2 mg/kg/day and gradually tapered over several months, according to disease activity. Arthritis usually responds to NSAIDs. Sunscreen lotions (with sun protection factor of 15–20) must be prescribed for all children with lupus and applied 3–4 times/day, even on cloudy days.

Life-threatening complications (e.g. class IV lupus nephritis, myocarditis, encephalopathy) require the use of intravenous pulses of methylprednisolone (30 mg/kg/day) for 3–5 days. Rituximab, a monoclonal antibody to CD20, has also been found to be effective in such situations.

Use of monthly pulses of IV cyclophosphamide (500 mg/m²) has considerably improved the long-term outcome in children with severe forms of lupus nephritis. Once remission is achieved, the patient can be maintained on mycophenolate mofetil or azathioprine. Mycophenolate mofetil is being increasingly used for therapy of severe forms of lupus nephritis in children.

Low dose prednisolone (2.5–5 mg/day) and hydroxychloroquine (5–6 mg/kg/day) may need to be continued for several years depending on the clinical response.

Infections must be treated aggressively with appropriate antimicrobials and the steroid dose increased during such episodes. With appropriate therapy, the long-term outlook of SLE in children is quite encouraging.

Antiphospholipid Syndrome

Antiphospholipid syndrome is a common accompaniment of SLE but can be seen in association with other rheumatological disorders as well. The syndrome can, at times, arise *de novo* when it is known as primary antiphospholipid syndrome. It is a common cause of acquired hypercoagulable states in children and is manifest with venous and arterial thrombosis, livedo reticularis and thrombocytopenia. The presentation is sometimes catastrophic and may result in fatality. Laboratory diagnosis is suggested by a typical coagulation profile (normal prothrombin and prolonged partial thromboplastin times) and confirmed by detection of anticardiolipin antibodies (IgM and IgG), anti-β₂ glycoprotein 1 antibodies (IgM and IgG) and the lupus anticoagulant test. Treatment is with long-term oral anticoagulation.

JUVENILE DERMATOMYOSITIS

Juvenile dermatomyositis (JDM) is not merely a disorder of muscle and skin, but a multisystem disease characterized by nonsuppurative inflammation of striated muscle and skin, and systemic vasculopathy. Unlike

adults, pure polymyositis (i.e. with no accompanying skin involvement) is uncommon in children. The diagnosis of JDM can be made on basis of the following criteria:

- i. Characteristic heliotrope discoloration over the upper eyelids (Fig. 22.2a) or a scaly, erythematous rash over dorsal aspects of metacarpophalangeal and proximal interphalangeal joints (Gottron papules; Fig. 22.2b)
- ii. Symmetrical proximal muscle weakness
- iii. Elevated levels of muscle enzymes (creatine kinase, alanine and aspartate aminotransferases aldolase)
- iv. Electromyographic evidence of myopathy
- v. Muscle biopsy showing myonecrosis, myophagocytosis and perifascicular atrophy

A definite diagnosis of JDM can be made, if a child fulfils the first criterion along with any three of the remaining four and it is considered *probable* if two of the four criteria are met. Other dermatological changes include edema over eyelids, photosensitivity, truncal rash and calcinosis. Magnetic resonance imaging (MRI) shows characteristic hyperintense signals on T2-weighted images suggestive of muscle edema and inflammation while T1 weighted images may show fibrosis, atrophy and fatty infiltration. Muscle biopsy is rarely required for diagnosis.

Treatment is with pulse intravenous methylprednisolone (30 mg/kg/day) for 3–5 days followed by gradually tapering doses of oral prednisolone (1.5–2 mg/kg/day). Weekly methotrexate (15–25 mg/m²/week given subcutaneously or orally) is the mainstay of maintenance therapy. Usual duration of therapy is 18–24 months. Rapid tapering of steroids may result in disease relapse. Long-term prognosis is excellent, if treatment is started early.

SCLERODERMA

Scleroderma refers to hardening of the skin. It can be classified as follows:

- i. Systemic scleroderma (e.g. diffuse cutaneous, limited cutaneous)
- ii. Overlap syndromes
- iii. Localized scleroderma (e.g. morphea, linear scleroderma, eosinophilic fasciitis)

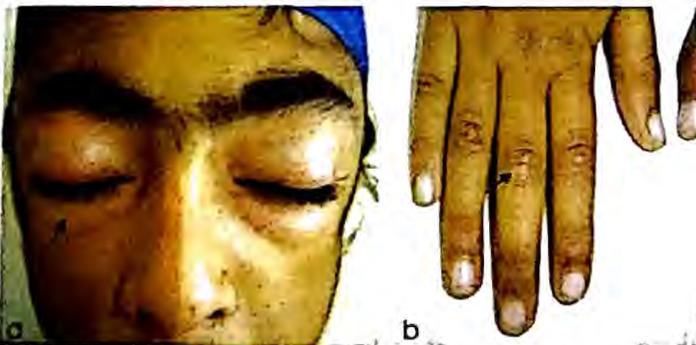


Fig. 22.2: Juvenile dermatomyositis. Note (a) Heliotrope rash; and (b) Gottron papules, indicated by black arrows

- iv. Chemically induced scleroderma (e.g. with polyvinyl chloride, pentazocine, bleomycin)
- v. Pseudosclerodermas (e.g. phenylketonuria, scleredema, progeria and porphyria cutanea tarda)

Diffuse cutaneous systemic scleroderma is usually associated with widespread visceral involvement including the gastrointestinal tract, heart, lungs and kidneys. It is believed that fetomaternal graft-versus-host reactions are involved in pathogenesis of this condition. Onset of disease is insidious and may be difficult to recognize in initial stages. The child presents with skin tightening (edema, atrophy and acrosclerosis), Raynaud phenomenon (i.e. blanching, cyanosis and erythema), soft tissue contractures, arthralgias and myalgias, dysphagia (regurgitation, reflux and aspiration), dyspnea (interstitial fibrosis, low diffusing capacity) and characteristic subcutaneous calcifications. Many children have abnormalities of nailfold capillaries, which can be seen as capillary dropouts and dilated loops with a nail-bed capillaroscope or +40 lens of an ophthalmoscope. Onset of hypertension and proteinuria usually indicates renal involvement, and should be a cause for concern.

Investigations show presence of ANA (with nucleolar pattern on immunofluorescence) and antibodies to Scl70 (DNA-topoisomerase I) or centromere. No form of drug therapy is curative. Penicillamine and colchicine can produce beneficial results in some patients, especially if used early in the course of disease. Monthly pulses of IV cyclophosphamide (followed by maintenance daily azathioprine or weekly methotrexate) can be life saving in patients with interstitial lung disease. Nifedipine is useful for management of Raynaud phenomenon while enalapril can result in control of blood pressure and stabilization of renal function. The latter is also the drug of choice for scleroderma renal crises. With appropriate management, 10 years survival rates of up to 90% have been reported in children.

Scleredema is a benign, self-limiting condition characterized by non-pitting indurated edema over face, neck, shoulders and chest, but excluding the hands and feet.

MIXED CONNECTIVE TISSUE DISEASE

This is a multisystemic overlap syndrome characterized by features of rheumatoid arthritis, systemic scleroderma, SLE and dermatomyositis occurring in conjunction with high titers of anti-ribonucleoprotein (RNP) antibodies (specific for U1 RNP). Nephritis is usually less common and less severe than in SLE. Many children show good response to low-dose glucocorticoids and NSAIDs. Oral weekly methotrexate is a useful therapeutic option. Treatment must be individualized and should focus on the particular disease component which is predominating in a given child.

VASCULITIDES

The vasculitides are best classified according to the size of the vessel involved:

- i. Large vessel (i.e. aorta and major branches) vasculitis e.g. Takayasu arteritis; giant cell arteritis
- ii. Medium vessel (i.e. coronary, renal, hepatic, mesenteric) vasculitis, e.g. Kawasaki disease, polyarteritis nodosa
- iii. Small vessel (i.e. arterioles, capillaries, venules) vasculitis, e.g. IgA vasculitis (Henoch-Schönlein purpura), granulomatosis with polyangiitis (Wegener granulomatosis), microscopic polyangiitis, Churg-Strauss syndrome, cutaneous leukocytoclastic angitis.

Takayasu Arteritis

This is characterized by a segmental inflammatory panarteritis resulting in stenosis and aneurysms of aorta and its major branches causing weak arterial pulses. It is believed to be the commonest cause of renovascular hypertension in India. It is classified according to the site of involvement: *Type I*: Aortic arch; *Type II*: Descending aorta; *Type III*: Aortic arch and descending aorta; *Type IV*: Aorta and pulmonary artery. Children with Takayasu arteritis often show a strongly positive tuberculin reaction. The classification criteria for childhood Takayasu arteritis are given in Table 22.5.

Diagnosis is confirmed by angiography. Treatment involves long-term immunosuppression with prednisolone and methotrexate (used in weekly doses). Mycophenolate mofetil has also been found to be useful. Angioplasty procedures are now being increasingly performed even in small children and show promising results. Cyclophosphamide or azathioprine may be required in children who fail to show an adequate response to steroids. Hypertension must be managed appropriately.

Kawasaki Disease

Kawasaki disease is an acute febrile mucocutaneous lymph node syndrome mainly affecting infants and young children. More than 80% of cases are seen in children under 5. It is the commonest vasculitic disorder of childhood and has replaced acute rheumatic fever as the leading cause of acquired heart disease in children in many countries. The basic lesion is a necrotizing vasculitis of

medium-sized muscular arteries (especially coronaries), which may result in aneurysms, dilations, and stenoses in untreated patients. In Japan, 1% of all children would develop Kawasaki disease before they reach 10 years of age. In India, this condition is now being increasingly recognized but the vast majority of patients still continue to remain undiagnosed probably because of lack of awareness amongst pediatricians.

It is important to remember that the diagnosis of Kawasaki disease is based entirely on recognition of a temporal sequence of characteristic clinical findings (Fig. 22.3) and that there is no specific laboratory test. The diagnostic criteria for KD are as follows:

- A. Fever lasting for at least 5 days
- B. Presence of any 4 of the following 5 conditions:
 - i. Bilateral nonpurulent conjunctival injection (without discharge)
 - ii. Changes of mucosae of oropharynx (e.g. injected pharynx, injected lips, strawberry tongue)
 - iii. Changes of peripheral extremities (acute stage: edema, erythema of hands or feet; convalescent stage: desquamation, which usually begins periungually)
 - iv. Polymorphous rash (never vesicular)
 - v. Cervical lymphadenopathy (at least 1 node ≥ 1.5 cm; usually unilateral)
- C. Illness not explained by any other known disease process.

These clinical features evolve sequentially over a period of days and all need not be present together at a given point of time. This partly explains the difficulty that the clinician experiences in arriving at a correct diagnosis. Most children have high grade fever and are extremely irritable. In fact it is this irritability that often provides the first clinical clue to diagnosis. Other characteristic clinical findings include perianal desquamation (in first few days of fever) and reactivation of BCG scar, usually seen in infants). Arthritis is often seen in children with Kawasaki disease and may result in diagnostic confusion. Hydrops of gall bladder can also occur. Sterile pyuria is common and, in the setting of ongoing fever, may lead to an erroneous diagnosis of urinary tract infection.

KD must be considered in differential diagnosis of all children, especially those below 5-year-old, who have fever without apparent focus lasting more than 5 days. Thrombocytosis with periungual peeling is characteristic of second week of illness. Beau lines may be seen during the convalescent phase (Fig. 22.4).

Treatment is with a single dose of intravenous immunoglobulin (2 g/kg) and aspirin in anti-inflammatory doses (30–50 mg/kg) until the child becomes afebrile. Low dose aspirin (3–5 mg/kg/day) is then continued for 4–6 weeks for its antiplatelet activity. In appropriately treated children, the long-term prognosis is excellent with less than 3% patients developing coronary artery abnormalities as compared to 15–25% in the untreated category.

Table 22.5: Classification criteria for childhood Takayasu arteritis

Angiographic abnormalities (conventional, CT or MRI) of the aorta or its main branches, plus at least one of the following 4 features:

- Decreased peripheral artery pulse(s) and/or claudication of extremities
- Blood pressure difference between both limbs >10 mm Hg
- Bruits over aorta and/or its major branches
- Hypertension



Fig. 22.3: Findings in acute phase of Kawasaki disease. (a) Red cracked lips; (b) Strawberry tongue; (c) Swelling on dorsum of hands; and (d) Periungual desquamation.



Fig. 22.4: Beau line in Kawasaki disease

Polyarteritis Nodosa

Polyarteritis nodosa (PAN) is rare in childhood. Clinical manifestations can be extremely variable because of multisystem involvement and include fever, hypertension (seen in 80%), abdominal pain, arthritis, myalgia, skin involvement (especially livedo reticularis,

Fig. 22.5a), neurological involvement (seizures, encephalopathy) and peripheral neuropathy (mononeuritis multiplex). Pathological diagnosis consists of demonstration of fibrinoid necrosis in medium-sized arteries with segmental involvement and a predilection for bifurcation of vessels. On angiography, aneurysms may be demonstrable in the renal arteries or celiac axis (Fig. 22.5b). The classification criteria for childhood PAN have been revised (Table 22.6). Treatment consists of long-term immunosuppression (initially with cyclophosphamide and prednisolone, followed by azathioprine).

IgA Vasculitis (Henoch-Schönlein purpura)

IgA vasculitis is a common vasculitic disorder of childhood and is characterized by presence of a non-thrombocytopenic and usually palpable purpura, transient arthralgia (occasionally, arthritis) and abdominal symptoms. The criteria for diagnosis of childhood HSP are given in Table 22.7.

The illness begins with a purpuric rash more prominent over the extensor aspects of lower extremities and buttocks. It may be macular, maculopapular or even urticarial to begin with and can be difficult to diagnose in



Fig. 22.5: Findings in polyarteritis nodosa include (a) Livedo reticularis; and (b) Microaneurysm (black arrow) on angiography

Table 22.6: Classification criteria for childhood polyarteritis nodosa

A childhood illness characterized by the presence of either a biopsy showing small and mid-size artery necrotizing vasculitis or angiographic abnormalities (aneurysms or occlusions),* plus at least 2 of the following:

- Skin involvement
- Myalgia or muscle tenderness
- Systemic hypertension
- Abnormal urinalysis and/or impaired renal function
- Mononeuropathy or polyneuropathy
- Testicular pain or tenderness
- Signs or symptoms suggesting vasculitis of any other major organ systems (gastrointestinal, cardiac, pulmonary or central nervous system)

*Should include conventional angiography if magnetic resonance angiography is negative

the first few days of illness. Glomerulonephritis is seen in approximately one-third, but only 10% patients have azotemia or nephrotic range proteinuria. Clinically, it may manifest as isolated hematuria, hypertension or a nephritic/nephrotic syndrome. Significant renal involvement is uncommon in children below 6 years old.

Gastrointestinal manifestations usually occur in first 7–10 days of the illness. Affected children may be erroneously diagnosed as having a 'surgical abdomen'. Abdominal pain is usually intermittent, colicky and periumbilical. Vomiting occurs in about 60% of patients but hematemesis and melena are relatively less common. Intussusception (ileoileal or ileocolic) can be seen in the acute phase.

Most clinical features of IgA vasculitis are self-limiting and resolve in a few days. Rare manifestations include

Table 22.7: Classification criteria for childhood Henoch-Schönlein purpura

Palpable purpura with at least one of the following:

- Diffuse abdominal pain
- Any biopsy showing predominant IgA deposition
- Arthritis or arthralgia
- Renal involvement (any hematuria and/or proteinuria)

CNS vasculitis, coma, Guillain-Barré syndrome, pulmonary hemorrhage, carditis and orchitis.

Laboratory Investigations

IgA vasculitis is a clinical diagnosis and none of the laboratory features are pathognomonic. There may be a nonspecific increase in total serum IgA levels. Many children may have microscopic hematuria and proteinuria. Skin biopsy from the involved sites shows leukocytoclastic vasculitis. On indirect immunofluorescence, there are deposits of IgA in skin as well as renal biopsies. Ultrasound examinations may need to be repeated for evolving abdominal findings.

Treatment

Management is generally supportive with maintenance of hydration and pain relief. Prednisolone (1–1.5 mg/kg/day) is often given in children with gastrointestinal involvement and is usually continued for 2–3 weeks (in gradually tapering doses) depending on the clinical response. There is, however, no clear evidence that steroids alter the natural course of disease.

Nephritis due to IgA vasculitis may need aggressive management with immunosuppressants (prednisolone and azathioprine).

Prognosis

The disease usually runs its entire course in 4 weeks and majority of children have no permanent sequelae even when the short-term morbidity is quite significant. Children older than 6 years with significant renal involvement (especially children with rapidly progressive glomerulonephritis and crescents) need to be closely followed up; the long-term prognosis is guarded in such situations. Overall 1–5% of children with nephritis due to IgA vasculitis progress to end stage renal disease.

Granulomatosis with Polyangiitis (Wegener granulomatosis)

This condition is characterized by necrotizing granulomatous angiitis affecting the respiratory tract and kidneys. It is rare in children. Constitutional symptoms are quite prominent. Presence of anti-neutrophil cytoplasmic antibodies (ANCA), especially c-ANCA, are virtually pathognomonic. With steroids and cyclophosphamide and occasionally, intravenous immunoglobulin, the long-term outlook is satisfactory.

Behçet Disease

This is an extremely uncommon vasculitic disorder, with variable clinical manifestations.

- i. *Major*: Aphthous stomatitis, genital ulceration, cutaneous manifestations and ocular disease
- ii. *Minor*: Gastrointestinal disease, thrombophlebitis, arthritis, family history and neurological involvement.

Behçet disease is characterized by multiple relapses with significant disability from ocular and neurological manifestations. Widespread thrombosis (venous and arterial) of large vessels may be life-threatening. Many patients show a positive pathergy test (cutaneous pustular reaction following needle pricks). HLAB5 and B51 haplotypes have been associated with this syndrome. Drug therapy involves use of colchicine and thalidomide. Methotrexate and chlorambucil have also been used.

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Genetic Disorders

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CHROMOSOMES AND GENES

Of 23 pairs of human chromosomes, the two members of 22 pairs that are apparently alike (or homologous) are called autosomes. The 23rd pair is homologous only in females with two X chromosomes. In males, the 23rd pair has one X chromosome and a much smaller Y chromosome. Each chromosome has a short arm (p) and a long arm (q) joined by a centromere (Fig. 23.1). Based on the position of the centromere, chromosomes are categorized as metacentric (centromere in the middle), submetacentric (centromere distant from centre) and acrocentric (centromere at the end). Chromosomes are numbered based on their size and position of the centromere.

Chemically, the chromosomes are made up of deoxyribonucleic acid (DNA) and histones. Only about 3% of DNA in the human genome symbolizes genes; the rest does not have a clear-cut function (often termed junk DNA). There are about 20000–25000 genes in the human genome, each gene being the functional unit of heredity. Gene is a sequence of several nucleotides, and its position on a chromosome is called its locus. Each individual has two copies of genes on the two parental chromosomes (one each from mother and father). Alternative forms of a gene are known as alleles (Fig. 23.2). For instance, one allele may code for black iris and another for blue iris. If the alleles code for the same forms, these are called homozygous; if they code for different traits, they are

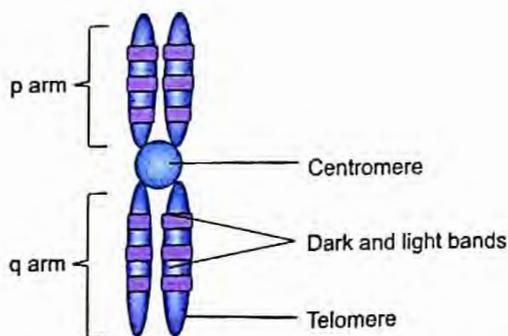


Fig. 23.1: Schematic structure of a chromosome

heterozygous. If an allele clinically manifests itself even in the heterozygous state, it is called a dominant gene or character. Its alternate form or allele which does not express itself clinically when the other allele from the other parent is normal is called a recessive gene. Recessive genes will manifest features of disease only when present in homozygous state or when the abnormal gene is inherited from both parents. The genetic makeup of a person is called the genotype and the clinical characters are known as phenotype. Sometimes a gene may express itself in several slightly modified forms without adverse effect on health of the individual, known as genetic polymorphism.

Genetics and Disease

Most diseases have probable genetic and environmental basis. The genetic component may be the major or the only factor leading to manifestation(s) of the disease, or it may merely predispose the individual to get a disease in response to environmental stresses. Based on genetic mechanism, diseases may be of 5 types: (i) Chromosomal disorders, (ii) single gene disorders, (iii) polygenic disorders, (iv) mitochondrial disorders and (v) somatic cell disorders.

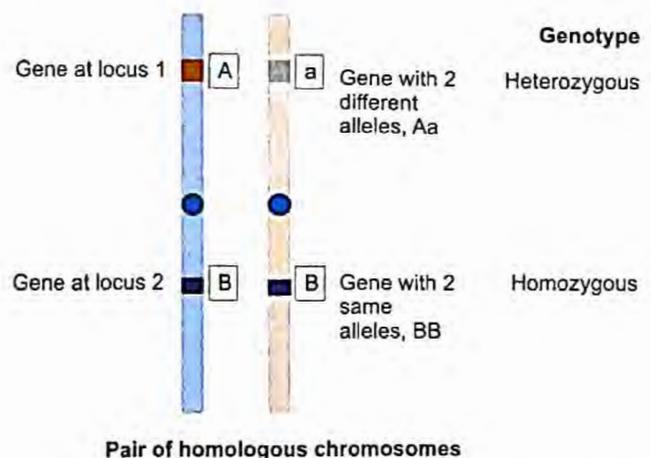


Fig. 23.2: Concept of locus, gene, allele and genotype

CHROMOSOMAL DISORDERS

Mechanisms of Chromosomal Anomalies

Chromosomes contain a large number of genes. Loss or gain of a whole chromosome due to abnormalities in cell division may cause profound disturbances in the genetic constitution of the fetus and affect its survival. Depending upon the type of abnormality, the chromosome involved and the type of imbalance, there may be an early abortion, still birth, neonatal death, malformations or intellectual disability. At times, only a part of the chromosome may be deleted or lost, causing less severe genetic disturbances. Generally, loss of a whole chromosome, except the X chromosome (as in Turner syndrome), is lethal. Surveys in still-born or abortuses show chromosomal anomalies in a large proportion. Five of 1000 live newborns, have chromosomal anomaly. There are two types of chromosomal abnormalities—numerical (aneuploidies) and structural.

Aneuploidies result from failure of chromosomes to separate normally during cell division. This phenomenon is known as nondisjunction. Nondisjunction during meiosis I leads to formation of disomic or nullisomic gametes, resulting in trisomic and monosomic zygotes, respectively; nondisjunction during meiosis II results in monosomic, disomic and nullisomic gametes, leading to disomic (46 chromosomes), trisomic (47 chromosomes) and monosomic (45 chromosomes) zygotes, respectively, as shown in Fig. 23.3. Nondisjunction may occur in maternal or paternal germ cells, but is more common in the former and with increasing age. Common aneuploidies in live born babies include Down syndrome (trisomy 21), Edward syndrome (trisomy 18), Patau syndrome (trisomy 13, Fig. 23.4) and Turner syndrome (monosomy X).

Mosaicism: If nondisjunction occurs in the first mitotic division instead of meiosis, of the two new cells formed, one has 47 chromosomes and the other has 45 chromosomes. The error is perpetuated by repeated mitotic divisions. Thus, two cell lines with 47 and 45 chromosomes are observed in the same individual. If the nondisjunction occurs after a few mitotic divisions have already occurred, more than two cell lines are observed, some with normal and others with abnormal complement of chromosomes.

Structural Chromosome Abnormalities

Chief types of structural chromosome abnormalities are: (i) translocation, (ii) inversion, (iii) deletion, (iv) duplication, (v) ring chromosome and (vi) isochromosomes.

Translocation (Fig. 23.5): A chromosome or segment of a chromosome may break off from the parent chromosome and join another chromosome, in a process called translocation. One chromosome may appear shortened in this process. If no loss or gain of the genetic material occurs, the translocation is *balanced* and the person is phenotypically normal. Translocated chromosome may be transmitted to either gamete during meiosis, such that when it mates with a normal gamete, the resulting zygote may have either excess or deficiency of the genetic material. Such an offspring is abnormal. Viability of such zygotes would depend on the essentiality of the genes carried on translocated portion of the chromosome.

Deletion (Fig. 23.6): A segment of chromosome may break off and be lost. Loss of a portion of chromosomal material large enough to be seen by light microscope is often lethal or poorly tolerated. Gene deletion syndromes are characterized by loss of a cluster of genes, giving rise to a

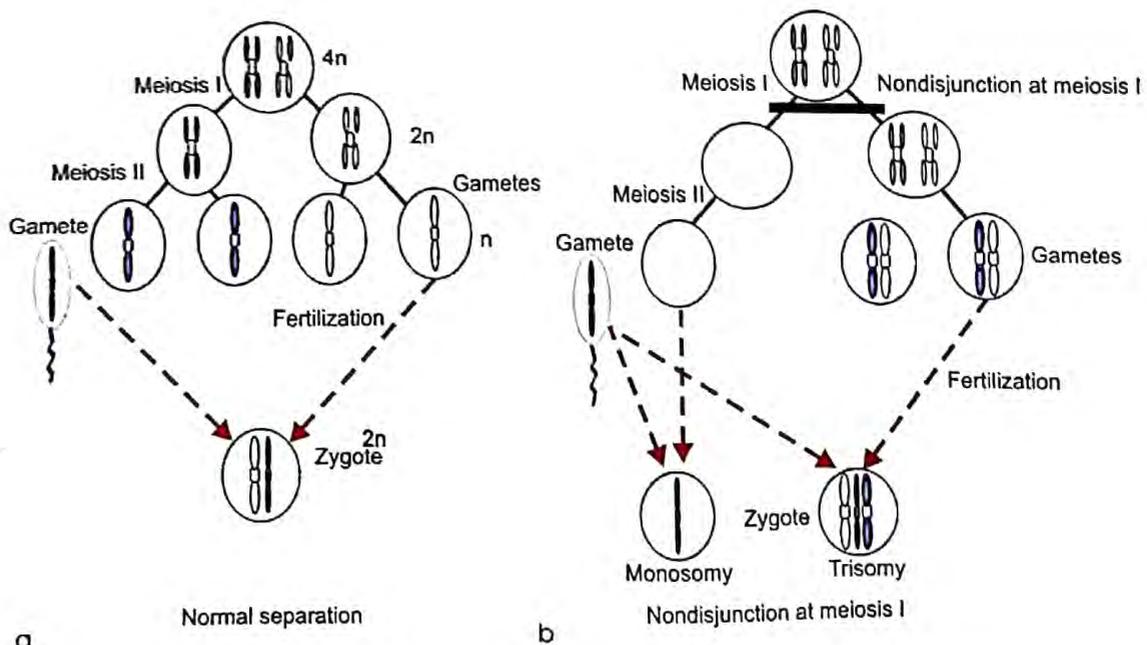


Fig. 23.3: (a) Normal separation; and (b) Nondisjunction of chromosomes

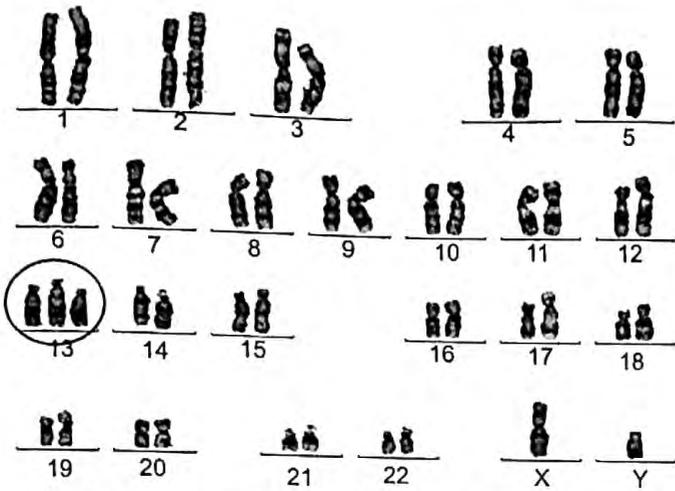


Fig. 23.4: Aneuploidy of chromosome 13 (trisomy 13)

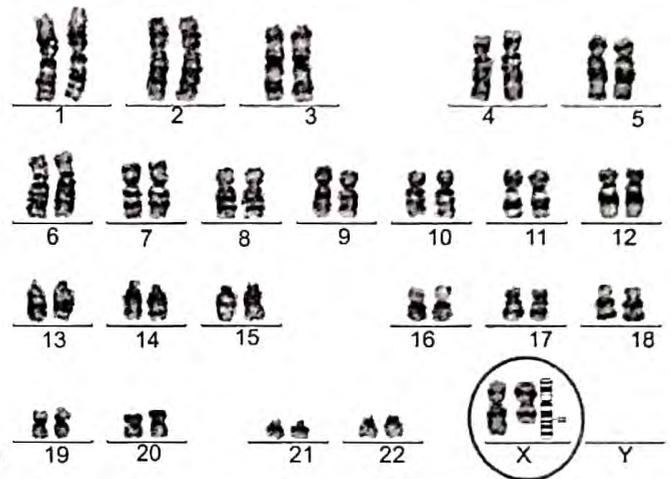
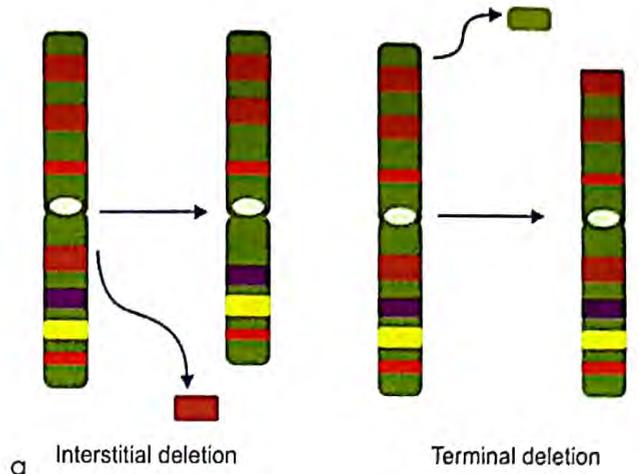


Fig. 23.6: (a) Schematic diagram of deletion; (b) Karyotype with deletion of long arm of X chromosome

of parathyroid and thymus, facial and palate anomalies; 22q11). Submicroscopic deletions are detected on special chromosomal staining or fluorescent *in situ* hybridization (FISH) (Fig. 23.7). DNA probes make it possible for FISH to be used for diagnosis for aneuploidies and micro-deletion syndromes.

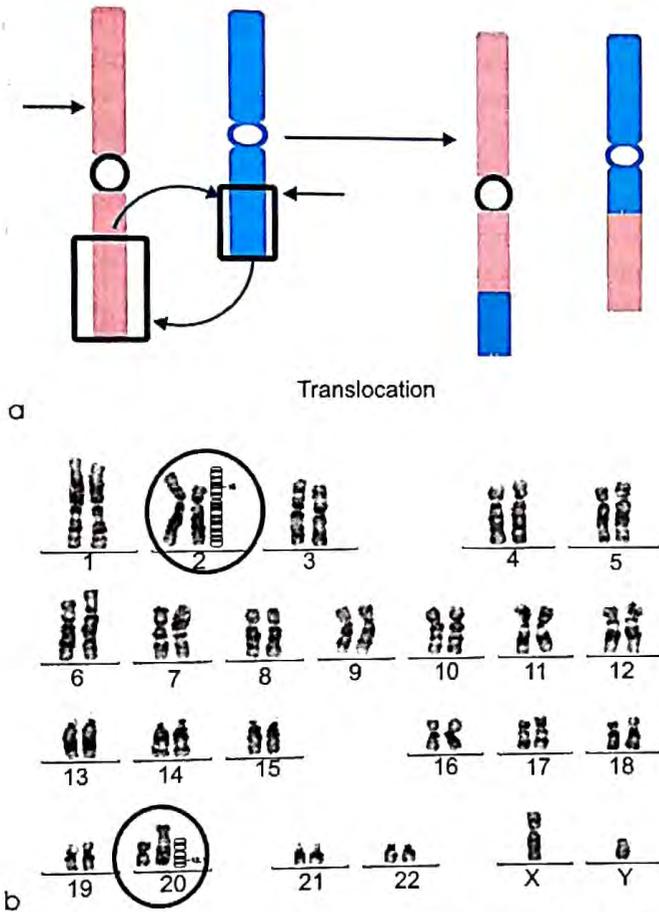


Fig. 23.5: Translocation. (a) Cartoon indicating exchange of parts of chromosomes. (b) Karyotype showing translocation between chromosomes 2 and 20 [t(2;20)]

consistent pattern of anomalies and developmental problems. Examples are William syndrome (7q11.23); retinoblastoma with mental retardation and dysmorphic facies (13q14.1); Prader-Willi syndrome (hypotonia, mental retardation and obesity, 15q11); Rubinstein Taybi syndrome (microcephaly, broad thumbs, big toes, dysmorphism and mental retardation; 16q13); and DiGeorge syndrome (congenital heart defect, hypoplasia

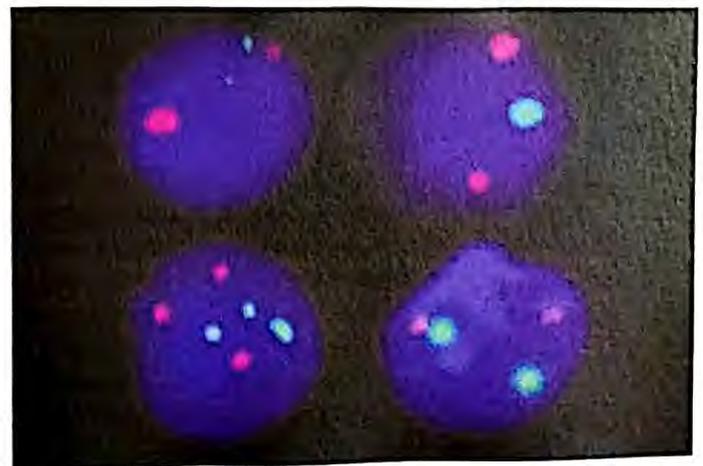


Fig. 23.7: Signals on fluorescent *in situ* hybridization (FISH) testing. Reduced or increased number of signals indicates aneuploidy

Duplications are abnormal duplication or copy of part of a particular chromosome that result in extra genetic material.

Ring chromosome (Fig. 23.8) occurs due to a two breakpoint event involving the ends of the p and q arm which leaves two sticky chromosomal ends that join to form a ring.

Inversion (Fig. 23.9a) results from one or two breaks along the length of the chromosome arm. The broken pieces rotate by 180 degrees and reinsert in a novel way. If there is no loss or gain of genetic material, there may be no significant clinical manifestations. Break point is important if it disrupts a vital gene.

Isochromosome (Fig. 23.9b). During mitotic cell division, the chromosome divides longitudinally. Rarely it divides transversely across the centromere, with half of the chromosome replicating to form its complement. Thus instead of normal chromosomes, two new types of chromosomes are formed, one having both the long arms and the other with both the short arms. These are known as isochromosomes. Each isochromosome has excess of some genetic material and deficiency of other genetic material. For example, isochromosomes cause some cases of Turner syndrome.

Genomic imprinting: Maternal and paternal sets of genes are not always functionally equal. Some genes are preferentially expressed from maternal or paternal side. Examples include Prader-Willi syndrome (microdeletion on paternal side or inheritance of both copies from maternal side) and Angelman syndrome (microdeletion

on maternal side or inheritance of both copies from paternal side).

Chromosomal abnormalities are generally sporadic and therefore, the risk of their recurrence in offsprings is low, except when either parent is carrying a balanced translocation.

Testing for Chromosomal Disorders

Laboratory testing for chromosomal disorders includes conventional karyotyping, fluorescent in situ hybridization (FISH), quantitative PCR (qPCR), multiplex ligation probe amplification (MLPA) and chromosomal microarray (CMA).

The process of making chromosome preparations by in vitro culture, staining, identification and classification of chromosomes is called karyotyping. Karyotyping can be performed on peripheral blood lymphocytes, bone marrow aspirate and tissue biopsy material. The process is labor intensive and involves culture, followed by harvesting chromosomes after the cells are arrested in mitosis. After preparation of slides, staining (usually Giemsa stain) is done to produce a banding pattern unique for each chromosome (Fig. 23.10). This enables detection of numerical and structural abnormalities through the genome at a resolution of approximately 5 Mb. The chromosomes from one metaphase figure (a single cell) are classified according to their length (chromosome one is the longest) and banding features into groups called a karyotype.

Molecular cytogenetic techniques include FISH, quantitative polymerase chain reaction (qPCR) and

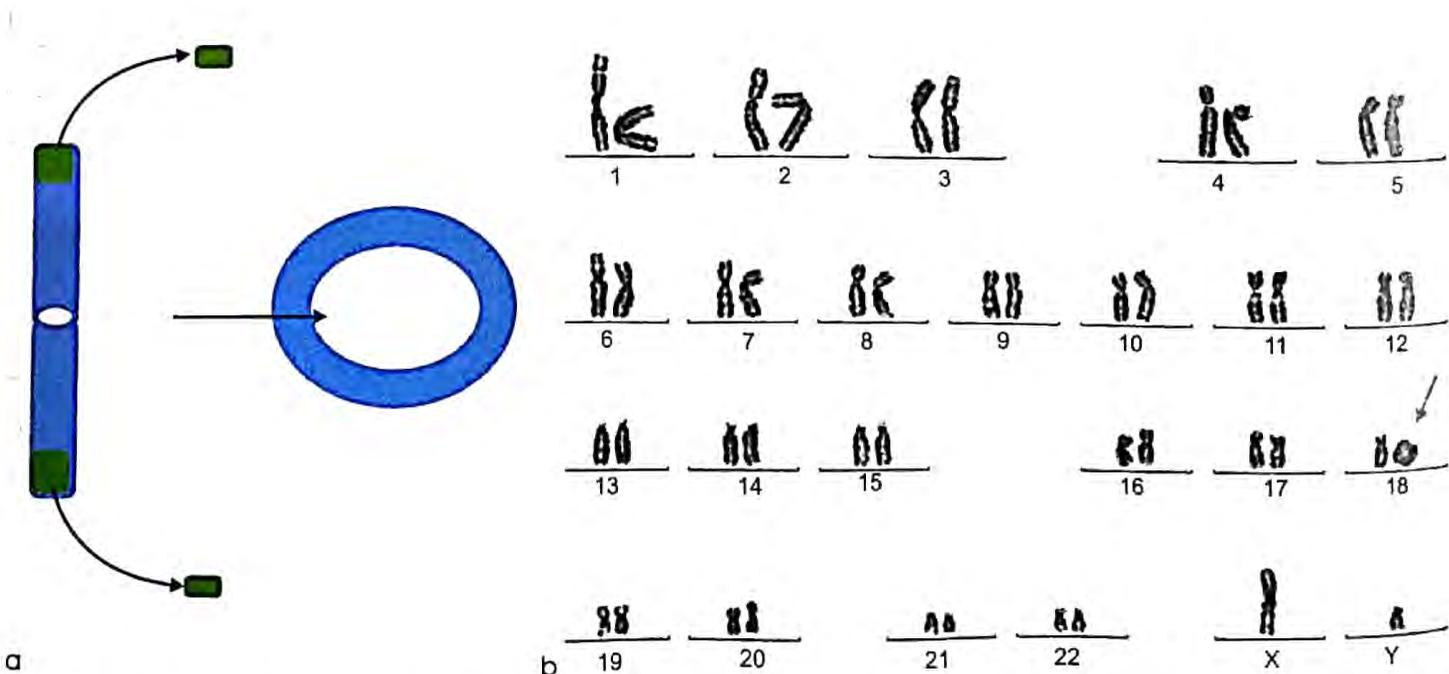


Fig. 23.8: (a) Schematic representation; and (b) Karyotype showing ring chromosome 18 in a child with developmental delay and seizures (see red arrow)

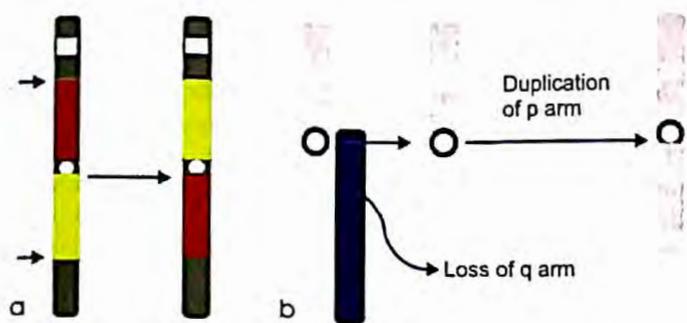


Fig. 23.9: (a) Inversion; and (b) Isochromosome

multiplex ligation dependent probe amplification (MLPA) (Fig. 23.10) detect chromosomal abnormalities in a targeted manner, since fluorescent probes (in case of FISH) and specific markers (qPCR and MLPA) are designed for a specific chromosome or region of chromosome, and can

be used for submicroscopic abnormalities. All these tests are rapid (results within 1–2 days) but are expensive and will detect abnormalities only in the desired chromosome(s) or regions. These are highly useful for rapid aneuploidy detection in prenatal diagnosis and for microdeletion syndromes (e.g. William syndrome).

Chromosomal microarray is a collection of microscopic DNA spots attached to a solid surface. It detects copy number variations, identifying both losses (deletions) and gains (duplications). It provides better diagnostic yield than conventional karyotype; it does not require dividing cells and the resolution is almost 50-fold higher. Chromosomal microarray is recommended for unexplained intellectual disability, multiple congenital anomalies and autistic spectrum disorders. DNA microarrays can be used to measure the expression of several genes simultaneously or to genotype multiple regions of a genome.

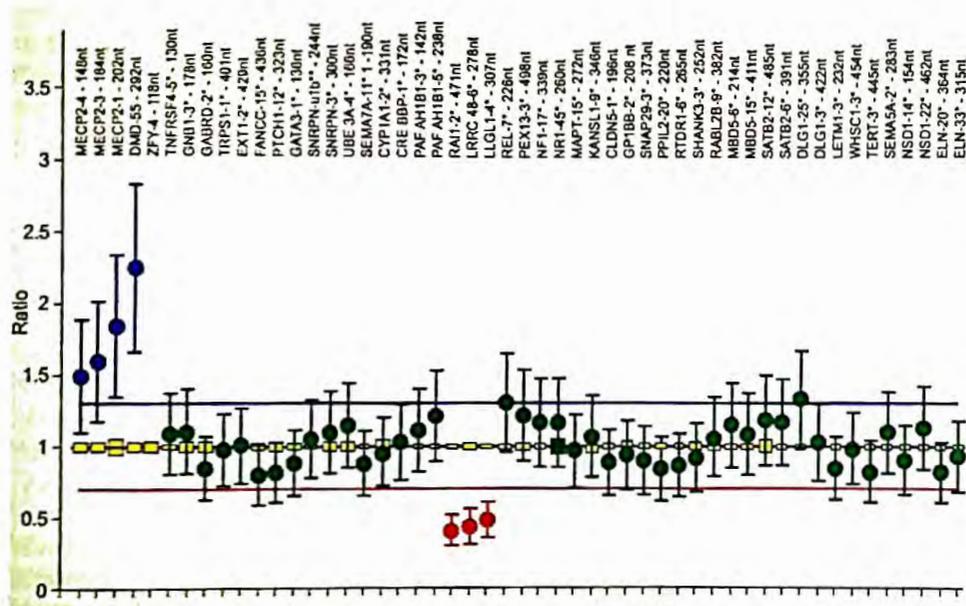


Fig. 23.10: MLPA analysis showing hemizygous deletion (indicated in red) in a patient with Smith-Magenis syndrome



DOWN SYNDROME

Down syndrome is the most common chromosomal disorder, occurring with a frequency of 1:800 to 1:1000 newborns. Chromosome number 21 is present in triplicate, usually because of meiotic non-disjunction in either maternal or parental gamete. In most cases the extra chromosome is from the mother. Down syndrome occurs more often in offspring of mothers conceiving at older age; the risk in the newborn is 1:1550 if maternal age is 15–29 years, 1:800 at 30–34 years, 1:270 at 35–39 years, 1:100 at 40–44 years and 1:50 after 45 years.

Cytogenetics

Trisomy 21 is found in 95% cases. Approximately 1% cases are mosaic and the rest (4%) are due to translocations, most

commonly involving chromosomes 21 and 14 (Fig. 23.11). Karyotype of the parents is only required if the affected child has translocation causing Down syndrome.

Clinical Features and Diagnosis

Patients with Down syndrome have intellectual disability and physical retardation, flat facial profile, an upward slant of eyes and epicanthic folds (Fig. 23.12). Oblique palpebral fissure is obvious only when the eyes are open. The nose is small with flat nasal bridge. Mouth shows a narrow short palate with small teeth and furrowed protruding tongue. There is significant hypotonia. The skull appears small and brachycephalic with flat occiput. Ears are small and dysplastic. There is a characteristic facial grimace on crying. Hands are short and broad.

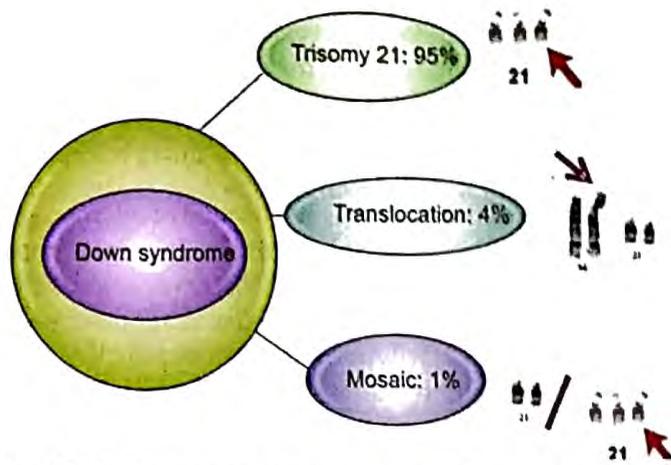


Fig. 23.11: Three types of chromosomal abnormalities found in children with Down syndrome. Arrows indicate the additional genetic material that results in the characteristic features

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Clinodactyly (hypoplasia of middle phalanx of fifth finger) and simian crease are usual. There is a wide gap between the first and the second toe (sandle gap).

Associated Abnormalities

Congenital heart disease: Approximately 40% children have congenital heart disease. Endocardial cushion defects account for 40–60% cases. Presence of heart disease is the chief factor in determining survival. All children should have a cardiac evaluation before 9 months of age, including echocardiography.

Gastrointestinal malformations: Atresias are present in 12% of cases, especially duodenal atresia. There is an increased risk of annular pancreas and Hirschsprung disease.

Ophthalmic problems: There is an increased risk of cataract, nystagmus, squint and abnormalities of visual acuity. Routine evaluation is performed in infancy and then yearly.

Hearing defects: 40–60% patients have conductive hearing loss and are prone to serous otitis media (commonly

during the first year). Routine evaluation is done before 6 months of age and then every year.

Thyroid dysfunction: About 13–54% patients with Down syndrome have hypothyroidism. Thyroid function tests (T_4 and TSH) are recommended once in the neonatal period or at first contact, every six months in infancy and then every year. This should ideally include antithyroid antibodies, especially in older children, as etiology is usually autoimmune.

Atlanto-occipital subluxation: The incidence is variable, reported in 10–30%. Lateral neck radiograph is recommended once at 3–5 years, before surgery, for participation in special games, or earlier, if signs and symptoms suggest cord compression.

Physical growth: Regular follow up for height and weight is necessary. Linear growth is retarded as compared to normal; children tend to become obese with age. Muscle tone tends to improve with age, while progress with development slows with age.

Malignancies: Patients with Down syndrome are at increased risk of development of lymphoproliferative disorders, including acute lymphoblastic leukemia, acute myeloid leukemia, myelodysplasia and transient lymphoproliferative syndrome.

Management and Prognosis

The principles of management are early stimulation, physiotherapy and speech therapy. Associated problems need to be treated as required. Social performance is usually achieved beyond that expected for mental age. Generally, they behave as happy children, like nursery, are friendly, have good sense of rhythm and enjoy music.

The chief cause for early mortality is congenital heart disease; almost 50% with cardiac anomalies die in infancy. Chronic rhinitis, conjunctivitis and periodontal disease are common. Lower respiratory tract infections pose a threat to life. Hematological malignancies are another cause of mortality. Table 23.1 outlines the protocol for usual children with Down syndrome.



Fig. 23.12: Children with Down syndrome at (a) 3 months; (b) 15 months; and (c) 2 years of age. Note the flat facies, upward slant and open mouth appearance

Table 23.1: Evaluation in patients with Down syndrome

Evaluation	Frequency of assessment
Growth	Twice a year in first year; annually till 5 years
Auditory (screen for hearing loss, otitis media)	
Ocular	
Thyroid profile	
Cardiac evaluation	At initial contact; follow up if congenital heart disease
Hematology	Screen for leukemia, twice a year in first year; monitor as per need
Dental	Annually
Additional evaluations	
Routine immunization as per schedule	
Vigilance about signs of gastroesophageal reflux disease, celiac disease, obstructive sleep apnea, atlantoaxial dislocation	
Early stimulation therapy	
Physiotherapy, occupational and speech therapy	
Guidance regarding vocational training, hygiene and self-care	
Discuss behavioral issues	
Counseling regarding future pregnancies and prenatal diagnosis	

Counseling

Parents of a child with Down syndrome should be counseled with tact, compassion and truthfulness. Briefly, one should: (i) inform about the disorder as early as possible after diagnosis is confirmed; (ii) counsel in presence of both the parents in privacy; (iii) talk in simple and positive language giving hope and allow sufficient time to the parents to ask questions; (iv) discuss known problems and associated disorders; (v) highlight the importance of early stimulation; (vi) not discuss institutionalization and adoption, unless asked, and discourage both the options; (vii) ask parents to contact the local Down syndrome association, if one exists; (viii) talk about genetics only after chromosomal analysis; (ix) inform about recurrence risks and possibilities of prenatal diagnosis; and (x) schedule future appointments.

Risk of recurrence: Women 35 years of age or less who have a child with trisomy 21 have a 1% risk of having another, which is significantly greater than the general population. The risk is little increased, if any, over the usual maternal age dependent frequency if the mother at risk is 35 years or older. For translocations inherited from the mother, the risk is about 10%, whereas it is about 4–5% when father is the carrier. Balanced translocation 21; 21 is the only situation where all viable fetuses will have Down syndrome.

Prenatal screening and diagnosis (also section: Prevention of Genetic Disorders). Parents who wish to get a prenatal diagnosis have a number of options. They can directly get a fetal karyotype either by chorionic villus sampling (by transcervical or transabdominal route) or amniocentesis. Alternatively (if the parents do not want invasive testing) an initial screening may be performed with maternal serum markers and ultrasonography (as discussed later).

Options for couples who come late or opt for initial screening with serum markers and ultrasonography are karyotyping by amniocentesis at 16–18 weeks, trans-abdominal chorionic villus sampling and cordocentesis after 18 weeks. Karyotype results are available within a week with cord blood samples and direct chorionic biopsy preparations. The results of amniotic fluid cultures take about two weeks. Rapid testing using FISH and quantitative PCR is very reliable and results are available in 24–48 hours.

TURNER SYNDROME

Turner syndrome, with 45 X chromosomal constitution, has an incidence of ~1:3000 newborns. However, chromosomal studies of spontaneous abortions have clearly shown that majority of 45 X fetuses are likely to be aborted. Since there is no apparent relationship to advanced maternal age, it is likely that the condition does not arise from gametic nondisjunction.

Cytogenetics

Many patients with Turner syndrome show considerable degree of chromosomal mosaicism, i.e. 45, X/46, XX or other karyotypes with multiple cell lines. Formation of isochromosome of long arms of X chromosome may lead to Turner phenotype with 46 chromosomes because of absence of short arms. Figure 23.6b shows a karyotype of a child with Turner syndrome with deletion of long arm of X chromosome

Clinical Features

Turner syndrome may be recognizable at birth. Lymphedema of the dorsum of hands and feet and loose skin folds at the nape of neck may be present. Other manifestations include short stature, short neck with



Fig. 23.13: Turner syndrome. Note (a) Ptosis in right eye, shield chest, increased carrying angle, webbed neck and short neck; and (b) Low posterior hair line

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webbing and low posterior hair line. Anomalous ears, prominent narrow and high arched palate, small mandible and epicanthic folds may be noted. Chest is broad shield-like with widely spaced hypoplastic nipples (Fig. 23.13a and b). There is increased carrying angle at elbow. Bony anomalies include medial tibial exostosis, and short fourth metacarpals and metatarsals. Pigmented nevi may appear in older patients. At puberty, sexual maturation fails to occur. The phenotype is highly variable. It has been recommended that the diagnosis of Turner syndrome should be considered in all girls with short stature.

Ultrasound may show streak ovaries and hypoplastic uterus. Levels of FSH and LH are increased (hypergonadotropic hypogonadism). Adult stature is usually below 145 cm. Associated congenital defects are common in kidneys (horseshoe kidney, double or cleft renal pelvis),

heart (coarctation aorta) and ears (perceptive hearing defect). Congenital lymphedema recedes in early infancy, leaving puffiness over dorsum of fingers and toes. Linear growth is at about half to three-fourths the usual rate. Hypothyroidism occurs in about 15–30% adults with Turner syndrome. The clinical features are milder in Turner syndrome with mosaicism; patients show may have normal stature and present with secondary amenorrhea.

Management

Height monitoring should be done using growth charts for Turner syndrome. Cardiac evaluation and measurement of blood pressure is recommended at baseline and every year. Treatment with growth hormone is recommended. While therapy may increase the final height by 8–10 cm, the cost is prohibitive. Thyroid testing should be done in infancy or early childhood, if the child is lagging in growth. Routine evaluation is required after 10 years of age. Counseling regarding behavioral problems due to short stature, amenorrhea and sterility is an integral part of management. Ovarian hormone replacement is advised around 14 years. Conjugated estrogen (0.3 mg/day) or ethinyl estradiol (5–10 ug/day) are given for 3–6 months; the dose of medications may be increased. After 6–12 months, cyclical therapy with estrogen and progesterone is started.

Regular audiometry is advised in adulthood or earlier, if indicated. Evaluation for renal malformation by ultrasonography should be done at first contact. Prophylactic gonadectomy is advised for patients with Y chromosome due to the risk of developing gonadoblastoma.

Table 23.2 gives brief description of some common aneuploidies.

Table 23.2: Clinical features of common aneuploidies

<i>Aneuploidy</i>	<i>Clinical features</i>	<i>Management</i>
<i>Trisomy 18</i> Edward syndrome	Failure to thrive, developmental retardation, hypertonia, micrognathia (Fig. 23.14a), shield-shaped chest, short sternum, joint abnormalities including flexion deformity of fingers (Fig. 23.14b and c), limited hip abduction and short dorsiflexed hallux. Congenital heart disease is common	Symptomatic, supportive
<i>Trisomy 13</i> Patau syndrome	Development and physical retardation, microcephaly, sloping forehead; cleft lip with/without cleft palate common Holo-prosencephaly; varying degree of incomplete development of forebrain, olfactory and optic nerves Microphthalmia, iris coloboma, retinal dysplasia and cataract; deafness Capillary hemangiomas (Fig. 23.15); polydactyly, flexion deformities Congenital heart disease (80%); most die by 6 months of life	Symptomatic, supportive
<i>Klinefelter syndrome</i> 47,XXY	Hypergonadotropic hypogonadism, small testes, fail to develop secondary sex characters; tall stature, gynecomastia Borderline intellectual disability, behavioral problems Consider diagnosis in boys with mental retardation, psychosocial or learning disability, or problems in school adjustment	Behavioral and psychosocial rehabilitation Testosterone therapy in middle-late adolescence



Fig. 23.14: Note the (a) Facial dysmorphism; (b and c) Overlapping of fingers in an infant with trisomy 18



Fig. 23.15: Note postaxial polydactyly and forehead hemangioma in an infant with trisomy 13

SINGLE GENE DISORDERS

Single gene disorders are inherited as autosomal dominant, autosomal recessive or X linked disorders, due to mutation(s) in the disease specific genes. Drawing and interpreting a pedigree is an integral part of diagnosis of single gene disorders. www.nature.com/scitable/content/standard.symbols-5526

Mutation refers to the heritable change in the DNA resulting in perturbed protein structure and function. There are three types of mutations: Single base substitution, deletions and insertions.

Substitution or point mutations, the most common type, result in replacement of a single nucleotide by another that results in formation of same amino acid (silent mutation), altered amino acid (missense mutation) or generate a stop codon (nonsense mutation).

Deletion mutations involve the loss of one or more nucleotides into a gene. If the deletion is a multiple of three

base pair deletion, then it is an in frame deletion, whereas if the deleted nucleotides are not the multiple of three, it results in disruption of the reading frame, known as frameshift mutation (out-of-frame deletions). Large deletions cause partial or whole gene deletion.

Insertion involves addition of one or more nucleotides into a gene. Frame shift mutations can also occur due to insertion of a nucleotide.

Triplet repeat expansions are dynamic mutations that expand over generations and become unstable on expansion, e.g. fragile X syndrome, myotonic dystrophy.

Autosomal Dominant Inheritance

Generally, autosomal dominant mutations impair the synthesis of structural or non-enzyme proteins, e.g. Huntington chorea and connective tissue disorders. These disorders manifest even if only one of the alleles of the abnormal gene is affected. Autosomal dominant disorders are generally milder than autosomal recessive disorders. Physical examination of other siblings and parents should be done to uncover milder forms of the disorder. Homozygotes for the dominant mutant genes usually die prenatally, as in the case of the gene for achondroplasia. If the child is the only affected member, it is very likely that the observed mutation has occurred *de novo* and is not inherited. In such cases other siblings are not likely to be affected. However, one-half of the offspring of the affected individual are likely to inherit the disorder. New dominant gene mutations are more likely to occur, if the paternal age is high. Examples include neurofibromatosis, achondroplasia, Marfan syndrome and Crouzon disease. A typical pedigree and its characteristic features are shown in Fig. 23.16.

Autosomal Recessive Inheritance

Autosomal recessive disorders manifest only in homozygous state, i.e. both the alleles are mutant genes. Generally, autosomal recessive mutations affect synthesis of enzyme, leading to inborn errors of metabolism. The parents of the affected individuals are apparently normal but carry the mutant genes. As they are heterozygous, the mutant recessive gene does not express itself in the phenotype. In such matings, one-fourth of the offspring are affected (homozygous for the mutant genes), one-

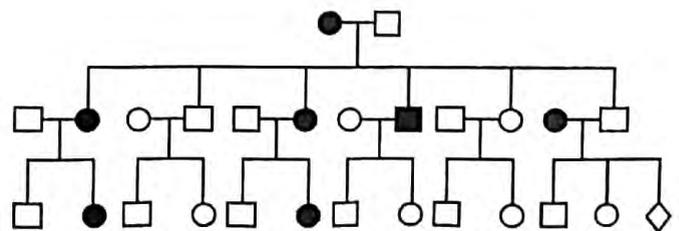


Fig. 23.16: Autosomal dominant Inheritance and its characteristics

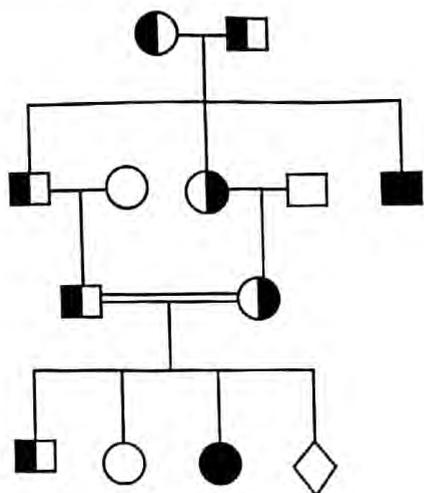


Fig. 23.17: Autosomal recessive inheritance and its characteristics. Carriers are indicated by partly shaded symbols

fourth are normal (both normal alleles) and half are carriers (heterozygote with one mutant allele and one normal allele). A classical pedigree is shown in Fig. 23.17. Recessive disorders are common in consanguineous marriage or in closed communities. It is now possible to detect carrier status by biochemical and molecular techniques in a number of autosomal recessive disorders. Common examples of autosomal recessive disorders are beta-thalassemia, sickle cell disease, spinal muscular atrophy, phenylketonuria and galactosemia.

X-Linked Recessive Inheritance

Since in males, there is no corresponding locus for a mutant allele of the X chromosome on the shorter Y chromosome, the mutant X-linked recessive gene expresses as a clinical disorder in the male child because it is not suppressed by a normal allele. In the female, the disorder does not manifest clinically since the mutant gene is compensated for by the normal allele in the other X chromosome. Females thus act as carriers of the mutant allele. Half of their male children inherit the mutant allele and are affected. Figure 23.18 shows a family with X-linked recessive inheritance. It is now possible to detect carrier state in females in some disorders, e.g. hemophilia, Duchenne muscular dystrophy and mucopolysaccharidosis type II (Hunter syndrome). Color blindness also has an X-linked recessive inheritance.

X-Linked Dominant Inheritance

Dominant X-linked conditions are rare. Both heterozygous female and hemizygous males are affected. All the sons of the affected males are normal and all daughters are affected. The affected females transmit the disease to half of the sons and half of the daughters, e.g. hypophosphatemic type of vitamin D resistant rickets, orofacioidigital syndrome and incontinentia pigmenti. In some cases, the effect of the mutant gene on development is severe, and

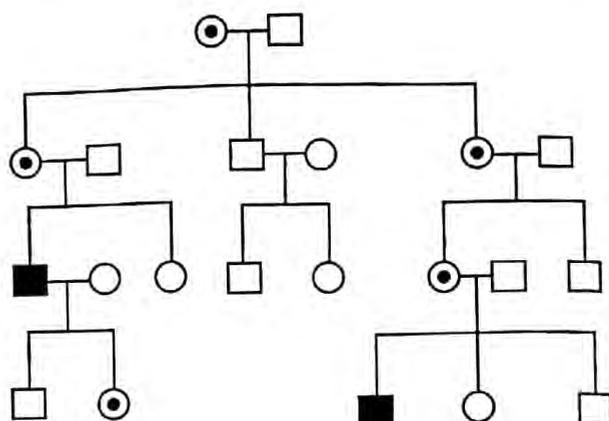


Fig. 23.18: X-linked recessive inheritance and its characteristics. Carriers are indicated by bold dot in the center

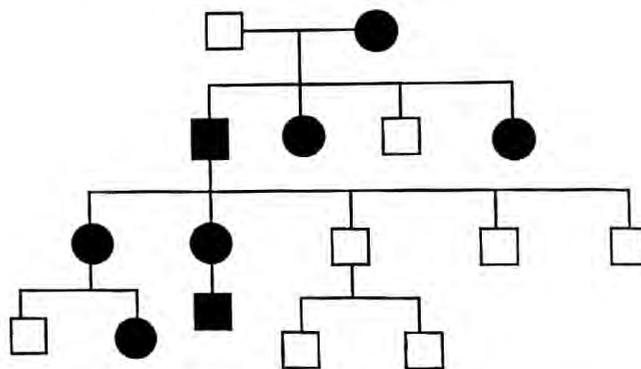


Fig. 23.19: X-linked dominant inheritance and its characteristics

affected males are seldom born alive. Majority of patients are heterozygous females (Fig. 23.19).

Mitochondrial Inheritance

Mutations within a mitochondrial gene can lead to phenotypic defects and show a pattern of maternal genetic transmission. Since mitochondria are only present in ovum and not sperms, the inheritance is maternal. All offspring of an affected female are affected. All affected daughters transmit the disease. Sons are affected but do not transmit the disease (Fig. 23.20). Examples include Leigh disease and mitochondrial encephalopathy, lactic acidosis and stroke (MELAS) like syndrome.

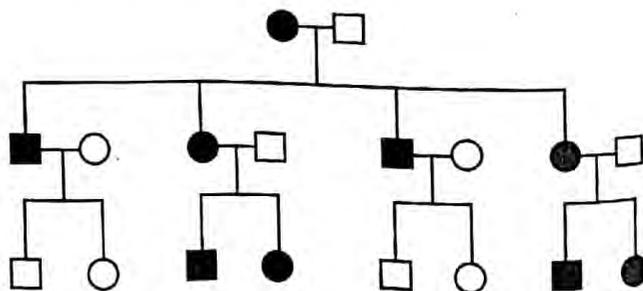


Fig. 23.20: Mitochondrial inheritance

Somatic Cell Genetic Disorders

In somatic cell disorders, the defects are restricted to specific somatic cells, in contrast to previous four types of genetic diseases (chromosomal, single gene, polygenic and mitochondrial) in which the abnormality is present in all cells, including germ line cells. These include cancers which can arise due to genetic changes in somatic cells alone.

Molecular Genetic Testing for Single Gene Disorders

DNA probes can be made to detect specific base sequences in the DNA. The most fascinating technique in molecular genetics is the ability to form large number of copies of DNA sequences in a short time. For DNA, blood sample is collected in EDTA, however, DNA can be extracted from virtually any tissue. Amplification of DNA is possible with polymerase chain reaction (PCR). Molecular genetic testing includes like allele specific amplification and restriction fragment length polymorphism. DNA sequencing includes conventional Sanger sequencing and newer high throughput technologies that rely on determining the order of the nucleotide bases in the DNA sequence of interest. High-throughput sequencing or next generation sequencing technologies can run thousands or millions of sequences in parallel, are very sensitive and lower the cost of DNA sequencing, hence, next-generation sequencing is being increasingly used in making genetic diagnosis. However, the technique is not useful for aneuploidy, and chromosomal rearrangement and large deletions. The use of these advanced is limited by need for expertise in analysing bioinformatic data and in interpretation of findings in clinical context. Such advanced studies are an adjunct but do not replace clinical phenotyping and analysis based upon detailed history and examination.

POLYGENIC INHERITANCE

In several conditions, the affected individuals do not have a sharp division between the normal and the abnormal, but merely represent a spectrum of a continuously varying attribute. Such conditions are likely to be inherited by alterations in many gene loci, each of them individually having only a small effect. Many of these conditions are also affected by numerous environmental factors, individually of small effect. Examples of polygenic disorders are neural tube defect, cleft lip, cleft palate, Hirschsprung disease, congenital hypertrophic pyloric stenosis, diabetes mellitus, ischemic heart disease, hypertension and schizophrenia.

In diseases with multifactorial etiology, the risk to progeny and siblings is higher if the malformation is severe, because a severe malformation is a bigger deviation from the normal, e.g. the risk of recurrence of Hirschsprung disease is higher if the aganglionic segment of the colon is longer. When these diseases have a marked sex predilection, the risk of recurrence in the family is higher if the index patient belongs to the less often affected sex. This is so, because the mutant genes are likely to be more severe so as to produce the disease in the sex with an inherent resistance to the disease. The usual risk of recurrence for malformations caused by a polygenic or multifactorial cause is 2–5%.

THERAPY FOR GENETIC DISORDERS

While genetic disorders cannot be cured completely, symptoms may be ameliorated and irreversible damage or handicap prevented or reduced through several therapeutic approaches (Table 23.3).

Specific diets: Metabolic manipulation involves diet modification with or without drugs to reduce the substrate

Table 23.3: Strategies for the therapy of genetic disorders

<i>Intervention</i>	<i>Examples</i>
Metabolic manipulation	Diet to reduce substrate accumulation (most inborn errors of metabolism); substrate reduction (lysosomal storage disorders)
Provide deficient protein	Hemophilia A and B; alpha-1 antitrypsin deficiency; growth hormone deficiency; lysosomal storage disorders
Avoid precipitating factors, drugs	Oxidants (glucose-6-phosphate dehydrogenase deficiency); avoid fasting in fatty acid oxidation defects and glycogen storage disorders
Promote excretion or removal of toxic substances	Penicillamine (Wilson disease); deferiprone (thalassemia); sodium benzoate (hyperammonemia); nitisinone (tyrosinemia)
Augmenting enzymes	Phenobarbitone (Crigler-Najjar syndrome); pyridoxine (homocystinuria)
Stem cell transplantation	Thalassemia major; severe form of Hurler syndrome
Organ transplantation (organ)	Specific malformations; maple syrup urine disease (liver or liver–kidney); polycystic kidney disease (kidney); cardiomyopathies (heart)
Remove diseased organ	Multiple endocrine neoplasia type II (thyroid); hereditary spherocytosis (spleen)
Molecular targeted therapies	Cystic fibrosis
Supportive, symptomatic care	Osteogenesis imperfecta and hemophilia (avoiding trauma); xeroderma pigmentosa (avoid sun exposure); cardiac conduction defects (pacemaker)

and is used mainly for metabolic disorders. The intake of substances which cannot be metabolized by the body should be reduced, especially if their accumulation is potentially toxic, e.g. in galactosemia, galactose cannot be metabolized adequately. As lactose in the milk is hydrolyzed in the body to glucose and galactose, milk in the diet of the affected infant is substituted by lactose free dietary formulae to obviate damage due to excess of galactose in tissues. The phenylketonuric infants placed on restricted phenylalanine in the diet may escape irreversible neurological damage.

Providing deficient proteins: Deficiency of the metabolic end product is managed by its replacement. Thus, thyroxine restores the thyroid function in familial hypothyroidism; cortisone suppresses excess ACTH production and androgen synthesis in adrenogenital syndrome and administration of factor VIII/IX prevents bleeding in cases of hemophilia. Enzyme replacement therapy, although expensive, has become feasible with the availability of deficient enzymes for Gaucher disease, Hurler syndrome, Hunter syndrome, mucopolysaccharidosis type VI, Fabry disease, MPS IV and Pompe disease.

Promoting excretion of toxic substances: The excretion of certain metabolites can be promoted by chelating agents, e.g. penicillamine promotes excretion of copper in patients with Wilson disease and desferrioxamine is used to chelate iron in patients with thalassemia and hemochromatosis.

Augmenting enzymes: Certain enzyme systems, which may be immature or reduced at certain phases of life may be induced or stabilized by the use of chemical agents. Phenobarbitone is used to induce hepatic microsomal enzymes like glucuronyl transferase in cases of neonatal hyperbilirubinemia or Crigler-Najjar syndrome. In some metabolic disorders, enzymatic block can be bypassed by administration of large quantities of the coenzyme, e.g. pyridoxine in homocystinuria.

Avoid precipitating factors and drugs: Certain drugs, which precipitate adverse symptoms in metabolic disorders, such as barbiturates in porphyria and oxidating agents in glucose-6-phosphate dehydrogenase deficiency, should not be given to affected patients.

Stem cell transplantation is recommended for many genetic disorders like thalassemia major, severe Hurler syndrome and some primary immunodeficiencies.

Surgery helps to reduce the functional or cosmetic disability in some structural defects, e.g. removing the spleen in hereditary spherocytosis. Solid organ transplantation, of liver, kidney and heart, is available across India. Conditions where transplantation may be useful include ornithine transcarbamylase deficiency, maple syrup urine disease, cardiomyopathies and polycystic kidney disease.

Supportive care: Patients with hemophilia and osteogenesis imperfecta should be protected from trauma and other

environmental hazards to prevent excessive bleeding and fractures, respectively. Supportive care includes physical therapy, stimulation and rehabilitation. Bisphosphonate therapy has been found useful in patients with osteogenesis imperfecta by reducing osteoclastic activity.

Targeted therapies for certain disorders, e.g. cystic fibrosis with specific mutations (Ivacaftor for G551D and Lumacaftor for delta F508del *CFTR* mutations) and hematological cancers (imatinib for chronic myeloid leukemia) have paved the way for research for several genetic and somatic disorders.

Gene therapy is possible in patients with adenosine deaminase deficiency, familial hypercholesterolemia and some cancers. The normal gene is introduced in affected individuals using viral or nonviral vectors.

PREVENTION OF GENETIC DISORDERS

Carrier Screening

It is now possible to detect the carrier state in a large number of autosomal recessive or X-linked recessive disorders. HbA2 levels are highly useful in identifying carriers of thalassemia trait pre-pregnancy or early in pregnancy. In India ideally all partners should be tested for beta-thalassemia carrier status as the condition is very common in North India. Female carriers of Duchenne muscular dystrophy may show high serum levels of the enzyme creatinine phosphokinase, but can be tested more precisely using molecular techniques. Such techniques are increasingly used for detection of individuals who are likely to give birth to offspring with hereditary disorders.

Newborn Screening

This is an example of secondary prevention by early diagnosis and treatment. Newborn infants are screened routinely for some endocrine disorders and inborn errors of metabolism in developed countries. This is of special value for detecting affected cases in the newborn period, so that handicap can be prevented or minimized by early treatment, e.g. congenital hypothyroidism, congenital adrenal hyperplasia, phenylketonuria, galactosemia and tyrosinemia.

Prevention of Neural Tube Defects

Folic acid supplementation is recommended at a dose of 0.4 mg daily from 1 month before to 3 months after conception to prevent neural tube defects. Expectant mothers at high-risk of such defects (e.g. previous fetus with neural tube defects) should consume 4 mg of folic acid daily to prevent recurrence.

Maternal Serum Screening

Estimation of pregnancy associated plasma protein A (PAPP-A) and free human chorionic gonadotropin (hCG) in the first trimester and serum alpha-fetoprotein, hCG,

unconjugated estriol and inhibin A in second trimester are useful biochemical markers to detect aneuploidies. If the risk of bearing a child with Down syndrome is more than 1:250, prenatal fetal karyotyping can be offered. Fetal ultrasonography helps to detect fetuses at high-risk for chromosomal abnormalities. Findings in the second trimester which suggest Down syndrome are increased nuchal fold thickness, short femur and humerus length and duodenal atresia. In the first trimester, nuchal translucency and nasal bone are robust markers.

Alpha-fetoprotein and estriol are low, whereas hCG is high, in pregnancies with Down syndrome fetuses. The detection rate of Down syndrome by triple test in the second trimester is about 65% with a false positive rate of 5%. All three markers are reduced in fetuses with trisomy 18. Ultrasound findings help in counseling, particularly if the parents have opted for initial screening with maternal serum markers. First trimester screening using dual markers has high detection rates, which improves further if ultrasound markers are combined. Elevated maternal serum alpha-fetoprotein level is a sensitive marker for fetuses with open neural tube defects.

Prenatal Diagnosis and Selective Termination of Affected Fetuses

This is a successfully used modality for preventing birth of affected babies and reducing the load of lethal, chronically disabling, untreatable or difficult-to-treat genetic disorders in the community. Non-invasive prenatal screening (NIPS) is also being used for screening high risk pregnancies for aneuploidies. This NGS-based technique evaluates mother's blood for common fetal aneuploidies after 10 weeks of gestation and has negative predictive value of 98–99%. Positive tests would need confirmation by invasive testing.

Invasive Prenatal Testing

This includes chorionic villus biopsy (at or after 10–12 weeks gestation), amniocentesis (16–20 weeks) and cord blood sampling (after 18 weeks). Procedure related risk is lowest with amniocentesis (~0.5%), while chorionic villus biopsy has a risk of fetal loss in about 1%. These samples can be used for chromosomal studies, DNA based tests or enzyme assays. Amniotic fluid is the preferred sample for chromosomal studies and chorionic villus tissue for DNA

based tests. Single gene disorders, e.g. thalassemia, sickle cell anemia, hemophilia, Duchenne muscular dystrophy and cystic fibrosis can be diagnosed prenatally.

Genetic Counseling

Genetic counseling is a communication process, which deals with problems associated with occurrence and recurrence of a genetic disorder in a family. It is the process by which patients or relatives are advised of the risk of transmission, occurrence and consequences of the disorder, and how this can be ameliorated or prevented. Genetic counseling is an important component of management of genetic disorders, since definitive therapy is not available for most cases.

The objectives of genetic counseling are:

- To provide information about the disease to the individual and the family
- Help the individual or family to choose a course of action that seems appropriate in view of disease risk, family goals, and ethical and religious standards
- To make the best possible adjustment to the illness in an affected family member, and risk of recurrence.

Counseling should be undertaken by a physician with proper understanding of the genetic mechanisms. Indications for genetic counseling include: (i) Known or suspected hereditary disease in a patient/family; (ii) birth defects in previous children; (iii) unexplained mental retardation, dysmorphism, multiple malformations; (iv) consanguinity; (v) exposure to a teratogen during pregnancy; and (vi) identification of malformation(s) by ultrasonography during pregnancy.

Suggested Reading

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Inborn Errors of Metabolism

Neerja Gupta • Madhulika Kabra

Inborn errors of metabolism (IEM) are conditions caused by the genetic errors related to synthesis, metabolism, transport or storage of biochemical compounds. The metabolic error usually results in the accumulation or deficiency of a specific metabolite. These disorders are individually rare, but collectively common, and manifest at any time from the fetal life to old age. Early recognition of signs and symptoms, prompt evaluation and management results in optimal outcome.

Classification

Intoxication group includes disorders of intermediary metabolism, with accumulation of toxic compounds resulting in acute or progressive symptoms. Amino-acidopathies (e.g. phenylketonuria, maple syrup urine disease), organic acidurias, urea cycle defects, disorders of carbohydrate and copper metabolism and porphyrias belong to this category. Symptoms are precipitated by catabolic state (fever, infections, immunization, dehydration or fasting).

Defects of energy metabolism include conditions with deficient energy production or utilization within liver, muscle, heart and brain, e.g. mitochondrial disorders, disorders of glycolysis, glycogen metabolism and gluconeogenesis, and hyperinsulinism. Failure to thrive, hypoglycemia with high lactate, hepatomegaly, hypotonia, cardiomyopathy, myopathy, neurological symptoms and circulatory collapse may occur.

Disorders of complex molecules include lysosomal storage diseases, peroxisomal disorders, α 1-antitrypsin deficiency and congenital disorders of glycosylation. Symptoms are progressive and permanent and do not have precipitating factors. Most disorders have multisystem involvement. Common features include developmental delay, organomegaly, coarse facies and arthropathy.

The onset of illness in the intoxication group and in defects of energy metabolism is often sudden, with nonspecific physical findings. The course may be recurrent and episodic, and response to supportive therapy is rapid. In disorders of complex molecules, the onset is gradual

with slow progression. They usually have characteristic findings that enable a specific clinical diagnosis.

Clinical Suspicion

The diagnosis of IEM is often delayed, and requires a high index of suspicion. Symptoms are often nonspecific, leading to evaluation for other disorders. Clues that suggest the presence of an IEM are listed in Table 24.1.

Table 24.1: Clinical clues suggesting IEM

Neonates

Unexpected deterioration after normal initial period
Nonspecific, unexplained features such as poor feeding, lethargy, vomiting, hypotonia, failure to thrive, respiratory abnormalities, apnea, bradycardia and hypothermia

Children

Sudden and rapid illness in a previously well child precipitated by fever, infection or fasting

Acute encephalopathy; previous similar episodes

Recurrent coma, stroke, ataxia, cramps

Worsening with intercurrent febrile illness

History of aversion to sweets, high protein

Developmental regression

Facial dysmorphism, structural anomalies of brain, cataract, retinopathy, deafness cardiomyopathy, hepatomegaly, myopathy

Peculiar odor (musty in phenylketonuria; cabbage like in tyrosinemia; maple syrup like in maple syrup urine disease; sweaty feet in isovaleric acidemia or glutaric acidemia type II; cat urine in multiple carboxylase deficiency)

Persistent or recurrent hypoglycemia, intractable metabolic acidosis, hyperammonemia, hyperkalemia

Reye syndrome like illness

E. coli sepsis

Others

Family history of similar illness, unexplained sib deaths, or progressive neurological disease

Parental consanguinity: Most acutely presenting metabolic disorders are autosomal recessive.

ACUTE PRESENTATION

Neonates with metabolic disorders are usually normal at birth since the small intermediary metabolites are eliminated by the placenta during fetal life. Disorders of glucose, protein and fat breakdown usually present early; premature neonates with transient hyperammonemia of newborn (THAN) and term babies with glutaric acidemia type II or pyruvate carboxylase deficiency may present on the first day of life. Early onset of symptoms is associated with severe disease. An important clue to diagnosis is unexpected deterioration after normal initial period in a full term baby. Neonates with organic aciduria, urea cycle disorders and some aminoacidurias may present with lethargy, poor feeding, persistent vomiting, seizures, tachypnea, floppiness and body or urine odor. Conditions such as sepsis, hypoxic ischemic encephalopathy and hypoglycemia should be excluded.

Older children show acute unexplained, recurrent episodes of altered sensorium, vomiting, lethargy progressing to coma, stroke or stroke-like episodes, ataxia, psychiatric features, exercise intolerance, abdominal pain, quadriparesis or arrhythmias (Table 24.1). The symptom free period may be prolonged, often longer than 1 year and patients are normal in between the episodes. Intercurrent illnesses, high protein intake, exercise, fasting and drug intake may precipitate symptoms. Encephalopathy occurs with little warning in previously healthy individuals, progresses rapidly, may be recurrent and is not associated with neurological deficits. Physical examination shows altered sensorium, apnea or hyperpnea and hypotonia.

Laboratory Investigations

Metabolic screening includes measurement of blood levels of glucose, electrolytes, lactate, pH, bicarbonate and ammonia. During neonatal period, ammonia levels are <200 µg/dL; subsequently levels <80 µg/dL are considered

normal. In urea cycle disorders, ammonia levels usually exceed 1000 µg/dL and cause respiratory alkalosis with compensatory metabolic acidosis. In organic acidurias, ammonia levels are <500 µg/dL and in fatty acid oxidation defects <250 µg/dL.

Urine metabolic screen includes pH, ketones and reducing substances. Urine is examined by ferric chloride, dinitrophenylhydrazine and nitroprusside tests for PKU, organic aciduria/maple syrup urine disease and homocystinuria, respectively. Biochemical screening may be normal in asymptomatic patients.

Specialized tests such as quantitative plasma amino acids analysis by high performance liquid chromatography (HPLC), acylcarnitine profile on plasma or dried blood spot by tandem mass spectrometry (TMS) and urinary organic acids by gas chromatography and mass spectrometry (GCMS) help in reaching a diagnosis. Urine samples should be obtained during the acute phase of illness and frozen at -20°C. It is advisable to provide details about drugs, diet and fluids given to the patient while ordering these tests. A pretransfusion sample is preferred, if blood transfusion is planned. All samples should be promptly transported to the lab. Examinations of cerebrospinal fluid, chest X-ray, echocardiography, ultrasound abdomen, computed tomography and magnetic resonance imaging of the head and electroencephalogram (EEG) are required in specific cases.

Based upon the abnormalities on basic metabolic screening, acutely presenting IEMs are classified into five major categories: Aminoacidopathies, organic acidemia, urea cycle disorders, mitochondrial disorders and fatty acid oxidation defects (Table 24.2). Figure 24.1 describes the initial approach in such patients.

Biochemical Autopsy

In a severely ill or dying child with suspected but undiagnosed IEM, parents should be advised of the need

Table 24.2: Differential diagnosis of metabolic disorders with acute presentation

Diagnosis	Acidosis	Ketosis	Plasma lactate	Plasma NH ₃	Plasma glucose	Special test
Aminoacidopathies	±	+	N	N	N/↓	Blood spot for TMS and plasma/urine amino acid; mutation analysis
Organic acidemia	+++	+	↑	↑↑	↓↓	Blood spot for TMS and urine GCMS; mutation analysis
Mitochondrial disorders	++	±	↑↑↑	N	N	Lactate: pyruvate ratio, blood spot for TMS, urine GCMS, muscle biopsy; mutation analysis
Urea cycle disorders	N	N	N	↑↑↑	N	Plasma amino acid, urine GCMS, urine orotic acid; mutation analysis
Fatty acid oxidation defects, glycogen storage disorders	±	N	±	↑	↓↓↓	Blood spot for TMS for acylcarnitines and urine organic acid; mutation analysis

GCMS: Gas chromatography and mass spectrometry; TMS: Tandem mass spectrometry

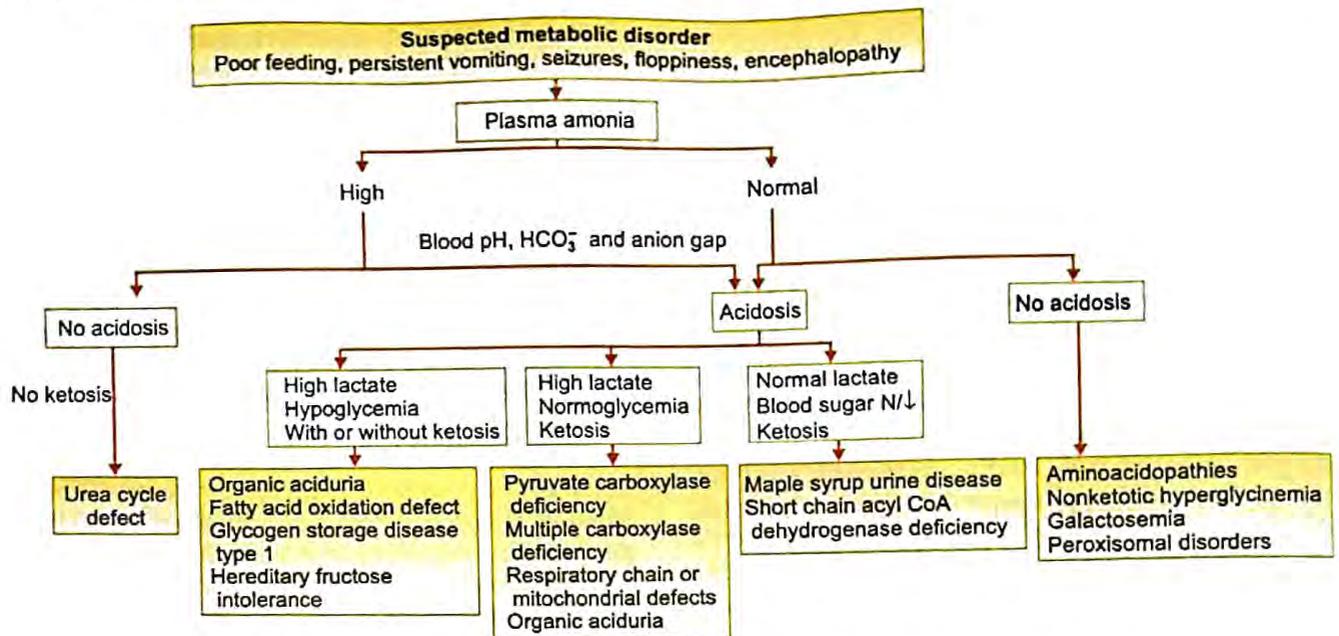


Fig. 24.1: Approach to a case with a suspected metabolic disorder. N: normal

Table 24.3: Specimens taken in critically sick children with undiagnosed IEM

Clinical photograph and infantogram

Blood: 5 mL in heparin, separated and stored at -70°C ; 5–10 mL EDTA blood (leukocytes), refrigerated and not frozen; few blood spots on filter paper (acyl carnitine analysis)

Urine: 5–10 mL frozen in plain sterile tubes

Cerebrospinal fluid: 3–5 mL in 1–2 aliquots frozen and stored at -70°C

Skin biopsy: ~3 mm diameter skin (include dermis) from the flexor aspect of the forearm or anterior aspect of thigh. Store at 37°C or refrigerate (not freeze) in culture medium or saline with glucose.

Liver, muscle, kidney, heart biopsy: At least two tissue biopsies of about 1 mm^3 , one immediately frozen in liquid nitrogen and other in the glutaraldehyde

for a biochemical autopsy for confirmation of diagnosis (Table 24.3). Specimens should be obtained before or within 1 to 2 hours of death to facilitate diagnosis.

Principles of Management

Specific treatment is directed towards reversing the basic pathophysiological process causing the disease. It includes reduction of substrate accumulation for a deficient enzyme, reduce accumulated toxic metabolites, supplement metabolites, replace deficient enzyme or enhance residual enzyme activity (Fig. 24.2). Treatment is symptomatic, supportive and often instituted empirically.

- i. Eliminate dietary or parenteral intake of potentially toxic agents (e.g. protein, fat, galactose, fructose).

- ii. Provide adequate calories (0.2% saline in 10% dextrose IV); intralipids (2–3 g/kg/day) may be infused if fatty acid oxidation defect is not suspected.

- iii. Correct metabolic acidosis, dehydration and electrolyte imbalance. Treat intercurrent illness, if any.

- iv. Enhance excretion of toxic metabolites. Immediate measures to reduce blood ammonia are necessary as the risk for irreversible brain damage is related to its concentration. IV phenylacetate and sodium benzoate with L-arginine (Table 24.4) are used as detoxifying agents, in urea cycle defects and organic acidemias. Dialysis is initiated if plasma ammonia levels >500 – $600\text{ }\mu\text{g/dL}$, or if levels do not fall within 2 hours after initiation of IV treatment. Hemodialysis is preferred to peritoneal dialysis and exchange transfusion.

Carnitine eliminates organic acids as carnitine esters, and is used in life-threatening situations associated with its deficiency, at a dose of 25–50 mg/kg IV over 2–3 minutes, followed by 25–100 mg/kg/day orally. L-carnitine should not be administered with sodium benzoate. Intractable seizures without metabolic acidosis or hyperammonemia are treated with pyridoxine 100–200 mg IV.

- v. Empiric cofactor or coenzyme therapy may be administered (Table 24.5) to maximize residual enzyme activity. Long-term adherence to dietary and pharmacologic regimen is recommended. Prompt recognition and avoidance of physiologic stresses (fever, infection, trauma, surgery, fasting) and changes in diet that may precipitate symptoms is important in preventing metabolic decompensation.

- vi. If clinical improvement is observed and a final diagnosis is not yet established, some amino acid intake is provided

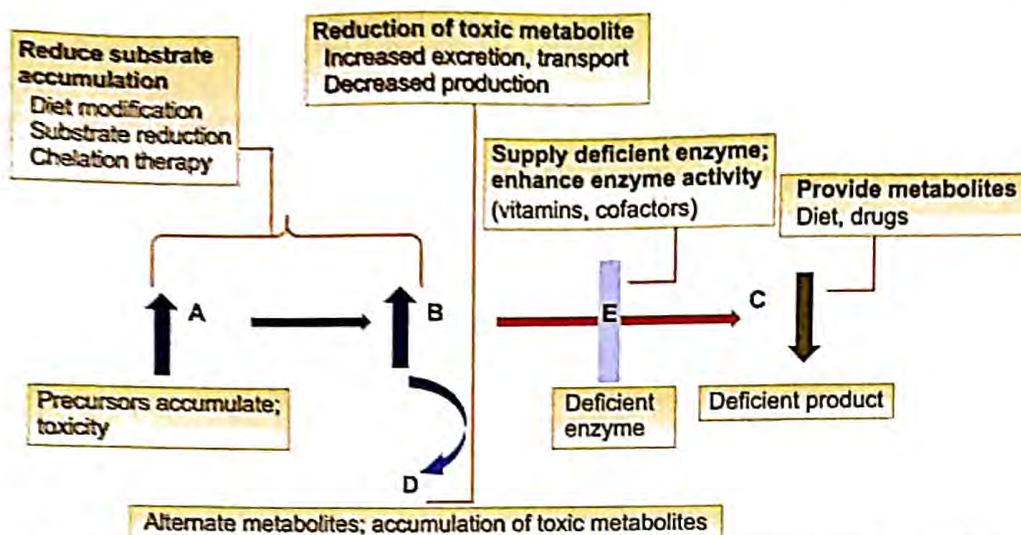


Fig. 24.2: Effect of deficient enzyme (E) on A, B and C of an affected pathway (lower panel) and different therapeutic modalities (upper panel)

Table 24.4: Management of hyperammonemia

Drug	Loading dose	Maintenance dose
Sodium benzoate and/or sodium phenylacetate	250 mg/kg (2.5 mL/kg) IV in 10% glucose over 2 hours	250–500 mg/kg in 24 hours (2.5 mL/kg /24 h) IV as continuous infusion
L-Arginine*	600 mg/kg (6 mL/kg) IV in 10% glucose over 2 hours	600 mg/kg/d IV as continuous infusion

IV: Intravenous

*Arginine HCl dose can be decreased to 200 mg/kg for carbamyl phosphate synthetase (CPS) or ornithine transcarbamylase (OTC) deficiency

Table 24.5: Cofactor and adjunctive therapy

Disorder	Oral cofactor/adjunctive therapy	Dosage (oral)
Maple syrup urine disease	Thiamine	10–15 mg/d
Methylmalonic acidemia	Vitamine B ₁₂ L-carnitine Metronidazole	1 mg/d 50–100 mg/kg/d 7.5–20 mg/kg once daily
Propionic acidemia	L-carnitine Metronidazole	50–100 mg/kg/d 10–20 mg/kg/d
Isovaleric acidemia	L-carnitine Glycine	50–100 mg/kg/d 150 mg/kg/d
Multiple carboxylase deficiency	Biotin	5–20 mg/d

after 2–3 days of complete protein restriction. Essential amino acids or total protein is provided orally or IV (begin at 0.5 g/kg/day, increased to 1–1.5 g/kg/day) until diagnostic evaluation is complete. Appropriate amino acid formula (free of precursor amino acids) or protein free infant formula with breast milk is introduced with clinical and laboratory monitoring. Expressed human milk is preferred as it can be measured and total protein intake can be quantified.

CHRONIC AND PROGRESSIVE PRESENTATION

This group of disorders is characterized by variable but insidious onset from birth to adulthood. Unexplained developmental delay with or without seizures,

organomegaly, coarse facies, cataract, dislocated lens, chronic skin lesions, abnormal hair or urine color, and failure to thrive are useful clues. These forms are divided into subgroups depending upon the involvement of specific system (Fig. 24.3).

Neurologic findings are developmental delay or progressive psychomotor retardation, seizures, ataxia, spasticity, variable hearing and visual impairment, and extrapyramidal symptoms. Psychomotor or developmental delay is the chief manifestation and tends to be global and progressive; regression of milestones may be present. Severe irritability, impulsivity, aggressiveness, hyperactivity and abnormal behavior (automatism, stereotypes, compulsive chewing of thumbs and fingers,

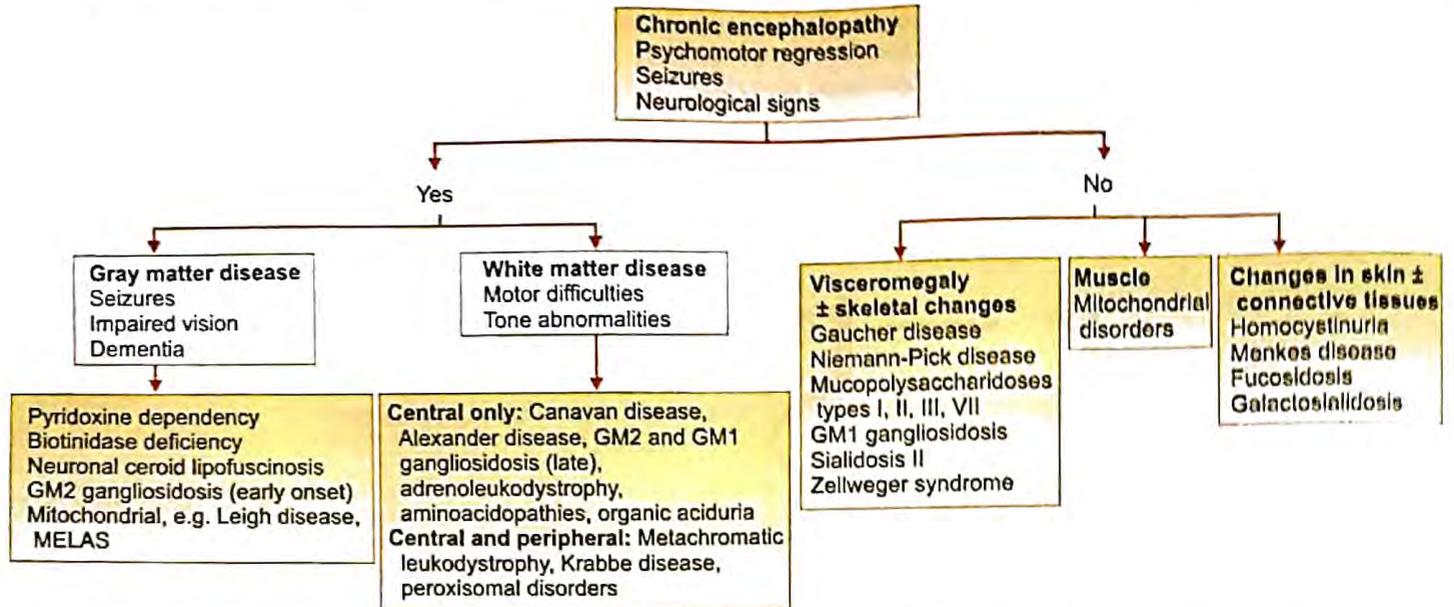


Fig. 24.3: Initial approach to a chronic encephalopathy. MLD metachromatic leukodystrophy; NCL neuronal ceroid lipofuscinosis; NPD Niemann-Pick disease; MPS mucopolysaccharidoses. Modified from: Clarke JTR. A clinical guide to inherited metabolic disease (Reference 1)

self-mutilation, nocturnal restlessness) are common. Complex partial or myoclonic seizures occur early in course of the disease and are often resistant to therapy. Differentiating between predominant involvement of grey and white matter helps in narrowing the diagnosis (Table 24.6). Movement disorders are intermittent or progressive, in form of ataxia, dystonia, choreoathetosis and Parkinsonism. Underlying conditions include late onset organic aciduria, neuronal ceroid lipofuscinosis and lysosomal storage disorders.

Muscular disorders presenting with myopathy are usually due to defects in energy metabolism. Myopathy may be progressive (glycogen storage disease, GSD types II and III), exercise intolerance with cramps and myoglobinuria (GSD V, VI) or part of multisystem disease (mitochondrial myopathies).

Hepatic presentations include presence of unconjugated or conjugated jaundice, hypoglycemia and hepatomegaly with or without hepatocellular dysfunction. Deranged lipid profile is seen in GSD types I and III, and hepatosplenomegaly in lysosomal storage disorders. Hepatocellular dysfunction is seen in galactosemia, GSD IV and III, Niemann-Pick type B and α_1 -antitrypsin deficiency. Disorders leading to cirrhosis include tyrosinemia, galactosemia, hereditary fructose intolerance and Wilson disease.

Cardiac manifestations may occur in fatty acid oxidation defects, mitochondrial disorders, GSD type II, methylmalonic acidemia, Fabry disease, Kearns-Sayre syndrome, familial hypercholesterolemia, mucopolysaccharidoses and GM1 gangliosidosis.

Table 24.6: Differentiating features of gray matter and white matter disorders

Clinical features	Gray matter disease (poliodystrophy)	White matter disease (leukodystrophy)
Age of onset	Early	Usually late (childhood)
Head size	Microcephaly (more common)	May have macrocephaly
Seizures	Early, severe	Late, uncommon
Cognitive functions	Progressive decline	Initially normal
Spasticity	At a later stage	Early, severe
Reflexes	Normal or brisk	Absent (neuropathy) or brisk (long tracts involved)
Eye	Retinal degeneration	Optic atrophy, cataract, cherry red spot
Peripheral neuropathy	Late	Early demyelination
Electromyography	Usually normal	Slowed nerve conduction velocity
Evoked potentials (VEP)	Usually normal	Prolonged or absent
Electroretinography	Abnormal	Normal
MRI brain	Cerebral atrophy mainly	White matter involvement (demyelination, dysmyelination)

Dysmorphic features are present in Zellweger syndrome, glutaric aciduria type 2 and storage syndromes.

Renal manifestations are seen in patients with cystinosis, galactosemia, hereditary fructose intolerance and tyrosinemia (renal tubular acidosis); progressive renal failure is common in cystinosis. Enlarged kidneys are seen in patients with GSD type I.

Ocular findings may be useful in ascertaining a diagnosis. Presence of cataract(s) suggests galactosemia, peroxisomal disorders, Lowe syndrome and Wilson disease; lens dislocation is seen in homocystinuria. Corneal abnormalities are seen in mucopolysaccharidoses, Wilson disease and Fabry disease. Cherry-red spots are found in various lysosomal storage diseases (Tay-Sachs disease, GM1 gangliosidosis and Niemann-Pick disease). Skin may show an eczematous rash associated with alopecia in biotinidase deficiency. Angiokeratoma are characteristic of Fabry disease, but are also seen in fucosidosis and β -mannosidosis.

Laboratory Investigations

Investigations include complete hemogram, liver and renal function tests and electrolytes. Anemia and thrombocytopenia are important features of Gaucher disease; pancytopenia may be seen in propionic and methylmalonic acidemia. Peripheral smear may show vacuolated lymphocytes in neuronal ceroid lipofuscinosis, fucosidosis and sialidosis; acanthocytosis in abetalipoproteinemia and Hallervorden Spatz disease. Adrenal insufficiency is frequent in patients with adrenoleukodystrophy. Metabolic acidosis with proximal tubular dysfunction is present in patients with Lowe syndrome, cystinosis, Wilson disease and galactosemia. Neuroimaging, electrophysiological studies and skeletal survey are useful for various neurodegenerative and storage disorders.

Bone marrow aspirate is useful to rule out specific storage disorders. Enzyme assays for various storage disorders are now available and provide definitive diagnosis. Estimation of plasma levels of lactate, ammonia, very long chain fatty acids and amino acids are useful in certain cases. DNA molecular testing is the most specific form of diagnostic testing and is useful for prenatal diagnosis.

Management

A multidisciplinary team of metabolic specialists, pediatric neurologists, clinical geneticist, cardiologist, orthopedic surgeon and physiotherapist is required to maximize the supportive care in these patients. Supply of deficient enzyme (enzyme replacement), enhancing residual enzyme activity through cofactor and megavitamin therapy (enzyme enhancement/organ transplantation), or reduction of substrate accumulation (substrate reduction) are available for these disorders (Fig. 24.2).

Since most IEMs are inherited in an autosomal recessive manner, the risk of recurrence in subsequent pregnancies is 25%. Few disorders show X-linked, autosomal dominant and mitochondrial inheritance. Prenatal diagnosis is possible by enzyme assays or mutation testing on fetal DNA, obtained through amniotic fluid or chorionic villus biopsy (Chapter 22).

Specific Disorders

Aminoacidopathies do not show a common phenotype but may have unique features (Table 24.7). Table 24.8 briefly describes urea cycle disorders and organic acidemias. Figures 24.5 and 24.6 indicate the enzymatic defects and an algorithmic approach to the diagnosis.

Defects of Carbohydrate Metabolism

These disorders include galactosemia, hereditary fructose intolerance and glycogen storage disorders. Major features include hypoglycemia, liver dysfunction with or without skeletal and/or cardiac muscle involvement.

Galactosemia

There are three disorders of galactose metabolism (Fig. 24.8), but it is the deficiency of the enzyme galactose-1-phosphate uridylyltransferase (GALT), that is referred to as classical galactosemia. Deficiency of GALT results in accumulation of galactose-1-phosphate and other metabolites (e.g. galactitol) that have toxic effects on the liver and other organs.

Patients are normal at birth, but by 3–4 days of breast milk or formula feeding show life-threatening disease with vomiting, diarrhea and poor weight gain. Jaundice and liver dysfunction are progressive and appear at the end of first or second week of life. The disease may present initially with indirect hyperbilirubinemia due to hemolysis secondary to high levels of galactose-1-phosphate in erythrocytes. Many affected infants die of *E. coli* sepsis in the neonatal period. Untreated infants, if surviving the neonatal period, have persistent liver disease, cataracts and mental retardation. Acute galactose toxicity may rarely cause chiefly neurologic symptoms. Proximal renal tubular disease presents with metabolic acidosis, galactosuria, glucosuria and aminoaciduria (Fanconi syndrome).

The diagnosis is confirmed by either enzyme or specific mutational analysis. A negative urine dipstick by glucose oxidase method with positive Benedict reaction indicates non-glucose reducing substances, e.g. galactose or fructose. A negative test does not eliminate the possibility, especially if the patient has received IV glucose for more than a few hours.

Management: If the diagnosis is suspected, whether or not urinary reducing substances are found, galactose-containing feedings should be discontinued and replaced

Table 24.7: Common aminoacidopathies

Disorder	Defect	Clinical features	Diagnosis, treatment
Phenylketonuria Autosomal recessive	Deficient phenylalanine hydroxylase; encoded by <i>PAH</i>	Profound, irreversible intellectual disability, microcephaly, epilepsy, behavioral problems Musty body odor; eczema; reduced skin, hair and eye pigmentation (Fig. 24.4)	Plasma phenylalanine >1000 $\mu\text{mol/L}$ Enzymatic; genetic testing Restrict dietary phenylalanine; aim for levels 120–360 $\mu\text{mol/L}$ Adjuvant therapy with tetrahydrobiopterin (7–20 mg/kg/day)
Maple syrup urine disease (MSUD) autosomal recessive	Low activity of branched chain alpha ketoacid dehydrogenase complex Mutations: <i>BCKDHA</i> ; <i>BCKDHB</i> ; <i>DBT</i>	Neonates: Poor feeding, ketonuria, irritability, drowsiness; progressive encephalopathy; apnea, hypertonia Typical urine smell by 5–7 days Chronic forms: Developmental delay, seizures, failure to thrive, sleep disturbances, mood swings, movement disorders	DNPH (2,4-dinitrophenylhydrazine) detects ketonuria (yellow white precipitate due to branched chain ketoacids) Elevated plasma leucine, isoleucine, valine Confirmation by genetic testing Therapy: Peritoneal or hemodialysis. Restrict dietary substrate Thiamine for milder forms Orthotopic liver transplant
Hepatorenal tyrosinemia type 1 Autosomal recessive	Deficient fumarylacetoacetate hydrolase, encoded by <i>FAH</i>	Infants: Vomiting, diarrhea, hypoglycemia, hepatomegaly, jaundice, ascites Repeated neurologic crises; change in mental status, peripheral neuropathy Death occurs <10 years from liver failure or cancer, neurologic crisis	Markedly elevated alpha-fetoprotein; high tyrosine, methionine and phenylalanine; high succinylacetone in blood, urine Confirmation by genetic testing Therapy: Nitisinone* (NTBC 1 mg/kg/day) Dietary restriction of phenylalanine and tyrosine Liver transplant for liver failure, cancer, failure to respond to NTBC
Homocystinuria Autosomal recessive	Deficient cystathionine β -synthase; encoded by <i>CBS</i>	Manifestation after 3–4 years of age Developmental delay, seizures, psychiatric problems, extrapyramidal signs, marfanoid, osteoporosis Ectopia lentis by 8 years; myopia Thromboembolism a cause of early death and morbidity	Urine nitroprusside test; high plasma levels of methionine, homocysteine Confirmation by genetic testing Therapy: Lower plasma homocysteine levels (<15 $\mu\text{mol/L}$) Methionine restricted diet; oral betaine B6 (200–1000 mg/d; responsive 50%) If folate, B12 deficiency: folate (5 mg/day), hydroxycobalamin (1 mg IM/month) Vitamin C for endothelial dysfunction GCMS can identify, quantify homogentisic acid No specific therapy; vitamin C prevents ochronosis
Alkaptonuria Autosomal recessive	Deficient homogentisate 1,2-dioxygenase	Urine turns brown black on standing; staining of diapers Grey discoloration of sclera, ear and nose cartilage (ochronosis) after 30 years Arthritis of shoulders, hips Renal stones	

by soy based or lactose free formula pending results of confirmatory enzyme assay or genetic studies. Galactose restricted diet is required throughout life.

Galactokinase deficiency: This deficiency is rare. The only significant abnormality is cataract due to accumulation of galactitol. Liver, kidney and brain symptoms are not seen. Galactose free diet, leads to improvement and prevents further damage. Galactose restricted diet is required throughout life.

Hereditary Fructose Intolerance

The condition occurs due to deficiency of the enzyme, aldolase B. Symptoms occur following ingestion of fructose or sucrose and present with intractable vomiting and symptomatic hypoglycemia. Prolonged exposure results in failure to thrive, dislike for fruits and sweets, irritability, hepatomegaly, abdominal distension, edema and jaundice. Investigations show hypoglycemia, lactic acidosis, hyperuricemia and deranged liver function tests,

Table 24.8: Urea cycle defects and organic acidemias

Disorder	Defect	Clinical features	Diagnosis, treatment
Urea cycle defects Urea cycle is the main pathway for removing highly toxic ammonia, derived from catabolism of amino acids	Urea cycle is composed of 6 enzymes (Fig. 24.5) Defects of these enzymes lead to hyperammonemia and deranged amino acid metabolism (Fig. 24.6)	Classic: Neonates have poor feeding, vomiting, tachypnea, hypothermia, irritability, seizures, lethargy and coma Partial deficiency: Symptoms delayed for months or years; often triggered by stress, high protein intake or illness Arginase deficiency: Specific symptoms; spastic diplegia, dystonia, ataxia	Hyperammonemia (ammonia >80 µg/dL after neonatal period) normal anion gap and glucose level Plasma amino acid analysis and urinary orotic acid can distinguish specific defects (Fig. 24.6) Enzyme activity; genetic testing Therapy: Removal of ammonia (Table 24.4) Restrict protein intake (essential amino acids 0.25 g/kg/d)
Organic acidemias Autosomal recessive disorders; excretion of non-amino organic acids in urine	Deficiency of specific enzyme in pathways of amino acid degradation, e.g. branched-chain amino acids (leucine, isoleucine, valine), tyrosine, homocysteine, methionine, threonine, lysine, hydroxy-lysine and tryptophan	Insidious onset with few/no acute crises or an acute metabolic encephalopathy that is precipitated by fever, fasting or infection. Multiple carboxylase deficiency and biotinidase deficiency: Additional hair and skin abnormalities (perioral eruption, alopecia) (Fig. 24.7)	Abnormal basic metabolic screening (acidosis, ketosis, hyperammonemia, hypoglycemia), abnormal liver function tests and neutropenia. Abnormal plasma acylcarnitine profile. Enzyme activity; genetic testing Acute phase: Adjunctive therapy with cofactors or vitamins (Table 24.5)



Fig. 24.4: Blond hair in a 6-year-old child with phenylketonuria including prolonged prothrombin and partial thromboplastin time. Proximal renal tubule dysfunction manifests as Fanconi syndrome. The diagnosis is confirmed by demonstration of deficiency of aldolase B in fresh liver biopsies. Fructose free diet is therapeutic.

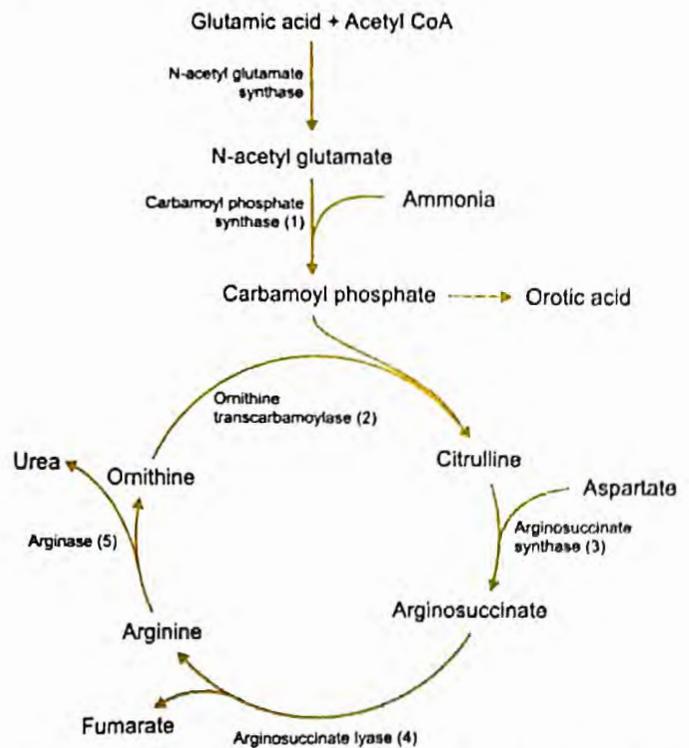
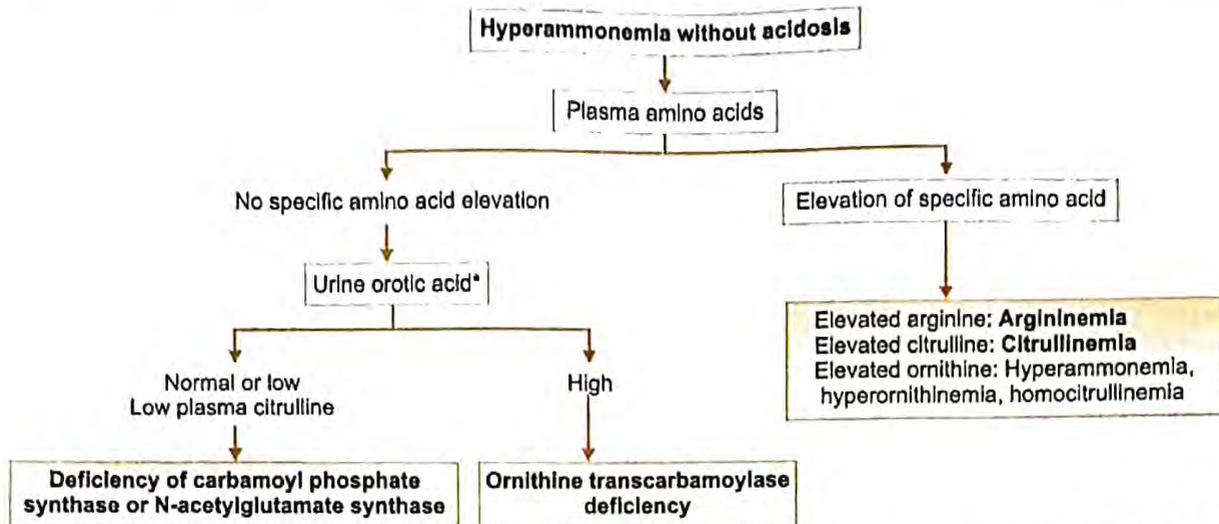


Fig. 24.5: Pathways for ammonia disposal and ornithine metabolism. Deficiency of enzymes results in the following: (1) CPS deficiency, (2) OTC deficiency, (3) citrullinemia, (4) argininosuccinic aciduria and (5) argininemia

Glycogen Storage Diseases

Glycogen is an extensively branched polysaccharide macromolecule formed by thousands of glucose units



*Transient hyperammonemia of newborns is characterized by hyperammonemia, normal levels of urine orotic acid, and normal or high plasma citrulline

Fig. 24.6: Algorithm to distinguish different urea cycle defects

joined into chains by α -1-4 and α -1-6 bond. Ingested carbohydrate is absorbed as glucose via the portal system, phosphorylated to intermediate compounds (glucose-6-phosphate and glucose-1-phosphate) and stored as glycogen. Glycogen is the main glucose reservoir in the liver and provides energy between meals or during fasting. In muscle, it provides energy for contraction. When peripheral glucose is utilized and its levels fall, glycogen is depolymerized, bonds at branch points are split and free glucose is released into blood by hydrolytic dephosphorylation (glycogenolysis) (Fig. 24.9). Defect in the synthesis and degradation of glycogen causes glycogen storage disease (GSD) or glycogenoses; most common types are I, III and IV (Table 24.9).

Fatty Acid Oxidation Defects

Fatty acid oxidation plays a major role in energy production during fasting or periods of high-energy



Fig. 24.7: Alopecia in a child with biotinidase deficiency

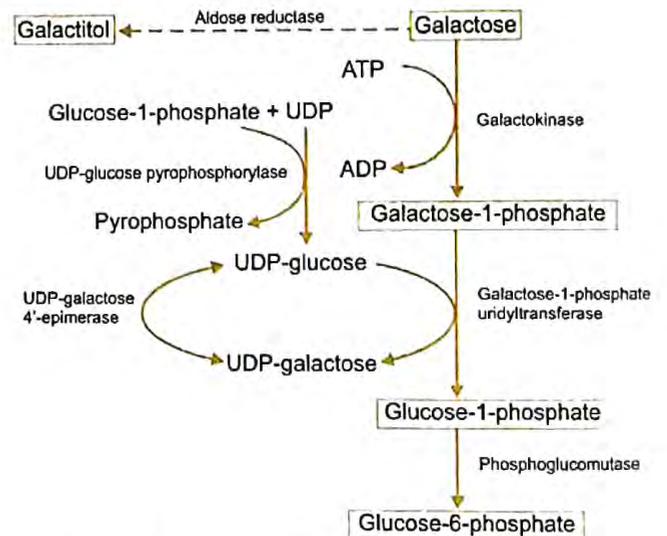


Fig. 24.8: Disorders of galactose metabolism

demand leading to glycogen depletion. It involves three processes:

Mobilization of fatty acids into mitochondria. Long chain fatty acids (C14-20) undergo active transport through carnitine shuttle; whereas short (C4 to C6) and medium chain (C12) fatty acids enter independently of carnitine and are activated to coenzyme A (CoA) esters. Disorders of carnitine cycle includes carnitine palmitoyl transferase I and II deficiency.

β oxidation. This involves removal of 2-carbon fragments (i.e. acetyl-CoA) from the transported saturated fatty acids via a four-step enzymatic reaction. Each enzyme has different chain length specificity. Deficiency of various acyl-CoA dehydrogenases (AD) results in short chain AD (SCAD) deficiency, medium chain AD (MCAD) deficiency, long chain AD (LCHAD) and very long chain AD (VLCAD) deficiency.

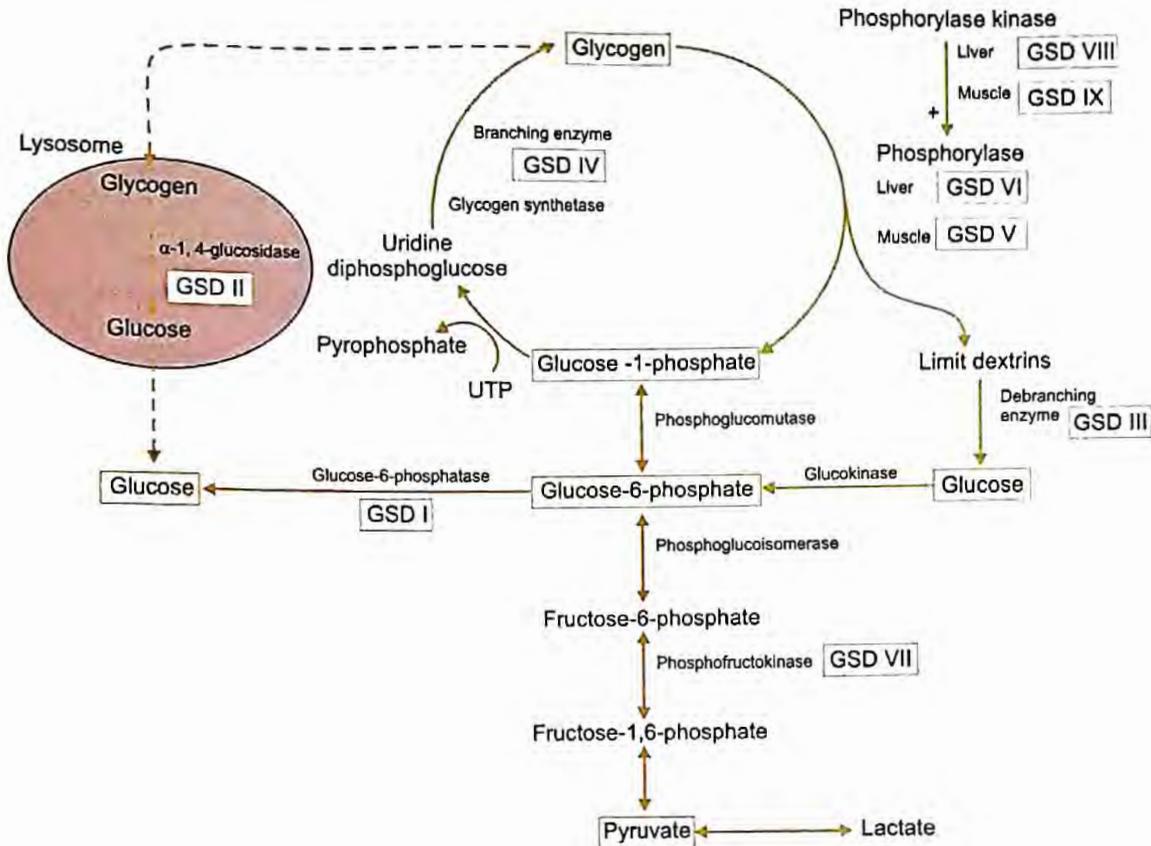


Fig. 24.9: Schematic glucose and glycogen metabolism in liver and lysosomes. Common enzyme defects and corresponding glycogenoses are depicted

Electron transfer to the respiratory chain. Acetyl-CoA is utilized as energy substrate in muscle and liver. Example glutaric acidurias type II (multiple acyl-CoA dehydrogenase or MAD deficiency).

Clinical Features

The illness may have varying severity and presents at any age. Symptoms are precipitated by fasting, exercise or intercurrent illness leading to episodes of metabolic decompensation.

- i. Acute hypoketotic hypoglycemia and encephalopathy, associated with Reye like illness, hepatomegaly and liver dysfunction.
- ii. Cardiomyopathy (hypertrophic more common than dilated) and conduction defects including arrhythmias causing sudden early death
- iii. Myopathy

The diagnosis is based on acylacrnitine profile in plasma and organic acid analysis in urine, and confirmed on enzyme assay or mutational analysis. Prolonged fasting should be avoided. Medium chain triglycerides (HCT) rich formula can be used; but is not effective is MCAD and MAD deficiency.

Mitochondrial Disorders

Mitochondria are mainly involved in the energy production pathway of oxidative phosphorylation (OXPHOS). Mitochondrial disorders refer to the defects in the OXPHOS pathway. Since mitochondria are mainly derived from the ovum, hence, mitochondrial DNA (mtDNA) disorders are maternally inherited.

Mitochondrial disorders can occur due to either alterations in mitochondrial DNA (mtDNA) or nuclear DNA (nDNA) mutations. Disorders that are due to nDNA mutations are autosomal recessive, autosomal dominant or X-linked. A mitochondrial disorder is often suspected with multisystem involvement such as stroke, hearing loss, muscle weakness, cardiomyopathy, liver dysfunction and/or endocrine dysfunction. Disorders due to mtDNA deletion/duplication mutations are chronic progressive external ophthalmoplegia, Kearns-Sayre syndrome and Pearson syndrome. Disorders caused by mtDNA point mutations include Leber hereditary optic neuropathy, maternally inherited Leigh syndrome, mitochondrial encephalopathy, lactic acidosis and stroke (MELAS), myoclonic epilepsy with ragged red fibres (MERRF), neurogenic weakness, ataxia and retinitis pigmentosa (NARP), hypertrophic cardiomyopathy, mitochondrial

Table 24.9: Clinical features and management of glycogen storage diseases

Type	Enzyme defect	Clinical features	Diagnosis
Liver glycogenoses with hepatomegaly and/or hypoglycemia			
von Gierke disease		Manifest ~3–4 months of age with hypoglycemia, seizures, doll like facies (Fig. 24.10a).	Hypoglycemia (glucose <80 mg/dL), lactic acidosis, high uric acid (>5 mg/dL), elevated cholesterol and triglycerides
Ia	Glucose-6-phosphatase		
Ib	Glucose-6-phosphate translocase	Marked hepatomegaly and growth retardation Kidneys may be enlarged Type 1b: neutropenia	Liver histology shows PAS positive, diastase sensitive glycogen and lipid laden vacuoles. Enzyme assay; DNA testing Monitor for hepatic adenomas by α -fetoprotein and ultrasound
Cori or Forbes disease		Hypoglycemia, hepatomegaly, growth retardation.	Normal or slightly increased lactic acid; normal uric acid; raised transaminases; deranged lipids
IIIa	Liver and muscle debrancher deficiency (Amylo-1, 6-glucosidase)	IIIa: associated myopathy, cardiomyopathy	Elevated creatine phosphokinase (CK) in IIIa Enzyme assay in fresh liver tissue; DNA testing
IIIb	Liver debrancher deficiency only		Liver histology shows increased glycogen with variable degree of fibrosis
Andersen disease IV	Brancher enzyme (Alpha-1, 4 glucan: alpha-1, 4 glucan-6-alpha glucosyl transferase)	Severe liver disease soon after birth; early cirrhosis and portal hypertension	Blood sugar, lipid profile, liver function tests, uric acid; urine ketones
Hers disease VI	Liver phosphorylase	Milder form; hypoglycemia, hepatomegaly	-do-
IX	Phosphorylase kinase		-do-
0	Hepatic glycogen synthase deficiency	Fasting ketotic hypoglycemia without hepatomegaly	-do-
Treatment: Continuous nasogastric infusion of glucose or uncooked starch maintains normoglycemia, especially in types I, III and IV (most demanding in type I).			
Mild to moderate restriction of lactose, fructose and sucrose. Ensure vitamins and minerals.			
Nicotinic acid, fibrates for triglyceride levels >900 mg/dL, despite dietary therapy			
Allopurinol (10 mg/kg/day) for hyperuricemia, if uncontrolled on dietary therapy			
Muscle glycogenoses; exercise intolerance often followed by rhabdomyolysis (types V, VII) and cardiomyopathy (type II)			
Pompe disease II	Lysosomal alpha-1, 4-glucosidase/acid maltase	Hypotonia, floppiness (Fig. 24.10); progressive cardiomyopathy (Fig. 24.10). EKG: Left axis deviation, short PR, large QRS complexes Tongue: large and protruding Death occurs before 1-year	Low levels of enzyme (acid maltase) in leukocytes and cultured skin fibroblasts; genetic studies Therapy: Mainly supportive; enzyme replacement
McArdle disease V	Muscle phosphorylase	Onset in adolescence; exercise intolerance, myoglobinuria Muscle weakness, hypotonia, easy fatigability and cramps	Muscle biopsy Genetic studies No specific therapy
Tarui disease VII	Phosphofructokinase		-do-

myopathy and nonsyndromic aminoglycoside-induced sensory neural hearing loss.

A markedly elevated blood lactate and lactate-to-pyruvate ratio >30 suggests an OXPHOS defect. Other biochemical features are metabolic acidosis, hypoglycemia

and ketosis. Muscle biopsy shows ragged red fibers as well as subsarcolemmal accumulation of mitochondria. Staining for succinate dehydrogenase and cytochrome C oxidase is useful. Brain magnetic resonance imaging (MRI) and/or spectroscopy are helpful in diagnosis.



Fig. 24.10: (a) A 4-year-old child with glycogen storage disease type I. Note the doll-like facies and protuberant abdomen due to hepatomegaly. (b and c) Pompe disease (type II) with marked hypotonia; and (d) Cardiomegaly

No specific therapy is available. Supportive treatment includes supplementation with cofactors such as riboflavin, coenzyme Q, folic acid, vitamin E, vitamin C, carnitine, high lipid, low carbohydrate diet and avoiding mitochondrial toxins such as sodium valproate and statins.

Lysosomal Storage Disorders

Lysosomes are one of the important cellular organelles responsible for degradation of complex cellular molecules using various acid hydrolases. Deficiency of these enzymes results in the accumulation or storage of an intermediate compound. Deposition of this stored material in several body tissues leads to cellular damage and disease symptoms.

Enzyme deficiencies in the degradation pathway of glycosaminoglycans cause *mucopolysaccharidoses*. In some glycolipid storage disorders, neurological functions are impaired due to abnormal deposition in the brain. The second category of *oligosaccharidoses* is the result of deficiencies of enzymes responsible for degradation of glycoproteins with a less complex polysaccharide (oligosaccharides) than glycosaminoglycans. The third category, *sphingolipidoses* is caused by deficiency of sphingolipid degrading enzymes. Accumulation of lipid inside the cells gives them a foamy appearance, chiefly seen in liver, spleen, lungs and marrow, with enlargement of these organs. All conditions have autosomal recessive inheritance except mucopolysaccharidosis II and Fabry disease (X-linked). Common disorders are discussed below and summarized in Table 24.10.

Mucopolysaccharidoses

Mucopolysaccharides constitute a major part of connective tissue and consist of units of disaccharides, nitrogen and esters. In mucopolysaccharidoses, acid mucopolysaccharides are deposited in the tissues and excreted in the urine. Due to lack of degradation, mucopolysaccharides accumulate in the lysosomes causing disorganization of the cell structure and function. Partially degraded

mucopolysaccharides are excreted in urine. Six different types of mucopolysaccharidoses with their subtypes are recognized. Their distinguishing features are described in Table 24.11 and are shown in Fig. 24.11.

Urinary excretion of glycosaminoglycans (GAG) by 2D electrophoresis is a useful screening test. Specific enzyme assays and DNA analyses confirm the diagnosis. Palliative care and multidisciplinary management are important. Enzyme replacement therapy is available for types I, II, IV, and VI, but the cost is prohibitive. An early bone marrow transplantation has been found to be effective in MPS III.

Sphingolipidoses

These are clinically heterogeneous disorders and include GM1 and GM2 gangliosidoses, Gaucher disease, Niemann-Pick diseases, Fabry disease, Farber disease, and Krabbe and metachromatic leukodystrophy. The most consistent feature is enlarged liver and spleen, with or without neurological involvement (Gaucher disease I and III, Niemann-Pick disease A and B, and GM1 gangliosidosis). Metachromatic leukodystrophy and Krabbe disease are characterized by white matter involvement and demyelination without organomegaly.

Gaucher disease: This is the commonest autosomal recessively inherited lysosomal storage disease. It occurs due to the deficiency of the tissue enzyme glucocerebrosidase that splits glucose from glucosylceramide, resulting in accumulation of the latter in cells of the reticuloendothelial system. Cerebroside-laden cells are large and have eccentric nuclei with vacuolated cytoplasm and 'wrinkled tissue paper' appearance (Gaucher cells). It is characterized by visceral (hepatosplenomegaly), and bone marrow involvement leading to anemia, thrombocytopenia, leukopenia, bony pains, fractures. There may be associated neurological symptoms like developmental delay, seizures and ocular involvement.

Non-neuronopathic (type I) is the commonest form and characterized by absence of neurological symptoms. Signs

Table 24.10: Clinical features of common lysosomal storage disorders

Disorder	Cherry-red spot	Visceromegaly	Skeletal changes	Developmental delay	Bulbar signs
Gangliosidosis GM1	+	+	+ (variable)	+	-
Gaucher disease	-	+	+	+	+ types II, III
Krabbe disease	-	-	-	+	-
Metachromatic leukodystrophy	+ occasionally	-	-	+	-
Multiple sulfatase deficiency	+	+	+	+	-
Niemann-Pick disease	+	+	-	+ types A, C	-
Sandhoff disease	+	+	+ variable	+	+ infantile forms in late stages
Tay-Sachs disease	+	-	-	+	+ infantile forms in late stages
Neuronal ceroid lipofuscinosis	Pigmentary retinopathy/ optic atrophy	-	-	+ regression	-

Table 24.11: Differentiating features of mucopolysaccharidosis

MPS type	Developmental delay	Coarse facies*	Viscero megaly	Joint contractures	Dysostosis multiplex**	Corneal clouding	Urine glyco-saminoglycans
Hurler/IH	+ (severe)	+ (severe)	+	+	+	+	Dermatan sulfate
Scheie/IS	-	+ (mild)	± (mild)	+	± (mild)	+	Keratan sulfate
Hunter/II	+ (mild to severe)	+	+	+	+	-	Keratan sulfate
Sanfilippo/III	+ (severe)	+ (mild)	±	-	± (minimal)	- (minimal)	Heparan sulfate
Morquio/IV	-	+ (mild)	-	-(laxity)	+	±	Keratan and chondroitin sulfate
Maroteaux-Lamy/VI	-	+	+	+	+	+	Dermatan sulfate
Sly/VII	+ (severe)	+	+	+	+	±	All except keratan sulfate

* Depressed nasal bridge, thick lips and ala nasi, enlarged tongue and peg-like teeth

** Dysostosis multiplex refers to thickened skull, deformity of sella turcica, broad spatulate ribs, beak shaped vertebrae and proximal tapering of metacarpals

and symptoms can develop at any age and include anemia, fatigue, poor growth, delayed puberty, easy bleeding and bruising, weak bones, bone and joint pain, fractures and enlarged liver and spleen (Fig. 24.12a).

Neuronopathic forms show involvement of the central nervous system. Two types are distinguished by the rate of neurological progression. Type II (acute neuronopathic) presents early in fetal life as hydrops or in early infancy with neurological signs and involvement of spleen and liver involvement. Course is rapidly progressive leading to early death by 2–4 years. Type III Gaucher disease (chronic neuronopathic, Fig. 24.12b) a chronic form with indolent course and manifestations in early childhood. Signs and symptoms are same as in type 1 except that neurological involvement is slowly progressive and leads to death by second or third decade. Neurological symptoms include developmental delay, stridor, squint

and swallowing difficulty, opisthotonus, head retroflexion, spasticity and trismus, abnormal eye movements, oculomotor apraxia (trouble in moving eyes to look side-to-side, need to turn head to see things on the side), saccadic initiation failure (failure in starting fast eye movements) and optokinetic nystagmus, dementia and ataxia, generalized tonic-clonic seizures and progressive myoclonic epilepsy.

Diagnosis is made by measuring glucocerebrosidase levels in leukocytes or skin fibroblasts. Serum chitotriosidase levels are elevated. Neuro-ophthalmological investigations, hearing assessment by brain evoked response audiometry, EEG and neuropsychometry tests are required. DNA analysis is helpful in assessment of phenotype and prenatal diagnosis.

This was the first storage disorder for which treatment was available, chiefly as enzyme replacement therapy and



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Fig. 24.11: Mucopolysaccharidoses: (a) Patient with type IH disease showing corneal clouding and coarse facial features; (b) MPS, type II without corneal clouding but with facial coarseness; (c) MPS IHS (milder phenotype) with restriction of joint movements; (d) Short trunk with barrel-shaped chest and sternum protruding forward in MPS IV (morquio disease); (e) Mild facial coarseness in A child with MPS III; (f) MPS VI (Marotaeux-Lamy) with abnormal skull and facial coarseness; (g) Beaking of the inferior margins of vertebrae and proximal pointing of metacarpals in MPS type I; (h) Central beaking of the lumbar vertebrae with proximally pointed metacarpals and short ulnae in MPS IV

substrate reduction therapy. The former provides deficient enzyme to allow breakdown of fat in cerebroside laden cells. Enzyme replacement does not have much effect on neurons so CNS manifestations are irreversible. Therapy is recommended in types I and III but not in type II. Substrate reduction therapy means reducing the production of fatty material, thereby avoiding cellular accumulation. Miglustat is oral treatment for adult patients

with type I Gaucher disease with mild to moderate manifestations for which enzyme therapy is not an option. Splenectomy increases the risk of progressive skeletal and pulmonary disease. Stem cell transplantation is a potential option.

Metachromatic leukodystrophy: Sulfated glycosphingolipids accumulate in white matter of the central nervous system,



Fig. 24.12: (a) Gaucher type I: Note protuberant abdomen due to hepatosplenomegaly; and (b) Gaucher type III: Note trismus and ophthalmoplegia

stains them purple with a brown background, resulting in metachromatic staining.

The disorder has infantile and juvenile forms. Early manifestations include disturbances of gait, incoordination and progressive mental deterioration in the second year of life. Knee jerk is brisk but ankle reflex and plantar response may be absent because of involvement of peripheral nerves. Diagnosis is confirmed by level of the enzyme, arylsulphatase A in white cells. There is no effective treatment; bone marrow transplantation has been tried.

GM₂ gangliosidosis: Inborn errors of GM₂ ganglioside metabolism result in accumulation of the metabolite within lysosomes of nerve cells. Most infants with Tay-Sachs form (type I) of the disease have severe deficiency of β -N-acetylhexosaminidase A (hexosaminidase A). Hexosaminidase A and B are deficient in Sandhoff disease (type II).

Tay-Sachs disease is an autosomal recessively inherited defect, which results from deficiency of hexosaminidase enzyme leading to accumulation of GM₂ ganglioside within ganglion cells of the nervous system. The disorder manifests by 6 months with loss of head control and the ability to sit. The head is disproportionately large. This is followed by progressive course with eventual spasticity, deafness and blindness. Fundus shows cherry-red spot. Death occurs within 4–5 years. In Sandhoff disease, visceral involvement is present in addition to features of Tay-Sachs disease.

Niemann-Pick disease: This is an autosomal recessive disorder of sphingomyelin and cholesterol in the lysosomes. In the classical form (type A), clinical features begin in early life with feeding difficulties, failure to thrive and developmental delay and later neuroregression. There is protuberant abdomen with hepatosplenomegaly. Cherry-red spot on fundus examination is seen in about half the cases. Diagnosis is confirmed by measurement of

sphingomyelinase levels. Type B disease is a milder form with hepatosplenomegaly but no neurological involvement. Late onset variants (type C) are associated with extrapyramidal manifestations. There is no specific treatment. Table 24.10 summarizes the clinical features of common sphingolipidosis.

Peroxisomal Disorders

Peroxisomes are involved in the oxidation (β -oxidation of phytanic acid and of very long-chain fatty acids, VLCFA) as well as synthesis of plasmalogens. Based upon their functioning, peroxisomal disorders can be divided into two major groups.

Disorders of peroxisomal biogenesis or importation are caused by defects in the transfer of proteins produced in the cytosol into the peroxisomes. This includes Zellweger syndrome (Fig. 24.13), neonatal adrenoleukodystrophy and infantile Refsum disease and rhizomelic chondrodysplasia punctata (Fig. 24.14). These disorders have autosomal recessive inheritance and are caused by defects in genes coding for peroxins (PEX). Defects interfere with peroxisomal biogenesis and import of proteins into peroxisome.

Disorders of individual peroxisomal enzymes include X-linked adrenoleukodystrophy and classical Refsum disease.

X-linked adrenoleukodystrophy (ALD) is an X-linked recessive disorder caused by tissue accumulation of VLCFA with a carbon chain length of 24 or more due to deficient peroxisomal degradation of fatty acids. The defective gene (ABCD1 gene) is located on Xq28. The childhood cerebral form usually manifests between 4 and 8 years of age with subtle initial manifestations of worsening school performance and behavioral problems such as hyperactivity and emotional lability. Auditory and visual disturbances may be associated. Seizures are often the initial manifestation. In most patients, adrenal dysfunction is noticed after the cerebral symptoms. Rapid neurological progression ensues causing increasing spasticity, visual and hearing impairment. MRI brain typically shows demyelination in the parieto-occipital areas (Fig. 24.15).

In adolescents, the usual age of manifestation is between 10 and 21 years and progression is much slower than the above form. Adrenomyeloneuropathy is a milder form with onset in late adolescence or adulthood and is characterized by progressive paraparesis due to long tract degeneration in the spinal cord.

Elevated plasma levels of VLCFA can identify patients and 85% of female carriers of X-adrenoleukodystrophy. Mutation analysis is the most reliable method to identify carriers. Corticosteroid replacement should be given for adrenal insufficiency. Bone marrow transplantation is curative but needs to be performed early in the disease. The role of Lorenzo oil is controversial.



Fig. 24.13: An infant with Zellweger syndrome. Note flat facial profile



Fig. 24.14: (a) One-month-old child with rhizomelic chondrodysplasia punctata. Note the facial dysmorphism and contractures at elbow and knee; and (b) X-ray showing rhizomelic shortening

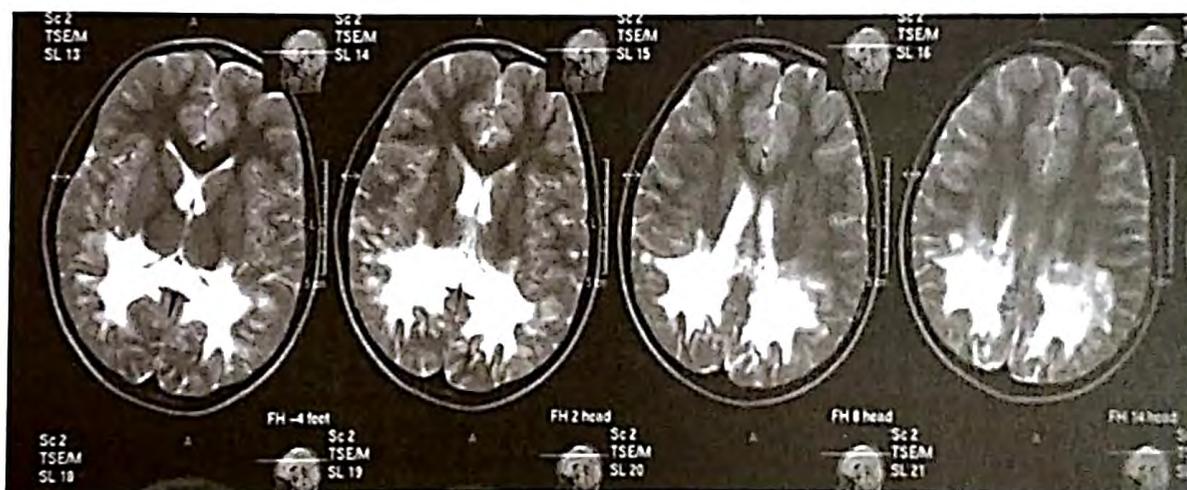


Fig. 24.15: Brain MRI findings in X-linked adrenoleukodystrophy. T2-weighted axial images show symmetrical hyperintense signal changes in bilateral perieto-occipital white matter and splenium of corpus callosum [Courtesy: Dr. Atin Kumar, AllMS, New Delhi]

Suggested Reading

- Clarke JTR. General principles. In: A clinical guide to inherited metabolic diseases, 3rd edn. New York: Cambridge University Press, 2006.
- Saudubray JM, van den Berghe G, Walter JH. Inborn metabolic diseases: Diagnosis and treatment, 5th edn. Springer Medizin; 2011.

Ophthalmic Disorders

Radhika Tandon

Children may present with varied primary eye problems. Several systemic diseases have ocular manifestations, some of which are very useful in making the correct diagnosis and instituting appropriate management. Also, therapies for some diseases are known to have ocular side effects which need to be recognized. Rarely, medications for eye diseases can have systemic side effects. Finally diseases beginning in the eyes and adnexa can have systemic complications.

PEDIATRIC EYE SCREENING

The concept of screening children for eye diseases is based on the awareness that infants and young children cannot communicate their symptoms and visual difficulties. In addition, several potentially blinding diseases manifest in this age group; their early detection and treatment can limit ocular morbidity and prevent irreversible blindness.

The goal of pediatric eye screening is to detect eye and visual disorders in children or identify their risk factors so that the child can be referred for detailed ophthalmic evaluation, confirmation of diagnosis and appropriate medical management.

Comprehensive Pediatric Eye Evaluation

Presence of any of the following risk factors is an indication for referral for comprehensive ophthalmic evaluation.

- I. *General health condition, systemic disease or use of medications associated with eye disease*
 - Extreme prematurity (gestational age ≤ 30 weeks); suspected retinopathy of prematurity
 - Intrauterine growth retardation
 - Perinatal complications
 - Neurological disorders
 - Juvenile rheumatoid arthritis
 - Thyroid disease
 - Craniofacial abnormalities
 - Diabetes mellitus
 - Syndromes with known ocular manifestations
 - Chronic steroid therapy; use of hydroxychloroquine or other medications known to affect eyes
 - Suspected child abuse

- II. *Family history of any of the following*

- Retinoblastoma
- Childhood cataract
- Childhood glaucoma
- Refractive errors in early childhood
- Retinal dystrophy or degeneration
- Strabismus and/or amblyopia
- Sickle cell disease
- Syndromes with ocular manifestations
- Nontraumatic childhood blindness

- III. *Signs or symptoms reported by the family, health care provider or school teacher*

- Defective ocular fixation or visual interactions
- Abnormal appearance of the eye(s)
- Squinting or tendency to close one eye in certain situations
- Any obvious ocular alignment, movement abnormality, head tilt or nystagmus
- Large and/or cloudy eye(s)
- Drooping of the eyelid(s)
- Lumps or swelling around the eye(s)
- Persistent or recurrent tearing, sticky discharge, redness, itching or photophobia
- Learning disabilities or dyslexia

Guidelines for Examination

Children are best examined in a comfortable and friendly environment. Very young children can remain in the lap of their mother while older children can be distracted with toys and colorful objects. When the child first enters the room, simple observation of behavior, fixation, movement and general awareness of the surroundings are good indicators of the child's visual status, and gross abnormalities can be detected.

Steady fixation and uniform steady alignment of the eyes develop in the first 4–6 weeks. Visual acuity assessment in children less than 6 months of age is limited to seeing if the child attempts to fix and follow light. A child 6–12 months of age can follow and even reach out towards colorful objects, and this permits a very crude assessment of gross visual ability. A more objective assessment can be made

Diseases Affecting the Conjunctiva and Anterior Segment

Some of the important conditions that may be seen include conjunctival telangiectasia, hazy or opaque cornea (causes of which can be memorized using the mnemonic STUMPED, i.e. sclerocornea, birth trauma, ulcer, mucopolysaccharidosis, Peter anomaly, endothelial dystrophy or endothelial dysfunction secondary to congenital glaucoma, and dermoid); flat cornea (cornea plana), anterior segment dysgenesis, aniridia, iris coloboma, primary congenital or juvenile developmental glaucoma, lens opacity or cataract, lens coloboma, displaced or subluxated lens or ectopia lentis, abnormal shape of lens such as microspherophakia, lens coloboma, lenticonus and persistent hyperplastic primary vitreous (Fig. 25.2).



Fig. 25.2: Child with bilateral congenital corneal opacity due to anterior segment dysgenesis. Differential diagnoses include all causes of congenital corneal opacity, congenital glaucoma with buphthalmos and corneal edema due to raised intraocular pressure



Fig. 25.3: Sequelae of keratomalacia causing corneal opacity right eye and phthisis bulbi left eye

child is vomiting and cannot retain oral supplement, an intramuscular injection of vitamin A may be given instead. For children less than 1 year of age and those weighing less than 10 kg, half the dose is given to avoid vitamin A toxicity and vitamin A induced intracranial hypertension.

Infections

Preseptal cellulitis and orbital cellulitis manifest as swelling and inflammation of the eyelids, are differentiated clinically, and often occur due to spread of infection from the lids, adnexa or paranasal sinuses or following trauma. These are potentially dangerous infections as they involve the anatomical 'dangerous area of the face' and if not treated promptly and adequately, can spread intracranially, resulting in meningitis or cavernous sinus thrombosis. Ultrasonography is required to detect an orbital abscess, which has to be drained. CT scan or MRI is required if involvement of adjacent paranasal sinuses or intracranial involvement is suspected. Treatment requires systemic antibiotics and anti-inflammatory agents, supplementation with topical antibiotics, and supportive measures, including lubricating eyedrops to prevent corneal damage.

Other infections involving the eyelids include blepharitis, hordeolum externum (stye), hordeolum internum (infected chalazion), molluscum contagiosum and phthiriasis of the eyelashes. Lid hygiene, hot fomentation and local antibiotic ointments are useful along with instructions for personal hygiene. Phthiriasis will require mechanical removal of nits adhering to the eyelashes, local application of 20% fluorescein sodium to the lid margins and systemic ivermectin therapy for recalcitrant cases, along with advice on hygiene and treatment of other affected family members.

Common infections of the ocular surface include conjunctivitis which could be bacterial, viral or chlamydial. Conjunctivitis occurring within the first month after birth is called *ophthalmia neonatorum*. Every effort should be made to identify the etiologic agent, especially in cases of *ophthalmia neonatorum*, since gonococcal conjunctivitis can

ACQUIRED EYE DISEASES

Nutritional Disorders

The most important condition in this category is vitamin A deficiency which can be catastrophic in young children if severe enough to produce keratomalacia. Up to the age of six months, children have adequate hepatic reserves of vitamin A. However, if the mother's nutrition is poor or the infant is not properly fed after birth, severe vitamin A deficiency may be precipitated by an attack of acute respiratory infection such as measles, pneumonia or acute gastroenteritis, which could lead to bilateral blindness due to severe keratomalacia (Fig. 25.3). Milder forms of vitamin A deficiency may manifest with xerosis of the conjunctiva, Bitot spot and nyctalopia or night blindness. Adequate nutritional advice to the pregnant and lactating mother and proper weaning with vitamin A rich fruits and vegetables is advised. Keratomalacia is treated with oral vitamin A 200,000 IU stat followed by a second dose after 24 hours and a third dose after 2 weeks. In case the

cause loss of vision in the newborn. Conjunctival smears and swabs can be sent for microbiological evaluation. Mucopurulent conjunctivitis is treated with topical antibiotic eyedrops and supportive measures such as cleansing the eye with clean water, lubricating eyedrops and cold compresses.

More severe infections include keratitis and corneal ulcers (Fig. 25.4). Trauma is the most common underlying predisposing factor, but poor hygiene and lowering of local immunity secondary to chronic inflammation, viral infections or use of topical steroids are other risk factors for bacterial and fungal infections of the cornea. Trauma with vegetative matter, such as a thorn, tree branch or wooden broomstick (often used for making 'bows and arrows' for playing), predisposes to fungal infections. Corneal ulcers require an examination under anesthesia for detailed evaluation and corneal scraping for microbiological analysis. Empirical therapy for bacterial corneal ulcers is started with a combination of freshly prepared fortified topical antibiotics such as 5% cephazolin and 1.3% tobramycin eye drops hourly and half hourly alternately round the clock for the first 48 hours. After 48 hours, the culture report and clinical response are reviewed. If there is no substantial clinical improvement, the antibiotic is changed based on microbiology results. If clinically responding to therapy, the frequency of antibiotics can be reduced to use during waking hours only, followed two days later by two hourly application, then reduced to 4 hourly or 6 hourly, and discontinued a week after the ulcer has healed. Supportive measures include topical cycloplegics, hot fomentation, analgesics, antiglaucoma medication if secondary glaucoma is present, and antibiotic ointment at night. Fungal keratitis is treated with topical



Fig. 25.4: A partially treated hypopyon corneal ulcer. The overlying epithelial defect has healed, but there is a deep corneal abscess, corneal edema and purulent fluid, i.e. hypopyon in the anterior chamber

natamycin (5%) 1 hourly with supportive measures. Herpes simplex viral keratitis is treated with topical acyclovir 3% eye ointment for epithelial involvement and systemic acyclovir for herpetic keratouveitis or recurrent disease.

Other infections include endophthalmitis (traumatic, metastatic, or iatrogenic following intraocular surgery) and parasitic infestations, such as toxoplasmosis, toxocariasis, and cysticercosis of the eye, extraocular muscles or orbit.

Allergic and Inflammatory Diseases

Children may develop allergic diseases of the skin around the eye and the ocular surface and conjunctiva. Dermatitis may be an allergic reaction to local ophthalmic medication or sometimes secondary to insect bite, application of traditional eye medicines or herbal remedies and use of local creams or lotions. In addition, a variety of environmental and hereditary factors may interplay to produce a variety of allergic conjunctival manifestations such as seasonal allergic conjunctivitis, hay fever conjunctivitis, perennial or chronic allergic conjunctivitis, atopic allergic conjunctivitis and vernal keratoconjunctivitis. Itching, redness, discomfort, gritty or foreign body sensation, watering, mucoid or thick ropy discharge, photophobia and blepharospasm are all seen in different combinations and varying degrees of severity. Treatment includes cold compresses, topical antihistaminic eyedrops for mild cases and counseling to avoid rubbing the eyes. Topical corticosteroid eyedrops give quick relief but are best avoided in mild cases because of the danger of self-medication and unsupervised chronic topical use complicated by steroid induced glaucoma and secondary corneal infection and ulceration. More severe allergies may have secondary consequences in the form of dry eye, keratopathy and corneal ulceration. These are best referred to ophthalmologists for expert management and careful follow-up.

Other inflammatory diseases include phlyctenular conjunctivitis or keratoconjunctivitis (believed to be an 'allergic' immunological reaction to tubercular antigen); interstitial keratitis secondary to infections like rubella, syphilis, leprosy and tuberculosis; and uveitis, either idiopathic or associated with juvenile chronic arthritis, psoriasis, tuberculosis, sarcoidosis and toxoplasmosis. Acute anterior uveitis (iritis, cyclitis and iridocyclitis) usually presents with a red inflamed eye with photophobia and diminution of vision. Chronic uveitis may be less symptomatic with decreased vision due to complicated cataract. Intermediate and posterior uveitis (pars planitis, vitritis, retinitis, choroiditis and retinochoroiditis) are usually painless with symptoms of decreased vision (due to hazy media and retinal or optic nerve swelling and inflammation) and floaters (due to inflammatory cells in the vitreous). Treatment is with topical cycloplegic agents and steroids, supplemented with systemic steroids and specific therapy for any underlying disease, such as

tuberculosis. Patients with uveitis need detailed examination with a slit lamp biomicroscope to identify the inflammatory response, ophthalmoscopy to view the fundus and specialist ophthalmic care and follow-up to control the inflammation and minimize the morbidity related to the disease and its treatment.

Intraocular (retinoblastoma or juvenile xanthogranuloma) or systemic malignant disorders may sometimes mimic uveitis syndrome due to malignant cells in the eye and vascular uveal tracts.

Optic neuritis is another important inflammatory disease which could be idiopathic, secondary to infections or associated with demyelinating disorders. Classical features include a rapid drop in vision, usually in one eye, which is accompanied by a relative afferent pupillary defect and normal fundus (retrobulbar neuritis) or inflammatory swelling of the optic disc (papillitis) and retinal edema and/or exudates (neuroretinitis). Patients need to be treated in consultation with a neuro-ophthalmologist after investigations to identify the cause.

Metabolic and Endocrine Disorders

Homocystinuria is associated with subluxation of the lens, and secondary glaucoma can be seen as a complication. The lens is usually subluxated downwards which causes poor vision due to displacement and astigmatism. Surgical lens removal has to be done under general anesthesia taking suitable precautions, as the patients are prone to thromboembolism. Optical rehabilitation is usually done with spectacles or contact lenses, though in some cases intraocular lenses can be fitted using scleral or bag fixation augmented with bag fixation devices.

Various storage disorders such as cerebral storage disease, lipidosis and gangliosidosis may be associated with a 'cherry red spot' due to abnormal deposition in the retina, corneal clouding as in some of the mucopolysaccharidoses, and Kayser-Fleischer ring in peripheral cornea in Wilson disease. Juvenile diabetes mellitus may be associated with cataract and diabetic retinopathy and thyroid dysfunction with dysthyroid eye disease. Tyrosinase deficiency might be associated with ocular albinism with foveal hypoplasia and poor vision.

Musculoskeletal and Neurodegenerative Diseases and Phakomatoses

Marfan and Ehlers-Danlos syndromes may be associated with subluxated lens and consequent secondary glaucoma. Marfan syndrome is usually associated with upward and outward displacement of the lenses and myopia with blurred vision. Retinal detachment is not connected also common. Surgical lens removal becomes necessary if the vision is not corrected with spectacles or contact lenses. Leukodystrophies and demyelinating diseases may be associated with extraocular muscle weakness, ptosis and optic neuropathy. Phakomatoses like neurofibromatosis,

Sturge-Weber syndrome and nevus of Ota may be associated with café au lait spots, plexiform neurofibromas of the lids and orbit and Lisch nodules on the iris and glaucoma.

Muscular dystrophies or degenerations such as chronic progressive external ophthalmoplegia result in ptosis and restriction of eye movements. Duchenne muscular dystrophy may be associated with cataracts.

Tumors and Neoplastic Diseases

Benign tumors include dermoids of orbit, lids or on cornea, hamartomas, osteoma, vascular malformations or hemangiomas of various types and neurofibromas. Malignant intraocular tumors are confined to retinoblastoma (Fig. 25.5), juvenile xanthogranuloma, medulloepithelioma and metastatic lesions from neuroblastomas, Ewing sarcoma, leukemias and lymphomas. Orbital tumors include rhabdomyosarcoma, Langerhans cell histiocytosis, extraocular spread of retinoblastoma, metastatic spread of Ewing sarcoma, neuroblastoma, leukemia and lymphoma.

Refractive Errors

An abnormality in the refractive and focusing apparatus makes it difficult for parallel rays of light from the distance to be accurately focused on the retina. This deviation from the normal emmetropic state is termed 'ametropia' or refractive error. This manifests as poor or blurred vision which may be noticed by parents, relatives, friends, school teachers or reported by the child as a difficulty in viewing clearly. Sometimes, indirect evidence is reported as eye rubbing, 'squinting', 'going too close to the television' or holding objects too close to the eyes. An assessment of visual acuity is followed by cycloplegic refraction; fundus evaluation is required in addition to routine ophthalmic evaluation. Refractive errors include myopia, hypermetropia and astigmatism, and spectacles must be prescribed accordingly. Associated amblyopia or strabismus must be taken care of and any additional features like nystagmus or extraocular muscle imbalance ruled out. Patients need to be carefully counseled with respect to improvement of vision with spectacles and need for compliance with follow-up. Failure to show an improvement of vision warrants investigations to rule out any associated subtle pathology



Fig. 25.5: 'Leukocoria' or white pupil in an infant secondary to retinoblastoma. Note the white appearance that appears to be from a structure located more posteriorly, has a slight yellowish pinkish tinge due to vascularization and has an appearance that is unlike that seen with a cataract. Ultrasonography of the orbits helps confirm the diagnosis

such as microstrabismus, retinal macular degeneration, retinitis pigmentosa, congenital hereditary cone dystrophy, delayed visual maturation, dyslexia or Leber amaurosis.

Strabismus and Amblyopia

Strabismus is defined as the condition when the visual axes of the two eyes do not meet at the point of regard. In other words, the motor and sensory alignment of the two eyes and their images in the brain are not synchronized. The cause may be a basic abnormality of development as in essential esotropia or exotropia (concomitant squint when the angle of deviation or separation of the two eyes is uniform, irrespective of the direction or position of gaze) or secondary to extraocular muscle paralysis, e.g. paralytic squint, orbital space occupying lesion, myositis or orbital inflammation as in orbital pseudotumor syndrome, orbital musculofascial abnormality like Duane retraction syndrome or Brown's superior oblique tendon sheath syndrome (causing an incomitant or nonconcomitant squint, where the deviation is more in certain positions and less or even absent in some positions of gaze).

An inward deviation of the eye is termed esotropia and outward deviation is termed exotropia. The child initially suffers diplopia due to the different images being presented to the visual cortex by the two eyes, but learns to suppress one image, eventually developing amblyopia or a 'lazy eye' with loss of binocularity and stereopsis. In very young children, the presence of an intermittent or constant squint or misalignment of the eyes should be indications for referral to an ophthalmologist.

Amblyopia or 'lazy eye' is a condition of subnormal vision defined as two lines less than normal or less than the fellow eye on the visual acuity chart with no anatomical cause detectable on examination, i.e. no media opacity and a normal fundus. Amblyogenic factors have their maximum impact on the immature developing visual system, i.e. during the first 6 yr of life and include sensory deprivation or abnormal binocular interaction. The former would refer to a corneal opacity or cataract which, even if taken care of surgically, do not indicate good chances of restoration of normal vision. Similarly, abnormal binocular interaction occurs in the presence of strabismus or anisometropia (difference in the refractive power of the two eyes), in which case one eye takes over and the visual cortical neurons meant to receive stimuli from the other eye are unable to develop normally, leading to a 'lazy eye'. These changes are potentially reversible with appropriate therapy in the first decade, but become irreversible and permanent later. Treatment involves restoration of vision with correction of refractive error, removal of media opacity if present (such as corneal opacity or cataract), patching therapy by part time patching of the 'good' eye to enable the 'lazy' eye to catch up, and strabismus surgery to restore ocular alignment if required.

Cataract

A visible lenticular opacity in the eye is termed as a cataract. It is congenital if present since birth, developmental if appearing later on, and traumatic if occurring after an episode of eye trauma. A central opacity is considered visually significant if it impairs visual acuity, and on clinical assessment obstructs a clear view of the fundus. A cataract may be unilateral or bilateral and symmetric or asymmetric. In view of the risk of sensory deprivation amblyopia, visually significant cataract should be treated surgically as soon as possible after birth. Functional success is highest if operated within the first few weeks after birth, provided the child is medically fit to undergo general anesthesia. Unilateral cataracts must be supplemented with postoperative patching therapy to take care of any amblyopic effect. Optical and visual rehabilitation for the aphakic state resulting from lens removal includes the implantation of an intraocular lens (IOL) for children above two years of age. Generally, intraocular lenses are avoided for children less than two years old as there are significant problems of change in lens power requirements as the maximum growth of the eyeball takes place during the first two years of life and the risk of complications of glaucoma and intraocular inflammation and fibrosis are higher. In very young children, therefore, a capsule rim is left for subsequent secondary IOL implantation, and temporary optical rehabilitation is provided with spectacles or contact lenses supplemented with patching for amblyopia in unilateral cases (Fig. 25.6).



Fig. 25.6: A child with bilateral developmental cataract. The cataract is partial and the condition was detected late. Also note that the child has a convergent squint. The child also has impaired hearing and congenital heart disease, suspected to be due to congenital rubella syndrome

Glaucoma

Primary congenital and developmental juvenile glaucoma are now recognized to be inherited diseases. Primary congenital glaucoma is associated with *CYP11B1* gene, (2p21) with a predominantly autosomal recessive mode of inheritance, and mutations in the myocillin (*MYOC*) gene. Photophobia, blepharospasm, watering and an enlarged eyeball are classic symptoms. Suspicion of glaucoma or buphthalmos warrants urgent referral to an ophthalmologist. An examination under anesthesia is required to measure the corneal diameter and intraocular pressure, and to visualize the optic disc. Once glaucoma is confirmed, medical therapy is started to lower the pressure and patient prepared for surgery. If the cornea is clear enough to allow visualization of the angle structures, a goniotomy is attempted. If the glaucoma is more severe or the cornea very edematous, a drainage procedure is undertaken to open alternative aqueous drainage channels such as trabeculectomy and trabeculotomy. If the cornea fails to clear after adequate control of the intraocular pressure, corneal transplantation is required to restore vision and prevent irreversible sensory deprivation amblyopia.

Children can also develop secondary glaucoma due to chronic use of topical corticosteroid eyedrops, following eye trauma particularly if associated with traumatic hyphema (blood in the anterior chamber) or angle recession, after surgery for developmental cataract and after chronic uveitis.

Eye Trauma and Related Problems

Eye injuries are common in children (Fig. 25.7). Eye injuries are considered to be an important cause of preventable blindness. Effort must be made to educate the community in general, and mothers in particular, about the importance of not allowing children to play with sharp pointed toys like bows and arrows, firecrackers, chemicals including colors during Holi festival or other chemicals like edible 'chuna'. Sharp and dangerous household objects like knives, scissors and needles, and chemicals like cleaning liquid, acid, whitewash paint and edible 'chuna' should be kept out of reach of children.

In case an injury is sustained, the eyes should be immediately washed thoroughly with locally available drinkable water, and the child should be rushed to the nearest hospital.

Perforating injuries of the globe require surgical repair under general anesthesia along with administration of systemic and topical antibiotics and tetanus prophylaxis. The child should be told not to rub the eyes and given only fluids while rushing the child to hospital so that there is no unnecessary delay in preparing the patient for general anesthesia and planning surgery. Meticulous repair of the wounds is undertaken as soon as possible to minimize the risk of secondary complications such as endophthalmitis, expulsion of intraocular contents and later risk of sympathetic ophthalmitis or an inflammatory panuveitis in the



Fig. 25.7a: The sequelae of ocular trauma. Following injury with a wooden stick, the child had corneal perforation, which was repaired. Traumatic cataract was surgically removed. Note the irreversible anatomical damage with corneal scar, distorted iris and pupil and lens capsular opacification



Fig. 25.7b: The sequelae of chemical injury, due to edible 'chuna'. Despite aggressive management, long-term sequelae include residual conjunctival inflammation with limbal stem cell deficiency and a scarred, irregular and opacified corneal surface

normal eye due to sensitization of the immune system to the sequestered antigens in the exposed uveal tissue.

Retinal Diseases

Children may be affected by a wide variety of retinal diseases. Retinal detachment can occur secondary to trauma or spontaneously in cases with high or pathological myopia. Classical symptoms such as sudden loss of vision with floaters and photopsia may not be reported by children and the detachment may not be detected till much later. Retinal detachment requires surgical treatment and the sooner the surgery is performed, the greater are the chances of functional recovery of vision. Other diseases that can affect the retina in childhood include degenerative and



Fig. 25.7c: Following trauma with a compass, this young teenager had to be operated for trauma-induced cataract and retinal detachment and subsequently developed a conjunctival inclusion cyst

hereditary conditions like retinitis pigmentosa and different forms of macular degeneration such as Stargardt disease. These diseases lead to gradual, painless, bilateral diminution of vision in the first or second decade of life which may be accompanied by defective dark adaptation or abnormal color vision. No specific treatment modalities are available, but refractive correction, low vision aids, visual rehabilitation and genetic counseling are ancillary measures.

Vascular abnormalities of the retina such as hemangiomas, arteriovenous malformations and exudative vitreoretinopathies like Coats disease may be seen. Retinal vasculitis may be seen in Eales disease and other inflammatory disorders. Diabetic retinopathy and hypertensive retinopathy can occur if these systemic disorders are present in sufficient grade of severity and for an adequate duration of time. An important disease seen only in children is ROP.

Retinopathy of Prematurity

This condition unique to children is seen in preterm babies due to early exposure to oxygen and other environmental

factors by a premature, underdeveloped retinal vascular system. The chief risk factors are prematurity, especially birth before 32 weeks of gestation, birth weight less than 1500 g and presence of other contributory risk factors such as supplemental oxygen therapy, hypoxemia, hypercarbia and concurrent illnesses like septicemia. The clinical features are graded in stages of severity depending on the retinal signs and the zone of retina involved. Children at risk should be screened periodically to look for evidence of developing what is considered as 'threshold' disease, i.e. requiring ablative laser treatment of the avascular zone of the retina to check further progression and prevent blinding stages of the disease which would then require surgical intervention to treat the ensuing retinal detachment and other complications.

Blindness and Low Vision in Children

The World Health Organization (WHO) has categorized blindness in different levels based on the extent of vision loss. Vision 2020: The Right to Sight is a global initiative for the elimination of avoidable blindness, a program jointly run by the WHO and The International Agency for

Table 25.1: WHO categories of visual acuity

Better eye	Worse eye	Disability category
6/6 –6/18	<6/18–6/60	0
6/6–6/18	<6/60–3/60	I
6/6–6/18	<3/60	II (one-eyed person)
<6/18–6/60 or field*	<6/18–6/60	III a (low vision)
6/24–6/60 or field*	<6/60–3/60	III b (low vision)
6/24–6/60 or field*	<3/60	III c (low vision)
6/36–3/60 or field†	<6/60–3/60	III d (low vision)
6/36–3/60 or field†	<3/60	III e (low vision)
<3/60 or field‡	<3/60	IV a (blindness)
Only HMCF	Only HMCF	IV b (blindness)
Only light perception	Light perception	
No light perception	No light perception	

*Visual field <40° up to 20° across, around centre of fixation or hemianopia involving macula

†Visual field <20° up to 10° across, around centre of fixation

‡Visual field <10° across, around centre of fixation

HMCF: Hand movement close to face



Fig. 25.8: Low vision and rehabilitation services: (a) Retinoscopy for refraction; (b) Checking acceptance; (c) Child wearing prescribed glasses; (d) Teenager using telescope; (e and f) Helping for near vision

Prevention of Blindness (IAPB). Priority diseases identified include cataract, trachoma, onchocerciasis, childhood blindness and refractive errors and low vision. The Government of India through the National Programme for Control of Blindness (NPCB), Ministry of Health and Family Welfare and the Ministry of Social Justice and Empowerment, arranges for periodic surveys and surveillance to monitor the progress in controlling the problem and also offers financial and technical assistance for treatment and rehabilitation. Integrating children into society even if blind is being recognized as important and efforts are being made to help with education, training and preparation for future employment. Various agencies are involved in developing measures to help the visually challenged negotiate activities of daily living with help of visual aids and navigational devices (Fig. 25.8).

Suggested Reading

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Skin Disorders

Neena Khanna • Neetu Bhari

Skin disorders account for a high proportion of ailments in children.

BASIC PRINCIPLES

Morphology of Lesions

Macules

Macule is a circumscribed area of change in skin color without any change in consistency (Fig. 26.1). A macule may be hyperpigmented (e.g. café au lait macule), hypopigmented (e.g. leprosy), depigmented (e.g. vitiligo), or erythematous (e.g. drug rash).

Papules and Nodules

Papule is a solid lesion < 0.5 cm in diameter with major part projecting above the skin (Fig. 26.2a). Papules may be dome-shaped (e.g. trichoepithelioma), flat-topped (e.g. verruca plana), conical (e.g. condyloma acuminata), filiform (e.g. filiform warts) or umbilicated (with crater on surface, e.g. molluscum contagiosum) or verrucous (with multiple closely packed firm elevations, e.g. verrucous warts). A papule which is > 0.5 cm in size and with the major part in the skin is called a nodule (Fig. 26.2b).



Fig. 26.1: Macule: Circumscribed area of change in skin color without any change in consistency



Fig. 26.2: (a) Papule: Solid lesion, ≤ 0.5 cm; (b) Nodule: Solid lesion, > 0.5 cm

Plaque

Plaque is an area of altered skin consistency, the surface area of which is greater than its depth (Fig. 26.3). A plaque can be elevated, depressed or flat.

Wheal

Wheal, the characteristic lesion in urticaria, is an evanescent, pale or erythematous raised lesion which



Fig. 26.3: Plaque: Area of altered skin consistency with a surface area greater than its depth

disappears within 24–48 hours (Fig. 26.4). Wheals are due to dermal edema, and when the edema extends into subcutis, it is called *angioedema*. When the wheals are linear, the phenomenon is called *dermographism*.

Blisters

Blister is a circumscribed elevated, superficial fluid filled cavity (Fig. 26.5). If ≤ 0.5 cm, it is a vesicle and if >0.5 cm, a bulla.

Scales

Scales are flakes of stratum corneum (Fig. 26.6) and are diagnostic in certain dermatoses, e.g. silver easily detachable flakes in psoriasis, branny scars in pityriasis versicolor and fish-like scales in ichthyosis.

Crusts

Crusts are formed when serum, blood or pus dries on the skin surface (Fig. 26.7).



Fig. 26.4: Wheal: Evanescent, pale/erythematous raised lesion which disappears within 24–48 hours



Fig. 26.5: Blister: Circumscribed, elevated, superficial fluid-filled lesion



Fig. 26.6: Scale: Appears as flakes of stratum corneum



Fig. 26.7: Crust: Yellow brown collection of keratin and serum

Erosions and Ulcers

A defect, which involves only the epidermis and heals without a scar (Fig. 26.8a) is called an erosion, while an ulcer is a defect in the skin which extends into the dermis or deeper, and heals with scarring (Fig. 26.8b).

Atrophy

Atrophy is the reduction of some or all layers of skin. In epidermal atrophy, thinning of the epidermis leads to loss of skin texture and cigarette-paper like wrinkling without depression. In dermal atrophy, loss of connective tissue of the dermis leads to depression of the lesion.

Lichenification

Lichenification, which is caused by repeated scratching, consists of a triad of skin thickening, hyperpigmentation and increased skin markings (Fig. 26.9).



Fig. 26.9: Lichenification: Thickening and hyperpigmentation of skin with increased skin markings

Burrow

Burrow is a dark serpentine, curvilinear lesion with a minute papule at one end and is diagnostic of scabies (Fig. 26.10).

Comedones

Comedones are due to keratin plugs that form within pilosebaceous apparatus. Comedones can be open or closed (Fig. 26.11) and are pathognomonic of acne.

Patterns Formed

Arrangement and configuration of skin lesions can help in diagnosis (Table 26.1).



Fig. 26.10: Burrow: Serpentine, thread-like, grayish curvilinear lesion, diagnostic of scabies



Fig. 26.8: Erosions and ulcers: (a) Erosions are due to complete or partial loss of epidermis with no loss of dermis; and (b) Ulcer is a defect in the skin which extends into the dermis or deeper and heals with scarring

Table 26.1: Arrangement and configuration of skin lesions

Arrangement	Example
Linear	Verrucous epidermal nevus
Grouped	Herpes simplex
Dermatomal	Herpes zoster
Arcuate	Granuloma annulare



Fig. 26.11: Comedones: Keratin plugs that form within follicular ostia

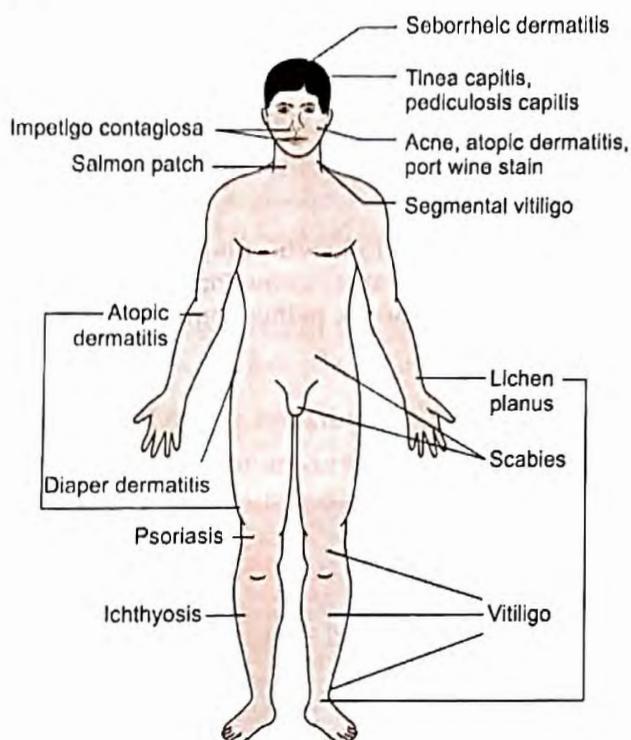


Fig. 26.12: Sites of predilection of common skin disease

Sites of Predilection

Sites of involvement often give important clues to the diagnosis (Fig. 26.12).

GENODERMATOSES

Genodermatoses are a group of inherited single gene cutaneous disorders that manifest themselves wholly or in part in skin, mucous membranes, hair and nails.

Ichthyoses

Ichthyoses are a heterogeneous group of disorders characterized by the presence of fish-like scales. Several variants of ichthyoses are recognized, based on inheritance, gene defects and clinical features (Table 26.2).



Fig. 26.13: Ichthyosis vulgaris: Large scales on extremities that are attached at the center and turned up at the edge



Fig. 26.14: X-linked ichthyosis: Large dark brown adherent scales encroaching flexures

The hallmark of the disease is presence of fish-like scales, but there are variations in the type of scales, their distribution and associated features (Table 26.2, Figs 26.13 to 26.17).

Treatment

Hydration (by immersing in water) followed by immediate lubrication with petroleum jelly or urea containing creams/lotions are useful. Keratolytic agents (hydroxyacids, propylene glycol) are used when lesions are moderately severe. Acitretin (a retinoid) is used in severe cases of congenital ichthyosiform erythroderma, lamellar ichthyosis and in keratinopathic ichthyosis. A short course of topical steroid and antibiotic combination is applied, if skin is eczematized.

Table 26.2: Clinical features of ichthyoses

	<i>Ichthyosis vulgaris</i>	<i>X-linked ichthyosis</i>	<i>Lamellar ichthyosis</i>	<i>Nonbullous ichthyosiform erythroderma</i>	<i>Keratinopathic ichthyosis</i>
Inheritance	Autosomal dominant	X-linked recessive	Autosomal recessive	Autosomal recessive	Autosomal recessive
Defect	Reduced or absent filaggrin that helps form keratin filament	Deficiency of steroid sulfatase enzyme	Defect/deficiency of transglutaminase	Mutation of <i>ABCA12</i> , <i>ALOX12B</i>	Keratin 1 and 10 defect
Age of onset	3–12 months	Birth	Birth	Birth	Birth
Sex	Equal in both sexes	Only males	Equal in both sexes	Equal in both sexes	Equal in both sexes
Incidence	Common	Rare	Very rare	Rare	Rare
Clinical features	Fine white scales on most parts of body Large mosaic-like scales, attached (at center and upturned at edges on extensors of lower extremities (Fig. 26.13)	Large dark brown adherent scales (Fig. 26.14)	Collodion baby at birth, onshoathed in shiny lacquer-like membrane which on shedding reveals diffuse large thick brown plate-like scales (Fig. 26.15) which persist for life; erythema minimal	Collodion baby at birth; followed by fine branny scales and marked erythema (Fig. 26.16)	Generalized erythema with blistering at birth. Followed by brown, warty, broad linear plaques (Fig. 26.17). Scales may fall off leaving skip areas
Sites of predilection	Extensors of limbs; major flexures always spared; face usually spared	Generalized involvement; encroachment of flexures; palms and soles spared	Generalized involvement; accentuation on lower limbs and flexures	Generalized erythema and scaling	Generalized involvement; accentuation in flexures
Associated features	Hyperlinear palms and soles; keratosis pilaris; atopic diathesis	Corneal opacities; cryptorchidism	Ectropion and eclabium; crumpled ears; palmoplantar keratoderma	Palmoplantar keratoderma less frequent	Palmoplantar keratoderma in >60%



Fig. 26.15: Lamellar ichthyosis: Large plate-like scales



Fig. 26.16: Congenital ichthyosiform erythroderma: Diffuse erythema with fine scales

Collodion Baby

Neonate is born completely covered with shiny (lacquer-like), taut membrane (Fig. 26.18), resulting in obliteration of normal skin markings. Ectropion, eclabium, flattening

of nose and ears, and sausage-shaped swelling of the digits are common. Over 1–2 weeks, the collodion membrane desiccates and is gradually shed, revealing underlying congenital ichthyosiform erythroderma or lamellar ichthyosis or sometimes normal skin.



Fig. 26.17: Keratinopathic ichthyosis: Brownish, warty, broad linear plaques



Fig. 26.18: Collodion baby: Baby is ensheathed in a shiny lacquer-like membrane

Collodion babies are at risk of thermoinstability, hypernatremic dehydration, skin infections, pneumonia and sepsis.

Treatment

Since collodion babies are frequently at risk of several complications, they are best managed in a controlled, humidified environment, carefully monitoring for fluid and electrolyte imbalance. Skin care (frequent application of emollients) and eye care are paramount. Oral acitretin is often needed.

Palmoplantar Keratoderma

PPKD may be inherited or acquired. Hereditary keratodermas are a heterogeneous group of disorders with AD or AR inheritance. While diffuse and focal types of PPKD inherited in an autosomal dominant manner, the mutilating and *transgradiens* variants have an AR inheritance. They may occur in isolation or be

part of a syndrome. Acquired PPKD may develop due to friction (corns and callosities) or be a manifestation of other inflammatory dermatoses, e.g. psoriasis.

Clinical Features

Inherited PPKD is characterized by thickening of palms and soles which usually manifest at birth or in the first few months of life. The thickening may vary from mild to moderate (Fig. 26.19) or may be severe, in which case it may be mutilating (Fig. 26.20). The keratoderma may be restricted to palms and soles or spill on to dorsae of hands and feet (*keratoderma transgradiens*; Fig. 26.21).

Treatment

Therapy for PPKD includes use of emollients, keratolytics (salicylic acid 6%, urea 30–40%), topical retinoids and vitamin D (calcipotriol), all used after soaking in water. In mutilating variants, treatment with oral acitretin may be warranted.



Fig. 26.19: Palmoplantar keratoderma: Autosomal dominant variant, with thickening of palms



Fig. 26.20: Palmoplantar keratoderma: Autosomal recessive, massive thickening and mutilation



Fig. 26.21: Palmoplantar keratoderma; Transgradient variant, with keratoderma spilling onto dorsae of feet

Epidermolysis Bullosa

Epidermolysis bullosa are a heterogeneous group of disorders defined by a tendency to develop blisters even on trivial trauma. Several variants of EB are recognized based on inheritance, gene defects and clinical features (Table 26.3). EB simplex and dominant dystrophic EB have an AD inheritance, while junctional EB and recessive dystrophic EB have an AR inheritance.

Clinical Features

The hallmark of the disease is tendency to develop blisters even on trivial injury, predominantly at sites of trauma. However, there are differences in type of blistering, their distribution and severity, evolution and sequelae as well as the degree of mucosal and nail involvement in the different variants (Table 26.3, Figs 26.22 to 26.25).

Treatment

General measures include avoiding friction and trauma, wearing soft, well-ventilated shoes and gentle handling. Prompt and appropriate use of antibiotics for blisters and infected lesions is necessary. Surgery may be required for release of fused digits, correction of limb contractures and esophageal strictures.

Gene therapy, intradermal collagen 7 injections and stem cell transplantation are being evaluated.

Ectodermal Dysplasias

Ectodermal dysplasias comprise a large, heterogeneous group of inherited disorders that are characterized by defects in development of 2 or more tissues derived from embryonic ectoderm. The disorders are classified based on either inheritance (AD, AR and XLR) or by structures involved (hair, teeth, nails, sweat glands).

Antibiotically Ectodermal Hypoplasia

The condition is inherited in an XLR manner. Child presents with intolerance to heat and episodes of high fever due to reduced sweating (hypohidrosis) because of presence of only a few sweat glands. The features distinctive with prominent forehead, thick lips and a flat nose. Additional features include thin, wrinkled, dark colored periorbital skin. The hairs are sparse, light colored, brittle and slow growing. The teeth may be absent (Fig. 26.26) or are peg-shaped.

Treatment: There is no specific treatment, but quality of life can be improved by maintenance of cool ambient temperature and managing fever by tepid sponging.

Table 26.3: Clinical features of epidermolysis bullosa (EB)

	<i>EB simplex</i>	<i>Junctional EB</i>	<i>Dominant dystrophic EB</i>	<i>Recessive dystrophic EB</i>
Age of onset	Early childhood	At birth	At birth, infancy	At birth
Skin lesions	Nonhemorrhagic bullae which heal without scarring (Fig. 26.22)	Large flaccid bullae which heal slowly (Fig. 26.23)	Hemorrhagic blisters which heal with some scarring and milia (Fig. 26.24)	Hemorrhagic blisters which heal with scarring (Fig. 26.25)
Sites	Hands and foot	Trunk and sites of trauma (knees, elbows, fingers). Periorificial granulation tissue	Sites of trauma	Generalized
Mucosal lesions	None	Involved	Minimal	Severe
Nail involvement	Absent	Present	Present	Present
Complications	Heal without scarring	One variant lethal	Scarring and milia formation	Severe scarring; development of contractures, fusion of digits and esophageal strictures
Level of split	Intraepidermal	Lamina lucida	Sublamina densa	Sublamina densa
Gene defect	Keratin 5 and 14	Laminin, collagen XVII	Collagen VII	Collagen VII



Fig. 26.22: Epidermolysis bullosa simplex: Bullae heal with minimal scarring



Fig. 26.25: Recessive dystrophic epidermolysis bullosa: Generalized involvement with bullae which heal with scarring. Note loss of nails

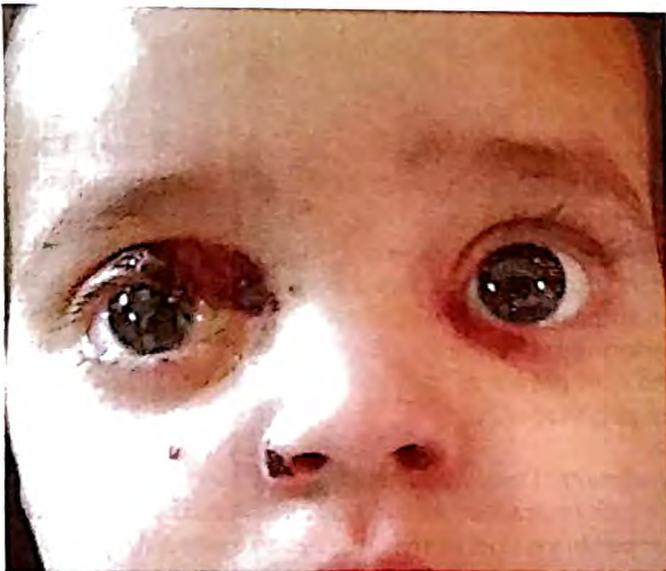


Fig. 26.23: Junctional epidermolysis bullosa: Periorificial granulation tissue



Fig. 26.26: Anhidrotic ectodermal hypoplasia: Typical facies, sparse hair and absence of teeth



Fig. 26.24: Dominant dystrophic epidermolysis bullosa: Localized involvement of trauma prone site, bullae heal with milia formation

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Dental restoration and use of artificial tears to prevent drying of eyes is often necessary.

Anhidrotic Ectodermal Dysplasia

This autosomal dominant disorder presents with patchy alopecia with sparse wiry hair, progressive palmar and plantar hyperkeratosis and dystrophic nails. Sweating and teeth are normal.

Neurocutaneous Syndromes

Neurofibromatosis

Neurofibromatosis encompasses eight inherited disorders, of which neurofibromatosis type 1 (NF1) is most common. NF1 is an autosomal dominant disorder with 100% penetrance. The defect is mutation/deletion of NF1 gene.

Clinical features: At least two of the following criteria should be met to reach a diagnosis of NF1:

1. Six or more café au lait macules (Fig. 26.27) which are >5 mm in prepubertal age group or >15 mm in post-pubertal age group.
2. Two or more neurofibromas (Fig. 26.27) of any type, or one or more plexiform neurofibromas.
3. Freckling in axillae or groin.
4. Optic glioma.
5. Two or more Lisch nodules on slit lamp examination.
6. Dysplasia of the sphenoid; dysplasia or thinning of long bone cortex.
7. First degree relative with NF1.

Neurofibromas which are symptomatic or have turned malignant need to be excised.

Tuberous Sclerosis Complex (TSC)

TSC is an AD inherited disorder with variable expressivity, even within the same family.

TSC may have protean manifestations involving several organ systems (Table 26.4, Fig. 26.28).



Fig. 26.27: Neurofibromatosis type 1: Presence of skin-colored soft papulonodular lesions associated with café au lait macules and lentigines

Table 26.4: Criteria for diagnosis of tuberous sclerosis complex

Major features	Minor features
Facial angiofibromas (Fig. 26.28a)/forehead plaque	Confetti skin lesions
Periungual fibromas	Gingival fibromas
Ash leaf macules (Fig. 26.28b)	Multiple dental pits
Shagreen patch	Rectal polyps
Multiple retinal hamartomas	Bone cysts
Cerebral tumors	Multiple renal cysts
Renal angiomyolipoma	Retinal achromic patch
Cardiac rhabdomyoma	

Definite TSC: Presence of either 2 major OR 1 major + 2 minor criteria

Probable TSC: Presence of 1 major + 1 minor criteria

Possible TSC: Presence of 1 major OR 2 minor criteria

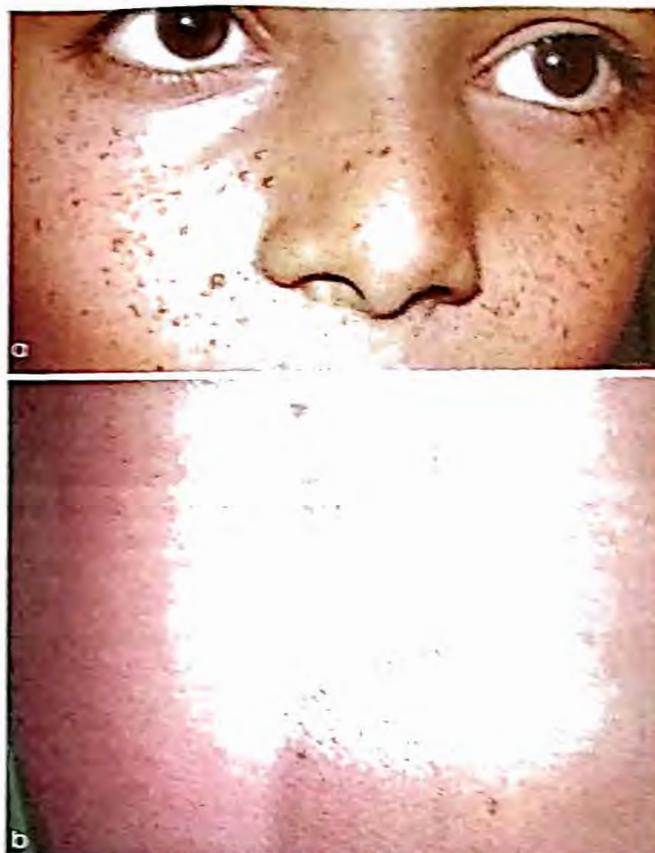


Fig. 26.28: Tuberous sclerosis. (a) Angiofibromas. Multiple small discrete erythematous papular lesions with regular surface over bilateral cheeks and dorsum of nose. (b) Ash leaf macule. Well defined, oval, hypopigmented macule over the trunk.

Treatment: Children with seizures need symptomatic treatment with anticonvulsants. Angiofibromas can be radiofrequency ablated. Rapamycin, administered by topical route for facial lesions and orally for cerebral lesions, has been used successfully.

Incontinentia Pigmenti

This is an X-linked dominant multisystem disorder, predominantly affecting females. Characteristic cutaneous manifestations occur in four stages: the vesicular (Fig. 26.29), verrucous, hyperpigmented and hypopigmented stages. There can be associated dental, ocular, neurological and developmental anomalies. Management includes genetic counseling of the parents and symptomatic care.

Xeroderma Pigmentosum

This is an AR condition, due to defective nucleotide excision repair of photodamaged DNA, and characterized by extreme photosensitivity (manifesting as acute sun burn) with onset in infancy. Over next 2-3 years the child develops hyperpigmented (freckle-like) and hypopigmented lesions predominantly on the photoexposed skin on a background of xerosis (Fig. 26.30). Over time, most children develop actinic keratoses (a premalignant



Fig. 26.29: Incontinentia pigmenti, vesicular phase: Multiple crusted vesicular lesions over the right lower limb of a female child



Fig. 26.30: Xeroderma pigmentosa: Multiple, brown to black freckle-like lesions over the face and lips, associated with conjunctival congestion

condition), basal cell carcinoma, squamous cell carcinoma and melanomas. Most children also have photophobia, conjunctivitis, keratitis, corneal opacities and develop malignancies of eyelids and conjunctiva. Neurological involvement is seen in a third of the patients.

Treatment Rigorous sun protection (lifestyle modifications and sunscreens) and use of topical and systemic retinoids delays and reduces development of neoplasias. Equally important is oncosurveillance and appropriate treatment of premalignant and malignant skin lesions.

NEVI

Nevus is a developmental disorder characterized by circumscribed hyperplasia of epidermal or dermal structures.

Melanocytic Nevus (MN)

MN are composed of nests of melanocytic nevus cells and may be *congenital* or *acquired*. Acquired MN may be *junctional* (with nevus cells at dermoepidermal junction), *compound* (with nevus cells at dermoepidermal junction and in dermis) and *dermal* (with nevus cells only in dermis). Of these, first two are seen in children while the dermal variant is seen only in adults.

The clinical presentation depends on the type of MN (Table 26.5, Fig. 26.31).

Treatment

Congenital MN especially those larger than 20 cm, need to be observed for malignant transformation. Acquired MN can be left alone.

Dermal Melanocytosis

Mongolian Spot

Mongolian spot is a dermal melanocytosis, due to entrapment of melanocytes in dermis during their migration from the neural crest into the epidermis. These spots present at birth (or soon thereafter) as gray blue macules, in the lumbosacral region and disappear spontaneously by early childhood.

Table 26.5: Clinical features of melanocytic nevi in children

	<i>Congenital nevus</i>	<i>Junctional nevus</i>	<i>Compound nevus</i>
Age of onset	Birth	Early childhood	Childhood
Morphology	Macules, papulonodules or plaques at birth; dark brown or black lesions	Macules with smooth margin; brown to dark brown-black, with color variation	Dome-shaped, smooth papules; brown-black with color variation
Hair	Usually have coarse hair which may appear whorled (Fig. 26.31)	No hair	May have hair
Site	Any part of the body	Palms, soles or genitals	Face
Complications	Malignant transformation in giant lesions; meningeal involvement; spina bifida, if on mid line on back	Malignant transformation rare	Inflammation; malignant transformation rare



Fig. 26.31: Congenital melanocytic nevus: Dark brown black plaques surmounted with coarse black hair which appear whorled

Nevus of Ota

Presents at birth or infancy (sometimes in adolescence) and consists of mottled slate-gray and brown hyperpigmented macules in the distribution of the maxillary division of trigeminal nerve (Fig. 26.32). Lesion persists for life and is frequently associated with pigmentation of sclera (slate-gray) and conjunctiva (brown). Pigmentation of nevus of Ota frequently impacts child's psychosocial development and can be reduced by treating with Nd:YAG laser.



Fig. 26.32: Nevus of Ota: Slate-gray, mottled hyperpigmentation of skin of periorbital skin with slate-gray pigmentation of sclera

Epidermal Nevi

These nevi usually present at birth, as multiple brown papules arranged linearly (Fig. 26.33). Several variants are described, including verrucous epidermal nevus, inflammatory linear verrucous epidermal nevus, naevus comedonicus and nevus sebaceous.

Topical retinoic acid and dermabrasion are helpful.



Fig. 26.33: Verrucous epidermal nevus: Multiple, brown papular lesions, arranged linearly

Vascular 'Birthmarks'

Vascular 'birthmarks' are classified based on the pathogenesis, evolution, clinical manifestations and on the presence of associations into vascular tumors and vascular malformations (Table 26.6).

Table 26.6: Classification of vascular 'birthmarks'

	<i>Vascular tumors</i>	<i>Vascular malformations</i>
Age of onset	After birth	Always present at birth
Evolution	Initial growth followed by involution	Growth proportionate to that of child and then persists (except Salmon patch)
Underlying defects	Infrequent	Frequent
Examples	Infantile hemangioma	<p><i>High flow</i></p> <ul style="list-style-type: none"> • Arteriovenous malformations <p><i>Low flow</i></p> <ul style="list-style-type: none"> • <i>Capillary</i> <ul style="list-style-type: none"> – Port-wine stain – Salmon patch • <i>Venous</i> • <i>Mixed</i> • <i>Lymphatic</i>

Clinical Features

The lesions could have one vascular component (e.g. capillaries) or have more than one component (mixed malformations). Diagnosis is based on morphology and progression of lesion(s) (Table 26.7, Figs 26.34 and 26.35).

Mixed malformations are characterized by presence of several vascular components (capillaries, veins and lymphatics) along with other nevi and are often associated with underlying skeletal abnormalities:

- **Klippel-Trénaunay syndrome** is characterized by presence of capillary malformations on the limbs in association with soft tissue swellings, venous varicosities with or without bony hypertrophy.
- **Proteus syndrome** is characterized by asymmetrical overgrowth (sometimes massive) of a part of the body (Fig. 26.36), associated with presence of epidermal nevi, hemangiomas, vascular malformations and lipoma-like

hamartomas. Extracutaneous findings include lung and renal cysts, skeletal and dental abnormalities, seizures and ocular complications.

Treatment

Salmon patch: No treatment required.

Infantile hemangioma: Small lesions resolve spontaneously. Large symptomatic lesions need treatment with systemic steroids in the proliferative phase. Propranolol used under supervision shows dramatic result. Pulsed-tunable dye laser is useful for cosmetic results.

Port wine stain: Cosmetic camouflage; laser ablation with pulsed-tunable dye laser.

Lymphangioma: Surgery, carbon dioxide laser, radiofrequency ablation.

Table 26.7: Clinical features of vascular 'birthmarks'

	<i>Infantile hemangioma</i>	<i>Salmon patch</i>	<i>Port wine stain</i>	<i>Lymphangioma</i>
Onset	After birth	At birth	At birth	At birth
Morphology	Soft, bright nodule with pale stippling (Fig. 26.34)	Telangiectatic macules	Light pink-deep red macules (Fig. 26.35); bosselated with age	Cluster of thin-walled vesicles
Site	Face forehead, eyelids and neck	Nape of neck	Face	Trunk
Complications	Interfere with function; bleeding or ulceration	None	Sturge-Weber syndrome associated with hamartomas; seizures, eye deficits	
Course	Grows for a few months; later regresses	Involutes by age of one year	Persists throughout life	Persists



Fig. 26.34: Infantile hemangioma: Soft bright red nodule with pale stippling



Fig. 26.35: Port-wine stain: Light pink to deep red macule often developing bosselation as child grows



Fig. 26.36: Proteus syndrome: Asymmetrical, disproportionate soft tissue overgrowth of left index finger associated with misalignment



Fig. 26.37: Infantile pattern of atopic dermatitis. Papulovesicular lesions on the face

DERMATITIS

Dermatitis manifests in acute phase as papulovesicular lesions, and in chronic phase as thickened, dry sometimes lichenified skin.

Atopic Dermatitis

Atopic dermatitis is an acute, subacute or chronic relapsing, endogenous eczema, characterized by dry skin and recurrent, pruritic, symmetric dermatitic lesions.

The condition is due to a complex interaction between genetic susceptibility and immunological changes with heightened IgE response.

Clinical Features

Lesions develop in infancy, anytime after 3 months of age. In children, two distinct patterns are recognized.

Infantile pattern: Manifests as itchy, erythematous papulovesicles, on the face (Fig. 26.37), but may become generalized. The lesions clear by 18 months of age in 40% and evolve into childhood pattern in the rest.

Childhood pattern: Childhood pattern is characterized by dry, lichenified and crusted plaques, seen mainly on antecubital (Fig. 26.38) and popliteal fossa, the neck and face. Most (70%) clear by 10 years of age.

The diagnosis is based on Hanifin and Rajka criteria (Table 26.8). Secondary bacterial and fungal infections are frequent. Viral infections like herpes simplex and molluscum contagiosum may become widespread.

Treatment

General measures: Care takers and the child should be counseled about the chronicity of the disease and that the child should avoid contact with irritants (woolens and chemicals). Measures to reduce exposure to house



Fig. 26.38: Childhood pattern of atopic dermatitis. Dry plaques in the flexures

dust mite (using barriers on pillows and mattresses, regular vacuuming of rooms) may help. There is no contraindications to vaccination except in children specifically allergic to eggs, in whom influenza and yellow fever vaccines are avoided. Dietary restrictions are usually not warranted and breast feeding is encouraged as it may decrease the chance of the infant developing the disease.

Skin care: Mild soaps and cleansing lotions are to be used for bathing followed immediately by application of moisturizers to skin. However, the cost-effectiveness of moisturizers which claim to replenish natural moisturizing factors is debatable.

Acute lesions are treated with wet dressing and topical steroids. Antibiotics and antifungals (topical/systemic) are used when indicated. Oral antihistamines are often prescribed.

Table 26.8: Hanifin and Rajka criteria for atopic dermatitis**Major features (must have ≥ 3)**

Pruritus

Typical morphology and distribution:

- Facial and extensor involvement in infants and children
- Flexural lichenification in adults

Dermatitis, chronic or chronically relapsing

Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis)

Minor features (must have ≥ 3)

Cataracts (anterior subcapsular)

Cheilitis

Conjunctivitis, recurrent

Facial pallor or erythema

Food intolerance

Hand dermatitis: Nonallergic, irritant

Ichthyosis

Elevated levels of IgE

Immediate (type I) skin test reactivity

Infections

Itching, when sweating

Keratoconus

Keratosis pilaris

Nipple dermatitis

Orbital darkening

Palmar hyperlinearity

Perifollicular accentuation

Pityriasis alba

White dermographism

Wool intolerance

Xerosis

Chronic lichenified lesions are managed by hydration followed by application of emollients (like petrolatum) and a short course of topical steroids. It is preferred to use the least potent steroid which reduces symptoms; potent steroids are avoided on face and genitalia. Topical immunomodulators (tacrolimus and pimecrolimus) are useful because of their steroid-sparing and antipruritic action. Oral antihistaminics are used to break the itch-scratch cycle. Narrow band UVB and systemic immunosuppressives (steroids, cyclosporine and azathioprine) may be needed in extensive/resistant disease.

Infantile Seborrheic Dermatitis

The onset is usually in the first 4 weeks of life, manifesting as erythema and yellow-orange scales and crusts (Fig. 26.39) on the scalp (*cradle cap*). Eczematous lesions may also develop in the major flexures and trunk. The illness is self-limiting and generally resolves by 12 weeks. *Malassezia furfur* is incriminated in pathogenesis.

**Fig. 26.39:** Infantile seborrheic dermatitis: Erythema with yellow-orange scales on the scalp**Treatment**

The crusts of cradle cap should be removed and this can be facilitated by pretreatment with an oil. Application of 2% ketoconazole shampoo, mild topical steroid or pimecrolimus/tacrolimus hastens subsidence.

Diaper Dermatitis**Etiology**

Diaper dermatitis is irritant dermatitis in infants due to prolonged contact with feces and ammonia (produced by the action of urea-splitting organisms in urine), often complicated by superadded candidal infection. Area in contact with diapers (convexity of buttocks) shows moist, glazed erythematous lesions with sparing of depth of flexures (Fig. 26.40).

Treatment

Diaper dermatitis is prevented by keeping area clean and dry and avoiding the use of disposable semiabsorbent occlusive diapers. Washed cotton diapers should be rinsed

**Fig. 26.40:** Diaper dermatitis: Moist, glazed erythematous lesions. Depth of folds typically spared

in dilute lemon juice/vinegar. Emollients and mild topical steroids with antifungal agents are useful in the acute phase.

Pityriasis Alba

Asymptomatic, ill-defined, hypopigmented macules with fine scales are seen on face, in children 2–6 years of age. The lesions are self-limiting, clearing spontaneously in a few months to couple of years.

Treatment

The family is reassured regarding the benign nature of the illness and that it is not vitiligo. Mild emollients may be used.

DISORDERS OF SKIN APPENDAGES

Acne Vulgaris

Acne vulgaris occurs in almost all peripubertal children. The age of onset is 12–14 years, being earlier in females and in about 70% of subjects, the lesions subside by early 3rd decade. It affects both sexes equally, but nodulocystic acne is more frequent in males.

Etiology and Pathogenesis

Lesions develop due to inflammation of the pilosebaceous units and etiology is multifactorial and includes:

Increased sebum secretion: Sebaceous glands in these patients show enhanced sensitivity to circulating androgens leading to increased sebum secretion.

Microbial colonization: *Propionibacterium acnes* (a normal commensal) is most commonly implicated.

Occlusion of pilosebaceous orifice: Pilosebaceous orifice is occluded by keratin plugs leading to retention of sebum and consequent growth of microbes, setting up a vicious cycle.

Release of inflammatory mediators: Distended follicle ruptures, releasing inflammatory chemicals into dermis, stimulating intense inflammation.

Clinical Features

Patients present with a polymorphic eruption of open and closed comedones, papules, pustules and nodules, on a background of oily skin (Fig. 26.41). The lesions usually heal with pitted scars. The lesions typically occur on face and upper trunk.

Infantile acne is caused by maternal hormones and presents at birth, lasting up to 3 years. It is common in males and lesions are similar to adolescent acne.

Acne conglobata is a severe form of acne characterized by abscesses, cysts and intercommunicating sinuses.

Drug-induced acne: Drugs causing acne include steroids, androgens, antituberculous and anticonvulsant drugs. The eruption consists of monomorphic lesions of papules or pustules.



Fig. 26.41: Acne vulgaris: Polymorphic eruption with comedones, papules and pustules

Therapy

General measures: Though there is no restriction on use of cleansers, it is best to use pH-balanced syndets and avoid oil and oil-based skin care products. No dietary restrictions are usually needed. Specific therapy depends on the severity of the disease (Table 26.9).

Alopecia Areata

Etiology

This is a skin-specific autoimmune disease, due to inappropriate immune response to hair follicle associated antigens.

The condition affects children and young adults, who present with discoid areas of non-inflammatory, non-cicatricial alopecia with exclamation mark hair at periphery (Fig. 26.42a). The common sites of involvement are scalp, eyelashes and eye brows. In ophiasis, there is a band-like alopecia in the periphery of the scalp, in alopecia

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Table 26.9: Management of acne

Severity	Subtype	Drug of choice
Mild	Comedonal	Topical retinoids like retinoic acid and adapalene
	Papulopustular	Topical retinoids/benzoyl peroxide. Oral antibiotics, if necessary
Moderate	Papulopustular	Oral antibiotics + topical retinoids and/or benzoyl peroxide
	Nodular	Oral antibiotics + topical retinoids and/or benzoyl peroxide In girls: Oral antiandrogens + topical retinoids
Severe	Nodular/acne conglobata	Oral retinoids* In girls: Oral antiandrogens + topical retinoids

* Oral retinoids may be used in females with moderate or severe lesions under supervision



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Fig. 26.42: (a) Alopecia areata: Noncicatricial, non-inflammatory, discoid lesions with exclamation mark hair at periphery; (b) Alopecia totalis: Total loss of terminal hair from scalp, face and body

totalis, there is total alopecia in the scalp, while in alopecia universalis there is total loss of terminal hair from scalp, eyebrows, eyelashes, beard and body (Fig. 26.42b). Nails may occasionally show fine pitting and thinning of the nail plate.

Spontaneous remission is common. Initially, the regrowing hairs are grey, but regain color over period of time. Poor prognostic features include onset in childhood, ophiasis, association with atopy and widespread alopecia.

Treatment

Treatment depends on extent and course of disease (Table 26.10).

Miliaria

Etiology

Miliaria is due to obstruction and rupture of eccrine sweat ducts resulting in spillage of sweat into adjacent epidermis/dermis. Depending on the level of rupture, miliaria is classified into:

- Miliaria crystallina
- Miliaria rubra
- Miliaria profundus

Table 26.10: Treatment of alopecia areata

Clinical severity	Management
Single or a few lesions of <6 months duration	Observe; spontaneous recovery common
Single or a few lesions of >6 months duration; rapid progression	<ul style="list-style-type: none"> • Topical corticosteroids • Intralesional triamcinolone • Topical minoxidil, 2–5% • Topical psoralens and ultraviolet A (PUVA/PUVA sol)
Extensive lesions	<ul style="list-style-type: none"> • Oral corticosteroids
Rapid progress	<ul style="list-style-type: none"> • Oral PUVA/PUVA sol • Induction of allergic contact dermatitis with diphencyprone

Miliaria crystallina: Usually seen during high fever, miliaria crystallina is characterized by tiny, noninflamed, superficial vesicles (Fig. 26.43).

Miliaria rubra: Usually seen during hot, humid climate, miliaria rubra is characterized by small erythematous papules, commonly surmounted by vesicles.

Miliaria profunda: Characterized by erythematous papules.

Therapy is symptomatic. Patients should avoid humidity and wear cotton clothes. Itching/ burning can be reduced with calamine lotion and topical steroids.

Trachyonychia

Most common associations are alopecia areata, psoriasis, and lichen planus. It is characterized by the presence of gray rough surface due to multiple, longitudinal, linear striations affecting all nail plates (hence also called *20-nail dystrophy*; Fig. 26.44). In children, it is a self-limiting condition.



Fig. 26.43: Miliaria crystallina: Tiny, non-inflamed superficial vesicles



Fig. 26.44: Trachyonychia: Multiple, longitudinal, linear striations over the fingernails associated with roughness of nail surface

Pachyonychia Congenita

It is a rare autosomal dominant disorder, characterized by gross thickening (tenting) of nail plates (Fig. 26.45a), oral lesions in form of leukoplakia (Fig. 26.45b) and keratoderma of palms and soles.

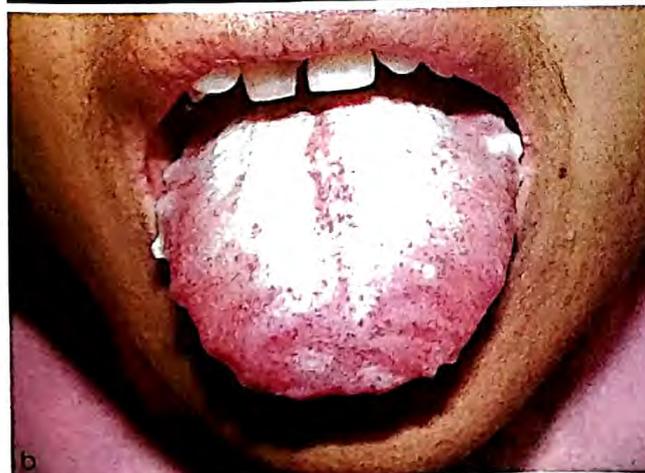


Fig. 26.45: (a) Pachyonychia congenita: Massive thickening of the nail plates resulting in tenting of nails; (b) Leukoplakia of the tongue

PAPULOSQUAMOUS DISORDERS

Psoriasis

Etiology

Psoriasis is a disease of T cells, with interplay of genetic factors (*PSORS1-8* genes, and several others) and environmental influences (physical trauma, infections and drugs).

Based on morphology of lesions, psoriasis is classified as chronic plaque psoriasis, guttate psoriasis and pustular psoriasis. Based on age of onset, chronic plaque psoriasis is classified into type I (onset in childhood or adolescence, positive family history, association with HLA-CW6, severe disease, prominent Koebner phenomenon and prolonged course, requiring aggressive therapy) and type II psoriasis (onset in adults).

Clinical Features

Chronic plaque psoriasis (CPP): CPP is characterized by well-demarcated, indurated, erythematous, plaques surmounted by silvery scales (Fig. 26.46), which are accentuated on grating the lesion with a glass slide (Grattage test). Removal of the scales by further scraping reveals a glistening white membrane and on removing the membrane, punctate bleeding points become visible (Auspitz sign). Lesions become polycyclic due to confluence and annular because of central clearing. Symmetrical involvement of knees, elbows and extensors, lower back, scalp and sites of trauma (Koebner or isomorphic phenomenon) is seen. Face and photo-exposed areas are generally spared.

Guttate psoriasis: It typically occurs in children and adolescents and is characterized by crops of small, erythematous scaly papules, predominantly on trunk. Guttate psoriasis is often triggered by streptococcal tonsillitis.



Fig. 26.46: Chronic plaque psoriasis: Well-demarcated, indurated, erythematous plaques surmounted by silvery scales

Pustular psoriasis: Though pustular psoriasis is rare in children, several variants are described. Annular pustular psoriasis, the variant typically seen in children, is characterized by subacute onset of fiery red erythema surmounted by cluster of very superficial creamy white pustules, which form circinate or annular lesions (Fig. 26.47). Infantile and juvenile pustular psoriasis is seen in infants and has a benign course. It is often confused with seborrheic and napkin dermatitis.

Nail changes: Include coarse irregular pits, thickening of nail plate, subungual hyperkeratosis, onycholysis, oil spots and discoloration of nail plates.

Joints: Ten percent of patients have joint involvement.

Treatment

It is important to counsel the parents and the child about the chronic nature of the disease and the likelihood of relapses. Several options are available for treatment depending on the type and extent of disease (Table 26.11).



Fig. 26.47: Annular pustular psoriasis: Superficial pustules which coalesce to form annular lesions

Lichen Planus

The etiology is unknown. A lichenoid eruption may be triggered by drugs like chloroquine and as a manifestation of graft versus host disease.

Lichen planus is characterized by presence of pruritic, polygonal, purple (violaceous) plane (flat) topped papules (Fig. 26.48) with white streaks (Wickham striae) on the surface. They are seen on wrists, around ankles and may appear at sites of trauma (Koebner phenomenon). Mucosal involvement is seen in 25% patients in form of reticulate lacey pattern on buccal mucosa, gingiva and gingiva or superficial erosions on tongue and buccal mucosa. Annular lesions may be seen on genitalia. Rarely scarring alopecia is present. Nail changes are infrequent in children.

Treatment

Therapy depends on the severity of the disease (Table 26.12).

Lichen Nitidus

Lichen nitidus most commonly presents in children and young adults. Classically, tiny 1–2 mm, monomorphic, hypopigmented/flesh-colored papules with a shiny surface are seen on the arms, chest and abdomen. The penile shaft is often involved (Fig. 26.49). Koebnerization with a linear arrangement of papules is a common finding. Lichen nitidus is a chronic, self-limiting disease, with an average course of about 1 year.

Mid-potent topical corticosteroid or topical tacrolimus can be used in children to relieve the pruritus. Phototherapy has been tried in refractory cases.

Lichen Striatus

Lichen striatus is characterized by presence of hypopigmented/erythematous papular lesions configured linearly usually on the limbs. Active lesions subside spontaneously, leaving behind atrophic, post-inflammatory hypopigmentation (Fig. 26.50). Counseling about the self-limiting nature and that it is not vitiligo is often all that is required.

Table 26.11: Treatment of psoriasis

	Treatment of choice	Alternative modalities
Psoriasis vulgaris Localised (<10% BSA) Extensive (>10% BSA)	Topical coal tar+ salicylic acid ointment Narrow band UVB	Topical steroids + salicylic acid Methotrexate Acitretin Cyclosporine A PUVA/PUVA sol*
Facial lesions Guttate psoriasis	Topical tacrolimus, pimecrolimus Antibiotics and emollients Narrow band UVB PUVA/PUVA sol*	Coal tar Tacrolimus Mild topical steroids Acitretin
Pustular psoriasis	Methotrexate Cyclosporine	

* PUVA: Psoralen + UVA should not be used in children <10 years of age



Fig. 26.48: Lichen planus: Polygonal, flat-topped, violaceous papules

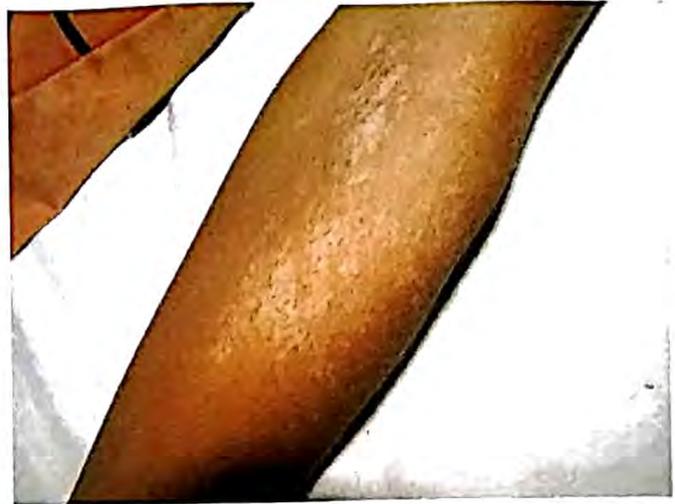


Fig. 26.50: Lichen striatus: Hypopigmented atrophic macules configured linearly over left forearm

Table 26.12: Treatment of lichen planus in children

Type of disease	Therapy*
Localized	Topical steroids
Extensive	Narrow band UVB Oral steroids Acitretin
Scalp lichen planus	Oral steroids
Mucosal lichen planus	Dapsone and topical steroids in orabase Oral steroids Acitretin

*Oral antihistamines to be added, if lesions itchy

Pityriasis Rosea

Etiology

The condition may be triggered by reactivation of human herpes viruses (HHV-7, HHV-6).

Clinical Features

PR begins with a 'herald patch' in 80% cases. Lesion is characteristically oval, wrinkled with a collarette of scales at the periphery. This is followed by multiple, smaller, oval to round scaly secondary eruptions. Their arrangement is characteristic as lesions run downwards and outwards from the spine (Christmas tree appearance) along lines of cleavage. The condition is self-limiting, with the lesions resolving spontaneously within 2–10 weeks.

No treatment is usually required. Oral antihistamines, calamine lotion and topical steroids may be used to decrease itching. Recalcitrant lesions may be treated with ultraviolet light.

Erythroderma

Childhood erythroderma may be a manifestation of several dermatoses including ichthyoses (nonbullous ichthyosiform erythroderma), dermatitis (atopic dermatitis, seborrheic dermatitis) and papulosquamous dermatoses (psoriasis, pityriasis rubra pilaris) and as an adverse effect to drugs.

Clinical Features

Erythroderma refers to a generalized erythema usually with, sometimes without, scaling that involves more than 90% of the child's body surface area (Fig. 26.51). Erythroderma is often complicated by thermodysgulation, sepsis and fluid, electrolyte and nutritional imbalance.

Treatment includes addressing the underlying disease and preventing complications. Treatment should be



Fig. 26.49: Lichen nitidus: Multiple, small, monomorphic, hypopigmented papules over the lower abdomen and shaft of penis



Fig. 26.51: Erythroderma: Generalized erythema associated with mild scaling in a newborn

initiated with bland applications and antihistamines but oral corticosteroids and other immunosuppressives may be needed in recalcitrant disease.

BULLOUS DISORDERS

26

Pemphigus Vulgaris

This is the most common variant of pemphigus, accounting for over 80% cases.

Pemphigus vulgaris is an autoimmune disease, characterized by acantholysis, induced by deposition of IgG autoantibodies against desmogleins 3 and 1 present in desmosomes, which are cell-to-cell adhesion molecules in epidermis.

Clinical Features

Patients develop flaccid bullae on non-erythematous skin (Fig. 26.52). The bulla spreads on tangential pressure (bulla spread sign) and can be induced (Nickolsky sign). These rupture easily to form crusted erosions. The usual sites are scalp, face, flexures and trunk. Oral lesions might antedate skin lesions in 50% of patients and eventually 80–90% of patients develop oral lesions. Mucosal lesions are characteristically painful erosions with ragged margins.

Treatment

General measures: Counseling the caretakers about course of disease and necessity of continuing therapy during asymptomatic maintenance phase is important. Supportive measures including barrier nursing, skin and mucosal care (measures to augment healing, prevent and treat skin infections), maintaining fluid and electrolyte balance help to improve response to therapy.



Fig. 26.52: Pemphigus vulgaris: Flaccid bullae on non-erythematous skin

Specific measures: Immunosuppressives including steroids systemically (daily doses or as monthly bolus) along with steroid-sparing immunosuppressive adjuvants (azathioprine, methotrexate, cyclosporine) form the mainstay of therapy. After control of active disease, maintenance therapy needs to be continued for several months. Rituximab, a biological and intravenous immunoglobulin has also been used successfully.

Chronic Bullous Disease of Childhood

This is an IgA-mediated blistering disorder, characterized by a dermoepidermal split. The condition is seen in children less than 5 years of age. The lesions are itchy, tense bullae on an erythematous skin. New lesions appear around previous lesions resulting in a 'string of pearl' appearance (Fig. 26.53). The lesions are usually grouped around the orifices (perioral, perinasal, perigenital or perianal). They



Fig. 26.53: Chronic bullous disease of childhood: Tense bullae on erythematous skin in perigenital area

are also frequently seen on lower abdomen, buttocks, knees and elbows. Oral mucosal involvement is seen in 50% of patients. The illness is self-limiting, with lesions generally resolving within 2 years of onset.

Patients with mild disease are treated with dapsone (1–2 mg/kg) while in those with extensive disease, oral corticosteroids are administered.

DISORDERS OF PIGMENTATION

Vitiligo

Vitiligo affects both sexes equally with peak incidence being between 10 and 30 years. A positive family history is present in 20–30% of patients. Vitiligo is classified into:

- *Segmental vitiligo*.
- *Nonsegmental vitiligo*: Which includes localized variants (focal and mucosal) and generalized variants (vulgaris, acrofacial and universalis).

Etiology

Nonsegmental vitiligo probably has an autoimmune pathogenesis with a polygenic predisposition. Segmental vitiligo has a neurogenic pathogenesis.

Clinical Features

The lesions are characterized by depigmented (chalky white or pale white) macules with sharp scalloped margins, which might coalesce to form geographical patterns (Fig. 26.54). Lesional hair may be depigmented (leukotrichia). Lesions may be present anywhere on the body, but areas prone to trauma are most susceptible. The lesion may be focal (1 macule at a single site), segmental (unilateral, dermatomal usually along distribution of mandibular division of the facial nerve), acrofacial (periorificial and acral) and universalis (extensive, generalized due to confluence of patches).



Fig. 26.54: Acrofacial vitiligo: Depigmented, scalloped macules on face and acral parts

Associations

Segmental vitiligo progresses initially for about 6 months and then stabilizes. Patients with vitiligo should be examined for cutaneous associations (alopecia areata, atopic dermatitis), endocrine disorders (diabetes mellitus, Addison disease, hypoparathyroidism and thyroid disorders) and pernicious anemia.

Course

Non-segmental vitiligo is slowly progressive, though it can sometimes progress rapidly. Spontaneous pigmentation is seen in 10% of patients. Predictors of poor prognosis include long-standing disease, leukotrichia and lesions on resistant areas (bony prominences, nonhairy, nonfleshy areas and mucosae).

Treatment

Patient and family need to be reassured. Sunscreens and cosmetic cover up may be needed. The treatment depends on the extent of involvement (Table 26.13). In patients whose disease is refractory but not progressing and in patients with segmental vitiligo, surgical techniques like blister grafting and melanocytes transfer can be tried.

Freckles and Lentigines

Both are characterized by presence of discrete hyperpigmented macules. Lesions of freckles are seen in red haired, very fair children. Lentigines show no such predilection. Lesions of freckles are seen in light exposed parts of body (face, V of neck and dorsolateral aspect of forearms) with conspicuous absence on covered skin. Lentigines do not show such a predilection and may be present even on mucosae (Peutz-Jeghers syndrome). Freckles (Fig. 26.55a) are lighter, with less delineated edges and show variegation in color including darkening on sun exposure. Lentigines are darker, sharply defined and do not darken on sun exposure. They may be a cutaneous marker of multisystem syndromes (Fig. 26.55b).

Table 26.13: Treatment of vitiligo

Localized disease	
New lesions	Topical steroids Topical calcineurin inhibitors
Old lesions	Topical PUVA*/PUVA sol
Extensive disease	
New lesions	Oral steroids + PUVA*/PUVA* sol or NB UVB**
Rapid increase	Oral steroids + PUVA*/PUVA* sol or NB UVB**
Old lesions	Oral PUVA*/ PUVA* sol or NB UVB **
Intolerance to PUVA	Oral steroids

*Oral PUVA/PUVA sol: Psoralen + UVA/psoralens + sunlight: not to be used in children <10 yr of age

**NB UVB: Narrow band UVB

ABNORMAL VASCULAR RESPONSES

Drug Eruptions

Drug eruptions are adverse events that occur after systemic or topical administration of a drug (Table 26.14).

Diagnosis is based on clinical features and temporal relation to drug use. Though any drug can cause a reaction after any length of treatment, some drugs are more suspect and the most recent introduction is the most likely cause. The role of drug provocation test is controversial but may be needed to find the culprit drug in patients on multiple drugs as well as to provide a list of safe alternative drugs.

Treatment

General measures: Withdrawal of drug is most effective approach but may not be easy as the child may be taking several drugs or the suspected drug may be essential and a chemically unrelated substitute may not be available. In severe reactions, maintenance of fluid-electrolyte balance, thermoregulation and skin care are very important. Symptomatic therapy is provided using antihistamines.

Specific treatment: In patients with erythroderma, local calamine lotion and topical steroids are instituted initially, but oral steroids may be required in recalcitrant patients. In Stevens-Johnson syndrome-toxic epidermal necrolysis complex, role of systemic steroids is only established in the early stage. Intravenous immunoglobulins and cyclosporine have also been used successfully.



Fig. 26.55: (a) Freckles: Discrete, light brown, ill-defined macules with variegation in color, on the face of a fair child; (b) Lentigines: Discrete, dark brown, sharply defined macules on mucosal surface of lips in a patient with Peutz-Jeghers syndrome

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Table 26.14: Common drug eruptions

Pattern	Morphology	Drugs implicated
Exanthematous	Symmetric erythematous macules and papules	Antibacterials (penicillins, sulfonamides, cephalosporins), antitubercular drugs anticonvulsants (barbiturates, carbamazepine, phenytoin, lamotrigene)
Erythroderma (exfoliative dermatitis)	Entire skin (>90%) is erythematous, scaly and edematous	Antibacterials, anticonvulsants, isoniazid, griseofulvin
Stevens-Johnson syndrome-toxic epidermal necrolysis (SJS-TEN) complex	Initial lesions often targetoid, followed by diffuse, intense erythema. Flaccid blisters, followed by large areas of skin denudation; mucosae always involved	Antibacterials (penicillins, sulfonamides, quinolones, cephalosporins), anticonvulsants, frusemide, hydralazine, NSAIDs (oxicam derivatives and COX-2 inhibitors), antifungal agents (terbinafine, griseofulvin)
Fixed drug eruption	Well demarcated, erythematous plaques; subside with hyperpigmentation; recur at same site each time the implicated drug is taken	Antibacterials (dapson, tetracyclines, penicillin, erythromycin), NSAIDs (salicylates, paracetamol), griseofulvin
Photosensitive eruption	Pruritic papules and plaques on sun-exposed areas	Antibacterials (sulphonamides, tetracyclines, quinolones), thiazides, phenothiazines, psoralens, NSAIDs, amlodaron
Vasculitis	Palpable purpura, urticarial vasculitis, necrotic ulcers, nodular vasculitis	Antibacterials (tetracyclines, ampicillin, erythromycin), NSAIDs, anticonvulsants, griseofulvin, levamisole
Urticaria and angioedema	Occur independently or along with bronchospasm and circulatory collapse (anaphylaxis)	Aspirin, penicillin, vaccines with egg proteins, ACE inhibitors, indomethacin, opiates, antifungals

Urticaria and Angioedema

Urticaria and angioedema are characterized by evanescent wheals which last 24–72 hours. Urticaria is due to edema of dermis while angioedema is due to edema of dermis and subcutis.

Both conditions are mediated by chemicals (especially histamine) released from mast cells, triggered either immunologically (via IgE/autoimmune/complement pathways) or non-immunologically (by drugs/chemicals). Often urticaria is idiopathic.

Urticaria is characterized by development of itchy, evanescent wheals (Fig. 26.56a) while the wheals in angioedema are less evanescent, not itchy (Fig. 26.56b). In dermographism the wheals are linear (Fig. 25.56c) and in cholinergic urticaria they are small.



Fig. 26.56: (a) Urticaria: Pale pink edematous wheals with a surrounding flare; (b) Angioedema: Pale pink swelling of genitals; (c) Dermographism: Linear wheals

Though removal of triggers seems a logical strategy of treatment, triggers are often difficult to identify. Antihistamines (preferably newer non-sedating ones), even in escalated doses (up to 4-times) are the mainstay of treatment. Oral steroids are used in anaphylaxis while immunosuppressives (methotrexate, azathioprine and cyclosporine) are used in resistant (autoimmune) urticaria. Montelukast (leukotriene receptor antagonist) and omalizumab (anti-IgE monoclonal antibody) are also used in recalcitrant patients.

Erythema Multiforme

Erythema multiforme has two main subtypes: Erythema multiforme (EM) minor, and EM major.

Etiology

Infections like herpes simplex virus, mostly, and less commonly, *Mycoplasma pneumoniae* and trigger EM.

Clinical Features

- **Cutaneous lesions:** Lesions usually appear in a single crop. Target lesions which consist of 3 concentric areas of varying degrees of erythema are characteristic (Fig. 26.57). Central bullous lesions are characteristic in EM major. Lesions are seen symmetrically on acral parts especially of upper extremities and on the face.
- **Mucosal lesions** are conspicuous in EM major (buccal erosions and hemorrhagic crusts of lips).
- **Constitutional symptoms** are present in EM major.

Most patients are managed symptomatically. In patients with recurrent EM, suppressive therapy with acyclovir may be instituted.



Fig. 26.57: Cutaneous lesions: Target lesions in acral parts. Inset: Target lesion consists of three concentric rings composed of central dusky erythema, sometimes surmounted with vesicle/bulla, surrounded by a pale edematous ring which is in turn surrounded by an erythematous halo

INFECTIONS

Pyodermas

Pyodermas are classified depending on whether they are follicular or non-follicular, and whether they are spreading or localized and the depth and extent of involvement (Table 26.15).

The chief causative organisms are *S. aureus* for folliculitis and furuncles, bullous impetigo, and some impetigo contagiosa and ecthyma.

S. pyogenes is causative for cellulitis and erysipelas and some impetigo contagiosa and ecthyma.

Table 26.15: Classification of pyodermas

	Superficial	Deep
	Follicular	
Folliculitis	Superficial folliculitis	Deep folliculitis
Perifolliculitis	Furuncle	Carbuncle
	Nonfollicular	
Spreading	Erysipelas	Cellulitis
Localized	Impetigo contagiosa Bullous impetigo	Ecthyma

Clinical Features

Manifestations depend on type of pyoderma (Tables 26.16 to 26.18, Figs 26.58 to 26.60).

Table 26.16: Clinical features of follicular pyodermas

	Folliculitis	Furuncle
Clinical features	Erythematous follicular papules, often surmounted by pustules	Firm red follicular nodules which discharge pus and heal with minimal scarring (Fig. 26.58)
Sites of predilection	Face, lower extremities	Buttocks, lower extremities

Table 26.17: Clinical features of spreading pyodermas

	Erysipelas	Cellulitis
Clinical features	Tender, warm, erythematous rapidly spreading plaques; superficial vesiculation. Constitutional symptoms	Tender, warm erythematous ill-defined plaques with superficial vesiculation. Constitutional symptoms
Sites of predilection	Face	Lower extremities

Table 26.18: Clinical features of nonfollicular pyoderma

	Impetigo contagiosa	Bullous impetigo	Ecthyma
Age	Children	Infants	Any age
Clinical features	Thin-walled blisters with erythematous halo; rupture to form honey colored crusts (Fig. 26.59) Lesions spread without central clearing Lymphadenopathy frequent	Thick-walled, persistent blisters on bland skin; rupture only after a few days to leave thin varnish like crusts (Fig. 26.60) Lesions heal in center to form annular plaques Lymphadenopathy rare	Crusted, tender erythematous indurated plaque with thick adherent crusts Lesions heal with scarring
Sites of predilection	Face, especially mouth and nose	Face, other parts of body	Frequent Thighs, legs
Complications	Post-streptococcal glomerulonephritis, eczematization	Staphylococcal scalded skin syndrome	Glomerulonephritis, eczematization, scarring



Fig. 26.58: Furuncle: Firm, red follicular nodules which discharge pus and heal with minimal scarring



Fig. 26.59: Impetigo contagiosa: Honey-colored crusted lesions around mouth



Fig. 26.60: Bullous impetigo: Thick-walled, persistent blisters on bland skin

Treatment

General measures include local hygiene, removal of crusts (in ecthyma), rest and limb elevation (for cellulitis). NSAIDs are used if pain and constitutional symptoms are present.

Topical antibiotics like mupirocin, sodium fusidate and nadifloxacin are used for localized lesions. Systemic therapy is required in patients with extensive lesions, in spreading lesions (erysipelas and cellulitis), and in presence of constitutional symptoms and lymphadenopathy. Follicular pyoderms and bullous impetigo warrant use of antistaphylococcal antibiotics (cloxacillin or coamoxiclav) while spreading pyoderms should be treated with injectable penicillins. For impetigo and ecthyma, macrolides usually suffice.

Staphylococcal Scalded Skin Syndrome

This condition is mediated by hematogenous spread of exotoxin produced by *S. aureus*, present usually in extracutaneous infections (e.g. otitis media, pneumonitis).

The illness is usually seen in newborns and infants younger than 2 years of age. Erythema and tenderness are followed by superficial peeling of skin in thin sheets, giving the appearance of scalding (Fig. 26.61). Constitutional symptoms are minimal.

Treatment is mainly supportive. Antistaphylococcal antibiotics are administered initially parenterally then orally. Fluid and electrolyte balance should be maintained.

Cutaneous Tuberculosis

Cutaneous tuberculosis caused by *M. tuberculosis* is classified based on host's immune status as well as route of inoculation into:

- Lupus vulgaris (Fig. 26.62)
- Scrofuloderma (Fig. 26.63)
- Tuberculosis verrucosa cutis
- Tuberculids



Fig. 26.61: Staphylococcal scalded skin syndrome: Erythema and superficial peeling of skin in thin sheets



Fig. 26.62: Lupus vulgaris: Solitary, well-defined annular plaque with central scarring



Fig. 26.63: Scrofuloderma: Sinus with mouth showing undermined edge and fixed to underlying lymph node

Table 26.19: Clinical features of tuberculosis

	<i>Lupus vulgaris</i>	<i>Scrofuloderma</i>	<i>Tuberculosis verrucosa cutis</i>	<i>Tuberculids</i>
Immune status of host	Moderate	Poor	Excellent	Excellent
Route of spread	Hematogenous/contiguous	Contiguous from lymph nodes, bones or joints	Inoculation	Hypersensitivity reaction
Morphology	Solitary, well defined, annular/arcuate plaque with atrophic/scarred center which typically develops nodules (Fig. 26.62). Periphery shows pink-brown, deep-seated nodules which on diascopy may exhibit an apple-jelly appearance	Firm, subcutaneous nodules which break open to form sinuses. Mouth of sinus is serpiginous with undermined edges (Fig. 26.63)	Single, warty firm plaque with a violaceous halo. The surface has clefts and fissures that discharge pus. There may be scarring at the center	Papular or papulonecrotic lesions
Sites of predilection	Head, neck and buttocks	Cervical lymph nodes most frequently, tibia and sternoclavicular joints	Sites of trauma	Trunk

The diagnosis is confirmed by histopathology. Patients should be evaluated for systemic tuberculosis. Therapy of cutaneous tuberculosis comprises use of four anti-tubercular medications (isoniazid, rifampicin, ethambutol and pyrazinamide) for 8 weeks followed by 2 agents (isoniazid and rifampicin) for the next 16 weeks.

26 Leprosy

The mode of transmission of *M. leprae* is uncertain but possibly nasal droplet infection is important. The clinical manifestations depend on the host immunological response. If the host mounts good cell-mediated immunity (CMI), the infection is localized (tuberculoid pole) while if the CMI is poor, the infection is extensive with visceral involvement (lepromatous pole).

The Ridley-Jopling classification, based on clinical, pathological, immunological and bacteriological parameters, classifies leprosy into:

- Indeterminate leprosy
- Determinate leprosy
 - Tuberculoid
 - Borderline tuberculoid
 - Borderline
 - Borderline lepromatous
 - Lepromatous

Tuberculoid and lepromatous leprosy are stable forms, while borderline forms of leprosy are unstable.

Prototype skin lesion is a hypopigmented/erythematous macule/plaque which is anesthetic/hypoaesthetic/normoaesthetic. Skin appendages (hair, sweating) on the lesions are reduced and there is epidermal atrophy. The nerves may be thickened and tender and there may be associated sensory and motor impairment. The clinical

presentation depends on the type of leprosy (Table 26.20, Figs 26.64 and 26.65).

Leprosy Reactions

Two types of acute episodes (lepra reactions) are recognized in leprosy. Type 1 reaction (T1R) which develops in patients with borderline leprosy (BT, BB, BL) is due to alteration in host CMI. T1R manifests as edema and erythema of pre-existing lesions along with neuritis which may result in development of new sensory and motor impairment. Type 2 lepra reaction (T2R, erythema nodosum leprosum, ENL) which occurs in highly bacillated patients (BL and LL) is an immune complex reaction and manifests as several tender, erythematous, transient nodules on face, flexures and legs. Patients may also show neuritis, orchitis, iridocyclitis, arthralgia and fever.

Complications

Patients may show the following complications:

- Trophic ulcers
- Deformities: Claw hand, clawing of toes, foot drop and saddle nose deformity
- Ophthalmologic complications: Diminished corneal sensation, lagophthalmos, recurrent iridocyclitis
- Renal involvement

Investigations

Slit skin smears: Slit skin smears, from the lesions and ear lobules, are stained with modified Ziehl-Neelsen method for acid fast bacilli (AFB). The smears are usually negative in TT/BT/most BB leprosy and usually positive in LL, BL and some BB.

Table 26.20: Clinical features of leprosy

	<i>Indeterminate</i>	<i>Tuberculoid</i>	<i>Borderline tuberculoid</i>	<i>Borderline</i>	<i>Borderline lepromatous</i>	<i>Lepromatous</i>
Skin lesions						
Number	Single	Single/Few	Few	Several	Numerous	Innumerable
Size	Variable	Variable	May be large	Variable	Small	Small
Sensations	Variable	Anesthetic	Hypoaesthetic	Hypoaesthetic	Hypoaesthetic	Normal
Symmetry	Asymmetrical	Asymmetrical	Asymmetrical	Bilateral, but asymmetrical	Tendency to symmetry	Symmetrical
Morphology	Hypopigmented macule; usually ill-defined hypoaesthetic; on face of child (Fig. 26.64)	Macule, plaque; well defined	Plaques; well defined; satellite lesions + (Fig. 26.65)	Macules, plaque; sloping edge (inverted saucer appearance)	Macules/papules, nodules, plaques; ill-defined	Macules, papules, nodules, plaques; ill-defined; diffuse infiltration of face
Nerves	+/-	Single trunk/feeder nerve related to lesion; thickened	Asymmetrical; few nerves thickened; anesthesia in its distribution	Asymmetrical; several nerves thickened	Several nerves, almost symmetrical, thickened; glove and stocking anesthesia	Several nerves asymmetrically thickened; glove and stocking anesthesia
Systemic Involvement	None	None	None	None	May be present	Lymphadenopathy, hepatosplenomegaly, ocular and testicular involvement
Reactions	-	-	T1R	T1R	T1R, T2R	T2R
Lepromin reaction	+/-	+	+/-	-	-	-
Presence of acid-fast bacilli	+/-	-	-	+/-	++	+++



Fig. 26.64: Indeterminate leprosy: Ill-defined hypopigmented, hypoesthetic lesion on the face

Skin biopsy: Presence of granuloma (epithelioid cells in tuberculoid leprosy and foamy cells in lepromatous leprosy) and nerve involvement are typical.

Treatment

Patient and parents are reassured and counseled regarding treatment compliance and care of hands, feet and eyes.



Fig. 26.65: Borderline tuberculoid: Well-defined erythematous plaque with satellite lesions

For the purpose of treatment, leprosy is classified into paucibacillary (PB) and multibacillary (MB) leprosy (Table 26.21) and based on this multidrug therapy (MDT) is instituted (Table 26.21).

Treatment of lepra reactions requires specific treatment (Table 26.22).

Table 26.21: WHO recommendations for treatment of leprosy in children aged 10–15 years

	<i>Paucibacillary</i>	<i>Multibacillary</i>
Definition	5 or less lesions	>5 lesions
Duration of therapy	6 months; to be completed in 9 months	12 months; to be completed in 18 months
Supervised (monthly)	Rifampicin 450 mg	Rifampicin 450 mg + clofazimine 150 mg
Unsupervised (daily)	Dapsone 50 mg	Dapsone 50 mg + and clofazimine 25 mg

Rifampicin 10 mg/kg; clofazimine 1 mg/kg daily, 6 mg/kg monthly; dapsone 2 mg/kg

Verruca (Warts)

Warts are caused by human papillomavirus, of which there are more than 100 types. They are transmitted by close contacts and autoinoculation. In children, non-genital warts are common, with an incidence of up to 10%.

Table 26.23: Clinical features and therapy of warts

	<i>Verruca vulgaris</i> (common warts)	<i>Verruca plana</i> (plane warts)	<i>Palmoplantar warts</i>	<i>Filiform warts</i>
Clinical features	Single or multiple firm papules with hyperkeratotic, clefted surface (Fig. 26.66)	Skin colored, flat smooth palpable papules (Fig. 26.67); Koebner phenomenon (pseudo) seen due to auto-inoculation	Superficial (mosaic): Painless, hyperkeratotic papules and plaques Deep (myrmecia): Painful, deep seated papules with a horny collar	Thin elongated, firm projections on a horny base
Site	Any part of body, most commonly on back of hands, fingers and knees	Face and back of hands	Soles and less often palms	Face
Therapy	Cryotherapy, mechanical removal and radio-frequency ablation (RFA)	Trichloroacetic acid touches; retinoic acid (0.025–0.05%) at night	Wart paint; cryotherapy; formalin soaks	RFA



Fig. 26.66: *Verruca vulgaris*: Firm papules with hyperkeratotic, clefted surface



Fig. 26.67: *Verruca plana*: Multiple, skin-colored papules

Table 26.22: Treatment of reactions in leprosy

	<i>Type 1 reaction</i>	<i>Type 2 reaction</i>
Mild	NSAIDs	NSAIDs
Moderate	NSAIDs Oral corticosteroids	NSAIDs Thalidomide* Chloroquine Clofazimine
Severe	NSAIDs Oral corticosteroids	Thalidomide* Oral corticosteroids

NSAIDs: Nonsteroidal anti-inflammatory drugs

*Thalidomide is a teratogenic agent and avoided in girls in the reproductive age

The clinical features differ in various types of warts (Table 26.23, Figs 26.66 and 26.67).

Modalities for treatment include cryotherapy, mechanical removal, radiofrequency ablation (RFA) and chemical cauterization (Table 26.23).

Molluscum Contagiosum

Caused by a poxvirus, patients show multiple, pearly white, dome-shaped papules with central umbilication (Fig. 26.68). Cheesy material can be expressed from the lesion. The lesions are seen on any part of the body. The condition is self-limiting and lesions usually clear within a year, but widespread lesions are seen in patients with atopic dermatitis and in those who are immunocompromised.

Treatment modalities used include wart paint or mechanical extirpation.

Hand-Foot-and-Mouth Disease

The illness is caused by coxsackie virus A16 infection, with feco-oral route being the predominant mode of transmission.

It most often affects children between 1 and 10 years of age during the summer and autumn months. The incubation period is 3–6 days. It manifests as an enanthem over the tongue and buccal mucosa, followed by painful vesicular exanthem involving lateral aspects of hands and feet (Fig. 26.69).

The disease usually runs a self-limiting course of 7–10 days, with a very rare incidence of cardiac and neurological complications.

Gianotti-Crosti Syndrome

Also known as papular acrodermatitis of childhood, the condition is associated with hepatitis B virus and Epstein-Barr virus.

The condition presents as characteristic lesions (Fig. 26.70) on the face, buttocks and limbs, associated with mild constitutional symptoms. The mucous membranes are not affected. The eruption fades with mild desquamation in 3–4 weeks.



Fig. 26.68: Molluscum contagiosum: Pearly white dome-shaped papules with central umbilication



Fig. 26.69: (a) Hand-foot-and-mouth disease: Skin lesions: Oblong vesicles with erythematous halo on palms; (b) Mucosal lesions: Oval, vesicular lesions with erythematous halo



Fig. 26.70: Gianotti-Crosti syndrome: Multiple, monomorphic, flat/umbilicated erythematous papules present symmetrically over the dorsae of hands

Herpes Simplex Virus (HSV) Infections

HSV type 1 infection is often asymptomatic but when symptomatic, the manifestations depend on whether the infection is primary or recurrent. Primary HSV infection presents as acute gingivostomatitis with tightly grouped vesicles on an edematous base which rupture to form polycyclic erosions (Fig. 26.71). There may be associated malaise, fever and lymphadenopathy. Patients with recurrent herpes labialis have a prodrome of burning and stinging followed by appearance of grouped vesicular lesions (Fig. 26.72) with background of slight erythema. These lesions may leave area of polycyclic depigmentation after healing.



Fig. 26.71: Herpes gingivostomatitis: Closed grouped vesicles on an edematous base which coalesce to form polycyclic erosions



Fig. 26.72: Herpes labialis: Polycyclic area of hypopigmentation and vesicular lesions

In patients with underlying dermatoses like atopic dermatitis and ichthyoses, HSV infection may become generalized (Kaposi varicelliform eruption or eczema herpeticum). Recurrent HSV infection may trigger episodes of erythema multiforme.

No treatment is generally required, except in primary infection, severe recurrent infection or in immunocompromised patients where treatment with oral acyclovir may be given for 5-7 days.

Dermatophytoses

Etiology

Three genera of fungi cause dermatophytoses: *Trichophyton*, *Epidermophyton* and *Microsporum*.

Clinical Features

The infection is given different names depending on the site affected. Dermatophyte infection of skin is known as *tinea corporis*, of groin as *tinea cruris*, of hands as *tinea manuum*, of feet as *tinea pedis* and of nails as *tinea unguium*. The classical lesion is an annular/arcuate/polycyclic plaque with a clear center and an active edge showing papulovesiculation and scaling.

Tinea capitis Three patterns are recognized:

- **Non-inflammatory or epidemic type** caused by anthropophilic organisms and so is responsible for epidemics. It presents as alopeciac patch, in which hairs break off easily (Fig. 26.73).
- **Inflammatory or kerion:** Caused by zoophilic organisms and so does not cause epidemics. It presents as a boggy swelling (Fig. 26.74) from which hair is easily pluckable without pain. Usually associated with occipital lymphadenopathy.
- **Favus:** Caused by *T. schoenleinii*, presents as yellowish, foul smelling cup-shaped crusts with matting of hair.



Fig. 26.73: Tinea capitis: Area of non-scarring alopecia with minimal inflammation with scaling at periphery

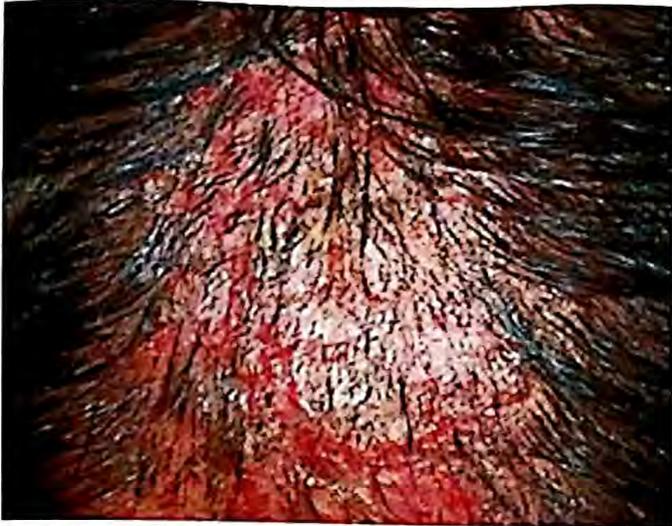


Fig. 26.74: Kerion: Boggy swelling of scalp which drains pus from multiple openings

Investigations

The diagnosis is confirmed by the KOH test that shows fungal hyphae. Culture helps in identification of species and this is important in patients with tinea capitis. Wood's lamp may help in diagnosis during epidemics.

Treatment

Tinea capitis Washing with ketoconazole shampoo and not sharing combs and head wear help to reduce transmission. Tinea capitis is always treated with systemic agents; griseofulvin (15 mg/kg/day of ultramicrocrystalline formulation) for 6 weeks is treatment of choice. Longer treatment (8 weeks) is needed for kerion. Terbinafine (5 mg/kg/day for 4–8 weeks) is effective in trichophyton (noninflammatory) but not in microsporum tinea capitis. Moreover, use of terbinafine in children is hindered by its unpleasant after taste.

Tinea corporis Localized lesions of tinea corporis are managed by topical therapy (azoles available as clotrimazole, miconazole or ketoconazole in lotion, gel and cream formulations). Widespread lesions require systemic antifungal therapy with terbinafine (2–6 weeks) or griseofulvin (4–8 weeks). Due to resistance to terbinafine, itraconazole is being used frequently.

Candidiasis

Candida albicans, a normal commensal becomes pathogenic in the presence of predisposing factors including obesity, diabetes and immunocompromised states. Less frequently other species like *C. glabrata* may be involved.

Candidiasis presents as oral thrush, vulvovaginitis, intertrigo, candidal diaper dermatitis or paronychia. Oral thrush presents as soft, creamy white to yellow, elevated plaques, that are easily wiped off to leave an erythematous, eroded or ulcerated surface. The lesions are seen on buccal mucosa, tongue, palate and gingiva.

Candidal intertrigo presents as erythematous, moist, macerated lesions with a frayed irregular edge with satellite pustules, present mainly in major skin folds, like axillae, groins and neck.

Candidal diaper dermatitis is characterized by well-defined weeping/eroded lesions with scalloped border and a collar of overhanging scales and satellite pustules. The lesion begins in the perianal region, spreading to perineum, upper thighs, lower abdomen and lower back.

Diagnosis

KOH mount shows budding yeasts and pseudohyphae. Culture is done in unresponsive cases to speciate the candida.

Treatment

Predisposing factors should be addressed and the area kept dry. Topical therapy includes imidazoles (clotrimazole, miconazole and ketoconazole) nystatin cream for folds and lotions for oral mucosa. Systemic therapy with weekly fluconazole is given in patients with extensive disease.

Pityriasis Versicolor

The condition is caused by *Malassezia furfur*, a commensal yeast. Patient presents with scaly, perifollicular macules with variable pigmentation (hypopigmented, erythematous or hyperpigmented). The fine branny scales are accentuated by gentle abrasion with a glass slide. The lesions are frequently seen on upper trunk (both anterior and posterior), neck and sometimes also on proximal part of upper extremities.

Diagnosis

KOH mount shows a mixture of short branched hyphae and spores (spaghetti and meatball appearance).

Treatment

Topical therapy with imidazoles (ketoconazole, 2%) for 3 consecutive days is sufficient in most cases. Systemic therapy with fluconazole is occasionally required in extensive and recurrent disease.

DISEASES CAUSED BY ARTHROPODS

Scabies

Scabies is caused by *Sarcoptes scabiei var hominis* and transmitted by close contact with infested humans.

Patient presents with itchy (worse at night) lesions, present in a characteristic distribution. The primary lesion is a burrow, a grey thread-like serpentine line with a minute papule at the end; papules and papulovesicles may also be seen. Secondary lesions consist of pustules, eczematized lesions and nodules. Lesions are seen in webs of hands, on wrists, ulnar aspects of forearms, elbows,

axillae, umbilical area, genitalia, feet and buttocks. Face is usually spared, except in infants in whom face, scalp, palms and soles (Fig. 26.75a) are also involved. Nodular lesions are seen on genitalia (Fig. 26.75b).

Secondary infections common. Secondary streptococcal infection may result in acute glomerulonephritis.

Treatment

General measures: All close contacts of the patient, even if asymptomatic, should be treated. Overzealous laundering of bed linen and clothes is not warranted.

Specific measure: Antibiotics are given, if secondary infection is present. Antihistamines are given for 1-2 weeks to reduce pruritus. The topical scabicide should be applied all over body below the neck, including on the free edge of nails, genitalia, soles of feet after hydration of body with a bath. Scabicides available include:



Fig. 26.75: (a) Infantile scabies: Multiple papulovesicular lesions on soles; (b) Infantile scabies: Nodular lesions of genitalia

Permethrin 5%: Overnight single application is treatment of choice in children older than 2 months of age.

Crotamiton 10%: Two applications daily for 14 days is recommended for infants less than 2 months.

Benzyl benzoate 25%: Three applications at 12 hourly intervals.

Ibermethin, single oral dose of 200 µg/kg body weight, in children older than 5 years is the treatment of choice for epidemics (as in orphanages).

Pediculosis

Louse is an obligate ectoparasite and two species infest humans: *Pediculus humanus* (*P. humanus capitis*, head louse and *P. humanus corporis*, body louse), and *Phthirus pubis* (pubic louse). Head louse infestation is transmitted by close contact and pubic louse infestation is acquired by children from infested parents.

Head louse infestation is common in children while pubic louse infestation is infrequent but when it occurs it also involves eyelashes and eyebrows. Head louse infestation manifests as severe scalp pruritus or recurrent pyoderma of scalp. Though adult lice are difficult to find, nits (egg capsules) are easily seen, firmly cemented to hair on which they can be slid but not slicked off. Secondary infection, eczematization and occipital lymphadenopathy are frequent.

Treatment

All family members should be treated. The chief pediculicides are:

- **Permethrin, 1% lotion,** single 10 minutes application to wet hair followed by rinsing. Repeat application after 7 days.
- **Gamma benzene hexachloride, 1% single overnight application** to dry hair followed by rinsing. Second application used after 7 days.
- **Malathion, 0.5% water-based lotion,** applied on dry hair for 6 hours. Has residual effect, so second application is not needed.
- **Sphosad, 0.9% suspension,** single 10 minutes application.

Popular Urticaria

Papular urticaria is due to bites of arthropods such as mosquitoes and fleas. An initial itchy, urticarial wheal that develops at the site of bite evolves into a firm pruritic papule, which persists for several days. The lesion often has a central hemorrhagic punctum (Fig. 26.76) and may be surmounted by a tiny vesicle.

Secondary infection, eczematization, hyper- and hypopigmentation, particularly in darkly pigmented individuals are not uncommon. New bites by the same species often cause a recrudescence of activity in existing and even healed lesions.



Fig. 26.76: Papular urticaria: Papule with a central hemorrhagic punctum

Treatment

Prevention of repeated insect bites through use of protective clothings, judicious use of insect repellents and treatment of pets with infestation is recommended. Topical steroid-antibiotic combination and oral antihistamines help in reducing pruritus and hypersensitivity reaction.

MISCELLANEOUS DERMATOSES

Protein-Energy Malnutrition

Marasmus is characterized by emaciation and dry, thin, pale, wrinkled skin while kwashiorkor manifests as generalized edema and areas of hyperpigmentation and occasional desquamation ('flaky paint appearance') predominantly at sites of pressure and friction (Fig. 26.77). Hairs may show alternate areas of discoloration (flag sign).

Acrodermatitis Enteropathica

This is an autosomal recessively inherited disorder resulting in deficiency of zinc transporter protein and resultant defective zinc absorption. The condition is characterized by the dermatitis, diarrhea, alopecia and irritability. Characteristics skin lesions include periorificial sharply demarcated, erythematous crusted plaques with fissured margins (Fig. 26.78).



Fig. 26.77: Protein-energy malnutrition: Generalized, areas of hyperpigmentation and occasional desquamation ('flaky paint appearance') in an irritable child



Fig. 26.78: Acrodermatitis enteropathica: Sharply demarcated erythematous plaque over the perianal area with fissured margins

Treatment

Oral administration of zinc sulfate or zinc gluconate.

Porphyria

Porphyrias are a group of diseases characterized by genetic or acquired enzyme deficiencies in the pathway of haem synthesis, resulting in accumulation of haem precursors: 5-aminolaevulinic acid (ALA), porphobilinogen and porphyrins.

Based on clinical and biochemical parameters, porphyrias are classified into:

1. *Erythropoietic porphyria*: Congenital erythropoietic porphyria (CEP), erythropoietic protoporphyria (EPP).
2. *Hepatic porphyria*: Porphyria cutanea tarda (PCT), variegate porphyria (VP), acute intermittent porphyria.

Porphyrias are characterized by extreme photosensitivity and blistering and scarring of photo-exposed areas (Fig. 26.79).

Treatment for all porphyrias includes genetic counseling, strict photoprotection and some specific measures (Table 26.24).

Mastocytoses

Etiology

Mastocytoses are a heterogeneous group of diseases characterized by localized or diffuse accumulation of clonal mast cells in the skin and/or in internal organs.

Urticaria pigmentosa is the most common variant (70–90%) of childhood mastocytosis. It may be seen at birth or appear in the first year of life and is characterized by itchy multiple, discrete, yellowish-brown hyperpigmented macules and slightly elevated plaques in a generalized distribution with a truncal predominance (Fig. 26.80). Dermographism is present in one-third of patients and in the first 2 years, pathognomonic Darier's sign may be present.

Diagnosis is confirmed with histological and immunohistochemical evaluation of skin biopsy.

Treatment is directed at alleviation of symptoms (pruritus) with antihistamines and/or disodium



Fig. 26.79: (a) Congenital erythropoietic porphyria: Hypertrichosis over the face; (b) Congenital erythropoietic porphyria: Hyperpigmentation, mutilating scarring

Table 26.24: Manifestations and treatment of porphyrias

	<i>Congenital erythropoietic porphyria</i>	<i>Erythropoietic protoporphyria</i>	<i>Porphyria cutanea tarda</i>	<i>Variegata porphyria</i>
Enzyme defect	Uroporphyrinogen synthase III	Ferrochelatase	Uroporphyrinogen decarboxylase	Protoporphyrinogen oxidase
Inheritance	Autosomal recessive	Autosomal dominant	Autosomal dominant, if early onset	Autosomal dominant
Onset	Soon after birth	Infancy or early childhood	Childhood	Post-pubertal
Cutaneous manifestations	Severe photosensitivity. Blisters on photoexposed areas, mutilation. Hypertrichosis conspicuous	Burning, edema and urticaria on sun exposure. Thickening of skin and superficial scarring	Blisters and fragility of skin on photoexposed areas. With time, skin becomes thickened, sclerodermoid and scarred. Hypertrichosis conspicuous	Some patients asymptomatic, others have only cutaneous manifestations, while some have both manifestations. Skin involvement like that in PCT
Associated features	<ul style="list-style-type: none"> Brown teeth, show fluorescence under Wood's lamp Hemolytic anemia 	<ul style="list-style-type: none"> Gall stones Liver disease, sometime fatal 		<ul style="list-style-type: none"> Abdominal pain Neuropsychiatric symptoms
Urine	Red coloured urine (also fluorescent)	Normal color	Pink (also fluorescent)	Red colored urine during acute attacks
Investigations	Estimation of porphyrins in blood, urine and stool			
Treatment	Bone marrow transplantation	Beta carotene	Blood letting and small dose of chloroquin	Avoiding triggers



Fig. 26.80: Urticaria pigmentosa: Multiple, discrete, yellow-brown hyperpigmented plaques over the chest and abdomen

cromoglycate. Systemic corticosteroid and oral PUVA are helpful in the cases with systemic symptoms.

Langerhans Cell Histiocytosis (LCH)

It is a multi-system infiltration with proliferating Langerhans cells.

Classification

Several subsets of LCH with overlapping features are recognized:

- *Letterer-Siwe disease* is generalized form, which occurs predominantly in children <2 years.
- *Hand-Schüller-Christian syndrome* is chronic, multifocal form, with peak onset in children aged 2–10 years.



Fig. 26.81: Langerhans cell histiocytosis: Multiple, small, erythematous, discrete, crusted papules over the chest and abdomen

- *Eosinophilic granuloma* is localized form, seen in children aged 5–15 years.

Letterer-Siwe disease is characterized by intractable 'seborrheic dermatitis-like' lesions with scaly/crusted yellowish reddish-brown (sometimes hemorrhagic) infiltrated papules over scalp and trunk (Fig. 26.81). Systemic manifestations include fever, anemia, diarrhea, thrombocytopenia, hepatosplenomegaly, lymphadenopathy and skeletal lesions.

Skin biopsy confirms the diagnosis. Systemic chemotherapy is indicated in children with disseminated multi-system involvement.

Suggested Reading

- Khanna N. Illustrated Synopsis of Dermatology and Sexually Transmitted Diseases. 5th edn. Elsevier, New Delhi, 2016.
- Khanna N, Saurabh S. Bhutani's Color Atlas of Dermatology, 6th edn. Jaypee, New Delhi, 2015.

Poisonings, Injuries and Accidents

Jhuma Sankar

INJURIES AND POISONING

Nearly 90% of childhood injuries are unintentional or accidental. Injuries account for 6–10% of all childhood deaths. A significant proportion of these children could be saved, if appropriate injury prevention measures were applied. Road traffic crashes, falls, drowning, burns and poisoning are the leading causes of child death from injuries. A large proportion (e.g. drowning, burns, falls) occur in or around the home. The following is a global resource on intentional injury and its prevention: http://www.who.int/violence_injury_prevention/child/injury/world_report/en/

ROAD TRAFFIC ACCIDENTS AND FALLS

Road traffic crashes are the leading cause of death among children aged 10 to 19 years. India has high rates of road traffic accidents in the world. Falls account for a significant proportion of visits by children to hospital emergencies. Seat-belts and child-restraints, helmets, pedestrian lanes, daytime running lights for vehicles, speed limits, laws against drinking alcohol and driving are among the successful interventions to prevent road traffic injuries. Severe falls can be avoided by changes in architectural designs, and specially designed child products and playground equipment.

Factors Predisposing Children to Trauma

Children have a pliable skeleton with less fat and more elastic connective tissue, protecting tightly packed

abdominal and thoracic structures. The impact of trauma is transmitted widely through the body resulting in multisystem injuries. Early recognition and aggressive management of emergencies like airway obstruction, hemorrhage including intra-abdominal and intracranial hemorrhages improve survival rates after major trauma. Subtle changes in heart rate and peripheral perfusion must be looked for, as these are signs of impending cardiorespiratory failure. Hypotension is a late sign of shock and blood pressure may remain normal despite 25–30% blood loss (Table 27.1).

Blunt injury is common compared to penetrating injury. Common visceral injuries include contusions, laceration or hematoma of liver, spleen, lungs as well as pneumothorax, rib fractures and gastrointestinal tract injury. Head injuries, alone or associated with multiple system injuries, are the most severe and cause most deaths. Head injuries also account for disability in children. Blunt trauma in children often results in airway and breathing compromise rather than bleeding and shock.

Management

Children may not cope well emotionally after an accident. They need to be managed in a calm, child-friendly environment, preferably in the presence of a parent or guardian. Initial management during 'the golden hour' in pediatric emergency includes primary survey and resuscitation by a well-organized team. The goal of the primary survey is to find and relieve immediate life-threatening conditions. It starts at the injury scene and

Table 27.1: Systemic response to blood loss in children

System	Mild blood loss (<30%)	Moderate blood loss (30–45%)	Severe blood loss (>45%)
Cardiovascular	Increased heart rate, weak peripheral pulses, normal systolic blood pressure	Markedly increased heart rate, weak central pulses, absent peripheral pulses, low normal systolic pressure	Tachycardia followed by bradycardia, weak or absent central pulses, hypotension
CNS	Anxiety, irritability, confusion	Lethargy, minimal response to pain	Coma
Skin	Cool, mottled, prolonged capillary refill	Cyanotic, markedly prolonged capillary refill	Pale and cold
Urine output	Low	Negligible	None

aims to maintain a patent airway, provide adequate breathing, circulatory support, and to assess major neurologic disability. Initial stabilization should proceed in ABC sequence. All patients should receive supplemental oxygen preferably with non-rebreathing mask (see Chapter 23).

Disability: A rapid neurological examination is carried out to assess level of sensorium with Glasgow Coma Scale and pupillary responses may indicate traumatic brain injury, hypoxemia or cerebral hypoperfusion. Various scores have been used to identify children at high risk of mortality of which the Pediatric Trauma score is widely used; score ≤ 6 significantly predicts mortality and morbidity (Table 27.2).

Secondary survey includes assessment as per the mnemonic, "SAMPLE" (symptoms, allergies, medications, past illness, last meal, and events leading to the illness) and head to toe examination to identify intrathoracic, intra-abdominal, and skeletal or skull injuries. Continued resuscitation and reassessment should proceed simultaneously. Radiologic examination involves use of X-ray, ultrasonography and CT scan to define anatomy and abnormalities. Focused assessment by sonography in trauma (FAST) may be useful in detecting intra-abdominal bleeding that can be performed serially at the bedside.

Management of injuries requires a specialist multidisciplinary team involving pediatric emergency physicians, anesthetists, surgeons, orthopedician, pediatric intensivists and trained nursing personnel. Life-threatening chest injuries, e.g. tension pneumothorax, flail chest, massive hemothorax and cardiac tamponade should be rapidly identified and managed. Abdominal blunt injury may result in contusions, hematomas or laceration of solid organs. Suitable analgesic medication is titrated to alleviate pain and anxiety. Availability of emergency medical services, transport systems and advanced trauma facilities has resulted in significant reduction in accident related mortality in developed countries. Polytrauma may have significant psychological and social impact on the developing brain and result in considerable morbidity. Psychological and social support, during resuscitation and afterwards, is important.

BURNS, ELECTRICAL AND INHALATIONAL INJURIES

WHO estimates approximately 10% of all unintentional injury related deaths are due to fire related burns. Children are at higher risk of death from burns with 3.9 deaths per

10000 population. Skin, the largest organ of the body, insulates and prevents heat and moisture loss and protects from invasion by harmful environmental microbes. Loss of integrity of the skin exposes the body to harmful agents, hypothermia and loss of body fluids. Of all types of burns, fire-related burns are the commonest, followed by scalds and electrical burns. Fireworks are a seasonal injury and over 40% of those injured by fireworks are children younger than 15 years. Prevention of child labor in firearm manufacturing units and strict legislative action has helped prevent firework-related injury in our country. Parental supervision of use of fireworks and community restriction on certain types of fireworks may further reduce these injuries. Children should use flame retardant or nonflammable fabrics to prevent burns.

Children with severe burns often have associated traumatic injuries which might be missed because of edema and charring nature of the burn. Electrical injuries can occur from direct contact or by an arc such as a lightning strike. Direct contact often has entry and exit site wound. The extent of injury depends on the voltage of current, and course of electric current through the body. Current passing in the region of the heart can cause arrhythmias and death. Tissues with high resistance like bone and tendons convert more electrical energy into thermal energy and sustain more damage. Inhalation injury, associated with large burns, includes upper airway direct thermal injury, chemical pneumonitis from harmful chemicals and systemic poisoning from inhalation of cyanide and carbon monoxide.

Classification of Burns

Thermal burns may be scalds (caused by hot liquid or steam), contact burns (contact with hot objects), flame burns, chemical burns (exposed to strong acids or alkalis) or electrical. Based on depth, burns are classified as:

1. **First degree or superficial burns** confined to the epidermis. Characterized as erythematous, painful and dry burns. They heal within a week not leaving any scar behind.
2. **Second degree or partial thickness burns** involve part of the dermis, and are characterized by erythematous, moist and painful burns. (a) *Superficial*: Take less than 3 weeks to heal; (b) *Deep*: Take more than 3 weeks to heal and leave scars.

Table 27.2: Pediatric trauma score

Component	+2	+1	-1
Size	>20 kg	10-20 kg	<10 kg
Airway	Normal	Maintainable	Not maintainable
Systolic BP	≤ 90 mm Hg	50-90 mm Hg	<50 mm Hg
Central nervous system	Awake	Obtunded, coma	Coma, decerebrate
Skeletal	None	Close fracture	Open or multiple fractures

3. **Third degree or full thickness burns** damage the full thickness of dermis. These are characterized as leathery, dry and insensate burn. They cannot regenerate themselves without grafting.

The "rule of nines" for calculating the surface area of burn is not applicable to children <15-year-old. The Lund and Browder chart can be used for the same. A practical approach is to consider the child's palm together with fingers as representing 1% of total body surface area (TBSA). The risk of mortality from burns covering 30% of body surface area is ~50% and that with more than 50% BSA is ~100%.

First Aid

Fire injuries: At the scene of fire, the child should be wrapped with a blanket or coat; attempt is made to extinguish the flames by rolling the victim on the ground. Running with clothes on fire should be avoided. The victim is rescued to a safe airy place away from the fire to prevent exposure to gases like carbon monoxide and cyanide. In the case of minor burns or scalds, pour cold water, apply cold-water soaks or submerge the burned portion immediately in cold water. Application of grease, soda, oil, powder, butter, toothpaste or herbs should be avoided. The wound is covered with clean sheets of sterile dressing and the patient wrapped in a blanket or foil. Management of patients requires assessment of the extent of injury, including surface area, depth and cause of burn.

Electrical injuries: The power supply should be switched off. Using a nonconductor material (dry wooden stick or dry cotton clothes), the victim is pulled from the electric source. The surface injury may be smaller and is often not indicative of the extent of injury to deeper tissues. Children should be monitored for arrhythmias, ongoing myolysis, and secondary organ dysfunction.

Inhalational injury: Children with inhalation injury may require to be intubated and provided supportive ventilation. Pneumonitis peaks after 3–5 days of injury. High blood levels of carboxyhemoglobin suggest carbon monoxide poisoning. Inhalation of 100% oxygen shortens the elimination half life of carbon monoxide from 4 hours to 40 minutes, and is thus recommended. Cyanide poisoning can occur when significant quantities of plastics are burned. The antidote, hydroxycobalamin, infused at a dose of 70 mg/kg IV, binds with cyanide forming cyanocobalamin that is stable and excreted in urine. Amyl nitrite and sodium nitrite may induce methemoglobinemia and are not recommended.

Hospitalization

Minor burns can be treated at home with topical ointments. Indications for inpatient care include: (i) third-degree burns at any age group; (ii) second-degree burns involving more than 10% TBSA; (iii) burn injuries involving the face, hands or genital areas; (iv) electrical

burns, chemical burns and inhalational injury; and (v) burn patients with concomitant trauma.

The goals of resuscitation and early management are: (i) adequate fluid replacement; (ii) correction of hypoxia and ventilatory disturbances; (iii) prevention of hypothermia; (iv) adequate control of pain and anxiety; (v) wound care; (vi) nutrition, and (vii) supportive care. IV access is established with the peripheral cannula and may be performed through burn-injured tissue, if required. Children with >10% burns should have urinary catheterization to titrate fluid resuscitation.

Fluid replacement: The goal of fluid resuscitation is to replenish the fluid loss and to restore and maintain perfusion, tissue oxygen delivery at optimal levels in order to protect the zone of ischemia in burnt tissues without overloading the circulation. Monitoring urine output and a nasogastric tube for continuous suction to prevent emesis and aspiration are essential. The adequacy of fluid resuscitation is based on urine output, which should be maintained above 1 mL/kg/hr in infants and young children. The Parkland formula estimates the amount of fluid to be replaced over 24 hours as follows:

Volume of Ringer lactate (mL) = 4 mL × weight (kg) × % TBSA burn

In addition, the child requires maintenance fluid therapy. Half of the resuscitation volume should be given in initial 8 hours and the other half in following 16 hours. Potassium is administered after normal kidney function is shown. Subsequent fluid management should account for ongoing fluid losses (Fig. 27.1).

Analgesia: Adequate control of pain is an essential component of burn management; opioids are commonly prescribed.

Wound care and topical therapy: Adequate wound care and topical therapy result in healing of first and second-degree burns, without need for skin grafting. The most commonly used topical agents are 0.5% silver sulfadiazine,

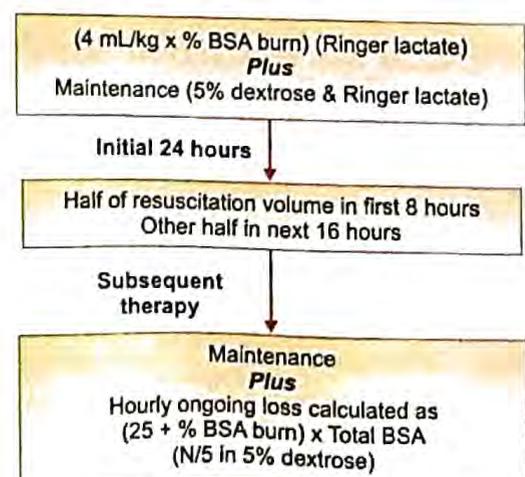


Fig. 27.1: Outline of fluid resuscitation in burns

0.5% silver nitrate and mafenide acetate. Application of silver sulfadiazine is painless and has a soothing effect, restricting fluid and heat loss from burn surface. However, it can cause skin rash, leukopenia, and thrombocytopenia. Silver nitrate is not an effective antibacterial agent because of poor penetration of the burn eschar. The medication can cause hyponatremia, hypokalemia, hypochloremia and hypocalcemia. Mafenide acetate penetrates the burn eschar effectively; its application may be painful and associated with skin reaction and metabolic acidosis.

Daily dressing changes are required; moist exposed burn ointment (MEBO) is promising. Treatment for small, deep second-degree burns has two components: Excising the burn wound before it is infected and covering the excised wound with synthetic or biological wound dressings. For circumferential burns of the chest, abdomen and extremities, decompressive escharotomy need to be performed.

Nutrition: High caloric and protein intake are crucial for survival and recovery. Caloric requirement in children with burns is estimated as follows:

Infants: 2100 Kcal/m² + 1000 Kcal/m² burn surface area

Children: 1800 Kcal/m² + 1300 Kcal/m² burn surface area

Adolescents: 1500 Kcal/m² surface area and burn surface area

Adequate protein intake (2–3 g/kg body weight) and supplementation of trace vitamins and minerals are necessary. Whenever feasible, particularly in children with less than 15–20% burns, nutrients are given enterally. Tube feeding is started on the first day of admission with rapid advancement towards intake goals. Parenteral nutrition is considered in children with extensive burns, inhalation injury or prolonged paralytic ileus.

Supportive measures: Assessment of physical abilities and enabling a full range of joint movements by physical and occupational therapy and play therapy is encouraged.

DROWNING AND NEAR DROWNING

Drowning is an asphyxial death from submersion or immersion in liquid. It is the leading cause of injury related death for young children under 5 years of age. Drowning rates in low-middle income countries are 6-time higher than in high-income countries. Risk factors for drowning include residence in densely populated areas with large amount of open water, young age, male sex and those with conditions such as epilepsy and autism. While drowning is most frequent in natural bodies like ponds, lakes and rivers, drowning in swimming pools and bathtubs is increasing.

Management includes immediate resuscitation and transfer to a tertiary care facility. In case of death due to drowning, parents need to be provided psychosocial support, as it is difficult to cope with the unexpected death. Successful interventions to prevent drowning include the

use of life jackets, fencing around swimming pools, covering water hazards and prompt first aid.

CHOKING AND SUFFOCATION

Choking, suffocation and strangulation are important causes of unintentional injuries, especially in infants. Complications include anoxic brain damage and esophageal perforations. Food (chiefly nuts), latex balloons, toys, lids and small containers are commonly involved in choking, while suffocation is commonly seen in a crib, waterbed or with playground equipment.

Ingestion or inhalation of button batteries is dangerous. Most batteries pass through the alimentary tract, but occasionally are impacted in the esophagus or cause gastric erosion. Batteries have also been inserted into the nose. Ingested small coins are usually passed safely but may become impacted and require surgical intervention. Prevention strategies include enforcing regulatory standards for baby and child product design and manufacture, appropriate labeling and parental education.

POISONING

Acute childhood poisoning is a common and challenging pediatric emergency. Children are susceptible to poisoning because of their curious and exploring nature, and propensity to put virtually everything in their mouths. Common poisoning agents in high-income countries include pharmaceuticals, household products and chemicals; in low and middle-income countries, pesticides, kerosene, cleaning agents and pharmaceuticals are commonly involved. Majority of poisonings in children <5 years of age are accidental, while in older children and teenagers, these are largely intentional.

Clinical Approach to Child with Suspected Poisoning

The initial approach includes stabilization and rapid assessment of the airway, breathing, circulation and mental status. After initial assessment and stabilization of vital signs, general physical and neurological examination is done. Physical examination may show pallor (hemolysis), cyanosis (methemoglobinemia) or icterus (hepatotoxic agents, hemolytic agents). Acidotic breathing suggests poisoning due to alcohols, salicylates or agents causing hypotension, hypoxia or seizures. Tachycardia or tachyarrhythmia may point towards sympathomimetic and anticholinergic agents, while bradycardia and bradyarrhythmia suggest toxicity with digitalis and cholinergic agents. Oral cavity examination may reveal signs of caustic ingestion such as excessive salivation and swallowing difficulties or indicate a poison by its odor. Characteristic features with commonly reported poisoning agents are shown in Table 27.3.

Often a particular poison produces a constellation of features (toxidromes) involving various organ systems that confirm the likely diagnosis. A history of vomiting,

Table 27.3: Key clinical features in poisoning

<i>Signs and symptoms</i>	<i>Toxin</i>
<i>Central nervous system</i>	
Ataxia	Anticonvulsants (phenytoin), alcohols, sedative-hypnotics
Coma	Opioids, sedative-hypnotics, anticonvulsants, antidepressants, antipsychotics
Seizures	Sympathomimetics, Ecstasy, anticholinergics
<i>Eyes</i>	
Miosis	Opioids, organophosphates
Mydriasis	Anticholinergics, sympathomimetics
Nystagmus	Phenytoin, alcohol, ketamine, sedative-hypnotics
<i>Cardiovascular system</i>	
Tachycardia	Sympathomimetics, anticholinergics, antipsychotics, antidepressants, serotonin syndrome
Bradycardia	Beta-blockers, calcium channel blockers, digoxin, organophosphates, opioids
Hypertension	Sympathomimetics, anticholinergics
Hypotension	Beta blockers, calcium channel blockers
<i>Respiratory system</i>	
Respiratory depression	Opioids, sedative-hypnotics
Tachypnea	Salicylates, sympathomimetics
<i>Gastrointestinal tract</i>	
Diarrhea	Opioid withdrawal, cholinergics
Constipation	Lead intoxication
Jaundice	Acetaminophen, carbon tetrachloride
<i>Cutaneous manifestations</i>	
Diaphoresis	Cholinergics, sympathomimetics
Cyanosis	Methemoglobinemia
Alopecia	Arsenic, thallium poisoning
<i>Oral cavity</i>	
Salivation	Organophosphates, salicylates
Oral burns	Corrosives
Gum lines	Lead, mercury, arsenic, bismuth
<i>Odor</i>	
Bitter almond	Cyanide
Acetone	Isopropyl alcohol, methanol, salicylates
Alcohol	Ethanol
Garlic	Organophosphates, arsenic, kerosene

diarrhea, excessive sweating or salivation, seizures and presence of miosis, coma and respiratory failure indicate anticholinergic (organophosphate) poisoning, while the presence of mydriasis, dry mouth, seizures, sensorial alteration and hypertension may point towards poisoning or overdose with cholinergic compounds (Datura, atropine or tricyclic antidepressants) (Table 27.4).

Laboratory Evaluation

Diagnosis of poisonings is chiefly clinical and quantitative estimation of most toxins is usually not possible or delayed. Laboratory evaluation is used to support the clinical diagnosis. Quantitative estimation of selected agents, such as heavy metals, salicylates, some anticonvulsants, digoxin and paracetamol is available at the toxicology laboratory at the All India Institute of Medical Sciences, New Delhi as well as a few private centers in the country. Samples for quantitative assessment

in a child with suspected poisoning should include vomitus or gastric aspirate, and urine and blood specimens. Simple bedside tests help in management and monitoring of these patients (Table 27.5).

Management

Emergency cardiorespiratory stabilization is the priority and should precede diagnostic tests. While the patient is being stabilized, a member of the team should contact the National Poisons Information Centre (NPIC) at AIIMS, New Delhi which has an emergency helpline available 24 × 7. Based on the information provided, advice on diagnosis and management of the child or adult patient is provided and the poisoning is recorded in the National Database. Helpline numbers are 1800-116-117, 011-26589391, and 011-26593677

<http://www.aiims.edu/aiims/departments/pharmacology/NPIC/home.htm>

Table 27.4: Common toxidromes

Toxin	Toxidrome
<i>Cholinergics</i> (organophosphates, carbamates)	<i>Muscarinic effects</i> (DUMBBELS) Diarrhea; urinary incontinence; miosis; bradycardia; bronchorrhea; emesis; lacrimation; salivation <i>Nicotinic effects</i> Fasciculations, weakness, paralysis Tachycardia, hypertension <i>Central nervous system effects</i> Lethargy, coma; agitation, seizures
<i>Anticholinergics</i> (atropine, tricyclic antidepressants, antihistaminics)	Delirium, agitation (mad as a hatter) Mydriasis (blind as a bat) Flushing (red as a beet) Hyperthermia (hot as a hare) Dry skin and oral mucosa (dry as bone) Tachycardia, hypertension, urinary incontinence, ileus
<i>Sympathomimetics</i> (amphetamines, cocaine, ADHD medications)	Agitation, seizures Mydriasis Tachycardia, hypertension Fever, diaphoresis Pallor, cool skin
<i>Opioids</i> (methadone, morphine, heroin)	Coma, respiratory depression Miosis Bradycardia, hypotension, hypothermia
<i>Sedative hypnotics</i> (barbiturates, benzodiazepines)	Coma, respiratory depression Arrhythmias, QT prolongation
<i>Serotonin syndrome</i> (SSRI, lithium, monoamine oxidase inhibitor, linezolid)	Agitation, confusion, coma Hyperthermia, tachycardia, hypertension or hypotension Mydriasis, diaphoresis Neuromuscular excitability

SSRI: Selective serotonin receptor inhibitor

Principles of management of patients with poisoning include: (i) initial assessment and rapid stabilization of airway, breathing and circulation (basic life support) and supportive care, (ii) decontamination, (iii) enhancement of excretion, and (iv) administration of antidotes. These are discussed below.

Basic Life Support

Airway and breathing: Early elective intubation is preferred in patients with high risk of aspiration and progression to respiratory failure. Rapid sequence intubation is preferred, due to potential loss of protective airway reflexes and expectation of a full stomach, with risk for aspiration. Specific indications for intubation include failure to maintain patent airway due to CNS depression or increased secretions; respiratory failure (hypoxemia or hypercapnia) and severe pulmonary edema (salicylates). Establishment of airway may be difficult in children with poisoning due to caustics and upper airway burns and/or angioedema. Adequacy of breathing should be assessed by respiratory efforts, chest excursions, air entry, and oxygen saturation. Mechanical ventilation

should be optimized to maintain adequate gas exchange and hemodynamics, taking care to avoid nosocomial infections.

Circulation: Causes for cardiovascular instability in poisoned patients include decreased systemic vascular resistance, myocardial depression (tricyclic antidepressants, calcium channel blockers) and arrhythmias (digoxin, tricyclic antidepressants). Priority is given towards optimization of preload before using vasoactive agents. In hypotensive patients, it should be remembered that patients are often not hypovolemic; aggressive fluid resuscitation can, therefore, lead to fluid overload. If hypotension persists after 1 or 2 standard crystalloid boluses, infusion of a direct acting vasopressor, such as epinephrine and norepinephrine, is preferred. Arrhythmias caused by agents that block fast sodium channels (tricyclic antidepressants) are managed with sodium bicarbonate therapy.

Supportive Care

The goals of care include post-stabilization care and monitoring for complications and organ dysfunction.

Table 27.5: Laboratory clues in poisoning

Laboratory abnormality	Causative agents
High anion gap metabolic acidosis	Methanol, metformin Uremia Diabetic ketoacidosis Paraldehyde, propylene glycol Isoniazid, iron Lactic acidosis Ethanol, ethylene glycol Salicylates
Elevated osmolar gap Hypoglycemia	Alcohols: Ethanol, methanol, isopropyl, ethylene glycol Oral hypoglycemics: Sulfonylurea, meglitinides Quinine, unripe Ackee fruit Beta blockers, insulin, ethanol, salicylates
Hyperglycemia	Salicylates (early) Calcium channel blockers, caffeine
Hypocalcemia Rhabdomyolysis Hyperkalemia	Ethylene glycol, fluoride Neuroleptic malignant syndrome, serotonin syndrome, statins Digoxin, beta blockers, alpha agonists
<i>Urine color</i>	
Orange to red-orange	Rifampin, deferoxamine, phenazopyridine, lead and mercury poisoning
Pink	Cephalosporins or ampicillin
Brown	Chloroquine or carbon tetrachloride
Green to blue	Amitriptyline
<i>ECG changes</i>	
Prolonged PR interval	Digoxin, lithium
Prolonged QRS complex	Membrane active agents like tricyclic antidepressants (TCA)
Prolonged QTc interval	Some macrolides and antifungals, amiodarone, antipsychotics
Radiopaque density	Chloral hydrate, calcium carbonate, heavy metals, iron Phenothiazines, potassium chloride, enteric-coated tablets Dental amalgam

Convulsions may occur due to hypoglycemia, hypoxia, cerebral edema, direct effect of toxin on the central nervous system, and hypo- or hypernatremia. Seizure control is achieved through administration of benzodiazepines (lorazepam 0.1 mg/kg IV, midazolam 0.15 mg/kg IV, rectal diazepam 0.2–0.5 mg/kg/dose). Status epilepticus is managed as per standard protocol.

Acid-base abnormalities are commonly observed with alcohols, salicylates and iron toxicity. The emphasis is directed at the underlying etiology rather than excessive use of sodium bicarbonate.

Electrolyte and metabolic abnormalities are anticipated in poisoning with drugs such as digoxin, beta-blockers, insulin and potassium chloride. Administration of antidotes, if applicable, and correction of the underlying abnormality is important.

Hypothermia is observed in poisoning with narcoleptic agents such as chlorpromazine. Management comprises of keeping the patient warm, administering pre-warmed IV/nasogastric fluids and monitoring for complications of hypothermia, e.g. hyperglycemia and disseminated intravascular coagulation.

Pulmonary edema is non-cardiogenic and occurs with substance abuse (heroin, cocaine) or with aspirin overdose. Treatment comprises of administration of 100% oxygen and positive pressure ventilation, if required. The use of furosemide and atropine (for organophosphate poisoning) may be helpful.

Pain is common with snake or scorpion bites and with ingestion of corrosives. Analgesics, narcotics (if no respiratory/CNS depression) and local anesthetics are often required.

Nausea, vomiting and upper GI bleeding may be observed with ingestion of corrosives or drugs causing gastric irritation, or due to stress of illness itself. The use of antiemetics, H₂ receptor antagonists and proton pump inhibitors should be considered.

Decontamination or Removal of Unabsorbed Poison

Decontamination is an important step that helps reduce further absorption of the poison. The method varies depending on the type and route of exposure, patient age and general condition, and the time elapsed since poisoning. However, decontamination should not be routinely employed for every patient.

Dermal and ocular decontamination: Dermal and ocular decontamination begin with removal of any contaminated clothing and particulate matter, followed by flushing of the affected area with tepid water or saline. A minimum of 10–20 minutes of flushing is recommended for most exposures, although some chemicals (e.g. alkaline corrosives) require longer periods of flushing. Dermal decontamination should include thorough cleansing with soap and water especially in case of organophosphate poisoning. Water should not be used for decontamination after exposure to highly reactive agents, such as elemental sodium, phosphorus, calcium oxide and titanium tetrachloride.

Gastrointestinal decontamination: GI decontamination strategies are most likely to be effective, if employed within the first hour after an acute ingestion. However, even rapid decontamination with activated charcoal will, at best, bind ~30% of the ingested substance. Of the methods of GI decontamination, only activated charcoal and whole-bowel irrigation (WBI) are of clinical benefit.

Gastric lavage may be employed for patients who arrive within 1 hour of toxin ingestion. Following insertion of a large-bore orogastric tube (preferably 28 Fr in infants and 36 Fr in older children) into the stomach, the gastric contents are aspirated and washed. Child is kept in lateral decubitus position with head end lowered. Contraindications to gastric lavage include unprotected airway, ingestion of corrosive substances or hydrocarbons, and patients at risk for GI perforation or hemorrhage. Complications include pulmonary aspiration, respiratory compromise, mechanical injury or perforation of esophagus, and electrolyte imbalances. There is limited evidence to suggest that its use improves clinical outcome, so gastric lavage should not be considered unless a patient has ingested a potentially life-threatening amount of poison.

Activated charcoal is a potentially useful method of GI decontamination. Charcoal is activated by heating to extreme temperatures, which lead to creation of extensive network of pores, providing large surface area for absorption. Charcoal is most likely to be effective when given within 1 hour of toxin ingestion. It adsorbs almost all toxins except *common electrolytes, iron, mineral acids or bases, alcohols, cyanide, most solvents, most water insoluble compounds (hydrocarbons), pesticides and lithium*. The dose of activated charcoal is 1g/kg in children or 50–100 g in adolescents and adults. A patent and stable airway must be ensured before administering activated charcoal. Its use is contraindicated in patients with intestinal obstruction, ileus, peritonitis and corrosive ingestions.

Whole bowel irrigation (WBI) involves instilling large volume of polyethylene glycol electrolyte solution (PEG-ES) rectally or orally to wash out the entire gut. Recommended doses of PEG-ES are 35 mL/kg/hr in children and approximately 1–2 L/hr in adolescents. In children, WBI is particularly useful in decontamination

of gut of a child with ingestion of *heavy metals, iron, sustained release or enteric-coated tablets and drug packets*. Careful attention should be paid to assessment of the airway and abdominal exam before initiating WBI, and it should never be done in a patient without bowel sounds or signs of obstruction or ileus, or without a protected airway. WBI is administered *via* a nasogastric tube and is continued until the rectal effluent is clear.

Syrup of ipecac or use of other emetics is no longer recommended as the amount of poison removed is highly variable and the outcomes do not seem to improve with administration. Induced emesis is also contraindicated in infants, comatose patients, and in children with corrosive and hydrocarbon ingestion.

Surgical decontamination comprises of endoscopic removal of toxins in case of ingestion of large quantities of the toxin or substance (body packers) or lethal amounts of heavy metals refractory to WBI.

Enhancement of Excretion

The technique of enhancing excretion is useful only for a few toxins where prolonged exposure can result in hemodynamic and respiratory compromise or organ failure. Commonly used methods for enhancing excretion are described below.

Urinary alkalization is used for enhancing excretion of weak bases and acids, respectively. Alkalinization is accomplished by continuous infusion of sodium bicarbonate, aiming for urine pH of 7.5–8. This procedure is used to enhance excretion of weak acids, e.g. salicylates, isoniazid, phenobarbitone and methotrexate. Sodium bicarbonate is given at a dose of 1–2 mg/kg in one liter of N/5 normal saline and infused at a rate of 0.5 to 1 liter per hour until desired pH is achieved. Serum pH should be closely monitored, since pH >7.5 is potentially dangerous for cellular function. Acidification of urine is not advised because of associated complications like acidosis, hyperammonemia and rhabdomyolysis.

Forced diuresis in order to ensure urine flow ~5 mL/kg/hr facilitates drug elimination. Brisk diuresis reduces drug concentration in distal tubules and decreases the concentration gradient, reducing chances of reabsorption and enhancing elimination. Diuresis is usually combined with urinary alkalization.

Hemodialysis is effective in removal of substances having the following properties: (i) low volume of distribution (<1 L/kg), (ii) low molecular weight, (iii) low degree of protein binding, and (iv) high degree of water solubility. Toxins removed by hemodialysis include barbiturates, carbon tetrachloride, digitalis, ethanol, ethylene glycol, salicylates, theophylline, bromide, lithium and valproic acid. In addition to enhancing elimination, hemodialysis benefits by correcting metabolic and electrolyte abnormalities resulting from ingestion of toxic substances.

Hemoperfusion involves circulating blood through a cartridge with large surface area coated with activated charcoal. Hemoperfusion enables removal of substances with: (i) low water solubility, (ii) high affinity for the adsorbent, (iii) faster rate of equilibrium between peripheral tissues and blood, and (iv) low affinity for plasma proteins. Toxins eliminated by this technique are carbamazepine, barbiturates and theophylline.

Hemofiltration removes compounds with molecular weight 500 to 40000 RMM, and is used for removal of aminoglycosides, theophylline, iron and lithium.

Exchange transfusion removes poisons affecting the red blood cells, as in methemoglobinemia or arsenic-induced hemolysis.

Multiple dose activated charcoal (MDAC) enhances elimination by 2 mechanisms, interruption of enterohepatic circulation and gastrointestinal dialysis where intestinal mucosa is used as the dialysis membrane. MDAC is given at a dose of 0.5 g/kg every 4–6 hours, until there is significant decline in serum drug concentrations. Chief complications include bowel obstruction and perforation. The technique is recommended for drugs like carbamazepine, dapsone, phenobarbital, quinine and theophylline. IV infusion of *intralipid* may be used for sequestering fat-soluble drugs (calcium channel blockers, tricyclic antidepressants) and reducing their impact on target organs.

Administration of Specific Antidotes

Antidotes are substances that counteract the effect of poisons, and where available, are of immense utility.

However, effective antidotes are not available for majority of poisonings, and symptomatic and supportive treatment remains the mainstay of management. Table 27.6 lists antidotes used commonly for management of various poisonings. A list of manufacturers of specific antidotes in India is maintained by the NPIC.

<http://www.allms.edu/allms/departments/pharmacology/NPIC/masspoisoning.htm>

COMMON POISONINGS

Hydrocarbon Poisoning

Hydrocarbon ingestions account for ~5% of accidental poisonings and ~25% of deaths related to ingestions in children <5 years globally. Children are often accidental victims of IIC poisoning as these products are inappropriately stored in unlabeled containers or drinking glasses and are often attractive in color or pleasant smelling, like furniture polishes. Hydrocarbons are categorized into aliphatic (kerosene), aromatic (benzene), halogenated (carbon tetrachloride) and mixed compounds. Aromatic and halogenated compounds have predominant effect on the central nervous system, while aliphatic hydrocarbons have risk of aspiration and pulmonary symptoms. The most important manifestation of hydrocarbon toxicity is aspiration pneumonitis *via* inactivation of type II pneumocytes and resulting surfactant deficiency. The propensity of a hydrocarbon to cause aspiration pneumonitis is inversely proportional to its viscosity, and

Table 27.6: Poisoning agents and their antidotes

Toxin	Antidote	Dosage
Acetaminophen	N-acetylcysteine	Oral: 140 mg/kg loading; then 70 mg/kg q4h (for 17 doses) IV: 150 mg/kg over 1 hr; then 50 mg/kg over 4 hr; followed by 100 mg/kg over 16 hr
Benzodiazepines	Flumazenil	IV: 0.2 mg over 30 sec; If response inadequate, repeat q1 minute to maximum dose of 1 mg
Anticholinergics	Physostigmine	IV, IM: 0.02 mg/kg over 5 minutes; may repeat q 5–10 minutes to 2 mg maximum
Carbon monoxide	Oxygen	100% oxygen via non-rebreathing mask or endotracheal tube (if intubated)
β Blockers	Glucagon	IV: 0.15 mg/kg bolus; then 0.05–0.15 mg/kg/hr infusion
Calcium channel blockers	Insulin	IV: 1 U/kg bolus; followed by infusion 0.5–1 U/kg/hr
Digitalis	Digoxin-specific Fab antibodies (Digibind; DigiFab)	1 vial binds 0.6 mg of digitalis #Vials = digitalis level Å ~ weight in kg/100
Methemoglobinemia	Methylene blue, 1% solution	IV: 0.1–0.2 mL/kg (1–2 mg/kg) over 5–10 minutes; may repeat q30–60 minutes
Opioids	Naloxone	IV: 0.01–0.1 mg/kg Adolescents, adults: 0.04–2 mg; repeat as needed; or infusion
Organophosphates	Atropine Pralidoxime	IV: 0.05–0.1 mg/kg; repeat q5–10 minutes, if needed IV: 25–50 mg/kg over 5–10 minutes (maximum 200 mg/minute); repeat after 1–2 hr, then q10–12 hr as needed
Salicylates	Sodium bicarbonate	IV: 1–2 mEq/kg bolus; followed by continuous infusion

directly proportional to its volatility. Compounds with high volatility, low viscosity and low surface tension (kerosene, gasoline, naphtha) are likely to be aspirated and cause severe lung injury.

Clinical and Laboratory Manifestations

- **Respiratory system:** Symptoms develop early (within 6 hours) due to aspiration during ingestion or following vomiting. Symptoms may vary from mild cough and respiratory distress to ARDS and respiratory failure. The chest radiograph may be normal initially or show infiltrates, pleural effusion, ARDS and pneumatoceles.
- **CNS:** Restlessness, drowsiness, seizures and coma due to hypoxia and acidosis.
- **CVS:** Dysrhythmias seen with aromatic hydrocarbon abuse.
- Fever and leukocytosis are common and do not necessarily imply bacterial superinfection.

Recovery usually takes 3 to 8 days, but may be prolonged due to superadded pneumonia. Male sex and malnutrition may prolong the length of stay in these children.

Treatment

Treatment is mainly supportive. Evacuation of stomach by gastric lavage or induction of emesis is not recommended because of risk of aspiration. Cautious evacuation of gastric contents is recommended in patients with poisoning by products contaminated by pesticides, heavy metals or other toxins. All patients with history of hydrocarbon ingestion should be observed for at least 6 hours irrespective of their clinical status. An approach to a case of hydrocarbon poisoning is shown in Fig. 27.2.

Corrosive Ingestion

Corrosives are a commonly reported agent of poisoning in children, especially in toddlers. Corrosives may be acidic or alkaline in nature. Acids are commonly found in various household or industrial products include batteries and acids for cleaning purposes. Phenols are used as antiseptics and alkalis may be found in bleaching agents, paint removing agents (sodium hydroxide), soaps and household cleaning products. Alkalis cause liquefaction necrosis while acids cause coagulation necrosis, followed by fibrosis and stricture formation.

Clinical and Laboratory Manifestations

Immediate effects may be burning pain at the site of ingestion or spill, and hoarseness of voice due to laryngeal edema. Excessive salivation, dysphagia, odynophagia, hematemesis and epigastric pain may be presenting features. There is risk of perforation of stomach and esophagus. Respiratory system involvement may manifest as dyspnea, pulmonary edema and chemical pneumonitis. Delayed effects include esophageal, laryngeal stricture and pulmonary fibrosis. Systemic effects include metabolic acidosis, hepatic and renal dysfunction.

Chest and abdominal radiographs or CT scan are done to screen for esophageal or intestinal perforation. Endoscopy is performed within 24 hours of ingestion to assess extent of esophageal injury. The procedure is contraindicated in patients with hemodynamic compromise, peritonitis and mediastinitis and in patients with mild ingestion. Zargar's classification of corrosive injury helps grade the severity: Grade 0 normal mucosa; Grade 1 erythema, hyperemia; Grade 2a superficial ulceration, erosion, hemorrhage; Grade 2b findings in 2a plus deep

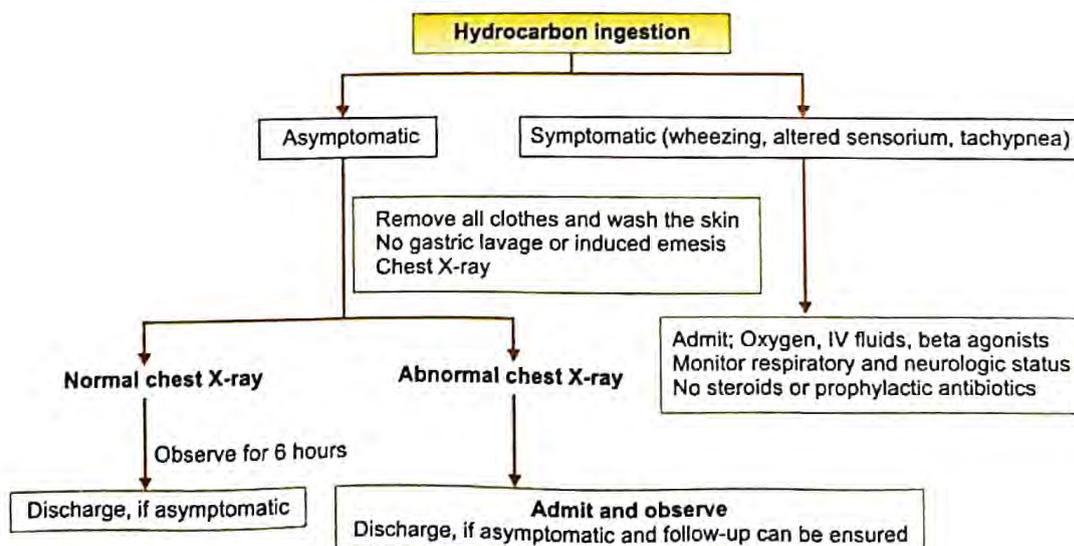


Fig. 27.2: Approach to a child with hydrocarbon poisoning

discrete or circumferential ulcers; Grade 3a scattered necrosis; and Grade 3b extensive, circumferential necrosis of mucosa.

Management

Management comprises of emergency care and supportive care (Fig. 27.3). Nasogastric tube should not be inserted and gastric lavage is contraindicated, as they increase the risk of injury and perforation. Exceptions are made in patients with mercury chloride, zinc chloride and phenol ingestion, as these compounds are associated with severe systemic toxicity and may be rapidly fatal. Airway protection is a priority as laryngeal edema may rapidly progress over minutes to hours and may cause airway obstruction and death. Elective intubation might be required in such cases, or in presence of respiratory distress or hoarseness of voice. Expertise to perform emergency tracheostomy or cricothyrotomy should be available at the time of elective intubation. There is no role for use of intravenous or nebulized corticosteroids or epinephrine in reducing the need for intubation.

Long-term management comprises of ensuring nutrition and therapy for strictures. Patients are initially kept nil orally and managed with IV fluids. Endoscopic grading helps in planning nutritional support. While patients with grade 1 and 2a are allowed oral feeds, those with grade 2b or 3a are fed by nasogastric tube that is inserted by endoscopy. Patients with grade 3b injury receive enteral feeding through gastrostomy; some patients require total parenteral nutrition prior to gastrostomy.

Stricture formation is the most important complication. Dilatation therapy and surgery are recommended for prevention and treatment of strictures. Dilatation is done

3–6 weeks after injury, progressively increasing the size of bougies passed over endoscopically placed guidewires. The risk of perforation and aspiration are high. Esophageal strictures refractory to dilatation may be surgically corrected by resection and esophageal bypass.

Organophosphate Poisoning

Organophosphates and carbamates are commonly used pesticide agents and a common cause of poisoning in developing nations. Organophosphates cause toxicity by inactivating acetylcholinesterase, resulting in excess of nicotinic and muscarinic activity in the peripheral and central nervous systems. These agents form an irreversible bond with and permanently inactivate the enzyme. On the other hand, carbamates reversibly bind with the enzyme.

Clinical Features

The symptoms of organophosphate toxicity depend upon the route, duration of exposure, and the absorbed dose. Acute poisoning is characterized by three phases: Cholinergic crisis, intermediate syndrome and delayed neuropathy. The features of acute cholinergic crisis include diarrhea, urination, miosis, bronchorrhea/bronchospasm, bradycardia, emesis, lacrimation and salivation (DUMBBELS). Some patients show nicotinic features with hypertension, tachycardia and dysrhythmia, muscle weakness, fasciculations, tremors and hypoventilation. Patients with severe poisoning may present with coma and respiratory failure which may rapidly progress. While recovering from cholinergic crisis, some patients may suddenly develop respiratory failure (intermediate syndrome). Late complications of poisoning include delayed polyneuropathy and a range of chronic neuropsychiatric symptoms.

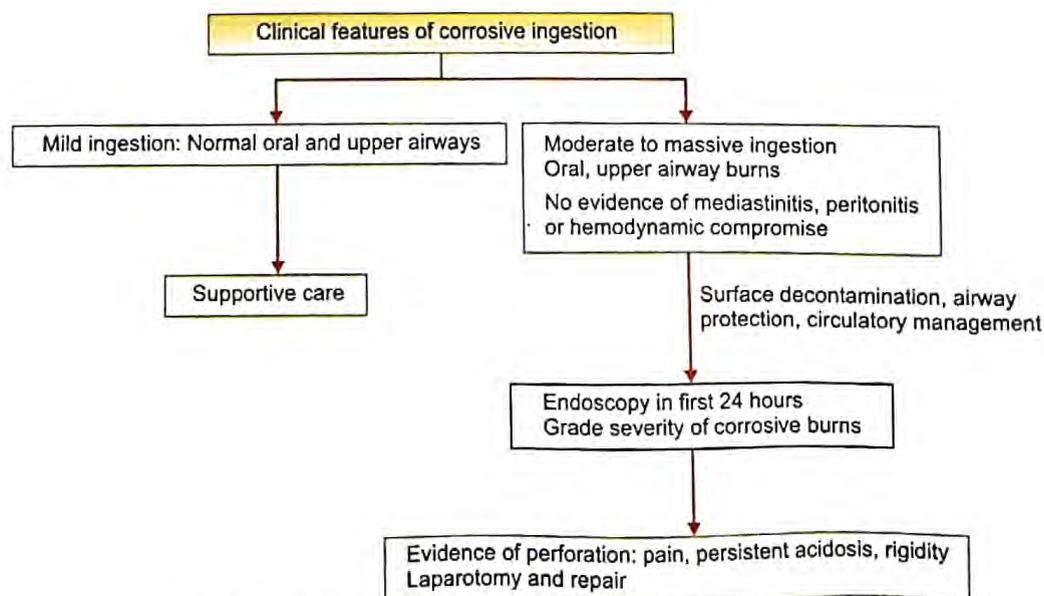


Fig. 27.3: Acute management in a child with corrosive ingestion

Laboratory Manifestations

The diagnosis of organophosphate poisoning is based on characteristic clinical signs, smell of the organophosphate compounds, and reduced butyrylcholinesterase in plasma or acetylcholinesterase activity in blood. The major differential diagnosis is carbamate poisoning, which is clinically indistinguishable.

Cholinesterase assays: There are two types of cholinesterases, acetylcholinesterase and butyrylcholinesterase; values <10% normal of either of the enzymes indicates severe poisoning. Emergency treatment should not be delayed while awaiting results of the enzyme assays.

Treatment

Management of organophosphate toxicity involves dermal and ocular decontamination and expeditious administration of two available antidotes, atropine (reverses muscarinic effects) and pralidoxime aldoxime methiodide (PAM), which facilitates reactivation of acetylcholinesterase. A stepwise approach to treatment of organophosphate poisoning is described in Box 27.1.

Pralidoxime is not administered in patients with carbamate toxicity, since patients usually recover within 24 hours with or without treatment. Since organophosphate and carbamate poisoning are clinically indistinguishable, the initial therapy should be as for the former poisoning. Since succinylcholine is metabolized by similar cholinesterase enzymes, its use should be avoided during rapid sequence intubation.

Acetaminophen (Paracetamol)

Acetaminophen is a widely used analgesic and antipyretic available in different strengths, formulations and combinations. Acetaminophen toxicity is the most common cause of acute liver failure in the western world. Acetaminophen toxicity results from formation of highly reactive metabolite, N-acetyl-p-benzoquinoneimine (NAPQI). NAPQI is normally detoxified by glutathione, but overdose of paracetamol leads to depletion of glutathione stores. Free NAPQI combines with hepatic macromolecules to produce hepatocellular necrosis. The toxic dose of acetaminophen in children is >200 mg/kg.

Clinical and Laboratory Manifestations

The clinical manifestations of acetaminophen intoxication are described in four stages (Table 27.7). Patients either

Box 27.1: Treatment of organophosphate poisoning

1. Check airway, breathing, circulation. Provide 100% oxygen and mechanical ventilation, as indicated.
2. IV access; administer IV fluids and atropine (0.02 mg/kg/dose as bolus). Record pupil size, sweat, pulse rate and blood pressure after first dose.
3. Pralidoxime (PAM, 25 mg/kg) IV over 20–30 minutes; then infusion at 10–20 mg/kg/hr in saline.
4. Repeat atropine (0.05 mg/kg/dose) after 5 minutes, if no improvement after first dose. Repeat boluses until heart rate is appropriate for age, systolic blood pressure >5th centile and chest is clear.
5. Once patient is stable, start infusion of atropine at 10–20% of the cumulative bolus doses administered.
6. Features of atropine toxicity: Stop infusion; wait 30 minutes; restart infusion at low doses.
7. Continue PAM infusion till atropine is no longer required for 12–24 hours and patient is extubated.
8. If tidal volume <6 mL/kg while weaning from mechanical ventilation (pressure support mode), continue to ventilate.
9. Sedation with benzodiazepines to combat atropine-induced agitation.
10. If features of cholinergic crisis recur, treat as above with PAM and atropine.

recover completely in 3 weeks time or progress to fulminant hepatic failure.

Treatment

The initial management of paracetamol overdose is like any other toxin comprising of gastric lavage (indicated in this case) within 4 hours of ingestion and therapy with its antidote, *N-acetyl cysteine* (NAC). NAC, a precursor for glutathione synthesis, reduces the incidence of hepatotoxicity, if administered promptly. A single acetaminophen blood level obtained at least 4 hours of ingestion and plotted on the Rumack-Matthew nomogram (Fig. 27.4) is used to decide treatment. The normal therapeutic level is 10–20 mg/mL. The nomogram predicts the risk of hepatotoxicity at a single point in time, and thus cannot predict hepatic failure during the illness or patient death. It cannot be used for multiple doses of paracetamol or after 24 hours of ingestion, and is not useful for associated ingestion with opioid or anticholinergic agents.

A stepwise approach to management of acetaminophen overdose is described in Fig. 27.5. NAC can be administered

Table 27.7: Clinical stages of acetaminophen toxicity

Stage	Time after ingestion	Characteristics
1	12–24 hours	Asymptomatic; nausea and vomiting
2	24–48 hours	Resolution of earlier symptoms; evidence of elevated liver transaminases
3	3–5 days	Anorexia, nausea, vomiting; multiorgan dysfunction; peak transaminase elevation
4	4–14 days	Recovery phase with resolution of clinical symptoms and improvement in hepatic functions

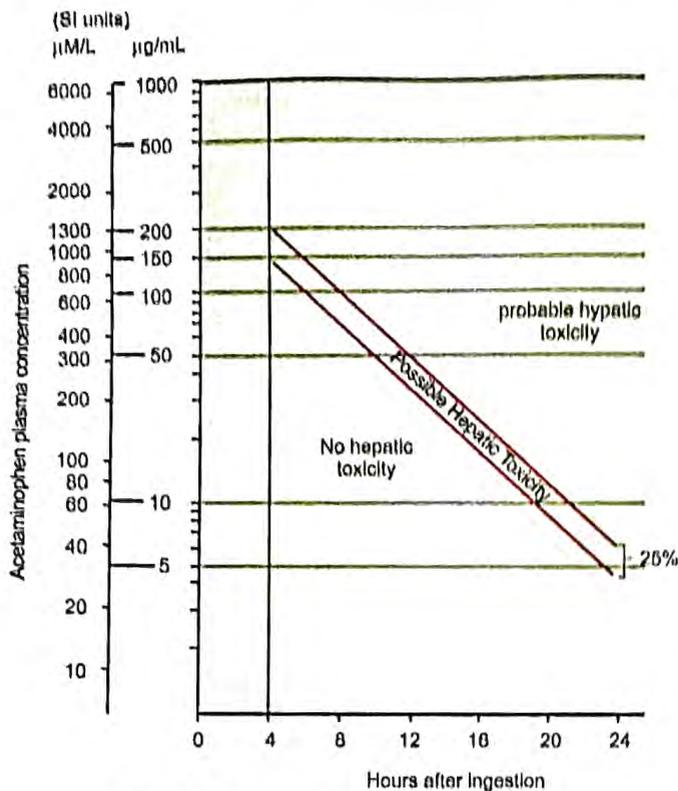


Fig. 27.4: Rumack-Matthew nomogram

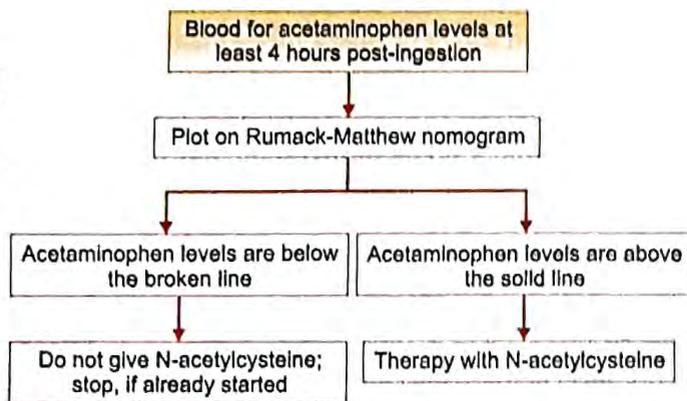


Fig. 27.5: Approach to a child with acetaminophen overdose

orally or intravenously. King's College criteria for acetaminophen toxicity are used for deciding referral for liver transplantation: (i) acidemia (serum pH <7.3) after adequate fluid resuscitation, (ii) coagulopathy (INR >6), (iii) renal dysfunction (creatinine >3.4 mg/dL), and (iv) grade III or IV hepatic encephalopathy. The degree of transaminase elevation is not involved in determining liver transplantation.

Methemoglobinemia

Methemoglobinemia is a condition where iron (within hemoglobin) is oxidized from ferrous (Fe^{2+}) to ferric (Fe^{3+}) state, resulting in inability to transport oxygen to

the tissues. The physiologic level of MetHb is <1% of the total hemoglobin concentration. MetHb is reduced to hemoglobin by cytochrome b5, nicotinamide adenine dinucleotide, ascorbic acid, glucose-6-phosphate dehydrogenase (G6PD), and glutathione reduction enzymes. Methemoglobinemia occurs when the capacity of these mechanisms is overwhelmed by intake of various drugs and toxins that cause an oxidative stress (e.g. lidocaine, prilocaine, antimalarials, pyridium, sulfonamides and metoclopramide). Acute methemoglobinemia may be life threatening when MetHb >50% of total circulating hemoglobin.

Clinical and Laboratory Manifestations

Clinical features range from asymptomatic with cyanosis to severe anoxic symptoms like lethargy, stupor and seizures. The patient appears cyanosed, which does not respond to 100% oxygen. The severity of symptoms depends upon blood MetHb levels; levels >70% result in vascular collapse and death. Arterial blood gas reveals normal PaO_2 and low SpO_2 . Bedside tests, such as the filter paper test, are useful for screening; blood is chocolate-colored and does not turn red on exposure to oxygen. The diagnosis is confirmed by multiple wavelength co-oximetry, which also gives MetHb levels in blood.

Treatment

Management comprises supportive care and administration of methylene blue, at a dose of 1–2 mg/kg followed by bolus of 25–30 mL normal saline. The dose can be repeated after 1 hr to maximum of 7 mg/kg over 24 hours; at higher dosage, the oxidizing action of methylene blue exceeds the reducing action of leukomethylene blue. Even after resolution of symptoms, patients should be observed for recurrences. Patients with G6PD deficiency should not receive methylene blue. Other therapies include ascorbic acid, hyperbaric oxygen and exchange transfusions.

ENVENOMATIONS

Snake Bites

The highest burden of envenomations exists in south and south-east Asia and sub-Saharan Africa. India has the highest number (46000 annually) snake bite-related deaths in south Asia. More than one-quarter of these deaths occur in children 5–14-year-old, mostly in rural areas and during the monsoon season. The four most important venomous snakes in India are Indian cobra (*Naja naja*), Indian krait (*Bungarus caeruleus*), Russell viper (*Daboia russelii*) and saw-scaled viper (*Echis carinatus*).

Clinical Features

As per WHO, the diagnosis of envenomation is based on one or more of the following: (i) history of snake bite, (ii)

presence of fang marks, (iii) local features such as pain and swelling at the site of bite, (iv) systemic manifestations such as spontaneous bleeding or neurotoxicity, or (v) if the dead snake is brought for identification. Systemic manifestations of snake bite depend on the species of snake.

- **Cardiovascular toxicity** is seen with cobra and viper bites and includes hypotension, bradycardia, arrhythmias and pulmonary edema.
- **Hemotoxic features** are seen with viper bites and include bleeding from the site of bite, spontaneous bleeding from gums, epistaxis, tears, intracranial bleeds, melena, hemoptysis, hematuria, and conjunctival and skin bleeds. Cerebral arterial thrombosis is seen with *D. russelii*.
- **Neurotoxic features** include ptosis, external ophthalmoplegia, mydriasis, and bulbar and respiratory paralysis is seen with cobra and krait bites.
- **Nephrotoxicity** is a common manifestation of bites from vipers and sea snakes, and includes features of lower back pain, hematuria, hemoglobinuria, myoglobinuria, oliguria and uremia.
- **Endocrine features** may occur due to infarction of the anterior pituitary following bites of Russell viper.

Laboratory Findings

The diagnostic test used to confirm hemotoxic bites is the 20 minutes whole blood clotting time. While the test it is useful to detect hemotoxic species, treatment with snake anti-venom (SAV) should be based on clinical assessment. Steps for performing the whole blood clotting time are as follows:

- Use a clean, new and dry test tube
 - Leave a few mL of venous blood undisturbed for 20 minutes
 - The test tube is tipped to see, if blood has clotted
 - **Interpretation:** Absence of clotting confirms hemotoxic envenomation (Viperine species)
- Other studies such as hemoglobin, hematocrit, platelet and leukocyte count, peripheral smear, muscle and liver enzymes, electrolytes and venous blood gases, and urinalysis are performed, if indicated.

Management

The 'National Snakebite Protocol' was developed in 2006 to optimize the management of snake bite victims and to improve outcomes. There is emphasis on the Do's and Don'ts of snake bite (Table 27.8), especially with regard to tourniquet application, prehospital treatment, administration of SAV and management of adverse events associated with its use. Principles of management are as follows:

Immobilization of the bitten limb retards systemic venom absorption. Walking for >10 minutes is a risk factor for severe envenomation. A stretcher, bicycle, cart or any motor vehicle should be used for transport; if none available, the patient should be carried (e.g. fireman's lift method).

Assessment: ABCDE approach should be used in all children presenting with history of snake bite. Detailed clinical assessment and, if possible, species diagnosis should be carried out. One should look for the clues to severe systemic envenoming as described above. The bitten part is examined for edema, tenderness, pulses and the compartment syndrome. Systemic examination includes assessment for spontaneous bleeding from the skin, mucosa and internal organs, and neurologic examination for ptosis, trismus, ophthalmoplegia, pooling of oral secretions, and paradoxical breathing. Some children with neurological symptoms may be unresponsive to painful stimuli, areflexic and show fixed dilated pupils.

Supportive care of victims of snake bite is important and determines outcomes. Care comprises of ventilation, inotropes, dialysis, administration of blood products, debridement as and when required, maintenance of asepsis, and prevention of nosocomial infections. Patients need to be monitored for complications such as respiratory failure, acute kidney injury, compartment syndrome, tissue necrosis, bleeding into internal organs, refractory shock, secondary infections and endocrine disturbances.

Table 27.8: Do's and Don'ts of snake bite

Do's	Don'ts
Do it RIGHT	Do NOT
Reassure patient (only 50% venomous snake bites actually envenomate)	Use traditional first aid measures, such as local incisions or pricks, punctures or tattooing at the site of bite or in the bitten limb
Immobilize as in a fractured limb; do not block blood supply	Attempt to suck the venom out of the wound
GH Get to Hospital immediately	Use (black) snake stones
T Tell the doctor of any systemic symptoms, such as ptosis	Tie tight bands (tourniquets) around bitten limb
	Give electric shock
	Apply or instill chemicals, herbs or ice packs

Specific Management

Snake anti-venom (SAV) is recommended in patients with systemic symptoms and/or extensive local involvement. Local involvement is considered extensive if: (i) there is severe local swelling that crosses a joint, or involves more than half the bitten limb within 48 hours of bite in absence of a tourniquet; (ii) tourniquet is in place, the swelling continues after 1 hour of removal, or (iii) lymph node(s) in the drainage area are tender and enlarged. In patients with systemic envenomation, the clinical features and whole blood clotting time should guide SAV therapy. Contraindications to SAV administration are prior history of severe reaction to horse or sheep serum (IT or anti-rabies) and history of atopic diseases.

In India, polyvalent SAV raised in horses using venom of 4 snakes (Indian cobra, Indian krait, Russell and saw-scaled viper) is used. Since the average amount of venom injected by Russell viper is ~60 mg, and each vial of polyvalent anti-venom neutralizes ~6 mg viper venom, 5-10 vials are initially given irrespective of age. Further doses are based on sequential estimation of whole blood clotting time, progression of weakness (repeat within 1-2 hours of first dose; no more than 2 doses required) and presence of cardiovascular signs (1-2 hours of first dose). SAV is administered, under supervision, as bolus (1 mL/minute) without dilution, or IV infusion (diluted in 5-10 mL/kg isotonic fluid) over 1 hr.

Adverse reactions and the number of vials of SAV used should be recorded. Early anaphylactoid reactions occur between 10 and 180 minutes of administration and manifest as itching, urticaria, vomiting, diarrhea and tachycardia; life-threatening anaphylaxis is rare. Some patients show pyrogenic reactions (shaking chills, fever and hypotension) that occur 1-2 hours after infusion or serum sickness (fever, vomiting, diarrhea, lymphadenopathy, nephritis, and encephalopathy) 1-12 days following therapy.

At the earliest sign of a reaction, SAV administration is temporarily suspended. Epinephrine (0.01 mg/kg, 1 in 1000) is given intramuscularly for early anaphylactic and pyrogenic reactions. Subsequently patients should receive treatment with an antihistamine (chlorpheniramine maleate, 0.2 mg/kg IV) and hydrocortisone (2 mg/kg body weight IV). In patients with systemic envenomation, therapy with SAV might require to be given for several days until hemostatic abnormalities persist.

Outcome

The mortality rates have varied between 5% and 15%. Among survivors, the main cause of permanent disability is local necrosis. Large areas of skin necrosis necessitate debridement and grafting whereas destruction of deep tissues might require amputation. Arthrodesis, chronic ulceration, osteomyelitis and malignant transformation are long-term consequences. Cerebral hypoxia from

delayed resuscitation and strokes may cause permanent neurological deficits. Some patients with marked hypotension and severe acute kidney injury may not recover and become dialysis dependent; others (Russell viper bite) may show acute hemorrhagic infarction of the pituitary and adrenal glands. Risk factors for adverse outcome in children include young age, vomiting, neurotoxicity, high creatinine, thrombocytopenia, ecchymosis at admission and delayed administration of SAV.

Scorpion Sting

Scorpion envenomation is common in tropical and subtropical regions of the world. Most cases are reported from Maharashtra, Karnataka, Tamil Nadu, West Bengal and Pondicherry. Of 86 species in India, the red (*Mesobuthus tamulus*) and less poisonous black scorpions (*Palaemonus swammerdami*) are implicated in most stings. Cardiac manifestations dominate clinical features in India, while neurologic symptoms are frequent in South Africa and USA. Stings are common during summer months and at night; scorpions sting when roughly handled or trodden. The case fatality rate is ~3-22%.

Clinical Features

The symptoms evolve over 30 minutes to 6 hours and subside within a day or two. Local features include severe pain and paresthesias. Systemic manifestations include a cholinergic storm with fever, shivering, sweating, salivation, vomiting, priapism, bradycardia and hypotension. This is followed by adrenergic stimulation, which start at 4 hours and last for 48 hours. Features include tachycardia, hypertension, myocardial dysfunction, arrhythmias, pulmonary edema (cardiogenic or non-cardiogenic), shock and hypotension. Complications include encephalopathy, convulsions, aphasia, hemiplegia, cerebral hemorrhage, DIC and respiratory failure (Table 27.9).

Management

Management is directed towards providing symptomatic relief as specific therapy (antivenom) is not available, nor recommended for routine use. Blood samples are taken for electrolytes (hyperkalemia), lipid profile (low serum cholesterol and triglycerides with rise in free fatty acids), and amylase, LDH, and transaminases (all elevated).

Table 27.9: Grading severity of scorpion stings

Grades	Clinical features
Grade I	Isolated pain
Grade II	Hypertension, sweating, vomiting, priapism, fever, shivering
Grade III	Cardiogenic shock, pulmonary edema, altered consciousness
Grade IV	Tachycardia, hypotension with or without pulmonary edema

Investigations, for identifying myocardial dysfunction, include chest X-ray, ECG and echocardiography. Myocardial perfusion and neurological abnormalities may be identified on nuclear scintigraphy and CT scans, respectively.

Local measures: The site of the sting is cleaned. Relief from pain allays anxiety and avoids myocardial stress. NSAIDs can be used for relief from severe pain. Local ice packs, xylocaine infiltration, dehydroemetine (counterirritant) and streptomycin (neuromuscular blockade) are reported to be useful.

General measures include:

- i. Oxygen administration by face mask or nasal cannula in case of respiratory distress, or impending shock.
- ii. Frequent monitoring of vital signs, fluid balance, blood levels of electrolytes, pH, liver and kidney functions, and DIC profile.
- iii. Sedation: Diazepam is recommended (in concert with GABA opens ion channels, antagonizing toxin action); long-acting sedatives are avoided.

Drug therapy: Various agents have been used in experimental animals and humans to treat systemic manifestations of scorpion envenomation. In our country, prazosin is the first-line agent because of predominant

cardiovascular manifestations. There is limited information on the efficacy and safety of scorpion antivenom in children. An algorithm based approach for management is given in Fig. 27.6.

Patients should be hemodynamically stable and show normal sensorium at discharge. Additional criteria for discharge include no respiratory distress and being free of complications.

INJURY CONTROL

Principles that deserve emphasis in planning injury prevention strategies are as follows:

- i. **Passive injury prevention**, such as automatic locks for medicine cabinets, is preferred over active strategies, e.g. "yuck" stickers on bottles.
- ii. **Specific instructions**, e.g. keep water heater temperature lower than 120°F, are more likely to be followed than general advice, e.g. reduce temperature of hot water tap in your home.
- iii. Reinforcement by **community wide education programs** is more effective than individual education sessions.

Targeted messages for prevention of injuries should be discussed with the parents (Table 27.10).

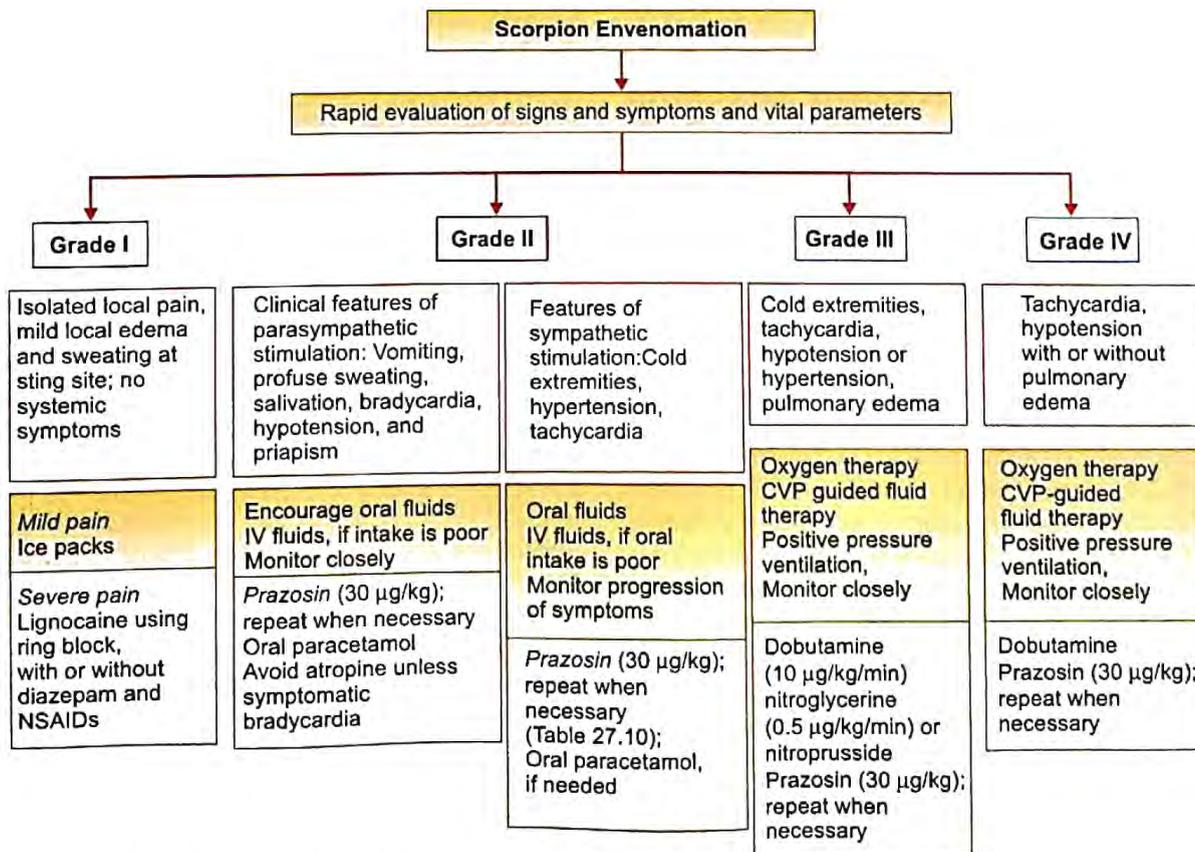


Fig. 27.6: Algorithm-based management of children with scorpion envenomation

Table 27.10: Do's and Don'ts of injury prevention**Do's**

- Use beds with rails for children aged <6 years
- Have safety gates at the top and bottom of the stairs, vertical bars on balconies
- Teach older children how to cross the road safely
- Ensure that your child's bicycle is maintained in good condition
- Teach the child how to handle tools and mechanical instruments safely
- Keep children far away from the stove while cooking
- Always turn off the gas after use into contact with it
- Always have an adequate fireguard hooked in place
- Check the temperature of milk before feeding the child
- Use electric points of the safe variety so that the child cannot insert a lead pencil or other object through the hole
- Keep all medicines out of reach of children
- Keep all poisons in their original containers and not in fruit juice/colored bottles
- Keep cleaning agents, drugs, kerosene and pesticides in a locked cupboard
- Keep plastic bags, scarves, ropes, cords out of reach of children

Don'ts

- Leave a small child alone in the house even for a few minutes
- Allow children to play on the stairs
- Keep the door open when the child is at home
- Allow young children to cross the streets alone
- Allow doubling on the bicycle
- Leave any sharp objects near the vicinity of the child
- Leave hot utensils or pans in the kitchen; electric iron switched on
- Allow him/her to ignite fireworks only under supervision
- Drink, or pass hot tea or coffee while holding the infant
- Keep electric equipment plugged on when not in use
- Allow children to run about with food in the mouth or to play while eating
- Give nuts and seeds to infants
- Leave medicines in the child's bedroom
- Take medicines in front of your child
- Leave young children unattended in bath tubs or near swimming pools/ponds/beaches
- Leave cupboards, wardrobes, refrigerators unlocked
- Let the child play with gas tap

Suggested Reading

- Murphy K. Management of musculoskeletal injuries. In: Behrman, Kliegman, Jenson, Stanton (eds) Nelson Textbook of Pediatrics, 20th edn. Philadelphia, Elsevier, 2016 pp 366–74.
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- Katz A, Kluger Y. Caustic material ingestion injuries-Paradigm shift in diagnosis and treatment. Health Care Current Reviews 2015; 3:152.
- Kajala P, Jhavar L, Singh S, et al. Demographic and clinical profile of children presenting with acute poisoning in a tertiary care hospital. IJEP 2011; 3: 55–9.

Pediatric Critical Care

Praveen Narsaria • Rakesh Lodha

Care for critically ill children has an important role in improving child survival. In tertiary care hospitals, 5–10% of pediatric beds are reserved for intensive care; higher numbers are required, if the hospital has surgical units. In order to optimize resource utilization in resource limited settings, it is useful to understand the indications of admission to PICU (Table 28.1).

The optimal number of beds in a PICU is 6–10. Attention is given to the layout, ensuring 200–250 square feet area per bed, with rapid access to head end for airway management. The unit should have uninterrupted power supply and preferably be air-conditioned. A crash cart having necessary drugs and resuscitation equipment should be available. The unit should have a central monitoring station and space for utilities and storage. Equipment required are cardiorespiratory and ECG monitors, oximeters, devices for oxygen therapy, mechanical ventilators, nebulizers, infusion pumps, weighing scales and enough disposables. The ICU should have access to laboratory facilities, including blood counts, glucose and electrolytes, and blood gases that require

small sample volumes. Portable X-ray and ultrasonography units are desirable. In addition to the primary disorder, it is necessary to ensure nutrition, sedation and effective analgesia and infection control. Communications with the parents is necessary to keep them informed about the condition of their child, and ensure their trust and cooperation.

Suggested Reading

- Slusher TM, Kiragu AW, Day LT, Bjorklund AR, Shirk A, Johansen C, Hagen SA. Pediatric critical care in resource-limited settings: Overview and lessons learned. *Front Pediatr* 2018;6:49.

ASSESSMENT OF A SERIOUSLY ILL CHILD

A sick child who is non-responsive to verbal and physical stimuli should be immediately checked for breathing efforts (gaspings, apneic) and central pulses (present, absent). If the child has abnormal respiration (gaspings or not breathing) or has absent central pulses, then child should receive CPR (cardiopulmonary resuscitation) immediately.

Further assessment comprises of the ABCDE approach. **A** stands for 'airway assessment' and should categorize the airway as 'clear', 'maintainable' and 'not maintainable'. **B** stands for 'breathing assessment' and includes respiratory rate and effort, abnormal sounds on auscultation and pulse oximetry. **C** stands for 'circulation assessment' including skin color and temperature, heart rate and rhythm, blood pressure, central and peripheral pulses, capillary refill time and assessment of end organ perfusion by mental status (brain perfusion), and urine output (renal perfusion). **D** stands for 'disability' that establishes the level of consciousness by AVPU pediatric response scale or Glasgow Coma Scale and pupillary response to light. **E** stands for 'exposure' where body parts are exposed to look for skin rashes or wounds. Features predictive of a serious illness, particularly in young infants are listed in Table 28.2. The history should focus on the underlying illness. Common investigations include blood counts, glucose, electrolytes and arterial blood gases.

Table 28.1: Indications for admission to the pediatric intensive care unit

- Hemodynamic instability or shock requiring inotropic support, e.g. cardiac arrhythmias, cardiorespiratory arrest, severe anemia or hemorrhage
- Respiratory distress requiring oxygen therapy and/or impending or established respiratory failure requiring mechanical ventilation
- Altered sensorium due to any cause, including encephalopathy, status epilepticus, raised intracranial pressure
- Acute hepatic or renal failure and complications
- Severe metabolic abnormalities, e.g. dyskalemia, dysnatremia, hypoglycemia, diabetic ketoacidosis; acute poisoning
- Severe infections, e.g. severe malaria, severe pneumonia
- Procedures: Peritoneal dialysis, exchange transfusion, central venous cannulation
- Postoperative monitoring

Table 28.2: Common danger signs

Seizure activity
Excessive, inconsolable cry
Decreased activity or drowsiness
Increased work of breathing
Abnormal sound on breathing
Apneic episodes or cyanosis
Cold extremities (particularly in absence of cold environment)
Decrease in the urine output
Decreased feeding, bilious vomiting

Monitoring*Respiratory*

The patient should be observed for respiratory rate and pattern, nasal flaring, use of accessory muscles and color (Table 28.3). Examination is done for symmetry of air entry, breath sounds and presence of stridor, rhonchi and crepitations. Respiratory rate is monitored continuously by impedance pneumography. Pulse oximetry allows non-invasive measurement of oxygen saturation. While reliable, some conditions lead to inaccuracies, e.g. dyshemoglobinemia (methemoglobin, carbon monoxide poisoning), dyes and pigments (methylene blue), poor peripheral perfusion, increased venous pulsations and interference with external light (phototherapy unit, fluorescent light). Chest radiography and arterial blood gas analyses are performed periodically.

Hemodynamic

Hemodynamic monitoring provides information about circulatory status and perfusion of vital organs. The rate and character of pulse should be examined. Blood pressure can be monitored manually or by oscillometry. The state of microcirculation is assessed by capillary refilling time. Pressure is applied with the index finger or ball of thumb

over sternum or forehead for 5 seconds to cause blanching. The normal capillary refill time is 3 seconds or lower; prolongation signifies impairment of microcirculation. Another way of determining adequacy of peripheral perfusion is noting the core-peripheral temperature gradient; gradient $>5^{\circ}\text{C}$ indicates hypoperfusion.

Continuous ECG monitoring is necessary in children admitted to the PICU. Central venous pressure (CVP) is monitored by placing a catheter through a large vein into the right atrium; the pressure informs about venous return and preload. Normal right atrial pressure is less than 6 mm Hg. Low CVP in a child with hypotension signifies low intravascular fluid volume. CVP may be increased due to myocardial dysfunction, fluid overload or increased pulmonary artery pressures. Renal perfusion is assessed by monitoring urine output; output <0.5 mL/kg/hr in a child with normal kidneys signifies poor perfusion. Monitoring of the sensorium and neurologic status also gives information about brain perfusion.

Suggested Reading

- Bronicki RA, Spenceley NC. Hemodynamic monitoring. *In:* Nichols DG, Shaffner DH, eds. *Roger's Textbook of Pediatric Intensive Care*, 5th edn. Lippincott Williams and Wilkins 2016: pp 1120–36.
- Cheifetz IM, Lee JH, Venkataraman ST. Respiratory monitoring. *In:* Nichols DG, Shaffner DH, eds. *Roger's Textbook of Pediatric Intensive Care*, 5th edn. Lippincott Williams and Wilkins 2016: pp 686–709.

PEDIATRIC BASIC AND ADVANCED LIFE SUPPORT

Cardiopulmonary arrest in children is much less common than adults and usually represents the terminal event of progressive shock or respiratory failure rather than a primary cardiac cause. The major causes in infants and children are respiratory failure, sudden infant death syndrome, sepsis, neurologic diseases, submersion or drowning and injuries. In contrast to adults, sudden cardiac arrest in children is uncommon. Basic life support (BLS) refers to a protocol of procedures performed in cases of cardiopulmonary arrest to provide cardiopulmonary resuscitation (CPR) with or without devices and bag-mask ventilation till advanced life support (ALS) can be provided. The major objectives of CPR are to preserve organ viability during cardiac arrest and to help return spontaneous circulation.

Basic Life Support

To maximize survival and intact neurological status in post-resuscitation stage, early recognition of cardiac arrest and strict adherence to the BLS sequence is necessary. BLS includes a series of skills performed sequentially to assess and restore effective ventilation and circulation to the child with respiratory or cardiorespiratory arrest. Evaluation and interventions in pediatric BLS are performed simultaneously, in the following sequence: (i) assessment, (ii) circulation, (iii) airway and (iv) breathing. The

Table 28.3: Respiratory rates (RR) and heart rates (HR) at different ages

Age, years	RR, breaths/min	HR, beats/min
1	30 (22–38)	120 (80–160)
2	25 (17–33)	110 (80–130)
4	23 (17–27)	100 (80–120)
6	21 (15–26)	100 (75–115)
8	20 (15–26)	90 (70–110)
10	18 (15–25)	90 (70–110)
12	18 (14–26)	85 (65–105)
14	17 (15–23)	80 (60–100)
16	17 (12–22)	75 (55–95)

sequence Circulation–Airway–Breathing (C–A–B) has been recommended in 2015 update of Pediatric Basic Life Support to maintain uniformity in CPR algorithm across all ages.

Assessment

Initial assessment is done to confirm cardiac arrest so that life-saving measures can be begun promptly to enable intact neurologic survival. The combination of unresponsiveness and absent or abnormal breathing most accurately identifies cardiac arrest. Palpation of the pulse for its absence is unreliable as the sole determinant of cardiac arrest. If the victim is unresponsive, not breathing normally, and there are no signs of life, lay rescuers should begin CPR; in such a setting, health care providers should begin CPR unless they definitely palpate a pulse within 10 seconds.

Circulation

CPR should begin with chest compression. Chest compressions are serial rhythmic compressions of the chest that allow blood flow to vital organs (heart, lungs and brain) in an attempt to keep them viable until ALS (advanced life support) is available. The victim should be laid supine on a hard and flat surface. Adequate chest compression is given by pushing hard, to a depth of at least one-third of anteroposterior dimension or approximately 1½ inches (4 cm) in infants and 2 inches (5 cm) in children. The rate should be 100–120 compressions per minute, allowing full chest recoil and minimizing interruptions in chest compressions. Compression of the xiphoid process should be avoided.

Chest compression in infants (<1 year)

Two-thumb technique: The infant's chest is encircled with both hands; fingers are spread around the thorax and the thumbs brought together over the lower half of the sternum, avoiding the xiphisternum. The sternum is compressed with the thumbs and the thorax with the fingers for counterpressure. The two-thumb-encircling hands technique is preferred because it produces higher coronary artery perfusion pressure, consistently appropriate depth and force of compression, and may generate higher systolic and diastolic pressures. While one provider should provide chest compressions, the other maintains the airway and provides ventilation at a ratio of 15:2 with as short a pause in compressions as possible. If the rescuer is unable to deliver breathes, the rescuer may continue with chest compressions only; however, one must remember that majority of pediatric cardiac arrests are secondary to hypoxia.

Two-finger technique: If the rescuer is alone or unable to physically encircle the chest, the chest is compressed with two fingers, placing them vertically over the sternum just below the intermammary line (between the two nipples) ensuring that they are away from xiphoid process. One

can use one hand to support the infant's body and head and the other hand to perform chest compression.

Chest compression technique in the child (1–8 years age) Fig. 28.1 indicates how the heel of one hand should be placed over lower half of sternum, avoiding pressure over xiphoid, and with fingers lifted above the chest wall to prevent compression of rib cage. Rescuer should position him/herself vertically above the victim's chest.

Large children and >8 years of age: The two-hand method for chest compression should be used to achieve an adequate depth of compression. This is achieved by placing the heel of one hand over the lower half of sternum and the heel of the other hand over the first hand, interlocking the fingers of both hands, with fingers lifted above the chest wall. External chest compression in children and infants should always be accompanied by rescue breathing. Ventilation is relatively less important during the first minute of CPR for victims of arrhythmia-induced cardiac arrest than it is after asphyxia-induced arrest. The lay rescuers should use a 30:2 compression-ventilation ratio for all (infant, child and adult) victims. For one healthcare provider, the compression-ventilation ratio should be 30:2 for all age groups and for two rescuers, the compression-ventilation ratio should be 30:2 in adults and 15:2 in infants, children and adolescents. Once an advanced airway (tracheal tube) is placed, chest compressions should not be interrupted for ventilation.

The victim should be reassessed after two minutes. If signs of spontaneous circulation have reappeared, chest compression should be discontinued and only ventilation continued till return of spontaneous breathing.

Airway

Infants and children are at increased risk of respiratory obstruction and failure compared to adults, for the following reasons: Smaller upper airway in comparison to adults; large tongue in relation to oropharynx; smaller

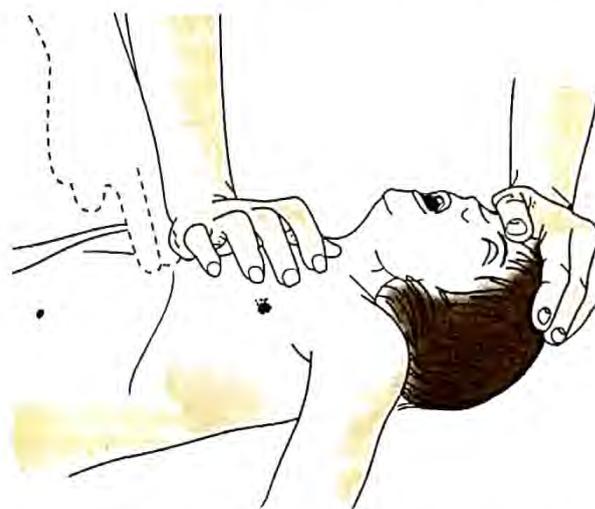


Fig. 28.1: Chest compression in a child (1–8-year-old)

and compliant subglottic area more prone for collapse and/or obstruction; relatively compliant chest wall and rib cage; and limited oxygen reserve.

Position of the victim: If the child is unresponsive but breathing or signs of life are present, he should be placed on a hard surface in supine position. If head or neck trauma is suspected, head and torso should be moved as a unit and the neck immobilized.

Open the airway: The tongue is lifted away from the posterior pharynx to keep the airway patent.

- i. **Head tilt chin lift maneuver** (Fig. 28.2): If the victim is found unresponsive and has signs of life, the airway is opened by tilting the head back and lifting the chin. One hand is placed over the forehead and head is gently tilted back. Simultaneously, the fingers of the other hand are placed on the lower jaw to lift the chin to open the airway. This maneuver should not be used, if there is suspicion of trauma to head and/or neck.
- ii. **Jaw thrust** (Fig. 28.3): Two or three fingers are placed under each side of lower jaw at its angle to lift the jaw



Fig. 28.2: Head tilt chin lift maneuver



Fig. 28.3: Opening the airway with jaw thrust

upwards and outwards. This method should be used in all victims with blunt trauma, craniofacial injury, and those having Glasgow Coma Score ≤ 7 . This method is not recommended for lay rescuer because it is difficult to learn and perform effectively and safely.

Foreign body airway obstruction: The mouth is opened and examined for presence of foreign body, which is removed, if visible; blind sweeping is not recommended. If the victim is an infant who is responsive and has features of airway obstruction, back slap and chest thrust are performed till the foreign body comes out or till the infant becomes unresponsive. If the victim is an older child or adolescent, an abdominal thrust is given by standing behind the victim till the foreign body is expelled out or till the patient becomes unresponsive (Chapter 29). If the victim becomes unresponsive, cardiopulmonary resuscitation should be begun with an additional maneuver of checking the airway for the foreign body after giving the chest compression and before breaths are given. Trained healthcare provider should perform a tongue-jaw lift to look for obstructing objects.

Breathing

After opening the airway, one should check for breathing. Periodic gasping, also called *agonal gasps*, is not breathing. If there is effective spontaneous breathing without evidence of trauma, the child is turned to recovery position, which helps maintain a patent airway and prevents aspiration.

Bag and mask ventilation (BMV): BMV remains the preferred technique for emergency ventilation during initial steps of resuscitation. In infants and children for whom BMV is unsuccessful, a laryngeal mask airway placed by appropriately trained providers may be considered for airway or support ventilation. Self-inflating bags are usually adequate in children. Flow inflating bags need oxygen flow and are used in hospitals. For term neonates, infants and children <8 years of age, ventilation bags of volume 450–500 mL should be used to deliver adequate amount of tidal volume. Neonatal size bags (250 mL) may be used in preterm neonates. An adequate amount of tidal volume should be used to cause visible chest rise. Excessive expansion may compromise cardiac output, increasing the chances of regurgitation and air leak. In patients with head injury or cardiac arrest, excessive ventilation may adversely affect neurological outcome.

The self-inflating bag delivers room air unless it is connected to an oxygen source. Pediatric bag-valve device, without a reservoir, if connected to an oxygen inflow of 10 L/min, delivers 30–80% of oxygen to the patient. If used with a reservoir, it may deliver 60–95% of oxygen, with an oxygen inflow of 15 L/min to provide adequate oxygen supply to the reservoir.

Pediatric Advanced Life Support (PALS)

PALS refers to the assessment and support of pulmonary and circulatory function in the periods before, during and after an arrest. PALS targets the prevention of causes of arrest and early detection and treatment of cardiopulmonary compromise and arrest in critically ill or injured children.

Components of PALS are: (i) Basic life support; (ii) use of equipment and techniques to establish and maintain effective oxygenation, ventilation and perfusion; (iii) clinical and ECG monitoring with arrhythmia detection and management; (iv) establishing and maintaining vascular access; (v) identification and treatment of reversible causes of cardiopulmonary arrest; (vi) emergency treatment of patients with cardiac and respiratory arrest; and (vii) treating patients with trauma, shock, respiratory failure or other pre-arrest conditions.

Adjuncts for Airway and Ventilation

Oxygen should be given to all seriously ill or injured children with respiratory insufficiency, shock and trauma. During mouth-to-mouth rescue breathings, only 16–17% oxygen is delivered, with alveolar oxygen pressure of 80 mm Hg, and optimal external chest compressions provide only a fraction of the cardiac output, resulting in reduced tissue perfusion and oxygen delivery. Ventilation-perfusion mismatch during CPR and underlying respiratory disorders causes right-to-left shunting that reduces oxygenation.

Endotracheal Intubation

If used properly, this is the most effective and reliable method of ventilation. The advantages of endotracheal intubation are: (i) it ensures adequate ventilation; (ii) reduced risk of aspiration of gastric contents; (iii) inspiratory time and peak inspiratory pressure can be controlled; (iv) suction can be done to keep airway patent; and (v) positive end-expiratory pressure can be provided. However, a skilled person is required for intubation. Hence, it is recommended that bag and mask ventilation should be continued in children who require ventilatory support in the out-of-hospital setting, when transport time is short or when an expert is not available for intubation. Indications for endotracheal intubation are listed in Table 28.4.

Table 28.4: Indications for endotracheal intubation

Excessive work of breathing leading to fatigue
Inadequate neurologic control of ventilation, and poor respiratory effort
Functional or anatomical airway obstruction
Need for high peak inspiratory pressure or positive end expiratory pressure
Lack of protective airway reflexes
For prolonged duration cardiopulmonary resuscitation

Table 28.5: Size of ET tube and suction catheter in infants

Age; weight	Tracheal tube mm	Suction catheter Fr
Premature newborn; <1 kg	2.5	5
Premature newborn; 1–2 kg	3.0	5–6
Newborn; 2–3 kg	3.0–3.5	6–8
Newborn; >3 kg	3.5–4.0	8
Infant	3.5–4.0	8

An appropriate sized endotracheal tube is used (Table 28.5). Beyond 1 year, the size of the tube is:

$$\text{Tracheal tube size (in mm)} = \frac{(\text{Age in year})}{4} + 4$$

Tubes 0.5 mm smaller and 0.5 mm larger than the estimated size should be available for use. The size of suction catheter is usually twice the internal diameter of the tracheal tube in mm, e.g. 8 Fr suction catheter for tracheal tube of size 4 mm. Cuffed tubes are preferred in patients with poor lung compliance, high airway resistance and large glottic air leak.

The depth of insertion of the tube is approximately three times its inner diameter. In neonates, the endotracheal tube is inserted to a depth of:

$$\text{Depth of insertion (cm)} = \text{birth weight (kg)} + 6$$

In children >2-year-old, the depth of insertion of the endotracheal tube is:

$$\text{Depth of insertion (cm)} = \frac{(\text{Age in years})}{2} + 12$$

Tube placement is confirmed by looking for symmetrical chest rise and auscultating for air entry on both sides. Auscultation over upper abdomen is required to rule out esophageal intubation. Other markers of proper tube placement are improving heart rate, color, perfusion and oxygen saturation. The position of the tube should be confirmed on chest radiograph.

Vascular Access

During CPR, the preferred access is the largest easily accessible vein, cannulating which does not require interruption of resuscitation. Central venous lines provide secure access, rapid action, higher peak drug levels, and permit administration of drugs that might injure peripheral veins (vasopressors, calcium gluconate, hypertonic solutions like sodium bicarbonate). Femoral vein is the safest and easiest to access (Chapter 29). Agents with short half-life such as vasopressors, adrenaline and adenosine act better, if given through central venous access. Catheter lengths of 5 cm in infant, 8 cm in a young child and 12 cm in an older child are usually suitable.

Intraosseous access should be tried in patients, if the central or peripheral venous access is not achieved. The usual site for intraosseous access is upper end of tibia medial to tibial tuberosity (Chapter 29). Other sites include the distal end of femur, lower end of tibia above medial

malleolus and anterior superior iliac spine. Drugs like adrenaline, adenosine, and vasopressors can be transfused by this route. Samples for chemical analysis, blood grouping and crossmatching may be taken from these sites.

Tracheal route is not a preferred route of administration of medications even in emergencies. If intravenous or intraosseous access is not established, the tracheal route may be used for lipid-soluble agents like lidocaine, epinephrine, atropine and naloxone.

Post-arrest Care

Fever is common after cardiac arrest and should be controlled aggressively. After return of spontaneous circulation, hypoxia or hyperoxia should be avoided and oxygen saturation should be maintained between 94 and 100%. Continuous arterial pressure monitoring is done to maintain blood pressure above the 5th centile. Table 28.6 shows doses for commonly used drugs during resuscitation.

Fluid Therapy

Early restoration of the circulating blood volume is important to prevent progression to refractory shock or cardiac arrest. An initial fluid bolus of 20 mL/kg is recommended in shock, and after each bolus, the patient is reassessed. Volume expansion is best achieved with isotonic crystalloid fluids, such as Ringer lactate or normal saline. Blood replacement is indicated in patients with severe hemorrhagic shock who remain in shock despite

infusing 40–60 mL/kg of crystalloids. Dextrose solutions should not be used for initial resuscitation as they do not expand the intravascular volume effectively and may cause hyperglycemia, leading to osmotic diuresis and a vicious cycle of polyuria and hypovolemia. Hypoglycemia, if suspected or documented, should be managed rapidly with intravenous glucose and measures to prevent recurrence.

Arrhythmias

Most pediatric arrhythmias are the consequence of hypoxemia, acidosis or hypotension. Children with myocarditis, cardiomyopathy or following cardiac surgery are also at risk of arrhythmia. Drugs in therapeutic or toxic doses can cause arrhythmia. About 10% of pediatric cardiac arrest patients have ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT).

Bradycardia: Hypoxemia, hypothermia, acidosis, hypotension and hypoglycemia depress sinus node function and slow conduction through the myocardium. Excessive vagal stimulation, raised intracranial pressure or brainstem compression may cause bradycardia. Sinus bradycardia, sinus node arrest with junctional or idioventricular rhythm and AV blocks are usually preterminal rhythms. All slow rhythms resulting in hemodynamic instability require immediate treatment. Epinephrine is the most useful drug in treating symptomatic bradycardia, unless due to heart block or vagal overtone. For bradycardia due to vagal overtone,

Table 28.6: Drugs used during cardiopulmonary resuscitation

Drug	Indications	Dosage	Remarks
Epinephrine	Symptomatic bradycardia, pulseless arrest	IV/IO: 0.01 mg/kg (1:10,000; 0.1 mL/kg) ET: 0.1 mg/kg (1:1000 flush with 1–2 mL of saline); repeat 3–5 minutes, if required	Tachyarrhythmia and hypertension may occur
Atropine	Bradycardias	0.02 mg/kg	Tachycardia, pupil dilatation may occur
Calcium gluconate (10%, 9 mg/mL calcium)	Hypocalcemia, hypermagnesemia, hyperkalemia	1 mL/kg IV or IO (slow push)	Monitor heart rate; flush line with saline before and after infusing calcium gluconate; avoid extravasation
Glucose	Suspected, documented hypoglycemia	0.5–1 g/kg	Avoid hyperglycemia
Sodium bicarbonate	Severe metabolic acidosis, hyperkalemia	1 mEq/kg IV/IO slowly	Use once ventilation is adequate; dilute 1:1 with 5% dextrose
Adenosine	Supraventricular tachycardia	0.1 mg/kg; repeat dose 0.2 mg/kg; rapid bolus IV/IO	Monitor ECG during dose; give through vein close to heart
Amiodarone	Pulseless VF or VT	5 mg/kg IV/IO	Monitor ECG during dose
Lidocaine	VF or VT	1 mg/kg IV/IO; follow by infusion at 20–50 µg/kg/min	Monitor ECG during dose
Naloxone	Opioid intoxication	0.1 mg/kg IV/IO/ET	Repeated doses may be required
Magnesium sulfate	Torsades, suspected hypomagnesemia, severe asthma	25–50 mg/kg rapid push for first two indications; infusion over 30 min for asthma	Watch for respiratory depression and hypotension

ET: Endotracheal; IO: Intraosseous; IV: Intravenous; VF: Ventricular fibrillation; VT: Ventricular tachycardia

atropine is the drug of choice. If no positive or transient effect is observed after ventilation and oxygenation, continuous infusion of epinephrine or dopamine should be considered.

Pulseless electrical activity: It is a state of electrical activity observed on a monitor or ECG in absence of detectable cardiac activity. This is often a preterminal state preceding asystole, representing the electrical activity of a hypoxic and acidotic myocardium. Occasionally, pulseless electrical activity may be due to sudden impairment of cardiac output with normal ECG rhythm, with heart rate increased or rapidly decreasing. Pulses or other evidence of cardiac output are absent and child appears lifeless. This state is called electromechanical dissociation. Reversible causes of electromechanical dissociation are best remembered as 4Hs and 4Ts. The 4Hs are severe hypovolemia, hypoxia, hypothermia and hyperkalemia and other metabolic imbalances, while the 4Ts are tension pneumothorax, toxins and drugs, pericardial tamponade, and pulmonary thromboembolism. Treatment of pulseless electrical activity and electromechanical dissociation is the same as treatment of asystole; reversible causes should be identified and treated appropriately.

Defibrillation: Defibrillation is the asynchronous depolarization of a critical mass of myocardium in order to terminate VF or pulseless VT. It is successful in cases of sudden onset VF having oxygenated normothermic myocardium without significant acidosis. Larger size defibrillator paddles, 8 to 10 cm in diameter, are recommended in children weighing more than 10 kg to maximize current flow. Smaller paddles are used in infants. One paddle is placed over the right side of the upper chest and the other over the apex of the heart. Alternatively, electrodes are placed in anterior-posterior position with one placed to the left of the sternum and the other one over the back.

The optimal electrical energy dose to defibrillate is not established in children. Available data suggest an initial dose of 2 J/kg, second dose of 4 J/kg and subsequent doses of >4 J/kg, to a maximum of 10 J/kg (adult dose). Children >8-year-old or those weighing >50 kg should receive adult doses of defibrillation. Single shock strategy followed by immediate CPR (beginning with chest compressions) is recommended for children with out-of-hospital or in-hospital VF/pulseless VT. After 5 cycles or 2 minutes of CPR, the rhythm is checked to look for reversion to sinus rhythm. If the rhythm is still VF or pulseless VF, another shock is given, followed by chest compressions, a dose of epinephrine and establishing an advanced airway, provided it does not interrupt the CPR. If after 2 minutes or 5 cycles of CPR, VF or pulseless VF persists, another shock may be given followed by chest compressions and administration of amiodarone or lidocaine. Simultaneous correction of hypoxia, acidosis and hypothermia is necessary to improve the outcome of defibrillation.

Suggested Reading

- 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care: Part 11: Pediatric Basic Life Support and Cardiopulmonary Resuscitation. *Circulation* 2015; 132: S519–25.
- 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care: Part 12: Pediatric Advanced Life Support. *Circulation* 2015; 132: S526–42.

SHOCK

This is an acute syndrome that occurs because of cardiovascular dysfunction and inability of circulatory system to provide adequate oxygen and nutrients to meet the metabolic needs of vital organs. Shock, however, is a clinical diagnosis that can exist without hypotension. The chief types of shock are listed in Table 28.7.

Blood Pressure Regulation

A host of neural and humoral reflexes maintain perfusion to vital vascular beds. Neural sympathetic reflexes act *via* the vasomotor center and include: (i) baroreceptors in the carotid body and aortic arch; (ii) volume receptors in right atrium and pulmonary bed; (iii) chemoreceptors in aortic and carotid body; and (iv) cerebral ischemic response. Humoral responses are mediated by: (i) adrenal medulla through catecholamines; (ii) hypothalamus and pituitary through ACTH and vasopressin; and (iii) renin-angiotensin-aldosterone system.

Baroreceptors: Reduction in mean arterial or pulse pressure results in decreased stimulation of carotid sinus and aortic arch baroreceptors, and vasoconstriction through inhibition of the vasomotor center. Vasoconstriction is severe in skeletal muscles, splanchnic and cutaneous vascular beds, while flow is preserved in cerebral, coronary and retinal circulation.

Chemoreceptors: Hypotension and reduced perfusion cause local tissue hypoxia and acidosis, activating chemoreceptors that stimulate respiration, induce vasoconstriction and enhance cardiac function.

Table 28.7: Types of shock

Type of shock	Clinical syndromes
Hypovolemic	Hemorrhage Dehydration due to diarrhea, vomiting, starvation, polyuria, burns, heat stroke
Cardiogenic	Congenital heart disease, cardiomyopathy, cardiac arrhythmias, tamponade, anoxia
Distributive	Anaphylaxis Neurogenic Drug toxicity Burns Toxic shock syndrome
Septic shock*	Bacterial, viral, fungal

*This has components of distributive, cardiogenic and hypovolemic shock

Humoral receptors: Hypotension-induced release of epinephrine and norepinephrine from adrenal medulla and systemic adrenergic nerve endings lead to vasoconstriction and inotropic and chronotropic effects. Release of vasopressin from neurohypophysis causes vasoconstriction and stimulates free water reabsorption in the distal nephron.

Renin-angiotensin-aldosterone system: Reduced renal perfusion results in release of renin from the juxtaglomerular apparatus, that helps convert angiotensinogen to angiotensin I and angiotensin II. Angiotensin II is a potent vasoconstrictor and stimulates release of aldosterone, enhancing sodium reabsorption.

Diagnosis of Shock

An early diagnosis of shock or impending shock and its appropriate management improve outcomes. Early diagnosis of shock requires a high degree of suspicion and knowledge of predisposing conditions. Children who are febrile, have an identifiable source of infection or are hypovolemic due to any cause are at increased risk. Signs of early shock include tachycardia, mild tachypnea, prolonged capillary refill (>2–3 seconds), orthostatic change in blood pressure or pulse, and mild irritability. Decreased tissue perfusion is identified by change in body temperature (cold extremities) and decreased capillary refill. Vital organ hypoperfusion is assumed in presence of oliguria or altered mentation. Narrowing of pulse pressure is an early finding due to reduced systolic and mild increase in diastolic blood pressures. Patients with early septic shock show increased peripheral pulses, warm and over perfused extremities, wide pulse pressure and hyperdynamic precordium.

If shock continues, the compensatory mechanisms are insufficient to maintain the metabolic needs of tissues. Cellular ischemia and inflammation affect brain, kidney and cardiac microcirculation. Tachypnea due to metabolic acidosis leads to respiratory alkalosis. Skin shows features of reduced capillary refill and mottling. Hypotension, oliguria and hypothermia set in. Mental changes include agitation, confusion, stupor and finally coma (Table 28.8).

Classification

Recognition and treatment of shock depends upon the etiology of shock.

Hypovolemic shock arises from loss of preload. Clues that suggest hypovolemic shock are (i) fluid losses due to diarrhea, vomiting, blood loss, profuse and prolonged sweating, polyuria or a combination of these, or (ii) reduced intake due to vomiting, poor appetite or fluid deprivation. Physical examination shows dry mucous membranes, absence of tears, delayed capillary refill, diminished peripheral pulses and poor color. The CVP is low. Investigations show high blood urea and creatinine, elevated uric acid and small cardiac silhouette on chest X-ray.

Cardiogenic shock results from loss of cardiac contractility. Clues are history of congenital heart disease, recent cardiac surgery or diseases associated with cardiac disorders (e.g. Duchenne muscular dystrophy), presence of a murmur, S3, gallop or friction rub, elevated JVP and hepatomegaly. CVP is elevated and chest X-ray may show a large cardiac silhouette and pulmonary edema.

Distributive shock results from loss of afterload or systemic vascular resistance. Clues on history include recent allergies or spinal cord injury. Examination shows bounding pulses, well-perfused skin and low blood pressure requiring large volume of fluid.

Septic shock has components of all aforementioned types: Loss of preload, loss of afterload or systemic vascular resistance, and loss of contractility. Apart from fever and tachycardia, there may be features of decreased perfusion in form of altered sensorium, prolonged capillary refill >2 seconds (cold shock) or flush capillary refill (warm shock), diminished or bounding pulses, and/or decreased urine output. Hypotension is a late feature. A focus of infection should be looked for.

Monitoring

Monitoring of patients who are in shock or impending shock is necessary. Parameters to be monitored are pulse rate and volume, respiratory rate and pattern, temperature, skin color, blood pressure, sensorium, urine output, ECG and pulse oximetry. Metabolic parameters include blood glucose, electrolytes and arterial gases.

Therapy

Therapy depends on the type of shock. In hypovolemic shock, replacement of intravascular volume by isotonic

Table 28.8: Stages of shock

Clinical parameter	Compensated	Uncompensated	Irreversible
Mental status	Agitation or confusion	Drowsiness	Unresponsive
Heart rate	Tachycardia	Marked tachycardia	Bradycardia
Respiration	Normal or mild tachypnea	Tachypnea	Apnea
Skin and capillary refill time	Increased capillary refill time	Very slow capillary return with cold peripheral skin	Cold and cyanotic skin and mottling
Urinary output	Adequate	Oliguria or anuria	Anuria
Blood pressure	Normal	Hypotension	Unrecordable

fluids is necessary. In cardiogenic shock, inotropic support and reduction of afterload by use of vasodilators is beneficial.

Fluid Therapy

Vascular access: Large bore IV cannula or catheter is placed in a large peripheral vein, e.g. femoral vein. In older children and adolescents, cannulation of internal jugular, external jugular and subclavian veins can be considered.

Fluids and blood products: The first choice of fluid for the acute stage is 0.9% normal saline or Ringer lactate. Large volumes of fluid have been used for acute stabilization in children without increasing the risk of acute respiratory distress syndrome or cerebral edema. When fluid requirement is high, colloids (dextran, gelatin, 5% albumin) may be used. Packed red cells should be given at 10 mL/kg, to maintain hematocrit ~33%.

Volume of fluids: Normal saline or Ringer lactate, 20 mL/kg, is infused rapidly over 5–10 minutes, and titrated with changes in heart rate, capillary refill and sensorium. If no significant improvement is noticed, repeat boluses of 20 mL/kg are given. Large volume fluid deficits require 40 to 60 mL/kg and maximum up to 200 mL/kg over first-hour for replenishing the deficit. In situations where availability for ventilator support and inotropic drugs is limited, fluid boluses should be administered cautiously. Patients who do not respond to boluses of 40–60 mL/kg in 1 hour are labeled as *fluid refractory* and should receive inotropic support. These patients require careful

monitoring and are considered for intubation and mechanical ventilation.

Vasoactive Drugs

Vasopressors (Table 28.9) Dopamine is the first-line inotrope for managing shock associated with high cardiac output and low systemic vascular resistance. The medication increases cardiac output at doses of 5–10 µg/kg/min. Its vasoconstrictor effect of dopamine is seen at doses >15 µg/kg/minute and follow release of norepinephrine from sympathetic vesicles, which may not be well developed in young infants (<6 months). Low dose dopamine (2–5 µg/kg/min) does not significantly affect renal blood flow. Dopamine refractory shock responds to norepinephrine or high doses of epinephrine. Some clinicians prefer using low dose norepinephrine as the first line agent for warm hyperdynamic shock. Use of vasopressors can be titrated to maintain a perfusion pressure, that refers to mean arterial pressure minus CVP, or systemic vascular resistance that ensures adequate urine output and creatinine clearance.

Inotropes (Table 28.10): After initial fluid resuscitation, myocardial contractility needs to be augmented to improve cardiac output. Dobutamine and mid-dose dopamine are used as initial inotropic agents in adults, but children are less responsive. Epinephrine infusion usually works in dopamine or dobutamine refractory shock. Low dose epinephrine is used as first-line choice for cold hypodynamic shock, i.e. low cardiac output.

Table 28.9: Vasoactive agents

Drug	Dose	Receptors	Use	Risk
Dopamine	2–20 µg/kg/min	D ₁ /D ₂ > β > α	Renal effects, early inotropy needs, septic shock	Peripheral vasoconstriction
Epinephrine	0.01–2 µg/kg/min*	β ₁ = β ₂ > α	Anaphylaxis, cardiogenic shock	Ischemia, hypertension
Norepinephrine	0.05–1 µg/kg/min	β > α	Severe vasodilatation, hypotension	Acidosis from poor perfusion, ischemic injury
Phenylephrine	0.1–0.5 µg/kg/min	α selective	Severe hypotension, hypercyanotic spells	Acidosis, ischemic injury

*Vasoconstrictive dose >0.2 µg/kg/min

Table 28.10: Inotropic medications

Drug	Dosing	Receptors	Use	Risk
Dopamine	2–20 µg/kg/min	D ₁ /D ₂ > β > α	Renal effects, early inotropy needs, septic shock	Peripheral vasoconstriction
Dobutamine	3–20 µg/kg/min	β ₁ > β ₂ > α	Contractility	Tachycardia, vasodilation
Epinephrine	0.01–2 µg/kg/min	β ₁ = β ₂ > α, but both	Contractility, vasoconstriction (high dose)	Tachycardia, vasoconstriction
Milrinone	0.3–0.7 µg/kg/min	Phosphodiesterase inhibitor	Inotropy, vasodilation	Tachycardia, vasodilation
Amrinone	5–10 µg/kg/min	Phosphodiesterase inhibitor	Inotropy, vasodilation	

Table 28.11: Vasodilator agents

Drug	Dosage	Site of action	Use	Risk
Nitroprusside	0.3–7 µg/kg/min	Arteries > veins	Afterload reduction	Cyanide toxicity, hypotension
Nitroglycerin	0.5–5 µg/kg/min	Veins > arteries	Preload and afterload reduction	Hypotension, methemoglobinemia

Therapy with type III phosphodiesterase inhibitors is considered in patients who are normotensive with low output and high vascular resistance despite use of epinephrine and vasodilator. However, these agents have long half lives and should be discontinued at the first sign of tachyarrhythmia, hypotension or diminished systemic vascular resistance.

Vasodilators (Table 28.11) Vasodilators are useful in children with hypodynamic shock with high systemic vascular resistance shock despite therapy with IV fluids and inotropes.

Figure 28.4 outlines the management of a child with septic shock.

Correction of Metabolic Abnormalities

Infusion of sodium bicarbonate may be used to maintain arterial pH after optimizing perfusion and ventilation in patients with severe acidemia (pH <7.0). Hypoglycemia and hypocalcemia should be corrected.

Control of Infection

Patients with septic shock require prompt, appropriate and adequate antibiotic therapy. Even those without an obvious focus of infection must receive antibiotics that cover both gram-negative and gram-positive infections. Surgical drainage is ensured, if the child has pus collection (abscess, empyema, collection in soft tissues or abdomen).

Corticosteroids are reserved for catecholamine-resistant shock, and suspected or proven adrenal insufficiency. Adrenal insufficiency is perhaps more common in children with septic shock than previously thought. Methylene blue, which inhibits nitric oxide release, improves mean arterial pressure in adult patients with septic shock. The benefit of activated protein C infusion in severe sepsis is limited. If available, extracorporeal membrane oxygenation may be offered to neonates with refractory shock.

Suggested Reading

- Dellinger RP, Levy MM, Rhodes A, et al; Surviving Sepsis Guidelines Committee. Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock 2012. *Crit Care Med* 2013; 41:580–637.
- Kawasaki T. Update on pediatric sepsis: A review. *J Intensive Care* 2017;5:47.
- Khilnani P, Singhi S, Lodha R, et al. Pediatric sepsis guidelines: Summary for resource-limited countries. *Indian J Crit Care Med* 2010; 14:41–52.

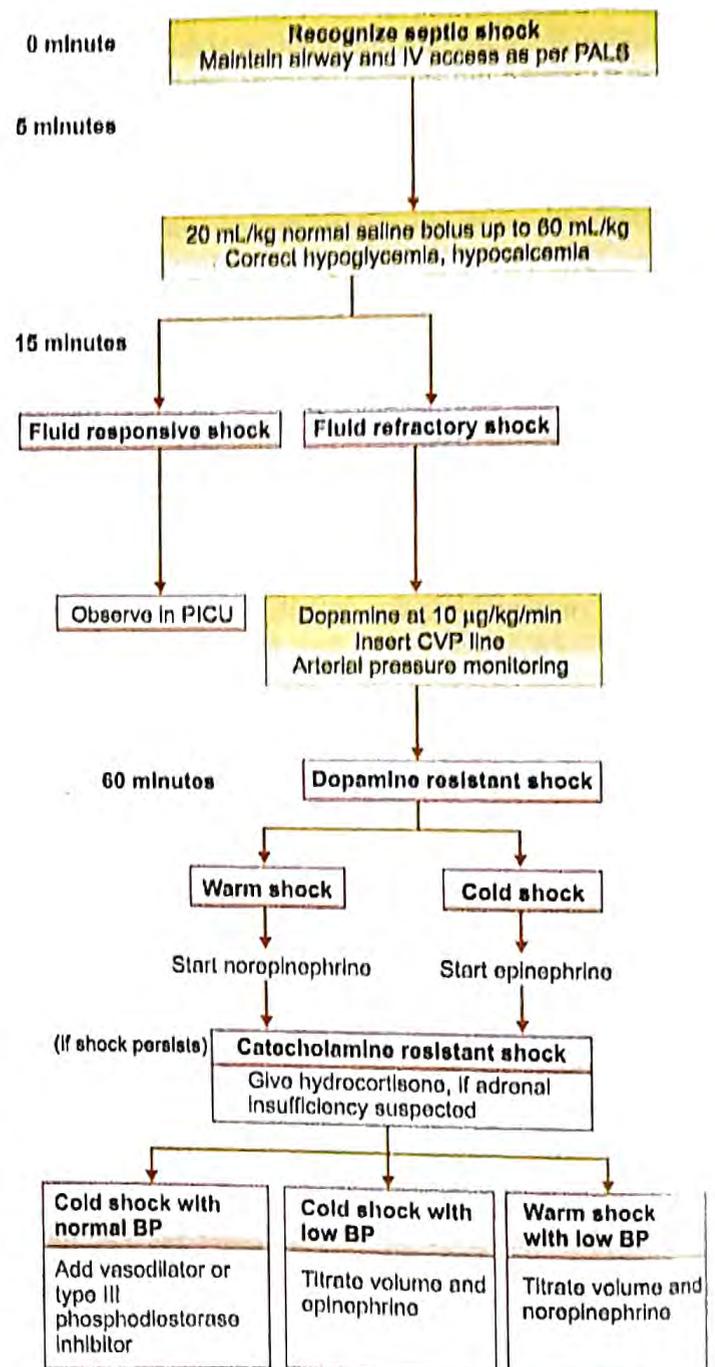


Fig. 28.4: Guidelines for management of septic shock. BP blood pressure; CVP central venous pressure; PALS pediatric advanced life support; PICU pediatric intensive care unit

- Zingarelli B. Shock, ischemia and reperfusion injury. In: Nichols DG, Shaffner DH, eds. *Roger's Textbook of Pediatric Intensive Care*, 5th edn. Lippincott Williams and Wilkins 2016; pp 253–268.

NUTRITION IN THE CRITICALLY ILL

Critically ill children are prone to malnutrition, due to reduced intake and accelerated demands, increased resting energy expenditure, proteolysis, and glucose and insulin intolerance. It is essential to provide adequate nutrition early in the course of illness in order to improve outcomes. The enteral route is preferred, since it is safer and more cost-effective than total parenteral nutrition. Enteral nutrition helps maintain the gut barrier, preserves indigenous flora and prevents overgrowth of pathogens, reducing the risk of bacteremia and pneumonia. By preventing atrophy of gut mucosa, resumption of oral feeds is easier during recovery. Supplementation of vitamins and minerals is also best done by the enteral route.

Apart from milk-based feeds, commercial formulae are available to supplement nutrition. Elemental formulae contain carbohydrates as oligosaccharides, maltodextrins or hydrolyzed cornstarch; nitrogen as peptides or amino acids; and lipids as oils or medium chain triglycerides. Low lactose or lactose-free diets are available. Feeding is initiated at 10–15 mL/kg/day and increased by 10–15 mL/kg/day until targets are achieved. Feeds may be delivered directly into the stomach by nasal or oral routes. Bolus feeding is preferred over continuous feeding as it is physiological and requires less expertise to administer. Small bowel feeds are useful in gastroparesis. Continuous feeding is preferred for small bowel feeding.

Conditions where enteral feeding is contraindicated are severe gastrointestinal hemorrhage, recent gastrointestinal surgery and intestinal obstruction. Complications of enteral feeding are intolerance, misplacement of the feeding tube, esophagitis and esophageal ulceration. Gastrointestinal reflux can lead to pulmonary aspiration. Diarrhea may occur because of hyperosmolar formulae, infection or malabsorption.

Parenteral nutrition refers to the delivery of nutrients directly into the bloodstream, including amino acid mixtures, lipids, glucose, trace minerals and vitamins. These are infused into a peripheral or central vein. A peripheral vein may be used, if the osmolality of infusate is less than 700 mOsm/kg. For delivery of adequate calories, central venous access is essential. For infants, glucose infusion is started at 5–6 mg/kg/min and increased gradually; insulin may be used, if there is hyperglycemia. Amino acids are begun at 1 g/kg/d and increased over 2–3 days to 2.5 g/kg/d. Lipids are given at 0.5 g/kg on day 1 and increased to 2–2.5 g/kg/d over 4–5 days. Appropriate combinations can be achieved by considering fluid requirements. In a critically ill child, the energy requirement is lower, as metabolism may be decreased, there is decreased activity due to illness, sedation and analgesia, and growth is lacking. The energy goal in the initial phase of acute illness is less than for a normal child and revised regularly to avoid overfeeding and underfeeding.

Use of TPN requires monitoring of blood glucose 2–3 times a day; electrolytes and urea twice a week; and weekly biochemistry, triglycerides and blood counts. Complications include catheter-related infections, liver dysfunction, hyperglycemia, acidosis, hyperlipidemia and electrolyte imbalance.

Suggested Reading

- de Carvalho WB, Delgado AE, Leite HP. Nutritional support. In: Nichols DG, Shaffner DH, eds. *Roger's Textbook of Pediatric Intensive Care*, 5th edn. Lippincott Williams and Wilkins 2016: pp 1615–32.
- Joffe A, Anton N, Lequier L, Vandermeer B, Tjosvold L, Larsen B, Hartling L. Nutritional support for critically ill children. *Cochrane Database Syst Rev*. 2016; 5: CD005144.

SEDATION, ANALGESIA, PARALYSIS

The goal of sedation is safe and effective control of pain, anxiety and motion, allowing necessary procedures to be performed and to provide appropriate amnesia or decreased awareness. The state of consciousness varies from mild to deep sedation to general anesthesia. In moderate sedation (conscious sedation), consciousness is depressed but protective airway reflexes are maintained and the child responds appropriately to verbal command or to light physical stimulation. Airway is maintained independently and spontaneous ventilation is adequate. Deep sedation refers to a medically controlled state of depressed consciousness from which the child is not easily aroused but responds purposefully to painful stimuli. The ability to maintain airway is impaired and requires assistance; spontaneous ventilation may be inadequate.

The child should be carefully assessed before sedation for underlying medical problems, medication use, allergies and time and nature of last oral intake. Monitoring is important during sedation and following procedures, including assessment of vital signs, movement of chest wall, ECG monitoring and pulse oximetry. Table 28.12 summarizes commonly used drugs for sedation and analgesia and Table 28.13 lists clinical scenarios requiring sedation and analgesia. For children on mechanical ventilation, continuous infusion of midazolam or diazepam is used for better control of ventilation. Intermittent doses or continuous infusion of fentanyl or morphine is used for pain control.

Neuromuscular Blocking Drugs

The use of neuromuscular blocking drugs is common in patients with artificial airway who are undergoing mechanical ventilation. Succinylcholine is the only depolarizing muscle relaxant available. Non-depolarizing drugs are pancuronium, atracurium, vecuronium and rocuronium. Short-term indications for these drugs include airway instrumentation and invasive procedures. Long-term use facilitates: (i) mechanical ventilation, overcoming patient ventilation dyssynchrony, and/or ensure high frequency ventilation; (ii) reduction of work

Table 28.12: Commonly used drugs for sedation and analgesia

Drug	Effects	Dose	Onset	Duration
Chloral hydrate	Sedation, motion control, anxiolysis; no analgesia	25–100 mg/kg PO	15–30 min	1–2 hours
Triclofos	Sedation, motion control; no analgesia	20–100 mg/kg PO	30–45 min	4–6 hours
Midazolam	Sedation, motion control, anxiolysis; no analgesia	IV 0.05–0.1 mg/kg; up to 0.4–0.6 mg/kg Infusion: 0.5–3.0 mg/kg/min	2–3 min	45–60 min
Diazepam	Sedation, motion control, anxiolysis; no analgesia	IV 0.2–0.3 mg/kg Infusion: 0.1–0.5 mg/kg/hr	2–5 min	1–2 hours
Propofol	Sedation, motion control; no analgesia	IV 0.5–1 mg/kg; then 0.1–0.5 mg/kg every 3–10 min Infusion: 5–10 mg/kg/min	1 min	10 min
Morphine	Analgesia, sedation	IV 0.1 mg/kg	2–3 min	4–5 hours
Fentanyl	Analgesia	IV 1 µg/kg/dose; repeat every 3 min Infusion: 1–5 µg/kg/hr	2–3 min	30–60 min
Ketamine	Analgesia, dissociation, amnesia, motion control	IV 1–1.5 mg/kg over 1–2 min	1 min	15–60 min
		IM 3–5 mg/kg	3–5 min	15–150 min

IM: Intramuscular; IV: Intravenous; PO: Per orally

Table 28.13: Clinical scenarios for sedation and analgesia

Clinical scenarios	Examples	Sedation strategy
Non-invasive procedures	CT scan Echocardiography EEG MRI Ultrasonography	Comforting alone in older children Chloral hydrate orally Triclofos orally Midazolam intravenous (IV) Comforting alone
Procedures associated with low level of pain and high level of anxiety	IV cannulation Phlebotomy Lumbar puncture Flexible bronchoscopy	Comforting and local anesthesia
Procedures associated with high level of pain and high level of anxiety	Central catheter placement Bone marrow aspiration Endoscopy Abscess: Incision and drainage Interventional radiology procedures Intercostal drainage Paracentesis	Midazolam and fentanyl or morphine IV Ketamine IV or intramuscular

of breathing and metabolic demands; (iii) treatment of agitation unresponsive to sedation and analgesia; and (iv) treatment of tetanus and status epilepticus, under continuous EEG monitoring. Children receiving these agents should be monitored carefully, particularly for position of artificial airway and adequate ventilation. Patients who require paralysis should also be sedated.

Suggested Reading

- McPherson C, Inder T. Perinatal and neonatal use of sedation and analgesia. *Semin Fetal Neonatal Med* 2017;22:314–20.
- Zuppa AF, Curley MAQ. Sedation, analgesia and neuromuscular blockade in pediatric critical care: Overview and current landscape. *Pediatr Clin North Am* 2017;64:1103–16.

HEALTHCARE-ASSOCIATED INFECTIONS

Healthcare-associated infections (HAI; earlier called nosocomial infections) are not present or incubating at admission, but occur during hospitalization. Infections diagnosed 48 hours after admission until 72 hours after discharge are considered as health care associated (also see Chapter). Up to 6–10% patients admitted to PICUs develop HAI. Bloodstream infections are the most common (25–30%), followed by infections of lower respiratory (20–25%) and urinary tracts (15–20%). Important pathogens are coagulase negative and positive staphylococci, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella*, enterococci and *Candida* sp.

Table 28.14: Strategies to reduce HAI

- Hand washing, hand hygiene, hand disinfection
- Aseptic precautions during invasive procedures
- Ensure nutrition: Prefer enteral to parenteral nutrition
- Appropriate and rational prescription of antibiotics
- Regular training: Infection control, procedure specific guidelines
- Surveillance for HAI
- Health care associated pneumonia: Avoid antacids and H₂ blockers; disinfect respiratory therapy equipment; sterile fluids for nebulization and humidifiers; change ventilator circuit tubing every 48 hours; care during suctioning; head end at 30–45° elevation; cuffed endotracheal tube; selective decontamination of gut (tobramycin, gentamicin, polymyxin, nystatin)
- Bloodstream infection: Care of vascular access; use of Teflon or polyurethane catheters; avoid multilumen catheters; use transparent dressings; minimal “break in” into catheter and intravenous tubing; avoid TPN catheters for other infusions
- Urinary tract infections: Minimal catheterization; asepsis during insertion; closed drainage; early removal of catheter

The risk of HAI is related to the severity of underlying illness, length of PICU stay, invasive monitoring and diagnostic procedures, and indiscriminate use of antimicrobials. Almost 90% of bloodstream infections occur in children with central venous lines, 95% of pneumonia in those on mechanical ventilation and 75% of UTI in children with catheters. HAI may be caused by organisms that originate from exogenous sources in the hospital or from patient’s own flora. Apart from increased duration of hospital stay and cost of therapy, mortality attributed to HAI ranges between 10 and 20%.

It is important for ICUs to have infection control programs to reduce the risk of HAI. A team of health professionals should ensure implementation and compliance on part of the PICU team. Infection control activities (Table 28.14) can reduce HAI rates by ~50%.

Suggested Reading

- Joram N, de Saint Blanquat L, Stamm D, Launay E, Gras-Le Guen C. Healthcare-associated infection prevention in pediatric intensive care units: a review. *Eur J Clin Microbiol Infect Dis* 2012; 31: 2481–90.

BLOOD TRANSFUSIONS

Blood component transfusion is an integral part of treatment for many patients cared for in PICU. Blood products are prepared from collected whole blood or apheresis donation. Whole blood units are separated into red cells (RBC) and plasma and platelet components by differential centrifugation. Automated apheresis procedures are used to collect platelets, granulocytes or plasma. Cryoprecipitate is prepared from a plasma unit. Plasma proteins, e.g. albumin, anti-D immunoglobulins, IV immunoglobulins and concentrated coagulation factors

are prepared by processing large pools of donor plasma obtained from whole blood or plasmapheresis.

Indications for red cell transfusion are listed in Table 28.15.

Transfusion for acute blood loss: If patient is not stabilized after 2 boluses of 20 mL/kg of isotonic crystalloids, it is likely that the blood loss is >30% and the patient should receive fresh blood.

Transfusion for chronic anemia: Children with chronic anemia usually tolerate hemoglobin levels as low as 4 g/dL. Investigations for the underlying cause of anemia should be sent, prior to instituting transfusions. Patients are screened for cardiovascular decompensation, an indication for emergency transfusion.

Choice of blood group: For red cell transfusions, the choices are based on the principle that the recipient plasma must not contain antibodies corresponding to donor A or B antigens. For plasma and platelet transfusion, donor plasma must not contain A or B antibodies corresponding to recipient A or B antigens (Table 28.16). Patients who are RhD negative should receive only RhD negative red cells. Ideally, the same blood group red cells that are compatible with the recipient plasma should be transfused.

Quantity of transfusion: The quantity of blood administered depends on hematocrit of the blood unit,

Table 28.15: Indications for red blood cell transfusion in children

- Infants**
- Hematocrit <20 and asymptomatic with reticulocytes <100000/cu mm
 - Hematocrit <30 and requiring oxygen
 - Hematocrit <35 and requiring CPAP or mechanical ventilation; heart rate >180/min or respiratory rate >80/min persisting for >24 hours; weight gain <10 g/day over 4 days while on >100 Cal/kg/d; or if undergoing surgery
- Children**
- Hemoglobin level ≤4 g/dL (hematocrit ≤12) irrespective of clinical condition
 - Hemoglobin 4–6 g/dL (hematocrit 13–18) with features of hypoxia, acidosis, dyspnea or impaired consciousness
 - Malaria with hyperparasitemia >20%
 - Features of cardiac decompensation

Table 28.16: Choices of ABO blood groups for red cells, plasma and platelet transfusions

Recipient blood group	Acceptable ABO group of component		
	Red blood cells	Plasma	Platelets
O	O	O, A, B, AB	O, A, B, AB
A	A, O	A, AB	A, AB
B	B, O	B, AB	B, AB
AB	AB, A, B, O	AB	AB

pretransfusion hemoglobin level and patient weight. If the hemoglobin level is ≥ 5 g/dL and citrate phosphate dextrose red cells (hematocrit 70–75) are used, a transfusion of 10 mL/kg raises hemoglobin level by 2.5 g/dL. If anemia has developed slowly and hemoglobin level is < 5 g/dL, red cell transfusion should be given slowly or in small quantities to avoid precipitating cardiac failure from circulatory overload.

Platelets

Platelet concentrates are prepared from whole blood donation but these may also be collected by apheresis. The usual platelet bag (unit) contains 7.0×10^{10} platelets, about 50 mL plasma, trace to 0.5 mL of red cells and varying number of leukocytes (up to 10^8). Apheresis platelet units contain 3×10^{11} platelets, approximately 250–300 mL plasma, trace to 5 mL of RBCs and 10^6 – 10^9 leukocytes. It can be stored for 5 days at 20–24°C. The need for platelet transfusions depends on the platelet count, bleeding tendency, etiology and setting of interventions like invasive procedures or surgery (Table 28.17).

Plasma

Plasma is prepared from a whole blood donation by centrifugation or automated apheresis. A unit of plasma contains 150–250 mL when prepared from whole blood donations. Immediately following collection, plasma contains approximately 1 unit/mL of each of coagulation factors. Coagulation factors V and VIII are labile and are not stable in plasma stored at 1–6°C. Plasma frozen within 8 hours of donation (fresh frozen plasma, FFP) contains ≈ 0.7 U/mL factor VIII; this may be stored for 12 months at -20°C . The use of FFP is limited to treatment or prevention of significant bleeding due to deficiency of one or more plasma coagulation factors (Table 28.18).

Compatibility tests before plasma transfusion are not necessary and plasma should be ABO compatible with recipients red cells. Usually, RhD group need not be considered unless in cases where large volume of FFP is needed. FFP may be thawed in a water bath at 30–70°C or in microwaves designed for this purpose. The dose of FFP depends on the clinical situation and the underlying disease. If used at a dose 10–20 mL/kg, it increases the level at coagulation factors by 20% immediately after infusion.

Cryoprecipitate

Cryoprecipitate is the precipitate formed when FFP is thawed at 4°C. It is then refrozen within 1 hour in 10–15

Table 28.17: Indications for platelet transfusion

Platelet count $< 10 \times 10^9/\text{L}$ due to any cause
Platelet count $< 20 \times 10^9/\text{L}$ and bone marrow infiltration, severe mucositis or anticoagulant use
Platelet count < 30 – $40 \times 10^9/\text{L}$ and disseminated intravascular coagulation
Platelet count < 50 – $60 \times 10^9/\text{L}$ and major surgical intervention

Table 28.18: Indications for transfusion of fresh frozen plasma

Coagulation factor deficiency when individual factor replacement is not available
Anticoagulant (vitamin K antagonist) related bleeding
Severe liver disease with prolonged prothrombin time or bleeding tendency
Disseminated intravascular coagulation with active bleeding
C1 esterase deficiency in hereditary angioneurotic edema

mL of donor plasma and stored at -20°C for up to 1 year. This unit contains 80–100 units of factor VIII, 100–250 mg of fibrinogen, 40–60 mg of fibronectin, 40–70% of vWF and 30% of factor XIII. Indications for use include hemophilia, von Willebrand disease and congenital deficiencies of fibrinogen or factor XIII. Compatibility testing of cryoprecipitate units is not necessary but ABO compatible units should be used. Cryoprecipitate is infused at the rate of 1 unit/5–10 kg of recipient weight, over 2–4 hours.

Risks of Transfusion

The chief risks of blood products include: (i) transfusion reactions; (ii) transmission of infectious agents, including HIV, cytomegalovirus, hepatitis B and C viruses, syphilis and malaria; and (iii) bacterial contamination due to inappropriate collection or storage.

Time limit for infusion: There is risk of bacterial proliferation or loss of function in blood products once they are removed from storage.

- Whole blood or packed red cell transfusion should begin within 30 minutes of removing from storage temperature (2 – 6°C) and completed within 4 hours, if ambient temperature is 22 – 25°C . In case of high ambient temperature, shorter 'out of refrigerator' times should be used.
- Platelets should be infused within 20–30 minutes of being received.
- Infusion of fresh frozen plasma should begin within 20–30 minutes of removal from refrigerator.

The products are infused through a sterile administration set containing a 170–200 μm filter. The set should be changed every 12 hours, if multiple transfusions are needed. For platelet transfusions, a fresh set primed with saline should be used.

Transfusion reactions: Tables 28.19 and 28.20 summarize adverse effects of transfusion of blood products. Hypersensitivity reactions cause mild and moderate reactions; life-threatening reactions can occur due to multiple causes, including intravascular hemolysis, bacterial contamination, fluid overload, anaphylaxis and transfusion associated lung injury.

Massive transfusion: This is the replacement of blood equivalent to or greater than the patients total blood volume (70 mL/kg in adults; 80–90 mL/kg in children)

Table 28.19: Adverse effects of use of blood and blood products

Category	Clinical features	Treatment
Mild	Pruritus, urticaria, rash	Slow transfusion Administer chlorpheniramine maleate 0.1 mg/kg If no improvement in 30 minutes, treat as next category
Moderately severe	Anxiety, itching, headache, mild dyspnea, palpitations, flushing, urticaria, rigors, tachycardia, fever, restlessness	Stop infusion, replace IV set; notify blood bank Take sample from bag and patient for repeat crossmatching; urine sample for hemolysis Administer antihistaminic and antipyretic Give IV steroids and bronchodilator, if needed If improves, restart transfusion slowly If no improvement in 15 minutes, treat as next category
Life threatening	Anxiety, chest pain, pain at transfusion site, headache, dyspnea, respiratory distress, backache, rigors, fever, restlessness, hypotension, tachycardia, hemoglobinuria, bleeding from one or more sites	Stop infusion, change IV set; notify blood bank Sample from bag and patient for repeat crossmatching; urine sample for hemolysis Ensure open airway; oxygen inhalation; elevate legs Normal saline 20 mL/kg; repeat if needed Inotropes, if required; adrenaline (1:1000) 0.01 mg/kg IV/SC IV steroids and bronchodilator, if needed <i>Bleeding (DIC):</i> Consider use of platelets, FFP, factor concentrates, cryoprecipitate <i>Acute renal failure:</i> Fluid balance; frusemide; dialysis <i>Bacteremia:</i> Send cultures; antibiotics

Table 28.20: Delayed complications

Delayed hemolytic reaction	5–10 days later Fever, anemia, jaundice	No treatment; if hypotension, treat as acute intravascular hemolysis
Post-transfusion purpura	5–10 days later Bleeding tendency Thrombocytopenia	High dose steroids Intravenous immunoglobulins Plasma exchange
Graft vs. host disease	10–12 days later Fever, rash, desquamation Diarrhea, hepatitis, pancytopenia	Supportive care
Iron overload	Cardiac and liver failure in transfusion dependent patients	Desferioxamine (subcutaneous infusion) Deferiprone (oral)

with stored blood in less than 24 hours. Complications of massive transfusion are acidosis, hypothermia, hyperkalemia, citrate toxicity and hypocalcemia, depletion of fibrinogen and coagulation factors, depletion of platelets and disseminated intravascular coagulation.

Suggested Reading

- Karam O, Spinella PC, Wong ECC. Blood products and transfusion therapy. In: Nichols DG, Shaffner DH, eds. *Roger's Textbook of Pediatric Intensive Care*, 5th edn. Lippincott Williams and Wilkins 2016: pp 621–40.

Important Medical Procedures

Arvind Bagga

Medical procedures involved in care of children include diagnostic procedures and therapeutic interventions, some of which may be critical or life-saving. It is important to observe universal sterile precautions during medical procedure and dispose waste articles appropriately.

Removal of an Aspirated Foreign Body

Foreign body airway obstruction is a common medical emergency, especially in children younger than 5-year-old. Most events are witnessed and may be caused by choking on toy parts, seeds, nuts, grapes, pebbles or buttons. The usual presentation is with sudden onset of cough, gagging or stridor with or without respiratory distress. A foreign body obstructing the upper airway completely can cause hypoxemia, cyanosis and secondary cardiac arrest. If the child can speak, breathe or cough, partial obstruction is likely. While this indicates that there is no immediate threat to life, the foreign body may get dislodged and obstruct the airway totally.

Indication: Patients with either complete airway obstruction or partial airway obstruction with poor air exchange require immediate relief.

Procedure: A choking infant younger than 1 year is placed face down over the rescuer's arm, with the head positioned below the trunk. Five measured back blows are delivered rapidly between the infant's scapulae using the heel of the hand (Fig. 29.1). If obstruction persists, the infant is rolled over and five rapid chest compressions are performed, similar to cardiopulmonary resuscitation. The sequence of back blows and chest compressions is repeated until the obstruction is relieved. Abdominal thrusts (Heimlich maneuver) may be performed in children older than 1 year (Fig. 29.2). When initial interventions fail, a jaw thrust is performed, since this may partially relieve the obstruction. If the foreign body can be visualized, it should be removed manually using Magill or other large forceps.

In the unconscious apneic child, a tongue-jaw lift can be performed by grasping both tongue and lower jaw between



Fig. 29.1: Back blows in a choking infant



Fig. 29.2: Heimlich maneuver in a child

the thumb and finger and lifting. Blind finger-sweeps are avoided in infants and young children because they may push the foreign body further back into the airway, worsening the obstruction. Children presenting with signs and symptoms of foreign body aspiration beyond the oropharynx into the trachea or bronchus require bronchoscopy by experienced personnel.

Complications: Chest compressions may cause rib and cardiac damage in infants, but are rare, if performed by experienced personnel. Uncommon complications of the Heimlich maneuver, if performed incorrectly, include pneumomediastinum, rupture of spleen or stomach and injury to the aorta.

Nasogastric Tube Insertion

Indications: Nasogastric intubation is usually performed for: (i) administration of medications or nutrients in unconscious or anorexic children; (ii) gastrointestinal decompression in case of intestinal obstruction or trauma; and (iii) gastric lavage in a patient with upper gastrointestinal bleeding or toxin ingestion.

Contraindication: (i) Suspected basilar skull fracture, (ii) maxillofacial trauma

Procedure: The largest size tube that does not cause undue discomfort to the child is chosen. Typically, an 8 Fr tube is used in neonates, 10 Fr for a 1-year-old and increasing sizes in childhood up to 14–16 Fr tubes in teenagers. The length of tubing to be passed is estimated by adding 8–10 cm to the distance between the nostrils to the xiphoid process. The child is prepared by explaining the procedure as fully as possible; sedation is rarely needed.

Infants and obtunded children are placed supine with the head turned to one side. The curved tube is straightened and its patency checked with a syringe. Application of a lubricant facilitates atraumatic nasal passage. The tube is grasped 5–6 cm from the distal end and advanced posteriorly along the floor of the nose. It is inserted with its natural curve pointing downward in order to go past the bend of the posterior pharynx easily. The procedure is discontinued temporarily, if the child coughs or gags or if the tube emerges from the mouth. When the tube is passed successfully to the measured length, its position is checked. Using a 5 mL syringe filled with air attached to the proximal

end, the plunger is depressed rapidly while one auscultates for gurgling over the stomach. The tube is taped securely to the nose.

Complications: The procedure may be associated with tracheal intubation, nasal or pharyngeal trauma, or vomiting.

Central Venous Cannulation

Indications: Usual indications include: (i) inability to establish venous access in the peripheral circulation; (ii) access for drugs and fluids that require central administration (e.g. vasopressors, hyperalimentation fluids, contrast medications); (iii) to monitor central venous pressure; and (iv) access for hemodialysis, plasmapheresis or continuous renal replacement therapies.

Procedure: Principles common to all central venous catheter procedures, regardless of site, include: (i) strict attention to asepsis; (ii) use of the Seldinger technique (placement over a guidewire minimizes trauma and hematoma formation and enhances successful cannulation); (iii) adequate sedation to minimize movements; (iv) attention to appropriate location of catheter tip, avoiding high-risk sites such as ventricles and left atrium, verifying tip position with a radiograph; (v) avoiding placement in presence of a bleeding diathesis; and (vi) continuous monitoring of vital signs and oxygen saturation.

Sites: The site of access depends on the indication (Table 29.1).

- i. **External jugular vein.** The external jugular vein can be identified easily. There is less risk of pneumothorax. Complications are minimal because of the superficial position of the vein and the ability to compress the vein to prevent hemorrhage.
- ii. **Internal jugular vein.** Internal jugular vein cannulation provides an excellent approach to the central circulation with a high success rate and minimal complications. Carotid artery puncture and pneumothorax are the most common complications. With left-sided cannulation, there is potential for injury to the thoracic duct and there is a higher risk for pneumothorax because the apex of the left lung is higher than on the right.

Table 29.1: Preferred choices for placement of central line

Indication	First choice	Second choice
Emergency airway management or cardiopulmonary resuscitation	Femoral vein	Subclavian vein
Long-term parenteral nutrition	Subclavian vein	Internal jugular vein
Acute hemodialysis or plasmapheresis	Internal jugular vein	Femoral vein
Coagulopathy	Femoral vein	External jugular vein
Other purposes, e.g. access for surgery or medications	Internal jugular vein	Femoral or subclavian vein

- iii. *Subclavian vein cannulation.* This vein is the preferred site in patients with long-term catheter requirements because of its relatively high level of patient comfort and ease of catheter maintenance. In patients with hypovolemia, the subclavian vein does not collapse as readily as other major vessels. Major complications include pneumothorax, subclavian artery puncture, or occasionally, hemothorax. The chief long-term risk is subclavian vein stenosis.
- iv. *Femoral vein cannulation.* Femoral vein cannulation is the most common site for central vein cannulation as it is easily accessible. Main complications are the risk of arterial puncture, infection, and rarely, deep vein thrombosis (more common with long-dwelling catheters in adolescents).

Capillary Blood (Heel Prick)

Indications: Heel prick is a useful technique to obtain arterialized capillary blood for blood gas analysis, bilirubin, glucose, hematocrit and other parameters in newborns.

Technique: Figure 29.3 indicates the appropriate areas to use for heel punctures for blood collection. Prewarming the infant's heel (using a cotton wad soaked in sterile warm water at 40°C or a hot towel) is important to obtain capillary blood gas samples as it increases the flow of blood, allowing collection of blood specimen. Hot water should not be used since baby skin is thin and susceptible to thermal injury. After ensuring asepsis, a sterile blood lancet or a needle is punctured at the side of the heel in the appropriate regions as shown in Fig. 29.3. The central portion of the heel is avoided as it might injure the underlying bone. Blood sample is obtained by alternate squeezing and releasing of calf muscles.

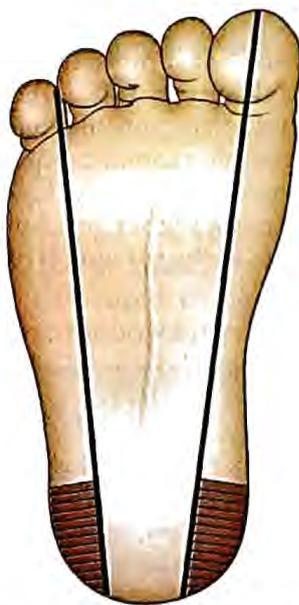


Fig. 29.3: Recommended sites for neonatal capillary blood sampling. Hatched areas indicate safe areas for puncture sites

Complications: The following complications may occur: (i) puncture of the calcaneus, resulting in necrotizing chondritis or osteomyelitis; (ii) calcified nodules of the heel; (iii) hemolysis, resulting in falsely elevated bilirubin and potassium levels from mechanical trauma; (iv) erroneously high glucose values due to alcohol in the swab; and (v) inaccurate pCO₂ and pO₂ values from poor blood flow.

Umbilical Vessel Catheterization

Indications: The umbilical vein is a convenient route for vascular access in newborns during the first 7–10 days of life. The route is used for administration of intravenous fluids or drugs during neonatal resuscitation, when establishing peripheral venous access is technically difficult. It is also employed as a route for central venous pressure monitoring and for performing exchange blood transfusion. Cannulation of the umbilical artery provides a route for arterial pressure monitoring or arterial blood sampling and alternative access for exchange transfusion.

Contraindications: Omphalitis is a contraindication; the procedure should also be avoided in presence of peritonitis or necrotizing enterocolitis.

Equipment: These include a 5 or 8 Fr catheter or feeding tube, 10 mL syringe, tape or silk suture to tie the base of the cord, normal saline for flushing, intravenous tubing and three-way connectors, a set of sterile drapes, sterile instruments (small iris forceps, needle holder and scalpel blade) and antiseptic for skin preparation.

Procedure: The neonate is placed beneath a radiant warmer. Anesthesia is not required; the limbs are restrained gently. The abdomen and umbilicus are cleaned with chlorhexidine gluconate or povidone-iodine and sterile drapes placed, leaving the umbilical area exposed. Vital signs are monitored continuously.

A suture is looped at the base of the cord with gentle constriction to anchor the cord and limit bleeding. The cord may need to be immobilized by two artery forceps grasping cord edges at 3 and 9 o'clock position. Using a scalpel blade, the cord is trimmed to 1–2 cm above the skin. The umbilical vessels are easily identified. The umbilical vein is a single, thin-walled, large diameter lumen, usually located at 12 o'clock position, while the two arteries have thicker walls with a small-diameter lumen (Fig. 29.4). The catheter or feeding tube is flushed with heparinized saline (1000 U/L) and attached to a three-way connector. A mark is placed at the length of insertion expected to place the catheter tip above the diaphragm but below the right atrium; this is calculated as 0.6 times the shoulder-to-umbilicus distance from the tip of the catheter. The closed ends of a pair of iris forceps are inserted into the lumen of the umbilical vein, and the lumen dilated by separating the ends of the forceps by

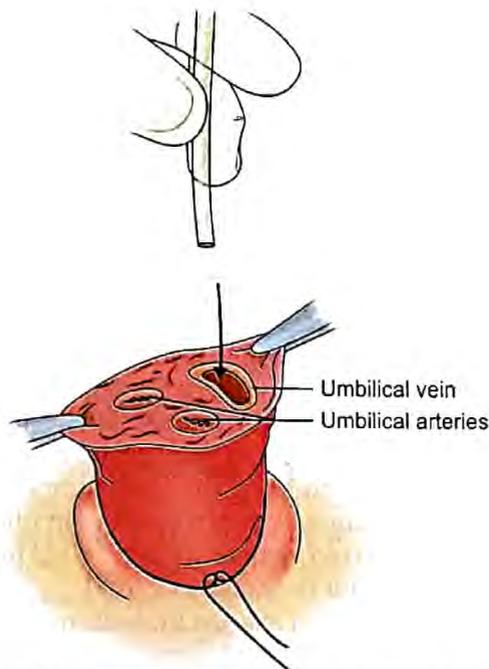


Fig. 29.4: Umbilical vein cannulation in a newborn. The umbilical vein is located at 12 o' clock position and is identified by its large lumen and thin walls

opening it gently. Grasping the catheter with iris forceps 1 cm from its distal end, the catheter is inserted into the lumen of the umbilical vein and advanced gently inward until blood returns freely. Resistance to advancement of the catheter indicates that the tip is in the portal vein or the ductus venosus; the catheter should be withdrawn until free flow of blood is noted. The catheter is flushed with saline and secured with a purse string suture. An X-ray is ordered to ensure that the tip of the catheter is in the inferior vena cava and not the hepatic vein or right atrium.

A similar procedure is followed for insertion of catheter into the umbilical artery. Since the lumen is smaller, the vessel is dilated carefully 2–3 times using a curved iris forceps and the catheter inserted gently, taking care to avoid vascular spasm. The catheter is advanced to either the high position (above the diaphragm between thoracic vertebrae T6 and T9) or the low position (above the aortic bifurcation between lumbar vertebral bodies L3 and L4).

Complications: During insertion, vascular spasm, arterial injury or air embolism may occur and a false tract may get created. Other complications include bleeding due to accidental disconnection of IV tubing; catheter-related infection, thrombosis and embolism; and incorrect position of the catheter tip causing cardiac arrhythmias, hepatic necrosis or portal hypertension. Vascular complications are common with the umbilical artery catheter, particularly if placed in the low position.

Arterial Catheterization

Indications: Arterial catheterization may be needed (i) to monitor blood pressure continuously, especially in hemodynamically unstable patients; and (ii) to frequently monitor arterial blood gas.

Sites and procedure: Radial artery cannulation is a primary site of arterial cannulation in infants and children. Right radial artery cannulation is performed when preductal arterial oxygen tension is required for evaluating and treating infants with congenital heart disease. It is often helpful to stabilize the hand and wrist on an arm board, placing the wrist in approximately 30°–45° extension over several gauze pads. Adequacy of the palmar arterial arch should be assessed by the Allen test before radial arterial puncture.

Complications:

- i. Disconnection of the catheter from the IV infusion.
- ii. Ischemia: The radial artery cannula should be withdrawn, if ischemic changes develop.
- iii. Emboli: Blood clot or air may embolize to the digits or centrally, resulting in arteriolar spasm or ischemic necrosis.
- iv. Infection may cause septicemia.

Intraosseous Infusion

Indications: The bone marrow cavity is effectively a vascular space that does not collapse even in the setting of shock or cardiac arrest. Intraosseous access is the vascular access of choice in patients with severe hypotension such as cardiopulmonary arrest or decompensated shock. Almost any medication that can be administered into a central or peripheral vein can be safely infused into the bone marrow. Crystalloid solutions, colloids and blood products can be safely infused, as can hypertonic solutions.

Procedure: The technique of intraosseous infusion is rapid and simple. The most common sites are the proximal tibia, distal tibia and distal femur (Fig. 29.5). Due to differences in cortical thickness, the proximal tibia along the flat anteromedial surface of the shaft, 1–2 cm below the tibial tuberosity, is the preferred site in infants and young children. The distal tibia at the junction of the medial malleolus and the shaft of the tibia is preferred in older children.

Technique: Using aseptic technique, the site is prepared with an iodine solution. The skin is injected with 1% lidocaine for anesthesia in the awake patient. The needle is inserted at a 10° to 15° angle to the vertical, away from the joint space (caudal for the proximal tibia, cephalad for the distal tibia and femur). Pressure is applied in a 'to and fro' rotary motion. As the needle passes into the marrow, a 'give away' will be felt. The needle should stand without support. Evidence for successful entrance into the marrow



Fig. 29.5: Insertion sites for Intraosseous Infusion in the proximal tibia, 1–2 cm anteromedial from the tibial tuberosity, the distal tibia at the junction of medial malleolus and the shaft of the tibia, and the distal one-third of the femur

include (i) the lack of resistance (or a 'give away') after the needle passes through the cortex, (ii) the ability of the needle to remain upright without support, (iii) aspiration of bone marrow into a syringe, and (iv) free flow of the infusion without significant subcutaneous infiltration. The stylet is removed. Proper placement is confirmed by aspiration of bone marrow into a 5 mL syringe and free flowing of a heparinized saline flush. The needle is connected to the desired intravenous tubing and solution. The site is observed for extravasation of fluids into the surrounding soft tissue.

Complications: Potential complications include osteomyelitis, subcutaneous abscess, extravasation of fluid into subcutaneous tissue, epiphyseal trauma and fat embolism.

Lumbar Puncture

Indications: The procedure is performed to obtain cerebrospinal fluid (CSF) for the diagnosis of meningitis, meningoencephalitis, subarachnoid hemorrhage, metastatic leukemia or benign intracranial hypertension.

Procedure: The spinal cord ends at approximately the level of the L1 and L2 vertebral bodies. Caudal to L2, only the filum terminale is present. The desired sites for lumbar puncture are the interspaces between the posterior elements of L3 and L4 or L4 and L5. These spaces are located by palpating the iliac crest. If one follows an imaginary 'plumb line' from the iliac crest to the spine, the interspace encountered is L4 to L5.

Lateral decubitus position: The patient is restrained in the lateral decubitus position as shown in Fig. 29.6a. The

spine is maximally flexed without compromising the upper airway.

The skin is cleaned with povidone-iodine solution and alcohol beginning at the intended puncture site and sponging in widening circles until an area of 10 cm in diameter has been cleaned. This is allowed to dry. Local anesthesia is used in children older than 1 year of age. The site is anesthetized by injecting 1% lidocaine intradermally to raise a wheal, then advancing the needle into the desired interspace and injecting the anesthetic, being careful not to inject it into a blood vessel or spinal canal.

The spinal needle is grasped firmly with the bevel facing 'up', parallel to the direction of the fibers of the ligamentum flavum. The needle is inserted into the selected interspace in the midline sagittal plane slowly, aiming slightly cephalad toward the umbilicus. When the ligamentum flavum and then the dura are punctured, a 'pop' and decreased resistance are felt. The stylet is removed to check for flow of spinal fluid.

About 1 mL of CSF is collected in sterile tubes for routine culture, glucose and protein determination and cell count. Additional samples are collected as indicated. The stylet is reinserted to remove the spinal needle with one quick motion. The back is cleaned and the puncture site covered.

Sitting position: The infant is restrained in the seated position with maximal spinal flexion (Fig. 29.6b). The

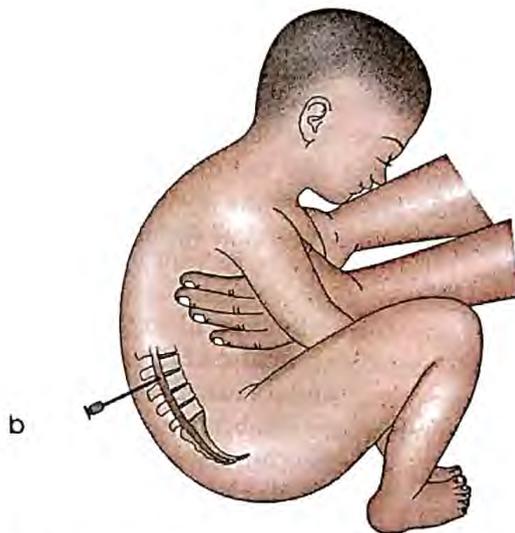
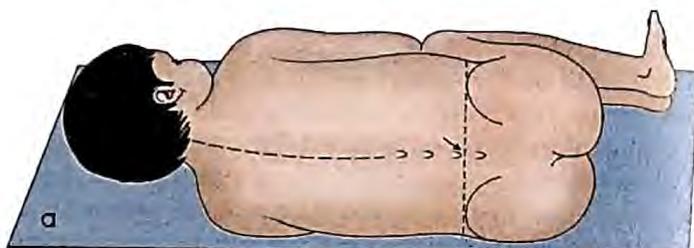


Fig. 29.6: Lumbar puncture with the child in (a) Decubitus position; and (b) Sitting position

assistant holds the infant's hands between his or her flexed legs with one hand and flexes the infant's head with the other hand. Drapes are placed underneath the child's buttocks and on the shoulders with an opening near the intended spinal puncture site. The interspace is chosen as noted earlier and the procedure follows steps as outlined for the lateral position. The needle is inserted so it runs parallel to the spinal cord.

Complications: Lumbar puncture may be associated with headache, local back pain or infection. Brainstem herniation may occur in the presence of symptomatic intracranial hypertension.

Thoracocentesis or Pleural Tap

Indications: Thoracocentesis is performed to evacuate fluid from the patient's pleural space for: (i) diagnostic purpose, e.g. pleural effusion or empyema; or (ii) therapeutic purpose, e.g. when large collections of pleural fluid compromise ventilatory function.

Contraindications: These include: (i) uncooperative child; (ii) uncorrected coagulopathy; and (iii) persistent inability to draw fluid (which suggests a loculated effusion). The operator should consider withholding further attempts until the procedure can be performed under radiographic guidance (CT scan, ultrasound).

Technique: The first step in thoracocentesis is to ensure by clinical and radiological methods that fluid is present in the area tapped. Decubitus films are helpful in demonstrating free fluid that shifts with movement.

The procedure (Fig. 29.7) is carried out with the patient appropriately positioned upright and leaning forward. The site of entry is anesthetized with local anesthetic. The landmark for evacuation of the fluid is the angle of the scapula that corresponds approximately to the eighth rib interspace. An appropriate catheter is used over a needle. The needle is introduced immediately above the superior edge of the rib to avoid puncturing the intercostal artery and vein. Once the pleural space is entered and fluid is aspirated, the catheter is advanced as the needle is withdrawn. The catheter is connected to a three-way stopcock and syringe (10–20 mL). It is important to control the aspiration of fluid such that air is not allowed to enter the pleural space from the outside.

Complications:

- i. Intercostal artery puncture with severe hemorrhage
- ii. Development of pneumo- or hemothorax
- iii. Malposition of the thoracocentesis needle, with injury of abdominal viscera or lung parenchyma.

Abdominal Paracentesis or Ascitic Tap

Indications: Ascitic tap is performed for diagnostic purpose, e.g. to determine the etiology of the peritoneal fluid and to determine whether infiltration is present, or for

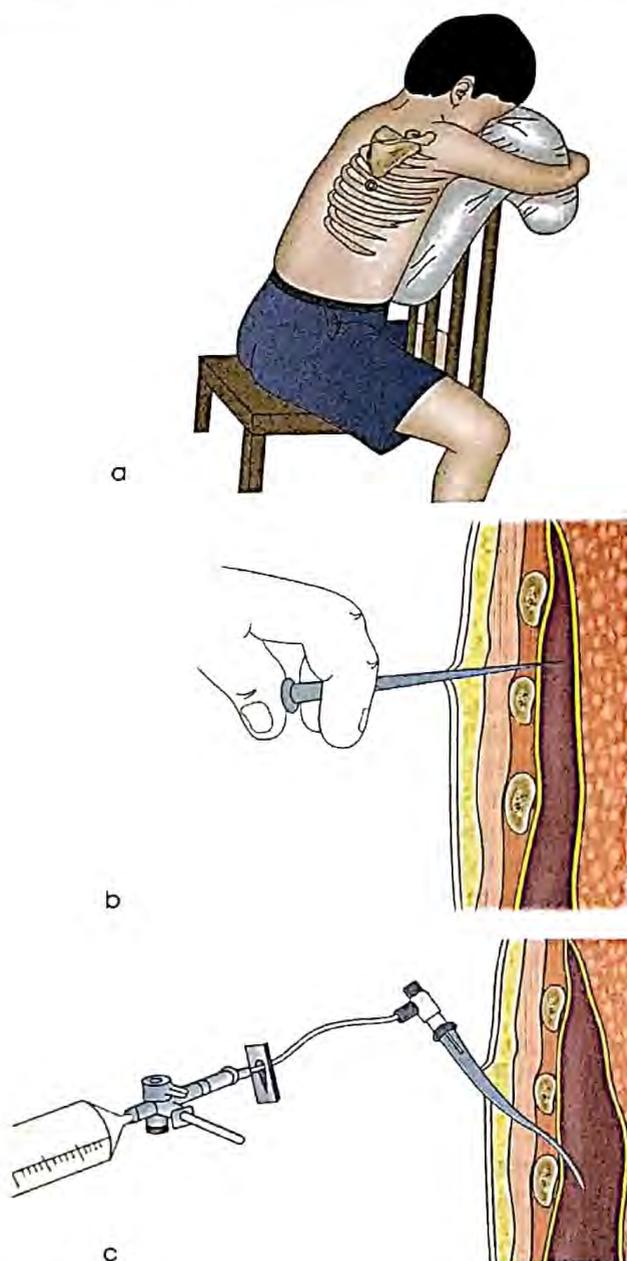


Fig. 29.7: Thoracocentesis: (a) The landmark for thoracocentesis is the angle of the scapula that corresponds approximately to the eighth rib interspace; (b) The needle is introduced immediately above the superior edge of the rib to avoid puncturing the intercostal vessels; and (c) After inserting the catheter in the pleural space, the catheter is connected to a three-way stopcock and a syringe

therapeutic reason, i.e. to remove large volumes of abdominal fluid which impair respiratory function.

Technique: The patient is placed in a supine position and the bladder is emptied. The common sites for paracentesis are shown in Fig. 29.8. These sites are chosen to avoid puncture of underlying vessels or viscera. Usually, the left lower quadrant is preferred, since critically ill children may have cecal distension.

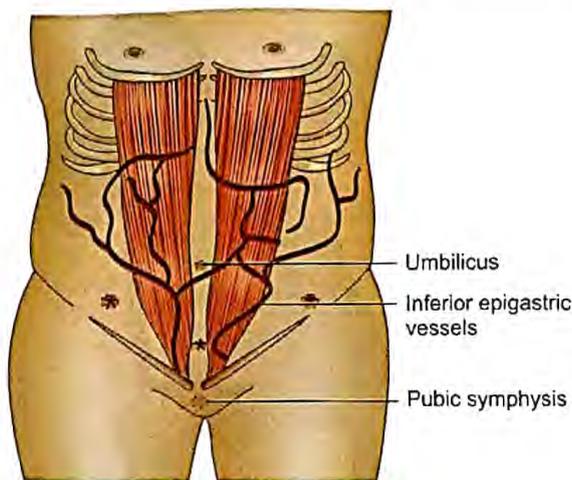


Fig. 29.8: Sites for abdominal paracentesis. The preferred sites are the linea alba (midway between the umbilicus and the pubic symphysis) and lateral to the rectus abdominis muscle

After the site is chosen, xylocaine is injected with a small needle to produce a skin wheal. The skin is then tilted anteriorly so that further infiltration into the subcutaneous tissue is in a different plane (Z tracking). A needle or over-the-needle catheter is then advanced using the Z tracking technique and at an angle perpendicular to the skin. Continued aspiration of the needle is used until peritoneal fluid is aspirated. Approximately 10–15 mL of fluid is aspirated for studies. Appropriate studies may include cultures and Gram stain, cell count, cytology, amylase, LDH, bilirubin, albumin and protein. If the paracentesis is performed for therapeutic purposes, a catheter should be placed.

Complications: Complications include hemorrhage, fluid leak, intestinal or bladder perforation, and hypotension, if large volumes are removed.

Catheterization of Bladder

Indications: Bladder catheterization is done in bedridden patients who need short-term assistance. It is also required in patients with (i) polytrauma, especially for evaluation of the urinary tract in an unconscious child; (ii) shock; (iii) acute urinary retention; (iv) to obtain a urine specimen for urinalysis; (v) in acute kidney injury, to monitor urine output; and (vi) for urodynamic studies.

Procedure: The patient is restrained as necessary. The urethral meatus, penis and the perineal area are cleaned thoroughly with a povidone-iodine solution. A Foley catheter of the appropriate size is selected (8 Fr in the newborn, 10 Fr in most children and 12 Fr in older children). The catheter tip should be lubricated with sterile lubricant to minimize local trauma.

Boys. The penile shaft is gently grasped and extended. The catheter is held near the distal tip and advanced up the urethra unless resistance or an obstruction is encountered. If resistance is encountered, a smaller catheter is selected.

The catheter should be passed into the bladder; this is important because urine may begin to flow while the catheter is in the proximal urethra and inflation of the balloon in the urethra may lead to urethral perforation. The balloon is inflated after advancing the catheter its entire length. The catheter is taped to the child's leg.

Girls. In girls, the principles of catheterization are similar to those in the male. An assistant carefully spreads the labia. A well-lubricated Foley catheter is introduced into the bladder. The catheter is advanced its entire length before inflating the balloon. A catheter that is passed in its entirety is unlikely to be inadvertently located in the small vagina of a young girl.

Complications: Injury to urethra or urinary bladder and inadvertent catheterization of the vagina may occur. Absence of aseptic precautions might result in urinary tract infection.

Peritoneal Dialysis

This modality of dialytic support is used for renal replacement therapy both in acute kidney injury (AKI) and end-stage renal disease. Catheters placed surgically for chronic ambulatory peritoneal dialysis are not discussed here.

Indications: The modality is used in patients with AKI in whom dialysis is indicated (Chapter 17) and hemodialysis and continuous renal replacement therapies are not available, or if hemodialysis is contraindicated. The technique is widely available, inexpensive and technically easy to perform even in newborns.

Contraindications: Relative contraindications to peritoneal dialysis include recent abdominal and/or cardiothoracic surgery, diaphragmatic peritoneal-pleural fistula, fecal or fungal peritonitis and abdominal wall cellulitis.

Procedure: Access for peritoneal dialysis can be achieved by inserting a rigid catheter (Fig. 29.9a) or a single cuff soft Tenckhoff catheter at the bedside (Fig. 29.9b). The double cuff Tenckhoff catheter, used for chronic peritoneal dialysis is placed in the operating room by a surgeon. A rigid acute PD catheter is easily available, inexpensive and relatively simple to insert. However, the risks of peritonitis are high, particularly if used for more than 48 hours.

The abdomen is cleansed with chlorhexidine and betadine and draped. Following administration of sedation and local anesthesia, an 18–22 gauge cannula is inserted below the umbilicus in the midline or lateral to the rectus abdominis muscle at two-thirds the distance between the umbilicus and the anterior superior iliac spine (Fig. 29.9c). About 20–30 mL/kg of peritoneal dialysis fluid is infused till the flanks appear full.

The cannula is removed and the stiff catheter is inserted using the trocar. Once a 'give away' sensation is felt, dialysis fluid flows freely back into the catheter lumen. The catheter is inserted carefully avoiding injury to viscus by the trocar



Fig. 29.9: Peritoneal dialysis: (a) Stiff uncuffed catheter used for acute peritoneal dialysis; (b) Soft single cuff Tenckhoff catheter inserted bedside for acute dialysis; (c) Usual site of catheter insertion is in midline below the umbilicus or two-thirds of the distance between umbilicus and anterior superior iliac spine; (d) Device for automated control of dialysis and aseptic handling; and (e) Infant undergoing dialysis with soft Tenckhoff catheter

and guiding the tip of the catheter into the left iliac fossa. The trocar is removed and the catheter attached to a three-way connection to the peritoneal dialysis fluid and the drain bag. Once easy inflow and outflow are confirmed, the catheter is secured with a purse-string suture and manual cycles of dialysis are initiated.

The soft single cuff catheter is inserted using an introducer kit using the modified Seldinger technique. A tunnel is created in the soft tissue so that the exit site is away from the entry point into the peritoneum and the cuff protects from bacterial migration. This catheter is associated with lower risk of peritonitis, particularly if used with an automated cyclor device (Fig. 29.9d). It can be capped when not in use, allows ease of nursing, and can be used for several weeks (Fig. 29.9e).

Prescription: Acute PD can be performed intermittently or continuously depending upon the desired amount of fluid and solute removal, and either manually by nurses or via an automated device. About 20–30 mL/kg is infused over 5 min, kept in the abdomen for 20–40 min, and then drained out. Ultrafiltration should not exceed 5–10% of body weight over 24–48 hours. The prescription is modified every 6–12 hours based on clinical evaluation and laboratory

parameters. Acute manual PD requires constant supervision to ensure accurate inflow, dwell and drain times and the maintenance of a record of exchange and drain volumes and net ultrafiltration. By comparison, the use of the automated cyclor reduces need for constant supervision and record maintenance and decreases the number of manual interruptions and risk of peritonitis.

Complications: Abdominal pain or discomfort may occur due to abdominal distension, improper position of the catheter or peritonitis. Mild hemorrhage is frequent during catheter placement, particularly with rigid acute catheters. Leakage around the PD catheter site is managed by reducing the exchange volume or placing a suture at the exit site. Inadequate drainage is due to improper placement of the catheter tip or decreased bowel motility. Bowel perforations is rare but may be observed with placement of stiff catheters. Metabolic complications include hyperglycemia, hypokalemia, protein losses and hyponatremia.

Bone Marrow Aspiration and Biopsy

A special bone marrow needle is introduced into the bone marrow space, and a sample aspirated for analysis. A marrow biopsy is taken to ascertain the cellularity and architecture of the marrow.

Indications: Bone marrow aspiration and biopsy are indicated in presence of pancytopenia, bicytopenia, unexplained thrombocytopenia or leukocytosis in order to rule out significant pathology such as lymphoreticular malignancy (acute lymphoblastic or myelogenous leukemia, Hodgkin or non-Hodgkin lymphoma, chronic myeloid leukemia, myelodysplasia, myelofibrosis); hypoplastic or aplastic anemia; megaloblastic anemia; sideroblastic anemia; Langerhans cell histiocytosis; hemophagocytosis syndrome; suspected metastasis (retinoblastoma, neuroblastoma); infiltrative storage diseases (Gaucher disease) or infections involving the bone marrow (kala-azar, tuberculosis).

Sites: The iliac crest is the most commonly used site. The sternum is not preferred in children because of associated pain and the risk of injuring underlying vital structures. Marrow may be aspirated from the proximal tibia medial to the tibial tuberosity in infants (<1-year-old). This site is preferred in infants since biopsy from the iliac site in young children is difficult as the iliac crest is small and carries risk of injuring pelvic viscera.

Equipment: Various types of bone marrow biopsy needles are available (Figs 29.10a and b). The Jamshidi needle and its modifications are used widely because of their light weight, sharp bevelled end that allows easy coring of bone, a tapering end that facilitates recovery of marrow specimen and suitability for both aspiration and biopsy.

Procedure: The child should be fasting for 3–4 hours before the procedure. The child is positioned prone with face turned to a side and the pelvis stabilized by folding a sheet below it. If tibia is to be aspirated, the leg is slightly flexed at the knee joint. Sedation with intravenous midazolam and ketamine is administered during continuous monitoring of vital signs and oxygen saturation.

The site is cleaned with chlorhexidine and betadine to include the lumbar spine, iliac crests and posterior iliac

spines (or for the tibial site, the entire leg up to the distal half of thigh) and draped. The posterior superior iliac spine is located by tracing the iliac crest backwards to its most prominent and elevated point. About 2 mL of 1% lidocaine is injected subcutaneously into the periosteum. The bone marrow needle is held firmly in the dominant hand with the index finger placed over the needle to act as a guard. The needle is advanced perpendicularly into the identified area with twisting motion till bone is felt. On advancing further, a 'give way' is felt that indicates that the needle is in the bone marrow. The stylet is removed and a 20 mL syringe attached. The piston is pulled to create negative pressure and aspirate slowly around 0.5 mL of marrow. The syringe is disconnected and the marrow placed on slides. To make a touch preparation, the marrow is spread on the slide by placing another glass slide so as to smear the marrow gently. Additional slides are prepared similar to a peripheral smear, using another glass slide at 30° angle to spread the marrow in a tongue-shaped projection on the slide.

To perform marrow biopsy, the stylet is replaced and the needle withdrawn slightly. The needle is advanced through another site in the bone. Once the needle is lodged in the bone, the stylet is removed and the needle advanced in rotatory motion through the marrow space. The needle is withdrawn and biopsy specimen placed in a vial containing formalin. Once the needle is removed, local pressure is applied to allow bleeding to stop. Drapes are removed, the skin is cleaned and pressure bandage applied.

Aspiration from the tibia is performed in a similar manner. The preferred site is medial to the tibial tubercle, one inch below the joint line to avoid the growth plate. The bone cortex is thinner and the marrow space is reached more quickly than with the pelvic site. Obtaining a biopsy is often difficult as the marrow is more spongy.

Complications: Bleeding and pain at the aspiration site are common. Bone injury with fractures of iliac bone and subcutaneous infections or osteomyelitis are rare.

Liver Biopsy

Indications: Liver biopsy is used to evaluate hepatic histology in order to: (i) diagnose parenchymal liver disease (e.g. neonatal hepatitis, suspected metabolic liver disease); (ii) understand the cause of persistently abnormal liver tests; (iii) determine the etiology of focal or diffuse abnormalities on imaging studies; (iv) assess the prognosis of known liver disease (e.g. extrahepatic biliary atresia, autoimmune hepatitis, chronic viral hepatitis); (v) determine response to therapeutic interventions; (vi) develop a treatment plan based on histology; and (vii) monitor effects of hepatotoxic drugs. Analysis of the biopsy specimen may include evaluation of histology, metal content, enzymatic assays and cultures for viral, bacterial, or fungal pathogen.

Contraindications: Absolute contraindications include coagulopathy, as suggested by low platelet count (<60,000/ μ L)

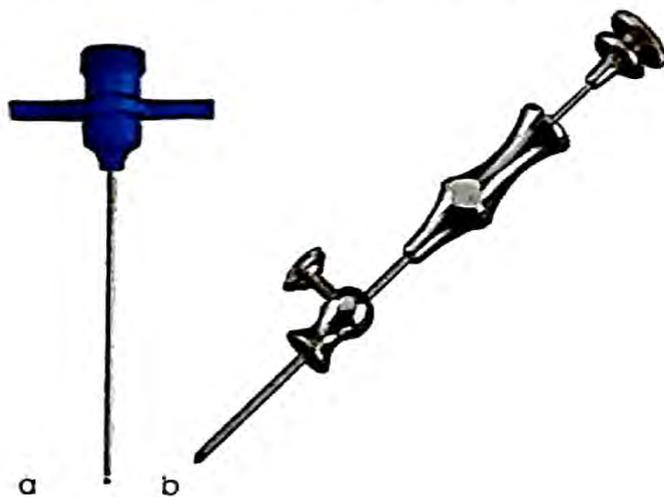


Fig. 29.10: Needles for bone marrow aspiration and biopsy. (a) Jamshidi needles; (b) Vim Silverman needle

or prolonged prothrombin time (international normalized ratio >1.5), and an inability to remain still (with or without sedation). Relative contraindications include anemia, peritonitis, marked ascites, high-grade biliary obstruction, and a subphrenic or right pleural infection or effusion.

Procedure: The biopsy may be performed percutaneously at bedside with or without ultrasound guidance. An ultrasound-guided biopsy carries lower risk of complications and allows visualization of the liver and any target lesions. Uncommonly, the biopsy is performed using the transjugular route, laparoscopically or by wedge resection during laparotomy. Transjugular venous biopsy is preferred in patients with severe coagulopathy.

The child should be fasting for 4–6 hours. An intravenous line is secured and the child made to lie supine. The abdominal girth is measured at the umbilicus to allow subsequent comparisons. The lower border of liver is localized by palpation or percussion, and its position on the midclavicular line marked.

During continuous monitoring of vital signs, sedation is administered. The site of biopsy is chosen based on the liver span. If the liver is palpable, a subcostal approach may be used. However, a right lateral transthoracic approach is most common, in which the needle is inserted in the tenth intercostal space in the midaxillary line, after confirming liver dullness. Local anesthesia is administered. The biopsy is usually performed using a spring-loaded semiautomatic biopsy gun (Fig. 29.11) of size 18 (infants) or 16 (children) gauge. The gun is loaded and its needle inserted through

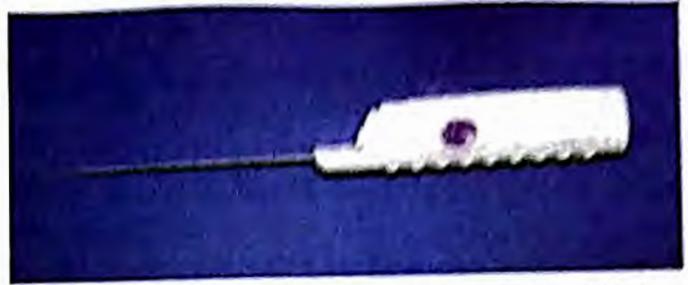


Fig. 29.11: Semiautomatic biopsy gun for liver biopsy

the marked intercostal site just above the border of the lower rib, so as to avoid injuring the neurovascular bundle running along the lower border of ribs. The needle is inserted carefully along a horizontal plane to a depth at which a 'give way' sensation is felt upon rupture of the liver capsule. The tip of the needle should rest just beyond the capsule and should move well with respiration. The gun is fired and the needle withdrawn quickly. The sample is transferred to vials, e.g. formalin for histopathology.

The biopsy site is sealed with tincture iodine and pressure dressing applied to prevent bleeding. The child is monitored over the next 6–8 hours for tachycardia, tachypnea, hypotension and increase in abdominal girth and excessive pain, which may suggest internal bleeding.

Complications: Complications include intra-abdominal hemorrhage, biliary peritonitis, hepatic laceration, hemothorax, hemobilia, pneumothorax, gallbladder or intestinal perforation and iatrogenic arteriovenous fistula.

Rational Drug Therapy

Anu Thukral • Kana Ram Jat

INTRODUCTION

Medications play an important role in protecting, maintaining and restoring health. Irrational and indiscriminate use may lead to toxicity and adverse reactions. It is better to use medications with which the physician is familiar. The expected benefits and side effects should always be kept in mind when prescribing. The principles of rational drug therapy can be summarized as:

- i. There should be a genuine indication for use of the medication.
- ii. Minimum number of appropriate, familiar and inexpensive agents of good quality should be used.
- iii. Drugs should be prescribed by their generic name.
- iv. Dosage should be optimum to achieve the desired benefits.
- v. It is desirable to administer medication, as far as possible, through oral route.
- vi. Adverse drug reactions should be anticipated, monitored and appropriately managed.

True synergism is rare; an exception is cotrimoxazole (trimethoprim and sulfamethoxazole). A combination of antibiotics may be necessary when the causative agent is not known. Multidrug therapy is indicated to prevent resistance to individual drugs, during long-term management of tuberculosis and leprosy and to reduce toxicity of individual drugs. Bactericidal drugs act best when the organism is actively multiplying and should ideally not be combined with bacteriostatic drugs.

Developmental and genetic factors affect the metabolism of drugs and thereby the response. Doses of drugs need to be modulated according to the individual responses. The dosages may vary in specific disease, e.g. pneumonia, meningitis, bacterial endocarditis and pyogenic arthritis.

The drugs, required dose and important side effects have been tabulated alphabetically below for the easy reading and referral. Details on the following categories of drugs are provided elsewhere: Antiepileptic drugs (Chapter 19), antihypertensive agents (Chapter 16), antitubercular, antiretroviral and antileprosy drugs (Chapter 11).

The reader is advised to consult detailed prescribing information for each medication.

Abbreviations: g gram; GI gastrointestinal; hr hour; IM intramuscular; IV intravenous; IO intraosseous; kg kilogram; m² square meter body surface; mg milligram; µg microgram, PO per oral; PR per rectal; q every; SC subcutaneous; T topical; wt weight; yr age in years; C/I contraindication; GERD gastroesophageal reflux disease.

ANALGESICS, ANTIPYRETICS, NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

Non-Narcotic Analgesics

Aspirin

Acute rheumatic fever: 90–120 mg/kg/day PO q 4 hr

Antipyretic dose: 30–60 mg/kg/day PO q 4–6 hr

Kawasaki disease: 80–100 mg/kg/day PO q 6 hr till afebrile or for 2 weeks followed by 3–5 mg/kg/day PO q 24 hr for 6–8 weeks until platelet count and ESR are normal.

Side effects: Hypersensitivity, hypoprothrombinemia. There is epidemiologic association between salicylate use and Reye encephalopathy. Therefore, use of aspirin for upper respiratory tract infections and fevers of undetermined origin in children is not advisable. Salicylates should be avoided empty stomach.

Paracetamol

Antipyretic/analgesic: 40–60 mg/kg/day PO q 4–6 hr or 15 mg/kg/dose PO q 4–6 hr; 5 mg/kg IM

Side effects: Skin rashes, hepatotoxicity, renal damage

Ibuprofen

Antipyretic/analgesic: 20–30 mg/kg/day PO q 6–8 hr or 10 mg/kg/dose PO q 4–6 hr; maximum dose 40–60 mg/kg/day

Juvenile idiopathic arthritis: 30–70 mg/kg/day PO q 4–6 hr

Closure of ductus arteriosus in neonates: 10 mg/kg/day PO followed by 5 mg/kg/day q 24 hr for 2 days
Side effects: Nausea, vomiting, rashes

Naproxen

Juvenile idiopathic arthritis: 10–20 mg/kg/day PO q 12 hr
Analgesia 5–7 mg/kg/dose PO q 8–12 hr (after meals)
Side effects: Nausea, vomiting, rashes

Diclofenac Sodium

1–3 mg/kg/day PO q 8 hr
Side effects: Gastric bleeding, ulcer

Mefenamic Acid

25 mg/kg/day PO q 6–8 hr
Antipyretic dose: 5–8 mg/kg/dose
Side effects: Gastric bleeding, rash, seizures

Indomethacin

1–3 mg/kg/day PO q 12–24 hr
Dose for ductal closure depends on the age of the neonate (Table 30.1)
Side effects: Oliguria, hypoglycemia, platelet dysfunction

Table 30.1: Indomethacin dose (mg/kg) in neonates

Age at first dose	1st	2nd	3rd
<48 hours	0.2	0.1	0.1
2–7 days	0.2	0.2	0.2
>7 days	0.2	0.25	0.25

Tamadol

1–2 mg/kg q 4–6 hr up to maximum of 400 mg/day; avoid below 14 yr of age
Side effect: Seizures, renal and hepatic dysfunction

Narcotic Analgesics (Opioids)

Fentanyl

0.5–5 µg/kg/dose q 1–4 hr IV; may be administered as a continuous infusion 1–5 µg/kg/hr
Potent narcotic analgesic; 0.1 mg dose possesses analgesic activity; equivalent to 10 mg of morphine.
Side effects: Rapid infusion may cause chest wall rigidity; respiratory distress and respiratory arrest.

Morphine

0.1–0.2 mg/kg/dose q 4 hr (maximum 15 mg) IV/IM/SC
Continuous infusion in neonates 0.01–0.02 mg/kg/hr, infants and children 0.01–0.04 mg/kg/hr
Naloxone (0.01 mg/kg IV) is an antidote in case of respiratory depression.

Side effects: Respiratory distress, increased intracranial pressure, seizures
Contraindication: Respiratory failure, obstructive airway disease

ANTIARRHYTHMICS

Adenosine

0.1 mg/kg/dose (initial maximum dose 6 mg) rapid IV (over 1–3 sec); if no response in 1–2 min 0.2 mg/kg bolus
To ensure that the drug reaches the circulation, administer directly into a vein with a three-way stop cock with 5–10 mL of saline flush ready to push immediately; maximum single dose 0.25 mg/kg or 12 mg
Side effects: Transient chest pain, dyspnea, flushing, bronchospasm. Carbamazepine and dipyridole increase the toxicity/effect of adenosine.

Atropine Sulfate

0.01 mg/kg/dose SC or IV
The dose can be repeated after 2 hr (max 4–6 times a day).
Organophosphorus poisoning: 0.02–0.05 mg/kg every 10–20 min until atropine effect, then q 1–4 hr for at least 24 hours
Side effects: Dry mouth, blurred vision, tachycardia, urinary retention, constipation, dizziness, hallucinations, restlessness

Lidocaine Hydrochloride

1 mg/kg/dose (maximum dose: 100 mg) slowly IV; repeat in 10–15 min for two times; maximum total dose 3–5 mg/kg within the first hr; endotracheal dose is two to three times the IV dose.
Continuous infusion 20–50 µg/kg/min IV/IO (do not exceed 20 µg/kg/min for patients with shock or CHF); administer 1 mg/kg bolus when infusion is initiated (bolus not given within previous 15 min)
Side effects: Hypotension, seizures, asystole, respiratory arrest

Phenytoin Sodium

Arrhythmia: Loading 1.25 mg/kg IV over 3 min and repeat every 5–10 min to a maximum total dose of 15 mg/kg or until arrhythmia reverts or hypotension develops; maintenance 5–10 mg/kg/day PO q 12 hr
Status epilepticus: Loading 15–20 mg/kg IV, do not exceed 1–3 mg/kg/min, maintain with 5–8 mg/kg/day PO or IV q 12–24 hr
Side effects: Gum hypertrophy, hirsutism, hypersensitivity, megaloblastic anemia, osteomalacia, vestibulocerebellar syndrome

Procalnamide

Arrhythmia: 3–6 mg/kg/dose over 5 mins, repeat q 5 min up to total of 15 mg/kg; IV infusion: 0.5 mg/kg/hr; oral 50 mg/kg/day PO q 3–4 hr

Side effects: Thrombocytopenia, Coombs positive hemolytic anemia, lupus-like syndrome

Contraindication: Heart block, myasthenia gravis

Propranolol

Arrhythmia: 0.01–0.25 mg/kg/dose; given as IV bolus over 10 min (max 1 mg in infants; 3 mg in children), may repeat in 15 min and then q 4–8 hr

Antihypertensive: 0.5–1 mg/kg/day PO q 6–8 hr

Thyrototoxicosis: 2–4 mg/kg/day PO q 6–8 hr

Tetralogy spells: 0.15–0.25 mg/kg/dose slow IV push, repeat q 15 min; 2–4 mg/kg/24 hr PO q 6–8 hr, increase to 4–8 mg/kg/day

Infantile hemangioma: 1 mg/kg/day PO q 8 hr. Increase to 2 mg/kg/day PO q 8 hr after 1 week, if well tolerated

Side effects: Increase in pulmonary resistance, fatigue and bradycardia

Quinidine Sulfate

Arrhythmia: Test dose 2 mg/kg PO followed by 30 mg/kg/day PO q 6 hr

Malaria: Loading dose 10 mg/kg/day IV over 1–2 hr (maximum dose 600 mg) followed by 0.02 mg/kg/min (10 mg/kg/dose q 8 hr), 10 mg/kg/dose PO q 8 hr

Side effects: Thrombocytopenia, anemia, tinnitus, hypotension, blood dyscrasias

Contraindication: Heart blocks, congestive heart failure

Verapamil

Arrhythmia: 0.1–0.3 mg/kg IV over 2 min

Hypertension: 4–8 mg/kg/day PO q 8 hr

Contraindication: Cardiogenic shock, AV block, children below 2 years of age

AGENTS FOR MYASTHENIA

Edrophonium Chloride

Initial dose: 0.04 mg/kg dose IV, IM (maximum 1 mg <30 kg); if no response after 1 min, may give 0.16 mg/kg/dose total of 0.2 mg/kg (maximum 5 mg for <30 kg)

Side effects: Arrhythmias, bronchospasm

Neostigmine Bromide

Myasthenia gravis: Neonate 0.05–0.1 mg IM/SC, then PO 1 mg 30 min before feed

Children 1–3 mg/kg/day PO q 4–6 hr; 0.01–0.04 mg/kg IV/IM/SC q 2–3 hr

Begin with lower dose and increase gradually till symptoms disappear.

Side effects: Cholinergic crisis, bronchospasm, respiratory depression, hypotension, seizures, salivation, vomiting, diarrhea and lacrimation

Contraindication: Urinary and intestinal obstruction

Pyridostigmine

Infants of myasthenic mothers 0.05–0.15 mg/kg/dose; max dose 5 mg PO q 4–6 hr (benzyl alcohol-free formulation should be used for neonates)

Children PO: 7 mg/kg/day in 5–6 divided doses; IM, IV: 0.05–0.15 mg/kg/dose (maximum dose 10 mg)

Side effects: Same as neostigmine

Physostigmine

Myasthenia: 0.001–0.03 mg/kg/dose IM, SC, IV

Repeat q 15–20 min to desired effect or maximum dose of 20 mg

Side effects: Same as neostigmine

ANTIMICROBIALS

Antibiotics

Penicillins (Table 30.2)

Penicillin may cause hypersensitivity reactions in about 1% of individuals. Acute symptoms include urticaria, angioneurotic edema, anaphylactic shock, asthma, laryngeal edema and hypotension. Delayed reactions are fixed drug eruption, serum sickness, hemolytic anemia and recurrent arthralgia. Sodium and potassium content of penicillin G is 1.68 mEq per million units; large doses may cause seizures. Side effects specific to piperacillin additionally include impaired platelet aggregation and deranged liver function. The dosing for piperacillin needs to be adjusted in renal impairment.

Cephalosporins (Table 30.3)

Approximately 10% patients with penicillin hypersensitivity show allergy to cephalosporin; fatal anaphylaxis may occur. Oral cephalosporins cause gastrointestinal symptoms such as loss of appetite, nausea, vomiting and diarrhea. Some parenteral cephalosporins cause serious renal toxicity.

Aminoglycosides (Table 30.4)

Side effects: Aminoglycosides cause variable degrees of auditory and vestibular toxicity, and reversible kidney dysfunction. Rashes and drug fevers occur in about 5% patients. Dosage should be reduced and interval between dosages increased in patients with impaired renal function. Administration of aminoglycoside dose once in 24 hours and as infusion reduces the risk of renal and auditory toxicity.

Chloramphenicol (Table 30.5)

Side effects: Idiosyncratic bone marrow depression. Hypersensitivity: fever, rash, angioneurotic edema; GI disturbances. Neonates, especially premature, may show grey baby syndrome with abdominal distension, vomiting, refusal to suck and dyspnea; cyanosis, peripheral circulatory collapse and death.

Table 30.2: Penicillins

Drug	Dose (mg/kg/day)	Route	Schedule
Penicillin G aqueous	Neonate: 50000–200000 U/kg/day (higher dose for meningitis)	IV	6–8 hr
	100,000–400,000 U/kg	IV/ IM	4–6 hr
	Meningitis and endocarditis: 200,000–400,000 U/kg		
Benzathine penicillin	Less than 6 years: 0.6 million units 6 years and above: 1.2 million units	IM	3 weekly
Procaine penicillin G	Neonates: 50,000 U 25,000–50,000 U	IM	1–2 doses maximum
Phenoxymethyl penicillin V	Infants: 62.5–125 mg/ dose	PO	12 hr
	Children less than 6 years: 125 mg/dose		
	6–12 years: 250 mg/dose		
	Rheumatic fever prophylaxis: 250 mg		
Methicillin sodium	100	IM or IV	6 hr
Oxacillin	50	PO or IV	6 hr
Cloxacillin	Child (<40 kg)	PO or IV	4–6 hr
	Mild/moderate infections: 12.5–50		
	Severe infections: 50–100	PO	6 hr;
	Child (≥40 kg) and adult: 125–500 mg/dose Maximum dose: 2 g/24 hr		
Ampicillin	100–200	PO or IV	6 hr
	Meningitis and enteric fever: 200–400	IV	4–6 hr
Amoxicillin	25–50	PO	8–12 hr
Co-amoxiclav (amoxicillin + clavulanic acid)	25–40	PO	8–12 hr
	75 of Amoxicillin	IV	8 hr
Ampicillin and sulbactam (100 mg ampicillin and 50 mg sulbactam)	150	IM, IV	8 hr
Carbenicillin	400–600	IV	6 hr
Ticarcillin	200–400	IV	6–8 hr
Ticarcillin (3 g) and clavulanate (100 mg)	240–320 of ticarcillin	IV	6–8 hr
Piperacillin	200–300	IV	4–6 hr
Piperacillin and tazobactam	300–400 of piperacillin	IV	6 hr

Macrolides (Table 30.6)

Side effects: Diarrhea, nausea and abnormal taste; raised transaminases and cholestatic jaundice. Drug interactions are less with azithromycin. Use with terfenadine, astemizole or cisapride may result in arrhythmias. Clarithromycin causes less abdominal discomfort.

Quinolones (Table 30.7)

Side effects: GI upset, renal failure, insomnia, dizziness and seizures; no concerns of arthropathy. Inhibition of liver enzymes can result in elevated levels of theophylline.

Other side effects include: Rash, photosensitivity, raised transaminases, neutropenia

Sulfonamides (Table 30.8)

Side effects: Blood dyscrasias, exfoliative dermatitis, serum sickness and drug fever

ANTIFUNGAL AGENTS*Amphotericin B*

Test dose 0.1 mg/kg IV; then start 0.25 mg/kg/day; increase by 0.25 mg/kg daily, until dose of 1 mg/kg/day; Dilute in 5% dextrose, saline; Protect from light

Total dose should not exceed 30–35 mg/kg over 4–6 weeks

Side effects: Febrile reactions, nephrotoxicity, hypokalemia, blood dyscrasias

Table 30.3: Cephalosporins

Drug	Dose (mg/kg/day)	Route	Schedule
First generation cephalosporins			
Cephalexin	25–50 (recommended for community acquired pneumonia)	PO	6–8 hr
Cefazolin (maximum 600 mg/24 hr)	50–100	IM or IV	6–8 hr
Cefadroxil (maximum 2 g/24 hr)	30	PO	12 hr
Second generation cephalosporins			
Cefaclor (maximum 2 g/24 hr)	20–40	PO q	6–8 hr
Cefuroxime	50–100	IM or IV	6–8 hr
	20–40 (enteric fever)	PO	12hr
Third generation cephalosporins (high CSF concentrations; widely used in meningitis)			
Cefdinir (maximum 600 mg/24 hr)	14	PO	12 hr
Cefditoren	3–10	PO	12 hr
Cefotaxime	100–150	IM, IV	8–12 hr
	200 mg/kg/day IV q 6 hr in meningitis	IV	6 hr
Cefoperazone	100–150	IV	8–12 hr
Cefoperazone, sulbactam	40–80	IV	12 hr
Cefprozil	15–30	PO	12 hr
Ceftriaxone	125 mg single dose (prophylaxis for <i>Neisseria meningitidis</i>)		
	25–50 (ophthalmia neonatorum)	IV	12 hr
	50–75	IV	12–24 hr
	100 (meningitis)	IV	12 hr
Ceftazidime	100–150	IV	8–12 hr
Ceftizoxime	100–200	IV/ IM	6–8 hr
Cefixime	8–10; enteric fever: 20	PO	12 hr
Fourth generation cephalosporins			
Cefpirome	30–60	IM or IV	12 hr
Cefpodoxime	8–10	PO	12 hr
Cefepime	≥2 months: 100–150 mg/kg/day <2 months: 60	IV	12 hr; 8 hr in meningitis, febrile neutropenia, serious infections

Table 30.4: Aminoglycosides

Drug	Dose (mg/kg/day)	Route	Schedule
Streptomycin (max 1 g)	15–20	IM	24 hr
Gentamicin	5–7.5	IM, IV	8–24 hr
Amikacin	15–20	IM, IV	24 hr
Tobramycin	5–7.5	IM, IV	8–12 hr
Netilmicin	5–7.5	IM, IV	12–24 hr
Kanamycin	15–20 (infusion)	IM, IV	8–12 hr

Table 30.5: Chloramphenicol

Dose (mg/kg/day)	Common route	Schedule
50–75	PO	6 hr
100	IM or IV	6 hr
Ointment available as 0.5 and 1%		

Table 30.6: Macrolides

Drug	Dose (mg/kg/day)	Route	Schedule
Erythromycin	30–50	PO	6–8 hr
Azithromycin	Otitis media: 10 on day 1; then 5 on day 2–5 Enteric fever: 20 (7–10 days) Pertussis <6 months: 10 (5 days) >6 months: 10 on day 1 then 5 on day 2–5	PO	24 hr
Clarithromycin	15 Maximum dose: 1 g/24 hr	PO	12 hr

Table 30.7: Quinolones

Drug	Dose (mg/kg/day)	Route	Schedule
Nalidixic acid	50–60	PO	8 hr
	UTI prophylaxis: 30	PO	12 hr
Ciprofloxacin	20–30; max 1.5 g/day	PO	12 hr
	10–20; max 800 mg/day	IV	12 hr
Gatifloxacin	10	PO	24 hr
Norfloxacin	10–15	PO	12 hr
Levofloxacin	10–15		
	6 mo–<5 yr: 20	PO/ IV	12hr
	5–12 yr: 10; max 500 mg/24 hr	PO/ IV	24 hr
Ofloxacin	15	PO	12 hr
	5–10	IV	12 hr
Sparfloxacin	4	PO	24 hr

Table 30.8: Sulfonamides

	Dose (mg/kg/day)	Route	Schedule
Sulfonamide	100–150	PO, IV	8 hr
Cotrimoxazole	Trimethoprim 5–8; sulfamethoxazole 25–40	PO, IV	8–12 hr
	Enteric fever: Trimethoprim 10		
	<i>Pneumocystis pneumonia</i> : Trimethoprim 20		
	Prophylaxis <i>Pneumocystis</i> : Trimethoprim 5 mg/kg alternate day Urinary infections: 1–2		

Table 30.9: Miscellaneous antibiotics

	Dose (mg/kg/day)	Route	Schedule	Major side effects	
Aztreonam	90–120	IV, IM	6–8 hr	Low cross antigenicity with beta lactams, thrombophlebitis, leukopenia, eosinophilia, neutropenia, hypotension, seizures <i>Adjust dose in renal impairment</i>	
	Cystic fibrosis: 150–200				
Clindamycin	10–30; max 1.8 g/day	PO	6 hr	Pseudomembranous colitis, rash, Stevens-Johnson syndrome, neutropenia, thrombocytopenia	
	25–40	IV	6 hr		
		IV	12 hr		
Colistin sodium	50,000 to 75,000 IU	IV	6 to 8 hr	Dizziness, paresthesia, nephrotoxicity and neurotoxicity	
	2.5–5 mg/kg/day 1 mg colistin base = 30,000 IU 1 mg colistimethate sodium = 12500 IU				
Imipenem	0–4 wk old and <1.2 kg: 50		IV	12 hr	Pruritus, urticaria, seizures, dizziness, hypotension, elevated liver enzymes
	<1 wk old and ≥1.2 kg: 50		IV	12 hr	
	≥1 wk old and ≥1.2 kg: 75		IV	8 hr	
	Child (4 wk–3 mo): 100 mg/kg/ day IV q 6 hr		IV	6 hr	
	Child (>3 mo): 60–100; Maximum 4 g/24 hr;		IV	6 hr	
	Cystic fibrosis: 90; Maximum 4 g/24 hr		IV	6 hr	

(Contd...)

Table 30.9: Miscellaneous antibiotics (contd.)

	Dose (mg/kg/day)	Route	Schedule	Major side effects
Meropenem	Neonatal sepsis Meningitis: 40 mg/kg/ dose	IV	8 hr	Nausea, vomiting, rarely seizures
Faropenem	200 increased to 300	PO	8–12 hr	Diarrhea, abdominal pain, loose bowel movement, nausea, and rash; safety in infants not established
Ertapenem	15–30	IV/IM	12 hr	Not approved for children less than 3 months, diarrhea, nausea, headache
Vancomycin	30–45 in neonate (dosage and frequency varies with gestation age); 40–60	IV	6–8 hr	Ototoxicity and nephrotoxicity (exacerbated with concomitant aminoglycosides); adjust dose in renal failure
Linezolid	10 mg/kg/dose	IV PO	12 hr 8–12 hr	Dysgeusia, constipation, diarrhea, dizziness, headache, anemia, leukopenia, thrombocytopenia
Teicoplanin	10 mg/kg 12 hr for 3 doses; then 6–10	IV, IM	24 hr	Long half life. Less nephrotoxic; less catheter-related phlebitis
Tigecycline	1.2 mg/kg/dose (Max dose 50 mg)	IV	12 hr	Hypersensitivity reactions, deranged liver function Use with caution in below 8 yrs
Nitrofurantoin	5–7 Prophylaxis: 1–2	PO	6 hr	Dizziness, hypersensitivity, icterus, interstitial pneumonitis, nausea, vomiting

Liposomal Amphotericin B

Systemic fungal infections: 3–5 mg/kg/dose; 24 hr;
Cryptococcal meningitis in HIV: 6 mg/kg/day IV q 24 hr
Side effects: Fever, flushing, chills, loss of appetite, nausea, headache, shortness of breath

Flucytosine

50–150 mg/kg/day PO q 6 hr
Side effects: Neutropenia, thrombocytopenia, colitis, hepatotoxicity

Griseofulvin

10 mg/kg/day; PO q 12 hr; double dose for extensive lesions

Microsize: Children >2 yr: 20–25 mg/kg/day q 8–12 hr
Ultramicrosize: Children >2 yr: 15 mg/kg/day q 8–12 hr
Side effects: Urticaria, paresthesia, proteinuria, leukopenia, photosensitivity; multiple drug interactions

Fluconazole

Loading dose 10 mg/kg IV/PO, then maintenance 6 mg/kg/day q 24 hr IV/PO
Side effects: Dizziness, skin rash, hepatic dysfunction; drug interactions

Ketoconazole

Oral: Child ≥2 yr: 3–6 mg/kg/day q 24 hr; maximum dose: 800 mg/day q 24 hr; Topical: 1–2 applications/24 hr.
Shampoo (dandruff): Twice weekly with at least 3 days

between applications for up to 8 weeks, thereafter, intermittently as needed to maintain control.

Suppressive therapy against mucocutaneous candidiasis in HIV: Child: 5–10 mg/kg/day PO q 12–24 hr; maximum dose: 800 mg/day q 12 hr.

Side effects: Abdominal pain, headache, dizziness, somnolence, photophobia, thrombocytopenia; gynecomastia; drug interactions.

Itraconazole

3–5 mg/kg/day (oral thrush); 5–10 mg/kg/day (histoplasmosis); maximum 400 mg/day. Prophylaxis: 2–5 mg/kg/dose; PO q 12–24 hr

Side effects: Hearing loss, arrhythmia, hepatotoxicity; use cautiously in patients with liver disease, cardiac dysfunction

Nystatin

1–2 million units/day PO q 8 hr for diarrhea due to *Candida albicans*

Mucosal application: Dissolve 100,000 units nystatin per mL glycerine

Side effects: Gastrointestinal disturbance, Stevens-Johnson syndrome

Voriconazole

>12 ys: 6 mg/kg/dose IV for 2 doses q 12 hr, then 3–4 mg/kg/dose IV q 12 hr; oral: 3–5 mg/kg/dose q 12 hr, 2–11 yr: 9 mg/kg/dose IV 2 doses q 12 hr, then 8 mg/kg/dose IV q 12 hr

Prophylaxis in pediatric leukemia: 6 mg/kg/dose PO q 12 hr for 2 doses followed by maintenance of 4 mg/kg q 12 hr.
Side effects: Blurred vision, photophobia, photosensitivity; hepatic impairment; flu-like symptoms

Caspofungin

Caspofungin <3 months: 25 mg/m²/dose (maximum 50 mg) once daily; older children: 70 mg/m² IV on day 1, followed by 50 mg/m² IV once daily (maximum 70 mg)
Side effects: Elevated transaminases; diarrhea, vomiting; flu-like symptoms; rash

To be used cautiously in patients with liver disease

Clotrimazole

Topical application for skin q 12 hr for 4–8 weeks; thrush >3 yr: Dissolve slowly (15–30 min) one troche in the mouth 5 times/day × 14 days

Side effects: Erythema, blistering

ANTHELMINTHICS

Albendazole

1–2 yr 200 mg single dose; >2 yr and adults 400 mg single dose; repeat after two weeks for roundworm

Strongyloides/H. nana/Taenia: 300 mg PO q 24 hr for 3 days.

Giardiasis: 400 mg PO q 24 hr for 5 days

Hydatidosis: 400 mg PO q 12 hr for 28 days: Repeat every two weeks for 3 cycles

Neurocysticercosis: 15 mg/kg/day PO q 12 hr for 7 days (with corticosteroids)

Side effects: Anorexia, vomiting

Dlethylcarbarnazine Citrate

Filariasis: 6 mg/kg/day q 8 hr for 2 weeks

Tropical eosinophilia: 10 mg/kg/day; PO q 8 hr for 1 month

Loeffler syndrome: 15 mg/kg single dose for 4 days

Side effects: Gastrointestinal upset, drowsiness

Ivermectin

Dose 200 µg/kg PO single dose

Contraindication: In children, <5 yr old

Mebendazole

100 mg; PO q 12 hr for 3 days; repeat after two weeks

Side effects: Pain abdomen, vomiting, diarrhea, headache

Praziquantel

Neurocysticercosis: 50 mg/kg/day q 8 hr; PO for 10–14 days.

Tapeworms: 10–20 mg/kg single dose

Liver fluke infestation: 75 mg/kg/day q 8 hr for 2 days

Side effects: Headache, vertigo, GI disturbance, urticaria, myalgia

Pyrantel Pamoate

10 mg/kg of pyrantel base; PO single dose with a maximum of 1 g; repeat after one week

Thiabendazole

50 mg/kg/day PO q 12 hr up to a maximum dose of 3 g/day

Duration of therapy for strongyloides 2 days, intestinal nematodes 2 days, cutaneous larva migrans 2–5 days, visceral larva migrans 5–7 days and trichinosis 2–4 days.

Side effects: GI disturbance, cholestasis, keratoconjunctivitis sicca, xerostomia, headache, giddiness

ANTIMALARIALS

Refer to Chapter 11.

ANTIPROTOZOAL

Chloroquine

10 mg/kg/day; PO q 8 hr for 14–21 days for extraintestinal amebiasis

Malaria treatment: Infant and child: 10 mg/kg/dose (maximum dose: 600 mg/dose) PO once; followed by 5 mg/kg/dose; Maximum dose: 300 mg/dose at 6 hr and then once daily for 2 days

Side effects: Nausea, vomiting, itching

IV administration has been reported to cause hypotension, arrhythmias, cardiac depression

Dlloxamide Furoate

Luminal amebic infection, cysts: 20 mg/kg/day PO q 8 hr for 10 days

Side effects: Nausea and flatulence

Dehydroemetine Dihydrochloride

1–3 mg/kg/day; PO q 8 hr for 10–15 days or 1 mg/kg/day IM for 7–10 days

Side effects: Renal and cardiac toxicity

Metronidazole

Giardiasis: 10 mg/kg/day; PO q 8 hr for 10 days

Amebiasis: 20 mg/kg/day; PO q 8 hr for 21 days or 50 mg/kg/day; PO q 8 hr for 7 days

Side effects: Diarrhea, leukopenia, metallic taste

Pentamidine

Leishmaniasis: 4 mg/kg/day IM or slow IV infusion daily dose for 12–15 doses

A second course may be given after 2 weeks

Side effects: Breathlessness, tachycardia, dizziness, fainting, headache, vomiting

Secnidazole

30 mg/kg; PO single dose; hepatic amebiasis treatment for 5 days

Side effects: Nausea, gastritis, metallic taste, rarely leukopenia and peripheral neuropathy

Sodium Stibogluconate

Cutaneous leishmaniasis: 20 mg/kg/day IM/IV for 20 days; mucocutaneous leishmaniasis and systemic infection: treat for 30 days

Side effects: Nausea, vomiting, prolonged QT interval

Tinidazole

50 mg/kg/day PO for 2–3 days

Giardiasis: 50 mg/kg single dose

Side effects: Same as for metronidazole

Nitazoxanide

1–4 yr: 100 mg; PO q 12 hr for 3 days

4–12 yr: 200 mg; PO q 12 hr for 3 days

Side effects: Gastrointestinal disturbance, discoloration of urine, headache

ANTIVIRAL AGENTS**Antiretroviral Drugs**

Refer Chapter 11

Aciclovir

HSV encephalitis >3 months, 20 mg/kg/dose IV q 8 hr; 21 days

Neonatal herpes simplex: <35 weeks-post-conceptional age 40 mg/kg/day IV q 12 hr 14–21 days ≥35 weeks post-conceptional age: 60 mg/kg/day IV q 8 hr 14–21 days

Herpes simplex: 1500 mg/m²/day IV q 8 hr

Varicella zoster: (≥2 yr) 30 mg/kg/24 hr or 1500 mg/m²/day q 8 hr IV × 7–10 days (≥2 yr), 80 mg/kg/day q 6 hr PO × 5 days (benefit if within 24 hr of onset of rash) maximum dose 3200 mg/24 hr

Adolescents: 800 mg PO q 6 hr for 7 days

Immunocompromised hosts: 1500 mg/m²/day IV q 8 hr for 7–10 days

Side effects: Seizures, congestive heart failure, urinary retention, leukopenia

Ganciclovir

10 mg/kg/day IV q 12 hr for 14–21 days; long term 6 mg/kg/dose once daily for 5 days in a week

Side effects: Bone marrow depression, rash, fever, vomiting

Valganciclovir

450 mg/m²/day or 30 mg/kg/day for 14–21 days

Side effects: Cytopenias, cholestasis, tremors, nausea, vomiting

Isoprinosine

Subacute sclerosing panencephalitis: 50–100 mg/kg/day PO q 12 hr

Side effects: Use cautiously in renal dysfunction

INTERFERONS**Interferon Alpha**

Chronic hepatitis B: 3–10 million units/m² thrice a week SC for 24 weeks

Chronic hepatitis C: Same dose with oral ribavirin for 24 weeks for genotypes 2 and 3; for 48 weeks for genotypes 1 and 4

Peg-IFN-2a: 180 µg/m² weekly (may be used for children with hepatitis B although it is approved for use only for the treatment of children with chronic hepatitis C. Treatment duration is 48 weeks)

Side effects: Flu-like symptoms, headache, body ache, malaise, fever and chills; Angioedema, urticaria, skin blistering or peeling; bone marrow depression; mood disorders; sepsis; seizures; arrhythmia; arthritis

ANTICANCER DRUGS

Refer Chapter 21

ANTICOAGULANTS**Heparin**

Heparin IV: 50 U/kg bolus; followed by 10–25 U/kg/hr as infusion or 50–100 U/kg/dose q 4 hr, 25–50 U/kg SC q 12 hr

Antidote: Protamine sulfate (1 mg neutralizes 1 mg heparin).

Side effects: Rash, alopecia, excessive bleeds, thrombocytopenia

Enoxaparin

Infants <2 months: Prophylaxis: 0.75 mg/kg/dose q 12 hr; Therapy: 1.5 mg/kg/dose q 12 hr

Older children: Prophylaxis: 0.5 mg/kg/dose q 12 hr; Therapy: 1 mg/kg/dose q 12 hr

Dosage titration with antifactor Xa level

Side effects: Bleeding, hypertension; use cautiously in patients with renal disease

Warfarin

0.05–0.34 mg/kg/day; PO

Adjust dose to maintain international normalized ratio (INR) 2–3

Side effects: Bleeding, epistaxis, internal hemorrhage

ANTICONVULSANTS

Refer Chapter 19

ANTIDOTES

Table 30.10.

Ipecac syrup is used to induce vomiting.

Table 30.10: Antidotes

Drug	Dosage	Side effects
Ipecac syrup	Infants 5–10 mL/dose; others 15–20 mL/dose. Do not use in semicomatose child or after charcoal administration	Diarrhea, vomiting, irregular heart beat, weakness, unusual tiredness
Deferoxamine	Acute iron poisoning 15 mg/kg/hr IV or 50 mg/kg/dose IM q 6 hr Maximum dose: 6 g/24 hr Chronic iron overload: IV: 15 mg/kg/hr; maximum dose: 6 g/24 hr SC: 20–40 mg/kg/dose once daily as infusion over 8–12 hr; maximum dose: 2 g/24 hr	Hypotension, shock, cramps, diarrhea. Contraindicated in renal failure
Dimercaprol	2.5 mg/kg PO q 4 hr on first day, q 6 hr on next 2 days, q 12 hr for 10 days; and q 24 hr for 10 days	Burning sensation, muscle aches, fever, hemolysis in G6PD deficiency
Edetate calcium disodium	12.5–30 mg/kg/dose IV q 12 hr for 5 days	Proteinuria and hematuria
Methylene blue	1–2 mg/kg/dose IV (in 5 min), if needed then repeat after 1 hour	Abnormal urine or stool color. Dizziness, headache, increased sweating and nausea
Naloxone	0.1 mg/kg/dose IM/IV; repeat if needed (maximum 2 mg)	May cause opioid withdrawal symptoms
Penicillamine	Wilson disease: 20–40 mg/kg/day PO q 6–12 hr; maximum dose 1 gm/day	Nephrotic range proteinuria, hepatotoxic, leukopenia, thrombocytopenia
Pralidoxime	Organophosphate poisoning: 25–50 mg/kg IM or IV as 5% solution over 15–30 min Dose may be repeated at 1–2 hr and then at 10–12 hr intervals, if cholinergic signs recur Continuous infusion 10–20 mg/kg/hr following loading dose	Nausea, hypertension, dizziness

ANTIEMETICS AND GASTROINTESTINAL MEDICATIONS*Domperidone*

0.2–0.5 mg/kg/dose PO q 6–8 hr; do not exceed 2.4 mg/kg/day or 80 mg

Side effects: Extrapyramidal disorders; angioedema, urticaria; rarely agitation, nervousness, arrhythmias, gynecomastia, amenorrhea

Metoclopramide

0.1–0.2 mg/kg/dose q 6–8 hr orally or IV; maximum dose 10 mg

Side effects: Extrapyramidal disorders including oculogyric crisis, tardive dyskinesia, dystonia, drowsiness

Ondansetron Hydrochloride

IV: 0.15–0.2 mg/kg/dose q 8–12 hr; Oral: 1.2–4 mg/dose q 8–12 hr

Side effects: Headache, diarrhea, constipation, fever, rash

Promethazine Hydrochloride

Nausea, vomiting, sedation: 0.25–1 mg/kg/dose PO/IM/IV/PR q 4–6 hr

Motion sickness: 0.5 mg/kg/dose PO q 12 hr. Max dose: 25 mg

Promethazine Theoclate

Antiemetic: Not approved for children below 2 yr

Children 2–5 yr: 5 mg q 6–8 hr; maximum daily dose 15 mg

Children 6–12 yr: 10 mg q 6–8 hr; maximum daily dose 25 mg

Motion sickness; administer 1–2 hr before travel

Side effects: Sedation, drowsiness, dry mouth, anorexia, blurred vision; rarely fever, jaundice, tremors, tinnitus, seizures, hallucinations and anxiety

Ranitidine

2–5 mg/kg/day; PO, IM or IV q 12 hr

Side effects: Headache, renal impairment

Famotidine

1–1.2 mg/kg/day, PO q 12 hr; maximum daily dose 40 mg

Omeprazole

5–10 kg: 5 mg q 24 hr

10–20 kg q 24 hr: 10 mg q 24 hr

≥20 kg: 20 mg q 24 hr

Side effects: Headache, dizziness, confusion, light headedness, tiredness

Lansoprazole

1 mg/kg/day in a single dose or 2 divided doses for GERD in infants

<30 kg: 15 mg, ≥30 kg: 30 mg

Side effects: Well tolerated, side effects as omeprazole

Sucralfate

1 month-2 yr: 250 mg PO 4-6 hr; 2-12 yr: 500 mg 4-6 hr; 12-18 yr: 1 g 4-6 hr

Side effects: Constipation, headache, dizziness, insomnia, vomiting

Lactulose

Constipation: 1-2 mL/kg/dose in hepatic coma and constipation

<2 yr 2.5 mL/day PO, PR q 12 hr

>2 yr 5-10 mL PO/PR q 12 hr; adult dose: 10-15 mL q 12-24 hr

Side effects: Diarrhea

Bisacodyl

5-10 mg bedtime; PO (Max—30 mg/day); Rectal suppository: 2-11 yr: 5-10 mg; >11 yr: 10 mg

Side effects: Abdominal pain, diarrhea, muscle pain, dizziness

Vasopressin

Catecholamine refractory septic shock: 0.3-2.0 mU/kg/minute IV infusion

Diabetes insipidus: 2.5-10 U SC/IM q 6-12 hr; 0.5-10 mU/kg/hr IV infusion

Bleeding esophageal varices: 20 U IV over 15 min, then 0.2 U/min or 0.33 U/kg/hr

Side effects: Hypertension, water intoxication, hyponatremia

ANTI-HISTAMINICS**Astemizole**

0.2 mg/kg/day taken half-hr before meals; not recommended <6 yr

Side effects: Weight gain with prolonged use

Cetirizine

6 months-2 yr: 2.5 mg PO once daily; 2-5 yr: 2.5 mg PO once daily, dose may be increased to 5 mg q 12-24 hr; ≥6 years: 5-10 mg; PO q 24 hr

Side effects: Drowsiness, dry mouth and nose

Levocetirizine

1-6 years: 0.125 mg/kg/day PO q 24 hr;

>6 years: 2.5 mg/day PO q 24 hr

Side effects: Headache, muscle ache, sleepiness, sore throat

Clemastine

1-3 yr: 0.25-0.5 mg q 12 hr

3-6 yr: 0.5 mg q 12 hr

6-12 yr: 0.5-1 q 12 hr

>12 yr: 1 mg q 12 hr

Contraindication: Patients with ventilator failure, obstructive airway disease

Chlorpheniramine Maleate

0.35 mg/kg/day PO q 4-6 hr; 2-5 yr: 1 mg/dose PO q 4-6 hr; maximum dose: 6 mg/24 hr; 6-11 yr: 2 mg/dose PO q 4-6 hr; maximum dose: 12 mg/24 hr; *sustained release* (6-12 yr): 8 mg/dose PO q 12 hr

Side effects: Hypotension, sedation, urinary retention, oculogyric spasms with high doses and after a few days of therapy

Diphenhydramine Hydrochloride

5 mg/kg/day q PO 6 hr oral; maximum daily dose 300 mg

Anaphylaxis or phenothiazine, overdose: 1-2 mg/kg IV slowly

Side effects: Dizziness, drowsiness, loss of co-ordination, dry mouth, nose or throat

Fexofenadine

<12 yr: 30 mg PO q 12 hr; >12 yr: 60 mg PO q 12 hr or 120 mg once daily

Side effects: Nausea, diarrhea, drowsiness, headache

Hydroxyzine Hydrochloride

2 mg/kg/day PO q 6 hr; 0.5-1 mg/kg/dose q 4-6 h IM

Side effects: Swelling over face, tremor, confusion, seizure

Loratadine

3-12 yr: 5 mg/day; >12 yr: 10 mg/day

Side effects: Diarrhea, epistaxis and flu-like symptoms

Methallazine Hydrochloride

>3 yr: 4 mg q 6-12 hr

Side effects: Sedation, urinary retention, leukopenia, agranulocytosis, glaucoma

Pseudoephedrine

<12 yr: 4 mg/kg/day PO q 6-8 hr oral; >12 yr: 30-60 mg/dose q 6-8 hr; maximum daily dose 240 mg

Side effects: Headache, tachycardia and tremor

ANTI-HYPERTENSIVES**Amlodipine**

0.1-0.2 mg/kg/dose (maximum dose 5 mg) PO q 24 hr, increase to 0.6 mg/kg/dose up to 20 mg/24 hr

Side effects: Edema, dizziness, flushing, palpitations; reduce dose in hepatic insufficiency

Atenolol

0.5–2 mg/kg/day PO q 12–24 hr

Side effects: Dizziness, light headedness, tiredness, and nausea. C/I in pulmonary edema, cardiogenic shock**Captopril**

Infant <6 months 0.01–0.5 mg/kg/dose PO q 8–12 hr, maximum dose 6 mg/kg/24 hr

Side effects: Dizziness, lightheadedness, or loss of taste, dry cough**Clonidine**

5–7 µg/kg/day q 6–12 hr, increase at 5–7 day interval to 5–25 µg/kg/day q 6 hr

Side effects: Dry mouth, dizziness, drowsiness, fatigue, rebound hypertension**Labetolol**

5–10 mg/kg/day PO q 12 hr after meals

Hypertensive crisis 0.25–1 mg/kg IV over 2 minutes, repeat after 5 minutes; may be administered as a continuous infusion (0.4–3 mg/kg/hr).

Side effects: Hypoglycemia, worsening asthma**Nitroprusside Sodium**

(Solution is light sensitive)

0.3–0.5 µg/kg/min infusion with blood pressure monitoring, maximum dose 8–10 µg/kg/min; titrate dose to desired effect

Side effects: Tachycardia, hypotension, acidosis**ANTITOXINS AND IMMUNOGLOBULINS****Anti-Rh D Immunoglobulin***Antenatal prophylaxis:* 300 µg IM at 28 weeks and 34 weeks gestation; or single dose within 72 hr of delivery*Twin pregnancy:* Double the dose. Abortion, evacuation, trauma*Other procedures (chorionic villus sampling, amniocentesis, external cephalic version):* 250 µg IM*Side effects:* Local site reactions (pain, discomfort, or tenderness), fever, joint or muscle pain, headache, dizziness, weakness, tiredness, itching, skin rash, nausea, diarrhea, vomiting**Anti-snake Venom**

Mixture of four enzyme-refined, lyophilized, polyvalent anti-snake venom (common Krait, cobra, Russell anti-snake venom)

5 vials (50 mL) for mild, 5–15 vials for moderate, 15–20 vials (150–200 mL)

For severe features; smaller children may require 50% more dose.

*Exclude horse serum allergy (0.02 mL of 1:10 diluted antivenin intradermally); then infuse antivenin diluted in 250 mL N/5 saline (20 mL/kg/hr)

Use steroids and antihistamines in addition

Side effects: Serum sickness, anaphylaxis**Diphtheria Antitoxin**

(Antitoxin is diluted 1:20 in isotonic saline and administered at 1 mL/min)

Schick test positive: One dose of diphtheria toxoid; diphtheria antitoxin 500–2000 units IM in other arm. Second and third doses of toxoid are given at 4–6 week intervals for active immunization

Dose is not related to patient age and weight

Pharyngeal or laryngeal diphtheria of 48 hr duration: 20,000–40,000 units IV

Nasopharyngeal diphtheria: 40,000–60,000 units IV

Extensive disease of >3 days duration with neck swelling: 80,000–120,000 units IV

Side effects: Coagulopathy, thrombocytopenia; contraindicated in IgA deficiency**Human Normal Immunoglobulin***Attenuation of disease among contacts of measles:* 0.25 mL/kg IM within 6 days of exposure*Hepatitis A:* 0.02–0.04 mL/kg/IM*Side effects:* Coagulopathy, thrombocytopenia; contraindicated in IgA deficiency*Hepatitis B (hepatitis B immunoglobulin):* 0.06 mL/kg IM, maximum 3–5 mL within 7 days of exposure

Human rabies specific immunoglobulin

If presents within 24 hr: 20 units/kg; one-half infiltrated at site of bite, other half IM in gluteal region

If presents between 1 and 7 days: Total dose given IM

Rabies vaccine is administered simultaneously

Side effects: Headache, vomiting, chills, rash**Human Tetanus Specific Immunoglobulin***Prophylactic:* 250 IU IM; *therapeutic:* 30–300 IU/kg IV; intrathecal: 250–500 IU single dose*Side effects:* As above**Intravenous Immunoglobulin (IVIg)***Primary immunodeficiency:* 400–500 mg/kg IV infusion every 3–4 weekly*Intravenous immunoglobulin (IVIg):* 0.4 g/kg IV infusion daily for 5 days; 1 g/kg/day for 2 days or 2 g/kg in one day as IV infusion over 10–12 hr as single dose*Side effects:* Hypersensitivity reactions**Tetanus Antitoxin***Prophylactic:* 3,000–5,000 U SC, IM; *Therapeutic:* 10,000 U IM, IV*Intrathecal:* 250–500 U q 24 hr for 3 day*Side effects:* Serum sickness, anaphylaxis

Varicella Zoster Immunoglobulin

125 U/kg IM within 48–72 hr of exposure to varicella

Side effects: Pain at injection side, hypersensitivity

BRONCHODILATORS, RESPIRATORY STIMULANTS AND ANTI-ASTHMA AGENTS**Adrenaline**

0.01 mL/kg/dose (max 0.5 mL/dose) of 1:1000 solution SC, repeat after 15–20 min

For resuscitation, 0.1–0.3 mL/kg/dose (1:10000) IV

Side effects: Tachycardia, palpitations and anxiety

Aminophylline

Status asthmaticus: 5–7 mg/kg IV loading, followed by infusion at 0.5–1 mg/kg/hr

Do not use loading dose, if already giving aminophylline.

Apneic spells in preterms: 5 mg/kg IV loading, followed by 1–2 mg/kg PO/IV q 8 hr

Side effects: Tachycardia, tremors, irritability, convulsions

Beclomethasone Dipropionate

MDI 50, 100, 200, 250 µg/puff: 100–1000 µg/day q 8 hr

Rotacaps 100, 200, 400 µg/cap: 100–1000 µg/day q 8 hr

Side effects: Dry/sore throat, hoarseness, a bad taste in the mouth, headache, and voice changes; not recommended for <5 yr children with oral inhalation and <6 yr with nasal administration due to unknown safety and efficacy.

Budesonide

MDI 50, 100, 200 µg/puff, rotacaps 100, 200, 400 µg/cap: 200–800 µg/day q 12 hr

Raspules 0.5 mg/mL, 1 mg/mL: 0.25–1 mg q 12 hr

Side effects: Dry/irritated throat, hoarseness, voice changes, bad taste

Caffeine

20 mg/kg (of caffeine citrate); then 5–10 mg/kg as IV/PO q 24 hr, to begin 24 hr after loading dose

Side effects: Hyperglycemia, hypoglycemia, gastrointestinal disturbances (nausea, vomiting, abdominal distension), irritability, sleeplessness, jitteriness, cardiac arrhythmias, tachycardia, rarely bradycardia, hypertension, diuresis and dehydration

Ciclesonide

MDI 80, 160 µg/puff: 80–640 µg/day q 12 hr; not approved below 12 years of age

Benefit of less oropharyngeal candidiasis and HPA axis suppression

Side effects: Benefit of less oropharyngeal candidiasis and hypothalamic–pituitary axis suppression

Fluticasone Propionate

MDI 25, 50, 125 µg/puff, rotacaps: 50, 100, 200 µg/puff: 100–1000 µg/day q 12 hr

Side effects: Hoarseness, throat irritation, headache, dryness in mouth/nose/throat, cough

Ipratropium Bromide

MDI 20 µg/puff: 2–4 puffs as needed

Rotacap 40 µg/cap: 1–2 cap as needed

Raspules 0.5 mg/2 mL, <1 yr: 125 µg/dose; >1 yr: 250 µg/dose, repeat q 20 minutes for 1 hr (during exacerbation); then q 6–8 hr

Side effects: Sinusitis, exacerbation of chronic obstructive pulmonary disease

Montelukast Sodium

1–5 yr: 4 mg PO once a day in evening; 6–14 yr: 5 mg once daily; >14 yr: 10 mg once daily

Side effects: Fever, upper respiratory infection, headache, pharyngitis, cough, abdominal pain, diarrhea, otitis media

Salbutamol

0.15 mg/kg/dose PO q 8 hr

MDI 100 µg/dose: 2–4 puffs as needed q 20 minutes for 1 hr (during exacerbation), then q 6–8 hr

Nebulizer solution: 0.15 mg/kg/dose (minimum 2.5 mg, as needed), q 20 minutes for 1 hr, followed q 6–8 hr

Side effects: Headache, tremor, irritability, hypokalemia

Levosalmbutamol

MDI 50 µg/puff: 2–4 puffs as needed

Side effects: Tachycardia, tremors, headache and hypokalemia

Terbutaline

0.1–0.15 mg/kg/day PO q 8 hr; 0.005–0.01 mg/kg SC q 6 hr; IV 0.4–1.0 µg/kg/min followed by infusion of 1–10 µg/kg/hr; nebulizer (10 mg/mL): 0.5–2 mg as needed. MDI 250 µg/puff; 2–4 puffs as needed

Side effects: Same as salbutamol

Magnesium Sulfate

Injection 25% (250 mg/mL), 50% (500 mg/mL)

IV 25–50 mg/kg diluted in saline infused over 30 minutes (maximum 2 g)

Side effects: Hypotension, respiratory depression, muscle weakness

Note

- Metered dose inhalers (MDI) should be used with large volume spacers. For infants, the spacer can be used with a face mask.
- Rotacap dose is double the inhaler dose; are administered using a Rotahaler.
- Nebulization: Final volume of 3–5 mL should be made by adding normal saline.

INOTROPIC AGENTS*Adrenaline*

Cardiac arrest: 0.1 mL/kg/dose of 1:10,000 solution IV/ intraosseous

Endotracheal use: 0.1 mL/kg/dose of 1:1000 solution (flush with 5 mL saline, followed by 5 ventilations) in case of non-response, repeat same dose q 3–5 minutes

Side effects:

Inotrope: 0.1–0.3 µg/kg/min IV infusion

Dobutamine

(Available as 250 mg powdered form; reconstitute ampoule with 10 mL saline to make 25 mg/mL)

2–20 µg/kg/min IV

Dosage (mg): 15 mg body weight dissolved in 24 mL of compatible solution (5% Dx/10% Dx/NS/DxNS), Infusion @ 0.5 mL/hr delivers 5 µg/kg/min

Side effects: Hypotension, if there is hypovolemia, tachycardia

Dopamine

(Available as 200 mg/5 mL ampoule)

2–20 µg/kg/min IV

Dosage (mg): 15 mg body weight dissolved in 24 mL of compatible solution (5% Dx/10% Dx/NS/DxNS), Infusion @ 0.5 mL/hr delivers 5 µg/kg/min

Side effects: Tachyarrhythmia, hypertension, vasoconstriction, vomiting. Extravasations may cause tissue necrosis

Digoxin

Digitalizing dose: Premature neonates 0.04 mg/kg/day; term neonates 0.06 mg/kg/day; infants 0.06–0.08 mg/kg/day; older children 0.04 mg/kg/day PO (parenteral dose is two-thirds of oral dose)

One-half of the digitalizing dose is given stat, followed by one-quarter each after 8 hr and 16 hr

Maintenance dose is one-quarter of digitalizing dose; given once a day

Digoxin specific fab antibody: IV infusion; 60 mg binds 1 mg of digoxin approximately

Side effects: Nausea, vomiting; bigeminy pulse, extrasystoles, partial or complete heart block, sinus arrhythmia, atrial or ventricular tachycardia

Millrinone

50–75 µg/kg loading dose followed by 0.25–1.0 µg/kg/min.

Side effects: Extravasations may cause tissue necrosis, dizziness, headache, rarely severe allergic reactions

Norepinephrine

0.05–0.1 µg/kg/min titrate dose to desired effect (maximum 2.0 µg/kg/min)

Side effects: Headache, bradycardia, hypertension

Isoproterenol Hydrochloride

0.5–5.0 µg/kg/min

Side effects: Cardiac dysrhythmias, rarely cardiac arrest, wheezing, bronchospasm

Vasopressin

Catecholamine refractory vasodilatory septic shock: 0.3–2.0 mU/kg/min IV infusion

Side effects: Hypertension, water intoxication, hyponatremia

DIURETICS*Acetazolamide*

Edema: 5 mg/kg/day PO q 24 hr or every other day

Epilepsy/glaucoma: 8–30 mg/kg/day PO q 6–8 hr

Hydrocephalus: 25–100 mg/kg/day PO q 8 hr

Seizures: 8–30 mg/kg/day PO q 6–12 hr

Pseudotumor cerebri: Start with 25 mg/kg/day PO q 6–24 hr, increase by 25 mg/kg/day until clinical response or as tolerated up to maximum of 100 mg/kg/day

Side effects: Sodium and potassium depletion, acidosis, GI irritation, paresthesia, sedation, C/I in marked hepatic and renal dysfunction

Bumetanide

≥6 months 0.01–0.05 mg/kg/dose PO q 24–48 hr;

>6 months 0.015–0.1 mg/kg/dose PO q 24–48 hr

Maximum dose 10 mg/24 hr

Side effects: Muscle cramps, nausea, vomiting, gynecostasia, leukopenia, thrombocytopenia

Chlorthalidide

20 mg/kg/day q 12 hr

Side effects: Hyperglycemia, glucosuria, neutropenia, neonatal thrombocytopenia, hypokalemia, hypotension

Furosemide

1–4 mg/kg/day in 1–2 divided doses; maximum 6 mg/kg/day. IV: 1–2 mg/kg/dose q 12 hr; infusion: 0.1–0.4 mg/kg/h

Side effects: Nausea, vomiting; hyponatremia, hypokalemia, metabolic alkalosis, hyperglycemia, hyperuricemia; pancreatitis, dizziness, vertigo, headache, tinnitus and hearing loss on prolonged use

Hydrochlorthiazide

Neonate and infant <6 mo: 2–4 mg/kg/day PO q 12 hr maximum dose 37.5 mg/24 hr

≥6 mo and child: 2 mg/kg/day PO q 12hr; maximum dose 100 mg/24 hr

Hypertension: Infant and child: Start at 0.5–1 mg/kg/day PO q 24 hr; maximum dose of 3 mg/kg/24 hr up to 50 mg/24 hr

Side effects: Almost similar to furosemide but less frequent

Metolazone

0.2–0.4 mg/kg/day PO q 24 hr

Side effects: Hypotension, palpitations and hypovolemia, hypokalemia, hyponatremia**Spironolactone***Neonates:* 1–3 mg/kg/day q 12–24 hr*Children:* 1.5–3 mg/kg/day or 60 mg/m²/day q 12–24 hr; not to exceed 100 mg/day*Side effects:* Dry mouth, dizziness, headache, irregular periods, gynecomastia, hirsutism, erectile dysfunction, hyperkalemia**Triamterene**

2–4 mg/kg/day q 12 hr

Side effects: Hyperkalemia, hyponatremia, dry mouth, headache**Mannitol**

0.5–3 g/kg/dose IV given over 30–60 min

Side effects: Hypotension, tachycardia, fluid and electrolyte imbalance**HORMONES****Betamethasone***Anti-inflammatory:* 0.0175–0.25 mg/kg/day or 0.5–7.5 mg/m²/day PO q 6–8 hr; 0.0175–0.25 mg/kg/day or 0.5–7.5 mg/m²/day IM q 6–12 hr

Fetal lung maturity (24–34 weeks); administer to mother 12 mg IM in 2 doses 24 hr apart

Side effects (short term): Sodium retention-related weight gain, glucose intolerance, hypokalemia, gastrointestinal upset and reversible depression of the hypothalamic-pituitary-adrenal axis*Side effects (long term):* Hypothalamic-pituitary-adrenal activity suppression, cushingoid appearance, hirsutism or virilism, impotence, cataracts and increased intraocular pressure, myopathy, osteoporosis**Cortisone Acetate***Physiological requirement:* 0.7 mg/kg/day*Therapeutic dose:* 2.5–10 mg/kg/day q 8 hr*Side effects (immediate):* Moon facies, acne, increased appetite, reduced resistance to infections, headache, gastritis, hypertension, electrolyte disturbances, glaucoma, pseudotumor cerebri*Side effects (prolonged therapy):* Myopathy, osteoporosis, growth retardation, cataract, adrenal cortical atrophy**Fludrocortisone***Infants:* 0.05–0.1 mg/day PO q 24 hr; *Children:* 0.05–0.2 mg/day PO q 24 hr*Side effects:* Hypertension, hypokalemia, acne, rash**Dexamethasone**

0.05–0.5 mg/kg/day PO q 6 hr

Congenital adrenal hyperplasia: 0.5–1.5 mg/day*Cerebral edema:* 0.5 mg/kg/dose IV/IM q 6 hr*Pulse dexamethasone:* 5 mg/kg as slow infusion (maximum dose 100 mg)*Side effects:* Weight gain, insomnia, mood changes, acne, dry skin, bruising or discoloration, slow wound healing, nausea
Croup: 0.3–0.6 mg/kg IM/oral, single dose**Hydrocortisone***Status asthmaticus:* 4–8 mg/kg/dose IV q 4–6 hr IV*Endotoxic shock:* 50 mg/m² initial dose followed by 50–150 mg/m²/day q 6 hr IV for 48–72 hr*Acute adrenal insufficiency:* 1–2 mg/kg/dose IV, then 25–150 mg/m²/day IV or IM*Side effects:* Hypertension, hyperglycemia, arrhythmias**Prednisolone**

(Prednisolone, 5 mg = 0.75 mg betamethasone or dexamethasone, 4 mg methylprednisolone or triamcinolone, 20 mg hydrocortisone and 25 mg cortisone acetate)

Acute asthma: 0.5–2 mg/kg/day PO q 12–24 hr*Anti-inflammatory:* 0.5–2 mg/kg/day PO q 8–12 hr*Nephrotic syndrome:* 2 mg/kg/day, q 12–24 hr daily; then on alternate days*Congenital adrenal hyperplasia:* 2 mg/kg/day PO q 6–8 hr or single dose in the morning*Side effects (immediate):* Moon facies, acne, increased appetite, gastritis, hypertension, electrolyte disturbances, glaucoma, pseudotumor cerebri*Side effects (prolonged therapy):* Myopathy, osteoporosis, stunting, cataract, adrenal cortical suppression**Methylprednisolone**

1–2 mg/kg/dose IM or IV

High dose (pulse) therapy: 15–30 mg/kg daily for 3–5 days*Side effects:* Hypertension, sweating, hyperglycemia, mood changes, dyselectrolytemia, rarely arrhythmias**Triamcinolone**

24 mg/day PO q 8–12 hr; deep IM 40 mg or intra-articular 2.5–15 mg; avoid <6 yr

Side effects: Fluid retention, hypokalemic alkalosis, aseptic necrosis of femoral heads, gastritis**ACTH***For infantile spasms:* 20–40 U/kg/day IM q 24 hr for 6 week or 150 U/m²/day q 12 hr for 2 weeks followed by a gradual tapering, for dynamic testing (short ACTH stimulation test)<6 months: 62.5 µg; 6 months–2 years: 125 µg; >2 years 250 µg
Side effects: C/I hepatic damage, nephropathy, acute psychosis, CHF, Cushing's disease, peptic ulcer, fungal infections, recent surgery

Vasopressin

Diabetes insipidus: 5–20 U q 12 h IM; 1.5–10 mU/kg/minute IV infusion

Side effects: Hypertension, water intoxication, hyponatremia

Desmopressin

Hemophilia: Infants >3 months of age and children: 0.3 µg/kg IV by slow infusion over 15–30 min beginning 30 min before procedure; may repeat dose, if needed.

Diabetes insipidus: Intranasal 5–30 µg/day

Side effects: Water intoxication, hyponatremia

Growth Hormone

0.09–0.2 unit/kg/day SC or IM till accepted height is achieved or bone fusion occurs

Turner syndrome: 0.11–0.14 unit/kg/day

Side effects: Abnormal bone growth, abnormal touch sensation, pseudotumor cerebri and hyperglycemia

Insulin

Refer to Chapter 18

Glucagon

Hypoglycemia (neonates/ infants): 0.025–0.3 mg/kg/dose q 30 min IM/IV/SC

Side effects: Nausea, vomiting, urticaria, respiratory distress

Diazoxide

Hypertensive crisis: 1–3 mg/kg/dose up to maximum of 150 mg/dose

Hyperinsulinemic hypoglycemia: 8–15 mg/kg/day PO q 8–12 hr

Hyponatremia, salt and water retention, gastrointestinal disturbance, hyperuricemia

Carbimazole

1–2 mg/kg/day q 8 hr

Side effects: Urticaria, ageusia, pigmentation, bone marrow depression

Thyroxine

10–15 µg/kg/day in newborn babies, 5 µg/kg/day in children, single dose PO empty stomach in the morning

Side effects: Tachycardia, headache, insomnia, muscle cramps

Potassium Iodide (SSKI) and Lugol's Iodine*

5 drops q 6 hr

Side effects: Hypo- or hyperthyroidism, GI disturbance, iododerma, hypersensitivity, interference with anion gap calculation

*SSKI (1 g/mL) contains 76.4% iodine. Five drops four times a day (assuming 20 drops/mL) contain about 764 mg iodine.

Lugol's solution (125 mg/mL of total iodine) contains, in each 100 mL, 5 g of iodine and 10 g of potassium iodide. Four drops four times a day contain about 134 mg of iodine

Propylthiouracil

Neonate: 5–10 mg/kg/day q 8hr; <10 yr: 50–150 mg/day q 8 hr; >10 yr: 150–300 mg/day q 8 hr

Maintenance: 50 mg q 12 hr

Side effects: Hepatitis, vertigo, rash, interstitial pneumonitis

Erythropoietin

Anemia of prematurity: 25–100 U/kg/dose SC or IV, 3 times a week

Chronic kidney disease: 50–150 U/kg/dose SC or IV, 2–3 times a week

SC route requires lower doses than IV; rotated through arm, thigh and anterior abdominal wall.

Side effects: Local swelling, dizziness, nausea, pain at the site of the injection, fever

Darbepoetin Alpha

Prolonged half life; administered less frequently; 0.45 µg/kg IV/SC once a week; 0.75 µg IV/SC once a fortnight

Side effects: Hypertension, seizures, venous thrombosis

Octreotide

1 µg/kg/hr (up to 50 µg/hr); given as continuous IV infusion

Side effects: Local pain, stinging, tingling at site of injection, hypothyroidism, conduction abnormalities, pancreatitis

Vitamin D

Treatment doses of vitamin D for nutritional rickets (dose in IU).

Age	Daily dose for 90 days	Single dose	Maintenance daily dose
<3 mo	2000	N/A	400
3–12 mo	2000	50,000	400
>12 mo–12 y	3000–6000	150,000	600
>12 y	6000	300,000	600

Dosing of 1, 25-dihydroxyvitamin D (calcitriol) in patients with chronic kidney disease: Chapter 17

Side effects: Hypercalcemia, nausea, vomiting, abdominal cramps

MICRONUTRIENTS**Magnesium Sulfate***

Protein energy malnutrition: 0.3 mL/kg (max 2 mL) of 50% magnesium sulfate on day 1, then 2–3 mEq/kg/day PO q 24 hr (maintenance requirement)

*Magnesium sulfate 50% solution provides 4 mEq/mL

Side effects: Hypotension, respiratory depression, muscle weakness

Zinc Sulfate

Therapy of deficiency: 0.5 mg/kg/day for infants; 10 mg/day for <6 months, 20 mg >6 months for two weeks

Acrodermatitis enteropathica (higher doses up to 6 mg/kg/day)

Side effects: Uncommon and include gastritis and vomiting; excessive doses may cause copper deficiency

Parenteral Iron Therapy

Parenteral: Iron dextran: 4 mg/kg/dose (maximum 100 mg); slow IV push at 1 mL (50 mg) per minute. The first dose for iron dextran is 10 mg (weight <10 kg), 15 mg (weight 10–20 kg) or 20–25 mg for older children

Polynuclear ferric hydroxide sucrose or iron sucrose: 0.5–2 mg/kg (maximum 7 mg/kg or 100 mg); diluted 20-fold with normal saline; infused over 30 minutes

Oral (ferrous sulfate): Prophylaxis: 1–2 mg/kg/day; treatment: 3–6 mg/kg/day

Side effects: Hypersensitivity reactions (bronchospasm, angioedema, urticaria, hypotension); pain and muscle spasms. Severe or persistent symptoms require therapy with antihistaminics. Iron sucrose preparation has lesser side effects.

The dose required for correction of iron deficiency is calculated as:

Total iron deficit (mg) = Weight in kg × (target Hb – actual Hb in g/dL) × 2.4 + depot iron in mg

The depot iron is 15 mg/kg body weight for children <35 kg, and 500 mg for >35 kg.

Calcium Gluconate (Elemental Calcium 9%)

1–2 mL/kg of 10% solution; slow IV infusion under cardiac monitoring

Side effects: Bradycardia, hypotension, local extravasation can cause tissue necrosis hence the patency of the line should be rechecked before every administration.

Contraindication: Ventricular fibrillation

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Potassium Chloride

1–2 mEq/kg/d PO q 8 hr; not to exceed 200 mEq/L in central line infusions

Side effects: Hyperkalemia, GI disturbances, phlebitis

Sodium Bicarbonate

1–2 mEq/kg/dose

The dose is calculated as:

Base deficit × weight in kg × 0.6 = mEq, or mL of 7.5% solution of sodium bicarbonate

Side effects: Metabolic alkalosis, hypernatremia, hypokalemia, thrombophlebitis, intracranial hemorrhage in neonates

Calcium Carbonate

Neonates: 50–150 mg/kg/day PO q 4–6 hr (maximum dose 1 g/24 hr); children 45–65 mg/kg/day PO q 6 hr

Side effects: Constipation, hypercalcemia, hyperphosphatemia, hypomagnesemia, vomiting, headache, confusion

Calcitriol

<1 yr: 0.04–0.08 µg/kg/dose PO q 24 hr; 1–5 yr: 0.25–0.75 µg/kg/dose PO q 24 hr >6yr: 0.5–2 µg/kg/dose PO q 24 hr; titrate in increments of 0.005–0.01 µg/kg/24 hr every 4–8 weeks based on clinical response

Side effects: Weakness, headache, vomiting, constipation, hypotonia, polydipsia, polyuria

Vitamin A

Prophylaxis: 100000 units at 9 months, then 200000 units every 6 months up to 3 yr; if measles: 100000 in <1 yr and 200000 in >2 yr at 0, 1 and 14 day

Side effects: Irritability, hypercalcemia, pseudotumor cerebri

Folic acid

0–6 months: 25–35 µg (PO q 24 hr)

6 months–2 years: 50 µg

4–6 years: 75 µg; 7–10 years: 100 µg; 11–14 years: 150 µg

Megaloblastic anemia: 0.5–1.0 mg for 4 weeks OD

Vitamin B₆

Pyridoxine: B₆ dependent seizures: 50–100 mg/day, IV/IM/PO

Isoniazid-induced neuritis: 1 mg/kg/day, PO

Side effect: Nausea, deranged liver function tests vitamin B₆.

SEDATIVES, HYPNOTICS, ANTIDEPRESSANTS AND ANTIPILEPTICS**Diazepam**

Sedation and anxiolysis: 2–5 mg PO

Anticonvulsant: 0.2 mg/kg/dose IV (maximum 10 mg); repeat in 15 minutes

Contraindication: Myasthenia gravis and acute narrow angle glaucoma

Flumazenil

Reversal of benzodiazepine sedation (IV):

Child: Initial dose: 0.01 mg/kg (max dose: 0.2 mg) given over 15 sec, if needed after 45 sec, 0.01 mg/kg (maximum dose: 0.2 mg) Q 1 min to a maximum total cumulative dose of 0.05 mg/kg or 1 mg, whichever is lower. Usual total dose: 0.08–1 mg (average 0.65 mg); as an alternative for repeat bolus doses, a continuous infusion of 0.005–0.01 mg/kg/hr has been used.

Side effects: Nausea, vomiting, dizziness, tremor, depression, euphoria, agitation, palpitations, dyspnea, hyperventilation

Lorazepam

0.1 mg/kg IV; repeat at 5 minutes; longer duration of action than diazepam; 0.03–0.05 mg/kg/dose PO q 8–12 hr

Side effects: Confusion, depressed mood, hyperactivity, agitation, hostility

Clonazepam

Infant and child <10 yr or <30 kg: initial: 0.01–0.03 mg/kg/day PO q 8 hr; increment: 0.25–0.5 mg/day q 72 hr, up to maximum maintenance dose of 0.1–0.2 mg/kg/day q 8 hr

Child ≥10 yr or ≥30 kg and adult: initial: 1.5 mg/24 hr PO q 8 hr; increment: 0.5–1 mg/day q 72 hr; maximum dose: 20 mg/24 hr

Side effects: Drowsiness, dizziness, muscle weakness, loss of balance or coordination

Chloral Hydrate

5–10 mg/kg/dose for sedation; 20–75 mg/kg/dose for heavy sedation

Side effects: Nausea and vomiting are more common, diarrhea; dizziness and drowsiness are less common

Chlorpromazine

2.5–6 mg/kg/day PO q 6 h

Chorea: Start with 50 mg/day PO; increase by 25 mg/day till controlled; maximum dose 300 mg/day

Neonatal tetanus: 1–2 mg/kg/dose q 2–4 hr

Side effects: Extrapyramidal reactions (e.g. Parkinson-like symptoms, dystonia, tardive dyskinesia), drowsiness, dizziness, skin reactions or rash, dry mouth, orthostatic hypotension, amenorrhea, galactorrhea, weight gain

Fluoxetine Hydrochloride

5–10 mg/day; maximum 20 mg/day

Side effects: Insomnia, weakness, anxiety, drowsiness, tremor, diarrhea, dyspepsia, nausea, nervousness, headache, xerostomia

Haloperidol

Psychotic disorder: 0.05–0.15 mg/kg/day PO q 8–12 hr; agitation: 0.01–0.03 mg/kg/day q 8–12 hr; chorea: 0.25 mg PO q 12 hr; 5–10 mg/day q 12 hr

Side effects: Extrapyramidal reactions, dyskinesia

Ketamine

IV induction: 0.5–2 mg/kg at a rate not to exceed 0.5 mg/kg/min; IM, oral, rectal: 3–10 mg/kg/dose; nasal and sublingual: 3–5 mg/kg/dose

Minor procedures 0.5–1.0 mg/kg; sedative dose 2 mg/kg

The concomitant use of midazolam is beneficial

Side effects: Hypertension, hypertonia, diplopia, increased intraocular pressure, salivary hypersecretion

Midazolam

0.07–0.2 mg/kg/dose IM or IV

Pre-operative sedation or conscious sedation (mechanical ventilation) above dose followed by 0.2–1 µg/kg/min for neonates and 0.5–3.0 µg/kg/min for infants and children
Status epilepticus 0.2 mg/kg IV or IM followed by 0.1–0.2 mg/kg/hr

Intranasal 0.2 mg/kg may be used for acute seizure control

Side effects: Respiratory depression, shock

Triclofos

20 mg/kg/dose for sedation PO q 12 hr

Side effects: Gastrointestinal disturbance, mild rash

Carbamazepine

<6 yr: 10–20 mg/kg/day PO q 8 hr, increment q 5–7 days up to maximum of 35 mg/kg/24 hr; 6–12 yr: 10 mg/kg/24 hr PO q 12 hr up to maximum 100 mg/dose q 12 hr; maintenance 20–30 mg/kg/day q 6–12 hr

Side effects: Dizziness, drowsiness, nausea, ataxia, and vomiting, pruritus, speech disturbance, xerostomia and amblyopia

Clobazam

<30 kg: 5 mg PO q 24 hr, increase to 20 mg q 24 hr

>30 kg: 10 mg PO q 24 hr, increase to 40 mg q 24 hr

Side effects: Dizziness, drowsiness, anxiety, suicidal thoughts, withdrawal symptoms, lower doses in liver diseases

Pentobarbital

Refractory status epilepticus: 10 mg/kg loading IV over 1 hr, maintenance 1–5 mg/kg/hr

Side effects: Hypotension, respiratory suppression, arrhythmia

Phenobarbital

Anticonvulsant: 20 mg/kg loading IV; 3–5 mg/kg/day IV q 12–24 hr as maintenance

Side effects: Dizziness, respiratory depression, hypotension

Phenytoin Sodium

Arrhythmia: Loading 1.25 mg/kg IV over 3 min and repeat every 5–10 min to a maximum total dose of 15 mg/kg or until arrhythmia reverts or hypotension develops; maintenance 5–10 mg/kg/day PO q 12 hr

Status epilepticus: Loading 15–20 mg/kg IV, do not exceed 1–3 mg/kg/min. Maintain with 5–8 mg/kg/day PO or IV q 12–24 hr

Side effects: Gum hypertrophy, hirsutism, hypersensitivity, megaloblastic anemia, osteomalacia and vestibulo-cerebellar syndrome

Fosphenytoin Sodium

15–20 mg/kg/day; then 4–6 mg/kg/day

Side effects: Pruritus, dizziness, ataxia, nystagmus, contraindicated in porphyria

Pentothal Sodium (Thiopental)

Refractory status epilepticus: 5–10 mg/kg loading dose IV over 2–5 minutes followed by 2–10 mg/kg/hr continuous infusion.

Side effects: Gastrointestinal disturbance, hypotension, respiratory depression, bronchospasm

Valproic Acid

Seizures (generalized, simple and complex partial): Start with 10–15 mg/kg/day PO q 8–12 hr, increase by 5–10 each week if required to maximum 60 mg/kg/day

Status epilepticus: 20 mg/kg loading followed by 10 mg/kg IV q 12 hr

Table 30.11: Miscellaneous drugs

Drug	Dosage	Side effects
Acetylcysteine	Meconium ileus: 5–10 mL/kg (10% soln PR) q 6 hr Nebulization: 3–5 mL/kg of 20% or 6–10 mL/kg (10%) q 6–8 hr Acetaminophen poisoning (see Chapter 27)	Bronchospasm, stomatitis, drowsiness, rhinorrhea, nausea, vomiting, hemoptysis Anaphylactic reactions with IV use Rapid infusion may lead to fluid overload; rarely hypersensitivity
Albumin (20%)	0.5–1 g/kg/dose over 30–120 minutes; coadministered with IV furosemide in patients with nephritic syndrome	Rash (frequent); nausea, diarrhea; allergic liver toxicity (increased risk with renal impairment)
Allopurinol	10 mg/kg/day PO q 8 hr, max dose 800 mg/24 hr; IV dosage is alkaline and should be diluted to minimum concentration of 6 mg/mL and infused over 30 min	Fever, apnea, flushing, bradycardia, hypotension, platelet aggregation defect
Alprostadil prostaglandin E1	Initial: 0.05–0.2 µg/kg/min; advance to 0.2 µg/kg/min, if necessary Maintenance: Decrease to lowest effective dose when increase in partial pressure of oxygen Usual dose 0.01–0.4 µg/kg/min	Restlessness, excitability, tremor, headache, anxiety, agitation, insomnia, dry mouth, palpitations C/I: Thyrotoxicosis, tachycardia due to cardiac insufficiency; obstructive gastrointestinal lesions
Amphetamine	0.15–0.5 mg/kg/day Children 3–5 years: 2.5 mg daily, increase by 2.5 mg q weekly Children >6 years: 5 mg once daily; increase by 5 mg q weekly	Drowsiness, weakness, tiredness, nausea, constipation, confusion
Atropine	Cardiopulmonary resuscitation: 0.01–0.03 mg/kg/dose IV every 2–5 minutes for 2–3 doses; maximum 1.0 mg Pre-anesthesia (30–60 min prior): 0.03–0.04 mg/kg/dose IV Bronchospasm: 0.02–0.05 mg/kg/dose (maximum 2.5 mg/dose)	Hypotension, seizures, asystole, respiratory arrest
Baclofen	0.75–2 mg PO q 8 hr; maximum dose 40 mg for <8 years and 60 mg for >8 years	
Lidocaine hydrochloride	<i>Without epinephrine:</i> Maximum dose 4.5 mg/kg/dose (up to 300 mg); do not repeat within 2 hr <i>With epinephrine:</i> maximum dose 7 mg/kg/dose (up to 500 mg); do not repeat within 2 hr <i>Topical:</i> Apply cream to affected intact skin q 6–12 hr <i>Oral:</i> 4.5 mg/kg/dose or 300 mg/dose swish and spit q 3 hr; maximum 4 doses per 12 hr	
Oxyphenonium bromide	0.8 mg/kg/day PO q 6 hr Preschool children: 5–10 drops; older children: 10–20 drops q 6 hr	Dry mouth, blurred vision, retention of urine, dizziness, fatigue, tremors
Pethidine	Analgesic 1–2 mg/kg/dose IM/IV	Seizures
Ribavirin	6 g in 300 mL sterile water; nebulize q 12–18 hr/day for 3–7 d Oral: 10 mg/kg/day q 6–8 hr (max <10 yr: 150 mg/d; >10 yr; 200 mg/d)	Seizures, congestive heart failure, urinary retention, leukopenia
Senna	Constipation: 10–20 mg/kg/dose, PO q 12–24 hr	Loose stools, cramping
Sildenafil	0.3–3 mg/kg/day PO q 8 hr, 0.3–2 mg/kg/dose PO q 6–12 hr IV bolus: 0.4 mg/kg over 3 hr; followed by 1.6 mg/kg/d infusion	Dizziness, light headed
Sotalol	Arrhythmia: 2–8 mg/kg/day, PO q 8–12 hr	May cause arrhythmia
Succinylcholine	Neuromuscular blocking agent: 1–2 mg bolus, maintenance 0.04–0.07 mg/kg/dose IV q 5–10 min as per desired effect	Hypotension, bronchospasm, hyperkalemia, malignant hyperthermia
Sulfasalazine	Inflammatory bowel disease: Start at 40–75 mg/kg/day, PO q 6 hr; maintenance: 30–50 mg/kg/day PO q 8 hr	Headache, nausea, rash, neutropenia
Theophylline	Apnea in preterm: Loading 6–10 mg/kg; maintenance 2–4 mg/kg/dose PO q 12 hr Bronchodilator: 10–20 mg/kg/day	GI disturbance, tachycardia, feeding intolerance, irritability
Tolazoline	1–2 mg/kg IV over 10 min followed by 1–2 mg/kg/hr continuous infusion	Dizziness, faintness

Side effects: Hepatotoxicity, irritability, hearing loss, nausea, vomiting, pyrexia

Vigabatrin

Infantile spasm: 40–150 mg/kg/day PO q 12–24 hr

Side effects: Visual field defects, GI and psychiatric symptoms

VASODILATORS

Isosorbide Dinitrate

0.1 mg/kg/day PO q 6–8 hr

Side effects: Flushing, headache

Nifedipine

0.3 mg/kg/dose oral q 6 hr

Antihypertensive: 0.25–0.5 mg/kg/dose (maximum 10 mg) PO q 6 hr

Vasodilator: 0.3 mg/kg/dose PO q 6 hr

Side effects: Hypotension, dizziness

Prazosin

Antihypertensive: 0.05–0.1 mg/kg/day q 8 hr (maximum 0.5 mg/kg/dose)

Side effects: Postural hypotension, dizziness, faintness, nasal stuffiness, priapism

Tolazoline

1–2 mg/kg IV over 10 min followed by 1–2 mg/kg/hour in continuous infusion

Side effect: Dizziness, faintness

Suggested Reading

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- Singh MB, Deorari AK. Drug dosages in children, 8th edn. New Delhi, Sagar Publications, 2009.
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Integrated Management of Neonatal and Childhood Illness

Ajay Khera • Varun Alwadhvi

Many well-known interventions like universal immunization, essential newborn care, exclusive breastfeeding during first 6 months of life, appropriate complementary feeding, oral rehydration therapy, and timely and appropriate use of antibiotics in pneumonia have proven to be effective in reducing child mortality. *While each of these interventions is successful, there is evidence to suggest that an integrated approach is needed to manage sick children.*

Sick children often present with overlapping signs and symptoms common to different illnesses and often suffer from more than one illness, which may necessitate different treatments. Another reason for integrated approach is the need for incorporating preventive strategies such as immunization and nutrition along with curative care.

INTEGRATED MANAGEMENT OF NEONATAL AND CHILDHOOD ILLNESS STRATEGY

Integrated Management of Childhood Illness (IMCI) strategy, developed by World Health Organization in collaboration with UNICEF and many other agencies in mid-1990s, combines improved management of common childhood illnesses with prevention of diseases and promotion of health by including counseling on feeding and immunization. This strategy has been adapted and expanded in India to include neonatal care at home as well as in the health facilities and renamed as Integrated Management of Neonatal and Childhood Illness (IMNCI).

Essential Components

The IMNCI strategy includes both preventive and curative interventions that aim to improve practices in health facilities, the health system and at home. At the core of the strategy is integrated case management of the most common neonatal and childhood problems with a focus on the most common causes of death in children <5 years of age.

The initial guidelines developed in 2003 were adapted in 2009 and have recently been revised again in 2017 and this chapter elaborates the clinical guidelines for the

treatment of sick children in an outpatient or primary care setting.

Clinical Guidelines

The clinical guidelines target children less than 5-year-old, the age group that bears the highest burden of morbidity and mortality. The guidelines represent an evidence-based syndromic approach to case management that includes rational, effective and affordable use of drugs. *Careful and systematic assessment of common symptoms, using selected reliable clinical signs, helps to guide rational and effective actions.*

An evidence-based syndromic approach can be used to determine: (i) Health problem(s) the child may have; (ii) severity of the child's condition; and (iii) actions that can be taken to care for the child (e.g. refer the child immediately, manage with available resources or manage at home). In addition the guidelines suggest the adjustments required to manage with the capacity of health system and active involvement of family members in health care practices.

Principles of Integrated Care

Depending on a child's age, various clinical signs and symptoms differ in their degrees of reliability and diagnostic value and importance. IMNCI clinical guidelines focus on children up to 5 years of age. The treatment guidelines have been broadly described under two age categories:

1. Young infants age up to 2 months
2. Children age 2 months up to 5 years

The IMNCI guidelines are based on the following principles:

- All children under 5 years of age must be examined for conditions which indicate immediate referral
- Children must be routinely assessed for major symptoms, nutritional, quality of interaction with a child, immunization status, feeding problems and other problems
- Only a limited number of carefully selected clinical signs are used for assessment

- A combination of individual signs is used to classify the severity of illness which calls for specific action rather than a 'diagnosis'. Classifications are color-coded and suggest referral (pink), initiation of treatment in health facility (yellow) or management at home (green)
- IMNCI guidelines address most common, but not all pediatric problems
- IMNCI management protocols use a limited number of essential drugs
- Caretakers are actively involved in the treatment of children
- IMNCI includes counseling of caretakers about home care including feeding, fluids and when to return to health facility.

The overall case management process is summarized in Fig. 31.1.

The case management of a sick child brought to a first-level health facility includes a number of important elements.

Outpatient health facility: Assessment; classification and identification of treatment; referral, treatment or counseling of the child's caretaker (depending on classification(s) identified); follow-up care

Referral health facility: Emergency triage assessment and treatment (ETAT); diagnosis, treatment and monitoring of patient progress.

Appropriate home management: Teaching mothers or other caretakers how to give oral drugs and treat local infections at home; counseling mothers or other caretakers about food (feeding advice, feeding problems); development support care (playing and communication) fluids; when to return to the health facility; and the mother's own health.

Classification Tables

IMNCI classification tables describe the steps of case management process: ASSESS, CLASSIFY and IDENTIFY

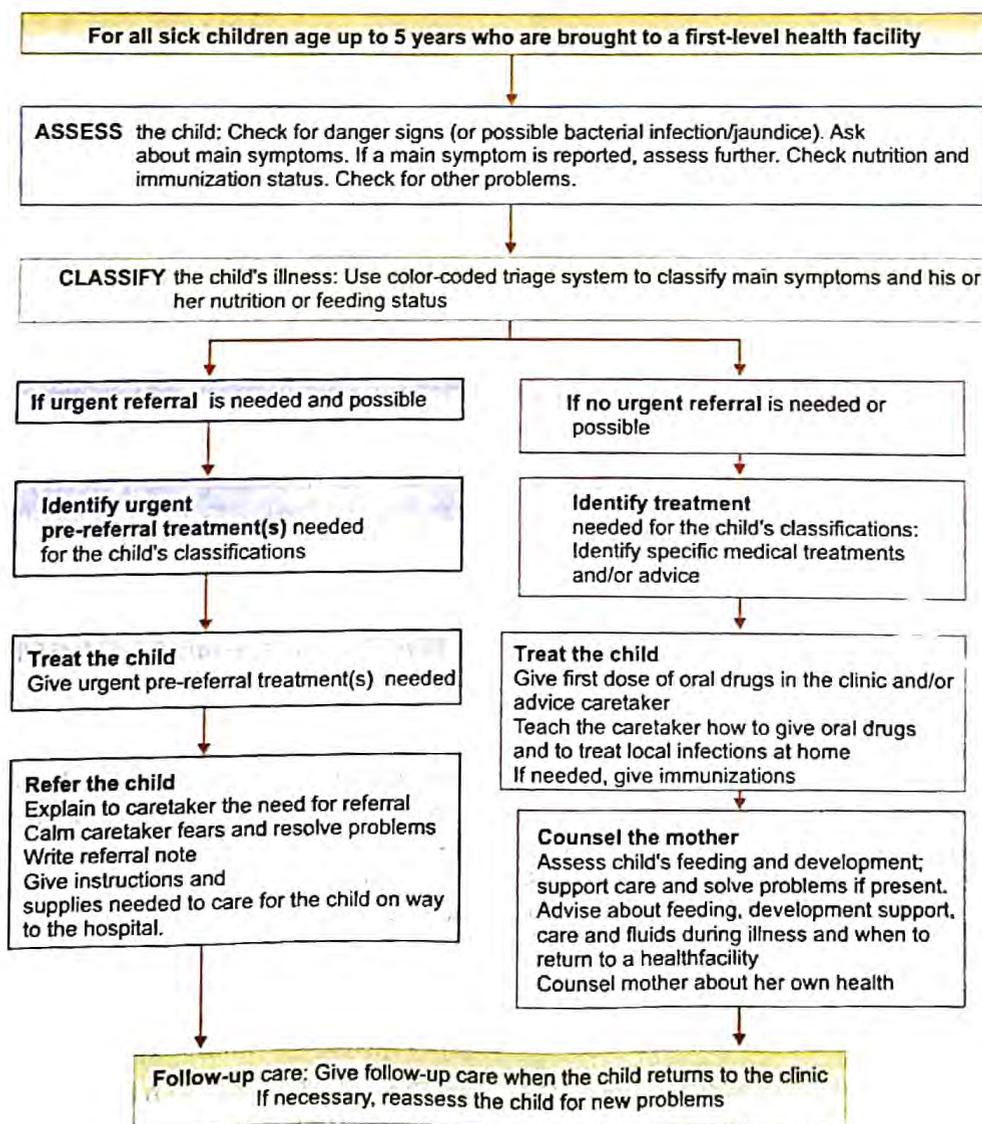


Fig. 31.1: Summary of the case management process

TREATMENT. There are separate classification boxes for main symptoms, nutritional status and anemia.

IMNCI classifications are not necessarily specific diagnoses, but they indicate what action needs to be taken. All classifications are color-coded: *pink* calls for hospital referral or admission, *yellow* for initiation of treatment, and *green* means that the child can be sent home with careful advice on when to return.

Classification tables are used starting with the *pink* rows. If the young infant or child does not have the severe classifications, look at the *yellow* rows. For the classification tables that have a *green* row, if the young infant or child does not have any of the signs in the pink or yellow rows, select the classification in the green row. If the young infant or child has signs from more than one row, the more severe classification is selected (Box 31.1). However, if the classification table has *more than one arm* (e.g. possible bacterial infection/jaundice, diarrhea in a sick child), one may have more than one classification from that box.

Box 31.1: Effective communication with care provider

It is critical to communicate effectively with the infant's mother or caretaker. Proper communication helps to reassure the mother or caretaker that the infant will receive appropriate care. In addition, the success of home treatment depends on how well the mother or caretaker knows about giving the treatment and understands its importance.

Parents, if correctly informed and counseled, can play an important role in improving the health status of their children by following the advice given by a health care provider, by applying appropriate feeding practices and by bringing sick children to a health facility as soon as symptoms arise.

OUTPATIENT MANAGEMENT OF YOUNG INFANTS AGE UP TO 2 MONTHS

Young infants have special characteristics that must be considered when classifying their illnesses. They can become sick and die very quickly from serious bacterial infections. They frequently have only general signs such as few movements, fever or low body temperature. Mild chest in drawing is normal in young infants because their chest wall is soft. The assessment procedure for this age group includes a number of important steps that must be taken by the health care provider, which are given below.

Communicating with the Caretaker

It is critical to communicate effectively with the infant's mother or caretaker. Good communication techniques and an integrated assessment are required to ensure that common problems or signs of disease or malnutrition are not overlooked.

Checking for Possible Bacterial Infection/Jaundice

A sick young infant with possible **serious bacterial infection** is one with any of the following signs: not feeding well, convulsions, fast breathing, severe chest in

drawing, fever, hypothermia, movement only when stimulated or no movement at all.

This infant should be referred urgently to the hospital after being given the first dose of intramuscular ampicillin/oral amoxicillin plus gentamicin, treatment to prevent hypoglycemia, and advice to the mother on keeping the young infant warm while arranging referral, and on the way to the hospital.

A sick young infant with **local bacterial infection** is the one with umbilicus red or draining pus or skin pustules. This infant may be treated at home with oral antibiotics but should be seen in follow-up after two days.

Additionally, if the sick young infant has jaundice, classify for **jaundice**.

There are two possible classifications

- A sick young infant with severe jaundice is one who has yellow palms and soles or has jaundice at age <24 hours or at age 14 days or more. This infant should be referred urgently to the hospital after being given treatment to prevent hypoglycemia and advice to the mother on keeping the young infant warm while arranging referral.
- A sick young infant with jaundice is one who has jaundice but the palms and soles are not yellow. This infant should be given home care, but mother should be advised when to return immediately and should be seen in follow-up in two days.

Assessing for Diarrhea

Diarrhea is a main symptom, which is assessed if the mother says it is present. Exclusively breast-fed infants normally pass frequent soft stools. This should not be confused with diarrhea. A young infant is said to have diarrhea if the stools have changed from usual pattern and the child is passing many watery stools (more water than fecal matter).

Clinical Assessment and Classification

All infants with diarrhea should be assessed for presence of dehydration. A number of clinical signs are used to determine the level of dehydration: infant's general condition (lethargic or unconscious or restless/irritable); sunken eyes and elasticity of skin (skin pinch goes back very slowly, slowly or immediately).

All young infants with diarrhea are classified for degree of dehydration. Young infants with severe dehydration will need IV fluids while those with some dehydration are treated as plan B with oral rehydration. Young infants with no dehydration will require more fluid to prevent dehydration.

Checking for Feeding Problems or Very Low Weight

All sick young infants seen in outpatient health facilities should be routinely evaluated for adequate feeding and have their weight checked). Infants who are very low

weight (weight <1800 g) are given pink classification and should be referred to a hospital. Infants who are low weight (weight 1800–2500 g) need special attention to how they are fed and on keeping them warm.

To assess the young infant for feeding problems the mother is asked specific questions about infant feeding to determine if the feeding practices are optimal. If there is no indication for referral the mother is observed for breastfeeding. Breastfeeding is observed to see the signs of attachment and whether the infant is suckling effectively. Mothers of infants with problem in feeding are counseled appropriately. Infants who are not low weight for age and have no feeding problem are classified as 'no feeding problem' and counseled about home care of young infant.

Checking Immunization Status

Immunization status should be checked in all sick young infants. A young infant who is not sick enough to be referred to a hospital should be given the necessary immunizations before he is sent home.

Assessing other Problems

All sick young infants need to be assessed for other potential problems mentioned by the mother or observed during the examination. If a potentially serious problem is found or there are no means in the clinic to help the infant, he should be referred to hospital.

Identify Treatment and Treat

The next step is to identify treatment required for the young infant according to the classification (*see* Charts). All the treatments required are listed in the 'Identify Treatment' column of the **ASSESS** and **CLASSIFY THE SICK YOUNG INFANT**. If a sick infant has more than one classification, treatment required for all the classifications must be identified. The first step is to determine if there is need to refer the child to hospital.

All infants and children with a severe classification (pink) are referred to a hospital as soon as assessment is completed and necessary pre-referral treatment is administered. Successful referral of severely ill infants to the hospital depends on effective counseling of the caretaker.

The first step is to give urgent prereferral treatment (written in bold font in identify treatment section of chart). This may be:

- Administering first dose of antibiotic
- Treatment of severe dehydration
- Prevention of hypoglycemia with breast milk; if young infant is not able to swallow give expressed breast milk/appropriate animal milk with added sugar by nasogastric tube
- In young infants with diarrhea, giving frequent sips of ORS solution on the way to the hospital.

Non-urgent treatments, e.g. applying gentian violet paint on skin pustules, should be deferred to avoid delaying referral or confusing the caretaker.

- If an infant does not need urgent referral, check to see if the infant needs non-urgent referral for further assessment. These referrals are not as urgent. Other necessary treatments may be done before referral.

Treatment in Outpatient Clinic and at Home

Young infants who have local infection, feeding problem or low weight, or diarrhea with some dehydration should have treatment initiated in clinic, which is continued at home. Counseling a mother/caretaker is critical for home care. The health professional should use good communication skills while counseling the mother/caretaker for treatment (Box 31.2).

Box 31.2: Effective communication and counseling—APAC

- *Ask and listen:* Ask the mother/caretaker and listen carefully to find out the young child's problems and what the mother/caretaker is already doing for the young infant
- *Praise:* Praise the mother/caretaker for what she has done well
- *Advise and teach:* Advise the mother/caretaker how to take care of young child at home (for tasks which require mother/caretaker to carry out treatment at home: give information, show an example, and let her practice)
- *Check:* Before the mother/caretaker leaves, always check understanding by asking questions to find out what she understands and what needs further explanation

Advise when to Return

Immediately: Return immediately if the infant has any of these signs: breastfeeding or drinking poorly, becomes sicker, develops a fever or feels cold to touch, fast breathing, difficult breathing, yellow palms and soles (if young infant has jaundice), diarrhea with blood in stool.

For follow-up visit: Return not later than 2 days if the infant has: Local bacterial infection or, jaundice or diarrhea or feeding problem or thrush; and not later than 14 days if low weight.

Next well child visit: For immunization and feeding counseling.

Counsel the Mother about her Own Health

During a sick infant visit, listen for any problems that the mother herself may be having. She may need treatment or referral for her own health problems. If the mother is sick, provide care for her, or refer her for help. Advise her to eat well to keep up her own strength and health. Check her immunization status and give tetanus toxoid if needed. Give the mother iron folic acid tablets if she is not taken them. Make sure she has access to family planning and counseling on STD and AIDS prevention.

OUTPATIENT MANAGEMENT OF SICK CHILD AGE 2 MONTHS TO 5 YEARS

The assessment procedure is similar to that of young infant including: (i) History taking and communicating with the caretaker about the child's problem; (ii) checking for general danger signs; (iii) checking main symptoms; (iv) checking for malnutrition; (v) checking for anemia; (vi) assessing the child's feeding; (vii) checking immunization status; and (viii) assessing other problems.

Communicating–History Taking

A sick child brought to an outpatient facility may have signs that clearly indicate a specific problem. However, some children may present with serious, nonspecific signs called **General Danger Signs** that do not point to a particular diagnosis. For example, a child who is lethargic or unconscious may have meningitis, severe pneumonia, cerebral malaria or any other severe disease. Great care should be taken to ensure that these general danger signs are not overlooked because they suggest that a child is severely ill and needs urgent attention.

Assessing for General Danger Signs

The following signs should be routinely checked in all children: (i) History of convulsions during the present illness, (ii) unconsciousness or lethargy, inability to drink or breastfeed when mother tries to breastfeed, or to give child something to drink; (iii) child vomits everything; and (iv) child is presently having convulsions.

If a child has one or more of these signs, he must be considered seriously ill and will almost always need referral.

Assessing for Main Symptoms

After checking for general danger signs, the health care provider must enquire about the following main symptoms: (i) Cough or difficult breathing; (ii) diarrhea; (iii) fever; and (iv) ear problems. If the symptom is present the child is evaluated for that symptom.

Cough or Difficult Breathing

Four key clinical signs are used to assess a sick child with cough or difficult breathing:

- **Fast breathing:** Cut-off respiratory rate for fast breathing is ≥ 50 breaths per minute for a child 2–12 months and ≥ 40 breaths per minute for 12 months up to 5 years
- **Lower chest wall indrawing**
- **Stridor**
- **Wheeze**

Patients with wheezing and either fast breathing or chest indrawing are given a trial of rapid acting inhaled bronchodilator for up to three times 15–20 minutes apart. The patient is observed again for respiratory rate and signs of chest indrawing, and reclassified as follows:

Classification of cough or difficult breathing: Those requiring referral for possible severe pneumonia or severe disease. This group includes children with any general danger sign, or stridor when calm. Children with severe pneumonia or severe disease most likely have an invasive bacterial organisms and diseases that may be life-threatening. The patient needs urgent referral to a hospital for treatment, such as oxygen, a bronchodilator or injectable antibiotics. **Pulse oximeter is used to determine oxygen saturation and patient referred if $< 90\%$.**

Those who require antibiotics as outpatients because they are highly likely to have **bacterial pneumonia**. A child with cough or difficult breathing who has fast breathing and or chest indrawing is classified as having pneumonia. This child should not have a general danger signs, or stridor and his oxygen saturation is $> 90\%$.

Those who simply have a cough or cold and do not require antibiotics. Such children may require a safe remedy to a relieve cough. A child with cough and cold normally improves in 1–2 weeks. However, a child with chronic cough (more than 14 days) needs to be further assessed (and, if needed, referred) to exclude tuberculosis, asthma, whooping cough or another problem.

Diarrhea

A child with diarrhea passes stools with more water than normal. A child with diarrhea may have (i) acute watery diarrhea (including cholera); (ii) dysentery (bloody diarrhea); or (iii) persistent diarrhea (diarrhea that lasts 14 days or more).

Clinical assessment and classification. All children with diarrhea should be assessed for dehydration based on the following clinical signs: General condition (lethargic or unconscious or restless/irritable); sunken eyes; child's reaction when offered to drink (not able to drink or drinking poorly or drinking eagerly/thirsty or drinking normally) and elasticity of skin (skin pinch goes back very slowly, slowly or immediately). In addition a child with diarrhea should be asked how long the child has had diarrhea and if there is blood in the stool. This will allow identification of children with persistent diarrhea and dysentery.

Fever

All cases with fever are suspected to have malaria after ruling out other common causes and should be investigated for confirmation of malaria by microscopy or rapid diagnostic kit (RDK) so as to ensure treatment with full therapeutic dose with appropriate drug to all confirmed cases.

History of duration of fever is important in evaluating fever. If fever has persisted daily for more than seven days the child needs to be referred to hospital for assessment and diagnostic tests. The other signs looked for in a child with fever include general danger signs (assessed earlier)

and signs of meningitis, e.g. stiff neck. Besides these, signs of measles such as cough/difficult breathing, diarrhea, cornea clouding, mouth ulcers and ear infections. Before classifying fever, one should check for other obvious causes of fever.

Ear Problems

A child with an ear problem may have otitis. It may be acute or chronic infection. If the infection is not treated, the ear drum may perforate. The mother is asked about history of ear pain and ear discharge or pus. The child is examined for tender swelling behind the ear. Based on these clinical findings a child can be classified as mastoiditis, acute ear infection, chronic ear infection or no ear infection. Children with mastoiditis are classified as severe illness and referred urgently to hospital. Children with acute ear infection are given oral antibiotics and those with chronic ear infection are advised to keep the ear dry by wicking.

Checking for Malnutrition

After assessing for general danger signs and the four main symptoms, all children should be assessed for malnutrition. There are two main reasons for routine assessment of nutritional status in sick children: (i) To identify children with severe malnutrition who are at increased risk of mortality and need urgent referral to provide active treatment; and (ii) to identify children with suboptimal nutritional status resulting from ongoing deficits in dietary intake plus repeated episodes of infection and who may benefit from nutritional counseling.

Clinical assessment and classification: Edema of both feet; weight for height; mid-upper arm circumference (only for children 6–59 months)

The child is classified as **Complicated Severe Acute Malnutrition** when they have severe acute malnutrition (edema of both feet, weight for height/length less than -3 SD scores, or mid-upper arm circumference less than 115 mm) and at least one medical complication, including any general danger sign, any severe classification, or pneumonia with chest indrawing or a feeding problem in children under 6 months. Children classified as having **complicated severe acute malnutrition** are at high risk of death from pneumonia, diarrhea, measles, and other severe diseases. These children need *urgent referral* to hospital where their treatment can be carefully monitored.

If the child has at least one sign of severe acute malnutrition, but does not have other signs of complication, they are classified as **Uncomplicated Severe Acute Malnutrition**. A child is classified as **Moderate Acute Malnutrition** if the weight-for-age is between -3 and -2 Z-scores or MUAC is between 115 and 125 mm. The child is classified as **No Acute Malnutrition** if the child has a weight-for-age over -2 Z-scores, and has no other signs of malnutrition.

Checking for Anemia

Palmar pallor can help to identify sick children with severe anemia. Wherever feasible, diagnosis of anemia can be supported by using a simple laboratory test for hemoglobin estimation. For clinical assessment of anemia the color of the child's palm is compared with examiner's own palm. If the skin of the child's palm is pale, the child has some palmar pallor. If the skin of the palm is very pale or so pale that it looks white, the child has severe palmar pallor. Pallor is classified as severe anemia, anemia or no anemia.

Assessing Child's Feeding and Development Support Care

All children less than 2 years old and all children classified as **moderate acute malnutrition** need to be assessed for feeding and development support care.

Feeding assessment includes questioning the mother or caretaker about: (i) Breastfeeding frequency and night feeds; (ii) types of complimentary foods or fluids, frequency of feeding and whether feeding is active; and (iii) feeding patterns during the current illness. The mother or caretaker should be given appropriate advice to help overcome any feeding problems found.

Assessment of development support care includes assessment of mother's sensitivity and responsiveness to the child's needs through questioning the mother or caretaker about: (i) Playing with the baby; (ii) talking to the baby, and (iii) making the baby smile and the learning pattern of the child. The mother or caretaker should be given appropriate advice to help overcome any playing and communication problems found (for more details, refer to the section on counselling the mother or caretaker).

Identify Feeding Problems

It is important to complete the assessment of feeding by referring to age appropriate feeding recommendations and identify all the feeding problems before giving advice. Other common feeding problems are: Difficulty breastfeeding, use of feeding bottle, lack of active feeding and not feeding well during illness.

Identify Developmentally Supportive (Family Interaction) Problems

It is important to complete the assessment of family interaction and identify all the problems before giving advice. Based on the mother's answers to the questions, identify any differences between the family's actual interaction (sensitivity and responsiveness) and the recommendations. These differences are problems. Some examples of interaction problems are listed in Box 31.3.

Box 31.3: Examples of Interaction problems

<i>Family interaction</i>	<i>Recommended action</i>
Mother reports, "she does not play with baby"	Discuss ways to help baby see, hear, feel and move, appropriate for age, ask caregiver to do play or communication activity, appropriate for age
Mother reports, "she does not talk to child or talks harshly to child"	If baby is less than 6 months ask caregiver to look into baby's eyes and talk to baby. For older children give caregiver and child an activity to do together. Help mother interpret what child is doing and thinking and see child respond and smile. If the mother scolds child, help caregiver distract child from unwanted actions by giving alternative toy or activity. If the mother is not able to comfort child and child does not look at the mother for comfort: help mother look into child's eyes and gently talk to child and hold child.
Mother tries to force smile or is not responsive to baby	Ask mother to make large gestures and cooing sounds; copy baby's sounds and gestures and see baby's responses.
Mother says the child is slow to learn	Encourage more activity with the child, check hearing and seeing. Refer child with difficulties

Checking Immunization, Vitamin A and Folic Acid Supplementation and Deworming Status

The immunization status of every sick child brought to a health facility should be checked. After checking immunization status, determine if the child needs vitamin A supplementation and/or prophylactic iron folic acid supplementation or deworming administration.

Assessing other Problems

The IMNCI clinical guidelines focus on five main symptoms. In addition, the assessment steps within each main symptom take into account several other common problems. For example, conditions such as meningitis, sepsis, tuberculosis, conjunctivitis, and different causes of fever such as ear infection and sore throat are routinely assessed within the IMNCI case management process.

Identify Treatment and Treat

All the treatments required are listed in the **Identify Treatment** column of the **Assess and Classify the Sick Child Age 2 months up to 5 years** (see Chart). All sick children with a severe classification (pink) are referred to a hospital as soon as assessment is completed and

necessary pre-referral treatment is administered. If a child only has severe dehydration and no other severe classification, and IV infusion is available in the outpatient clinic, an attempt should be made to rehydrate the sick child. The principles of referral of a sick child are similar to those described for a sick young infant.

Referral of Children Age 2 Months to 5 Years**For all children before referral**

1. Prevent low blood sugar by giving breast milk or sugar water.
2. For convulsions give diazepam (10 mg/2 mL solution) in dose 0.2 mg per kg (0.05 ml/kg) IV or rectally; if convulsions continue after 10 minutes, give a second dose of diazepam.
3. For severe pneumonia or severe disease (as also for mastoiditis), give first dose of IV or intramuscular antibiotic. Options for an intramuscular antibiotic for pre-referral use include (ampicillin plus gentamicin combination, OR ceftriaxone).
4. For very severe febrile disease, give one dose of paracetamol for high fever (38.5°C or above); give first dose of intramuscular quinine/artesunate for severe malaria in high *Plasmodium falciparum* area, and give first dose of an appropriate antibiotic.
5. For severe complicated measles, give first dose of appropriate antibiotic, give vitamin A, and if there is clouding of the cornea or pus draining from the eye, apply tetracycline eye ointment.
6. For severe dehydration, IV fluids should be given in the outpatient clinic according to WHO Treatment Plan C. Give 100 mL/kg IV fluids. Ringer's lactate solution is the preferred commercially available solution.
7. For severe persistent diarrhea, treat dehydration before referral using WHO Treatment Plan B for some dehydration and Plan C for severe dehydration.
8. For severe acute malnutrition, give first dose of intramuscular antibiotics. Options for an intramuscular antibiotic for pre-referral use include ampicillin plus gentamicin combination OR ceftriaxone. Oral amoxicillin can be an option.

Treatment in Outpatient Clinics and at Home

Identify the treatment associated with each nonreferral classification (yellow and green) in the IMNCI chart. Treatment uses a minimum of affordable essential drugs (Box 31.4).

Counseling a Mother or Caretaker

A child who is seen at the clinic needs to continue treatment, feeding and fluids at home. The child's mother or caretaker also needs to recognize when the child is not improving, or is becoming sicker. The success of home treatment depends on how well the mother or caretaker

Box 31.4: Treatment in outpatient clinics or at home

<i>Classification</i>	<i>Treatment</i>
Pneumonia	Oral amoxicillin for five days.
No pneumonia—cough or cold some dehydration	Soothe the throat and relieve the cough with a safe remedy. WHO Treatment Plan B Give initial treatment with ORS over a period of four hours; a total of 75 ml per kg. If the child is breastfed, breastfeeding should continue. After four hours, the child is reassessed and reclassified for dehydration, and feeding should begin; resuming feeding early is important to provide required amounts of potassium and glucose. When there are no signs of dehydration, the child is put on Plan A. If there is still some dehydration, Plan B should be repeated. If the child now has severe dehydration, the child should be put on Plan C. Zinc supplements are given to children with acute diarrhea, persistent diarrhea and dysentery for 14 days.
No dehydration	WHO Treatment Plan A Plan A focuses on the four rules of home treatment: Give extra fluids, zinc supplements, continue feeding, and advise the caretaker when to return to the doctor (if the child develops blood in the stool, drinks poorly, becomes sicker, or is not better in three days). Fluids should be given as soon as diarrhea starts; the child should take as much as she/he wants. Correct home therapy can prevent dehydration in many cases. ORS may be used at home to prevent dehydration. However, other fluids that are commonly available in the home may be less costly, more convenient and almost as effective. Most fluids that a child normally takes can also be used for home therapy especially when given with food. Zinc supplements are given to children with acute diarrhea, persistent diarrhea and dysentery for 14 days.
Persistent diarrhea	Encourage the mother to continue breastfeeding. If yoghurt is available, give it in place of any animal milk usually taken by the child; yoghurt contains less lactose and is better tolerated. If animal milk must be given, limit it to 50 ml/kg per day; greater amounts may aggravate the diarrhea. If milk is given, mix it with the child's cereal and do not dilute the milk. Food needs to be given in frequent, small meals, at least six times a day. All children with persistent diarrhea should receive supplementary multivitamins and minerals (copper, iron, magnesium, zinc) each day for two weeks.
Dysentery	The key elements of dysentery treatment are: Antibiotics, fluids, zinc supplements, feeding, and follow-up. Selection of an antibiotic is based on sensitivity patterns of strains of <i>Shigella</i> isolated in the area (cefixime or ciprofloxacin is the drug of choice in many areas) for 5 days.
Malaria/suspected malaria Fever—Malaria unlikely	Use drugs recommended by the National Anti-Malaria Program in India. Give one dose of paracetamol for high fever (38.5°C or above). Treat other obvious causes of fever.
Measles with eye or mouth complications	Give first dose of vitamin A. If clouding of cornea or pus draining from the eye, apply tetracycline eye ointment. If mouth ulcers, treat with gentian violet.
Measles currently (or within the last 3 months)	Give first dose of vitamin A.
Acute ear infection	Give appropriate antibiotic for five days; give one dose of paracetamol for pain; dry the ear by wicking.
Chronic ear infection	Dry the ear by wicking.
Uncomplicated severe acute malnutrition	Counsel the mother on how to feed the child
Moderate acute malnutrition	Assess the child's feeding and counsel the mother accordingly on feeding.
No acute malnutrition	If the child is less than 2 years old, assess the child's feeding and counsel the mother accordingly on feeding.
Anemia	Give iron folic acid therapy as per national guidelines.
No anemia	Give prophylactic iron folic acid as per national guidelines.

knows how to give treatment, understands its importance and knows when to return to a health care provider. Table 31.1 lists the specific times to advise a mother or caretaker to return to a health facility.

Table 31.1: Follow-up visits

When to return

Immediately

- Any sick child not able to drink or breastfeed, or becomes sicker or develops a fever
- If child has no pneumonia: Cough or cold, also return if fast breathing or difficult breathing
- If child has diarrhea, also return if blood in stool or drinking poorly

For follow-up visit (not later than ...)

- **2 days:** Pneumonia, dysentery, malaria/suspected malaria/fever; malaria unlikely if fever persists; measles with eye or mouth complications.
- **5 days:** Diarrhea, if not improving, persistent diarrhea, acute ear infection, chronic ear infection, uncomplicated acute malnutrition/feeding problem, any other illness, if not improving.
- **14 days:** Anemia
- **30 days:** Moderate acute malnutrition

Advise when to return for the next immunization according to immunization schedule.

Salient Adaptations in IMNCI (2017)

In general the adaptations were undertaken to update as per global advancements and in line with the various guidelines of India released from time to time. The adaptation took into consideration revised WHO IMCI charts released in 2014 and antimicrobial therapy advancements. A major adaptation included incorporation of Early Child Development messages along with nutritional counseling.

- Reduction of signs of possible severe bacterial infection (PSBI) in young infants
- Revised drug dosages for pre-referral treatment of possible severe bacterial infection
- Simplified classifications of diarrhea in young Infants
- Mandatory assessment of breastfeeding in all young infants
- Revised immunization schedule and addition of deworming as per immunization and deworming policy of India
- Removed weight for age as criteria for referral and referral of low birth weight aligned with other existing new-born training packages
- Added classifying danger signs as severe disease with addition of convulsing now
- Added use of rapid acting bronchodilator before classifying wheeze with fast breathing/chest indrawing in children presenting with cough or difficult breathing
- Revised signs for classifying pneumonia as per WHO recommendations
- Added use of pulse oximetry for classifying pneumonia
- Revised classification of fever as per National Anti-Malaria Program guidelines including use of RDT and drugs for treating malaria
- Signs for severe acute malnutrition revised
- Added early child development in the section on feeding counseling

Suggested Reading

- IMCI: Global Survey report. World Health Organization; 2017
- Integrated Management of Childhood Illness Chart Booklet. Geneva: World Health Organization; 2014
- Oxygen therapy for children: a manual for health workers. Geneva: World Health Organization; 2016
- Pediatric emergency triage, assessment and treatment: care of critically ill children: Updated guideline. Integrated Management of Child Illness. World Health Organization; 2016

IMNCI Charts are provided in the next few pages

ASSESS AND CLASSIFY THE SICK YOUNG INFANT AGE UP TO 2 MONTHS

ASSESS

- ASK THE MOTHER WHAT THE YOUNG INFANT'S PROBLEMS ARE
- Determine if this is an initial or follow-up visit for this problem.
 - if follow-up visit, use the follow-up instructions on the bottom of this chart.
 - if initial visit, assess the young infant as follows:

USE ALL BOXES THAT
MATCH INFANT'S
SYMPTOMS AND
PROBLEMS TO
CLASSIFY THE ILLNESS.

CLASSIFY IDENTIFY TREATMENT

A child with a pink classification needs URGENT attention, complete the assessment and prereferral treatment immediately so referral is not delayed

CHECK FOR POSSIBLE BACTERIAL INFECTION / JAUNDICE

ASK: LOOK, LISTEN, FEEL:

- Is the infant having difficulty in feeding?
- Has the infant had convulsions?
- Count the breaths in one minute. Repeat the count if elevated.
- Look for severe chest indrawing.
- Look at the umbilicus. Is it red or draining pus?
- Look for skin pustules
- Measure axillary temperature (if not possible, feel for fever or low body temperature).
- Look at the young infant's movements
If infant is sleeping, ask the mother to awake him/her.
 - Does the infant move on his/her own?
 - *If the young infant is not moving, gently stimulate him/her.*
 - Does the infant not move at all?
- Look for jaundice?
Are the palms and soles yellow?

YOUNG INFANT MUST BE CALM

Classify ALL YOUNG INFANTS

And if the infant has jaundice

SIGNS

CLASSIFY AS

IDENTIFY TREATMENT (Urgent pre-referral treatments are in bold print.)

<ul style="list-style-type: none"> • Not able to feed or • Convulsions or • Fast breathing (60 breaths per minute or more) or • Severe chest indrawing or • Axillary temperature 37.5°C or above (or feels hot to touch) or • Axillary temperature less than 35.5°C (or feels cold to touch) or • Movement only when stimulated or no movement at all. 	POSSIBLE SERIOUS BACTERIAL INFECTION	<ul style="list-style-type: none"> ➤ Give first dose of ampicillin /oral amoxycillin and intramuscular gentamicin. ➤ Treat to prevent low blood sugar. ➤ Warm the young infant by skin to skin contact while arranging referral. ➤ Advise mother how to keep the young infant warm on the way to the hospital. ➤ Refer URGENTLY to hospital
<ul style="list-style-type: none"> • Umbilicus red or draining pus or • Skin pustules. 	LOCAL BACTERIAL INFECTION	<ul style="list-style-type: none"> ➤ Give oral amoxycillin for 5 days. ➤ Teach mother to treat local infections at home. ➤ Follow up in 2 days.
<ul style="list-style-type: none"> • Palms and soles yellow or • Any jaundice at age < 24 hours or age 14 days or more 	SEVERE JAUNDICE	<ul style="list-style-type: none"> ➤ Treat to prevent low blood sugar. ➤ Warm the young infant by skin to skin contact while arranging referral. ➤ Advise mother how to keep the young infant warm on the way to the hospital. ➤ Refer URGENTLY to hospital
<ul style="list-style-type: none"> • Palms and soles not yellow 	JAUNDICE	<ul style="list-style-type: none"> ➤ Advise mother to give home care for the young infant. ➤ Follow up in 2 days.

AGE UP TO 2 MONTHS

THEN ASK:

Does the young infant have diarrhoea?*

IF YES LOOK AND FEEL:

- Look at the young infant's general condition: Infant's movements
 - ◆ Does the infant move on his/her own?
 - ◆ Does the infant move only when stimulated but then stops?
 - ◆ Does the infant not move at all?
 - ◆ Is the infant restless and irritable?
- Look for sunken eyes.
- Pinch the skin of the abdomen. Does it go back:
 - ◆ Very slowly (longer than 2 seconds)?
 - ◆ Slowly?

Classify DIARRHOEA

<p>Two of the following signs:</p> <ul style="list-style-type: none"> • Movement only when stimulated or no movement at all • Sunken eyes • Skin pinch goes back very slowly. 	<p>SEVERE DEHYDRATION</p>	<p>➤ Give first dose of intramuscular ampicillin (Oral Amoxycillin) and gentamicin.</p> <p>➤ If infant also has another severe classification:</p> <ul style="list-style-type: none"> - Refer URGENTLY to hospital with mother giving frequent sips of ORS on the way. - Advise mother to continue breastfeeding. - Advise mother how to keep the young infant warm on the way to the hospital. <p>➤ If infant does not have any other severe classification:</p> <ul style="list-style-type: none"> - Give fluid for severe dehydration (Plan C) and then refer to hospital after rehydration
<p>Two of the following signs:</p> <ul style="list-style-type: none"> • Restless, irritable. • Sunken eyes. • Skin pinch goes back slowly. 	<p>SOME DEHYDRATION</p>	<p>➤ If infant also has another severe classification or Low Weight:</p> <ul style="list-style-type: none"> - Give first dose of intramuscular ampicillin (Oral Amoxycillin) and gentamicin - Refer URGENTLY to hospital with mother giving frequent sips of ORS on the way. - Advise mother to continue breastfeeding. - Advise mother how to keep the young infant warm on the way to the hospital. <p>➤ If infant does not have low weight or another severe classification:</p> <ul style="list-style-type: none"> - Give fluids for some dehydration (Plan B). - Advise mother when to return immediately. - Follow up in 2 days
<p>• Not enough signs to classify as some or severe dehydration.</p>	<p>NO DEHYDRATION</p>	<p>➤ Give fluids to treat diarrhea at home (Plan A).</p> <p>➤ Follow up in 5 days if not improving.</p>

* What is diarrhea in a young infant?

If the stools have changed from usual pattern and are many and watery (more water than fecal matter). The normally frequent or loose stools of a breastfed baby are not diarrhea.

AGE UP TO 2 MONTHS

THEN CHECK FOR FEEDING PROBLEM OR VERY LOW WEIGHT:

ASK:

- Is the infant breastfed? If yes, how many times in 24 hours?
- Does the infant usually receive any other foods or drinks? If yes, how often?
- What do you use to feed the infant?

LOOK, FEEL:

- Determine weight
<1800 gm
1800–2500 gm
≥2500 gm

Classify
FEEDING

IF AN INFANT: Has no indications to refer urgently to hospital:

ASSESS BREASTFEEDING:

- Has the infant breastfed in the previous hour? If the infant has not fed in the previous hour, ask the mother to put her infant to the breast. Observe the breastfeed for 4 minutes. (If the infant was fed during the last hour, ask the mother if she can wait and tell you when the infant is willing to feed again.)

- Is the infant able to attach?
no attachment at all not well attached good attachment

TO CHECK ATTACHMENT, LOOK FOR:

- Chin touching breast
- Mouth wide open
- Lower lip turned outward
- More areola visible above than below the mouth

(All of these signs should be present if the attachment is good)

- Is the infant suckling effectively (that is, slow deep sucks, sometimes pausing)?
not suckling at all not suckling effectively suckling effectively
Clear a blocked nose if it interferes with breastfeeding.
- Look for ulcers or white patches in the mouth (thrush).

- Does the mother have pain while breastfeeding? If yes, look and feel for:
 - Flat or inverted nipples, or sore nipples
 - Engorged breasts or breast absces

<ul style="list-style-type: none"> • Weight <1800 gm 	Very Low Weight	<ul style="list-style-type: none"> ➢ Treat to prevent low blood sugar. ➢ Advise mother how to keep the young infant warm on the way to the hospital ➢ Refer URGENTLY to hospital
<ul style="list-style-type: none"> • Not well attached to breast or • Not suckling effectively or • Less than 8 breastfeeds in 24 hours or • Receives other foods or drinks or • Thrush (ulcers or white patches in mouth) or • Weight 1800–2500 gm or • Breast or nipple problems 	FEEDING PROBLEM OR LOW WEIGHT	<ul style="list-style-type: none"> ➢ If not well attached or not suckling effectively, teach correct position and attachment ➢ If breastfeeding less than 8 times in 24 hours, advise to increase frequency of feeding. ➢ If receiving other foods or drinks, counsel mother about breastfeeding more, reducing other foods or drinks, and using a cup and spoon. • If not breastfeeding at all, advise mother about giving locally appropriate animal milk and teach the mother to feed with a cup and spoon. ➢ If thrush, teach the mother to treat thrush at home. ➢ If low weight, teach the mother how to keep the young infant with low weight warm at home. ➢ If breast or nipple problem, teach the mother to treat breast or nipple problems. ➢ Advise mother to give home care for the young infant. ➢ Advise mother when to return immediately. ➢ Follow-up any feeding problem or thrush in 2 days. ➢ Follow-up low weight in 14 days.
<ul style="list-style-type: none"> • Weight ≥2500 gm and no other signs of inadequate feeding. 	NO FEEDING PROBLEM	<ul style="list-style-type: none"> ➢ Advise mother to give home care for the young infant. ➢ Praise the mother for feeding the infant well.

AGE UP TO 2 MONTHS

THEN CHECK THE YOUNG INFANT'S IMMUNIZATION STATUS:

	<u>AGE</u>	<u>VACCINE</u>		
IMMUNIZATION SCHEDULE*:	Birth	OPV 0	BCG	HEP-B 0
	6 weeks	OPV 1	Penta-1	Rota Virus

*Rotavirus to be given wherever included in the immunization schedule.

ASSESS OTHER PROBLEMS

ASSESS AND CLASSIFY THE SICK CHILD AGE 2 MONTHS UP TO 5 YEARS

ASSESS

ASK THE MOTHER WHAT THE CHILD'S PROBLEMS ARE

- Determine if this is an initial or follow-up visit for this problem.
 - if follow-up visit, use the follow-up instructions on *TREAT THE CHILD* chart.
 - if initial visit, assess the child as follows:

CHECK FOR GENERAL DANGER SIGNS

ASK:

- Is the child able to drink or breastfeed?
- Does the child vomit everything?
- Has the child had convulsions?

LOOK:

- See if the child is lethargic or unconscious.
- Is the child convulsing now?

Urgent attention

A child with any general danger sign needs **URGENT** attention; complete the assessment and any pre-referral treatment immediately so referral is not delayed.

CLASSIFY

USE ALL BOXES THAT MATCH THE CHILD'S SYMPTOMS AND PROBLEMS TO CLASSIFY THE ILLNESS.

IDENTIFY TREATMENT

SIGNS	CLASSIFY AS	IDENTIFY TREATMENT
<ul style="list-style-type: none"> • Any general danger sign 	<p>VERY SEVERE DISEASE</p>	<ul style="list-style-type: none"> ➤ Give diazepam if convulsing now and maintain airway ➤ Quickly complete the assessment ➤ Treat to prevent low blood sugar ➤ Refer URGENTLY to hospital



ASSESS AND CLASSIFY THE SICK CHILD AGE 2 MONTHS UP TO 5 YEARS

ASSESS

ASK THE MOTHER WHAT THE CHILD'S PROBLEMS ARE

- Determine if this is an initial or follow-up visit for this problem.
 - if follow-up visit, use the follow-up instructions on *TREAT THE CHILD* chart.
 - if initial visit, assess the child as follows:

CLASSIFY

USE ALL BOXES THAT MATCH THE CHILD'S SYMPTOMS AND PROBLEMS TO CLASSIFY THE ILLNESS.

IDENTIFY TREATMENT

THEN ASK ABOUT MAIN SYMPTOMS:
Does the child have cough or difficult breathing?

<p>IF YES, ASK:</p> <ul style="list-style-type: none"> • For how long? 	<p>LOOK, LISTEN:</p> <ul style="list-style-type: none"> • Count the breaths in one minute. • Look for chest indrawing. • Look and listen for stridor. • Look and listen for wheezing. <p>If wheezing with either fast breathing or chest indrawing: Give a trial of rapid acting inhaled bronchodilator for up to three times 15–20 minutes apart. Count the breaths and look for chest indrawing again, and then classify.</p> <p>Fast breathing is: 2 months up to 12 months: 50 breaths per minute or more 12 months up to 5 years: 40 breaths per minute or more</p>	<p>CHILD MUST BE CALM</p>
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**Classify
COUGH or
DIFFICULT
BREATHING**

SIGNS	CLASSIFY AS	IDENTIFY TREATMENT (Urgent pre-referral treatments are in bold print.)
<ul style="list-style-type: none"> • Any general danger sign or • Stridor in calm child. 	SEVERE PNEUMONIA OR VERY SEVERE DISEASE	<ul style="list-style-type: none"> > Give first dose of ampicillin/oral amoxycillin and intramuscular gentamicin. > Refer URGENTLY to hospital.
<ul style="list-style-type: none"> • Chest indrawing or • Fast breathing. 	PNEUMONIA	<ul style="list-style-type: none"> > Give Amoxycillin for 5 days. > If wheezing (or disappeared after rapidly acting bronchodilator) give an inhaled bronchodilator for 5 days* > Soothe the throat and relieve the cough with a safe remedy if child is 6 months or older. > If coughing more than 14 days or recurrent wheeze, refer for possible TB or asthma assessment > Advise mother when to return immediately. > Follow-up in 2 days. > If Oxygen saturation <90% by Pulse Oximeter refer urgently
No signs of pneumonia or very severe disease.	NO PNEUMONIA: COUGH OR COLD	<ul style="list-style-type: none"> > If wheezing (or disappeared after rapidly acting bronchodilator) give an inhaled bronchodilator for 5 days* > Soothe the throat and relieve the cough with a safe home remedy if child is 6 months or older. > If coughing more than 14 days or recurrent wheeze, refer for possible TB or asthma assessment > Advise mother when to return immediately. > Follow-up in 5 days if not improving.

*In settings where inhaled bronchodilator is not available, oral salbutamol may be tried but not recommended for treatment of severe acute wheeze

Ensure availability of pulse oximeter, determine oxygen saturation and refer if <90%.

AGE 2 MONTHS UP TO 5 YEARS

Does the child have diarrhoea?

IF YES, ASK: LOOK AND FEEL:

- For how long?
- Is there blood in the stool?
- Look at the child's general condition. Is the child:
 - Lethargic or unconscious?
 - Restless and irritable?
- Look for sunken eyes.
- Offer the child fluid. Is the child:
 - Not able to drink or drinking poorly?
 - Drinking eagerly, thirsty?
- Pinch the skin of the abdomen. Does it go back:
 - Very slowly (longer seconds)?
 - Slowly?

Classify DIARRHOEA

for DEHYDRATION

Two of the following signs: <ul style="list-style-type: none"> • Lethargic or unconscious • Sunken eyes • Not able to drink or drinking poorly • Skin pinch goes back very slowly. 	SEVERE DEHYDRATION	> If child has no other severe classification: <ul style="list-style-type: none"> - Give fluid for severe dehydration (Plan C). > If child also has another severe classification: <ul style="list-style-type: none"> Refer URGENTLY to hospital with mother giving frequent sips of ORS on the way. Advise the mother to continue breastfeeding. > If child is 2 years or older and there is cholera in your area, give doxycycline for cholera.
Two of the following signs: <ul style="list-style-type: none"> • Restless, irritable • Sunken eyes • Drinks eagerly, thirsty • Skin pinch goes back slowly. 	SOME DEHYDRATION	> Give fluid, zinc supplements and food for some dehydration (Plan B). <ul style="list-style-type: none"> > If child also has a severe classification: Refer URGENTLY to hospital with mother giving frequent sips of ORS on the way. Advise the mother to continue breastfeeding. > Advise mother when to return immediately. > Follow-up in 5 days if not improving.
Not enough signs to classify as some or severe dehydration.	NO DEHYDRATION	> Give fluid, zinc supplements and food to treat diarrhoea at home (Plan A). <ul style="list-style-type: none"> > Advise mother when to return immediately. > Follow-up in 5 days if not improving.
• Dehydration present.	SEVERE PERSISTENT DIARRHOEA	> Treat dehydration before referral unless the child has another severe classification. <ul style="list-style-type: none"> > Refer to hospital.
• No dehydration.	PERSISTENT DIARRHOEA	> Advise the mother on feeding a child who has PERSISTENT DIARRHOEA. <ul style="list-style-type: none"> > Give single dose of vitamin A. > Give zinc supplements daily for 14 days. > Follow-up in 5 days.
• Blood in the stool.	DYSENTERY	> Treat for 5 days with cefixime. <ul style="list-style-type: none"> > Treat dehydration > Give zinc supplements for 14 days > Follow-up in 2 days.

and if diarrhoea 14 days or more

and if blood in stool

AGE 2 MONTHS UP TO 5 YEARS

Does the child have fever? (by history or feels hot or temperature 37.5°C* or above)

IF YES:
Is it a PF (*p.falciparum*) predominant area? Yes/No

THEN ASK:

LOOK AND FEEL:

- Fever for how long?
- If more than 7 days, has fever been present every day?
- Has the child had measles within the last 3 months?

LOOK AND FEEL:

- Look or feel for stiff neck.
- Look for runny nose.
- Look for any bacterial cause of fever.

Look for signs of MEASLES

- ◆ Generalized rash and
- ◆ One of these: cough, runny nose, or red eyes.

Test POSITIVE /NEGATIVE/NA
P. falciparum/ *P. vivax*

If the child has measles now or within the last 3 months:

- Look for mouth ulcers. Are they deep and extensive?
- Look for pus draining from the eye.
- Look for clouding of the cornea.

Classify FEVER

Classify MEASLES

<ul style="list-style-type: none"> • Any general danger sign or • Stiff neck 	VERY SEVERE FEBRILE DISEASE	<ul style="list-style-type: none"> ➢ Give first dose of ampicillin / oral amoxycillin and intramuscular gentamicin. ➢ If PF Predominant area give first dose of IM quinine /artesunate after making a smear/RDT ➢ Treat the child to prevent low blood sugar. ➢ Give one dose of paracetamol in clinic for high fever (temp 38.5°C or above). ➢ Refer URGENTLY to hospital.
<ul style="list-style-type: none"> • Positive RDT 	MALARIA	<ul style="list-style-type: none"> ➢ Give antimalarial as per NAMP guidelines ➢ Give one dose of paracetamol in clinic for high fever. ➢ Advise extra fluids, continue feeding and advise about danger signs. ➢ Follow-up in 2 days if fever persists. ➢ If fever is present every day for more than 7 days, refer for assessment.
<ul style="list-style-type: none"> • Negative RDT/ RDT Not Available and • No other cause of fever. 	SUSPECTED MALARIA	<ul style="list-style-type: none"> ➢ Give one dose of paracetamol in clinic for high fever (temp. 38.5°C or above). ➢ Advise mother when to return immediately. ➢ Follow-up in 2 days if fever persists ➢ If fever is present every day for more than 7 days, refer for
<ul style="list-style-type: none"> • Negative RDT/ RDT Not Available and • Other cause of fever PRESENT** 	FEVER MALARIA UNLIKELY	<ul style="list-style-type: none"> ➢ Give first dose of Vitamin A. ➢ Give first dose of ampicillin / oral amoxycillin and intramuscular gentamicin. ➢ If clouding of the cornea or pus draining from the eye, apply tetracycline eye ointment. ➢ Refer URGENTLY to hospital
<ul style="list-style-type: none"> • Any general danger sign or • Clouding of cornea or • Deep or extensive mouth ulcers. 	SEVERE COMPLICATED MEASLES	<ul style="list-style-type: none"> ➢ Give first dose of Vitamin A. ➢ If pus draining from the eye, treat eye infection with tetracycline eye ointment ➢ If mouth ulcers, treat with gentian violet ➢ Follow-up in 2 days.
<ul style="list-style-type: none"> • Pus draining from the eye or • Mouth ulcers. 	MEASLES WITH EYE OR MOUTH COMPLICATIONS	<ul style="list-style-type: none"> ➢ Give first dose of Vitamin A. ➢ If pus draining from the eye, treat eye infection with tetracycline eye ointment ➢ If mouth ulcers, treat with gentian violet ➢ Follow-up in 2 days.
<ul style="list-style-type: none"> • Measles now or within the last 3 months. 	MEASLES	<ul style="list-style-type: none"> ➢ Give first dose of Vitamin A.

Does the child have an ear problem?

IF YES, ASK:

- Is there ear pain?
- Is there ear discharge? if yes, for how long?

LOOK AND FEEL:

- Look for pus draining from the ear.
- Feel for tender swelling behind the ear.

Classify EAR PROBLEM

<ul style="list-style-type: none"> • Tender swelling behind the ear. 	MASTOIDITIS	<ul style="list-style-type: none"> ➢ Give first dose of ampicillin/ oral amoxycillin and intramuscular gentamicin. ➢ Give first dose of paracetamol for pain. ➢ Refer URGENTLY to hospital
<ul style="list-style-type: none"> • Pus is seen draining from the ear and discharge is reported for less than 14 days, or • Ear pain. 	ACUTE EAR INFECTION	<ul style="list-style-type: none"> ➢ Give Amoxycillin for 5 days. ➢ Give paracetamol for pain. ➢ Dry the ear by wicking. ➢ Follow-up in 5 days.
<ul style="list-style-type: none"> • Pus is seen draining from the ear and discharge is reported for 14 days or more. 	CHRONIC EAR INFECTION	<ul style="list-style-type: none"> ➢ Dry the ear by wicking. ➢ Topical ciprofloxacin ear drops for 2 weeks . ➢ Follow-up in 5 days.
<ul style="list-style-type: none"> • No ear pain and No pus seen draining from the ear. 	NO EAR INFECTION	No additional treatment.

** Other causes of fever include cough or cold, pneumonia, diarrhoea, dysentery and skin infections.

AGE 2 MONTHS UP TO 5 YEARS

THEN CHECK FOR ACUTE MALNUTRITION

LOOK AND FEEL:

- Look for oedema of both feet.
- Determine weight for height/length*.....Z score
- Measure MUAC**..... mm in a child 6 months or older. If MUAC less than 115 mm, then:

- Check for any medical complication present:
 - ◆ Any general danger signs
 - ◆ Any severe classification
 - ◆ Pneumonia with chest indrawing
 - If no medical complications present:
 - ◆ Child is less than 6 months, assess breastfeeding.
- Does the child have a breastfeeding problem?

Classify
NUTRITIONAL
STATUS

<ul style="list-style-type: none"> • Oedema of both feet or • WFH/L less than -3SD scores or MUAC less than 115 mm, AND any one of the following: <ul style="list-style-type: none"> ◆ Medical complication present or ◆ Breastfeeding problem. 	COMPLICATED SEVERE ACUTE MALNUTRITION	<ul style="list-style-type: none"> ➢ Give first dose of appropriate antibiotic ➢ Treat the child to prevent low blood sugar. ➢ Refer URGENTLY to hospital ➢ While referral is being organized, warm the child. ➢ Keep the child warm on the way to hospital.
<ul style="list-style-type: none"> • WFH/L less than -3SD scores Or • MUAC less than 115 mm 	UNCOMPLICATED ACUTE MALNUTRITION	<ul style="list-style-type: none"> ➢ Give appropriate antibiotic for 5 days ➢ Counsel the mother on how to feed the child. ➢ Assess for possible TB infection. ➢ Advise mother when to return immediately ➢ Follow-up in 5 days.
<ul style="list-style-type: none"> • WFH/L between -3 and -2 SD scores Or • MUAC 115 up to 125 mm 	MODERATE ACUTE MALNUTRITION	<ul style="list-style-type: none"> ➢ Assess the child's feeding & development support care and counsel the mother. ➢ If feeding problem, follow-up in 5 days. ➢ Assess for possible TB infection. ➢ Advise mother when to return immediately ➢ Follow-up in 30 days.
<ul style="list-style-type: none"> • WFH/L -2 SD scores or more Or • MUAC 125 mm or more 	NO ACUTE MALNUTRITION	<ul style="list-style-type: none"> ➢ If child is less than 2 years old, assess child's feeding & development support care ➢ If feeding problem, follow-up in 5 days.

THEN CHECK FOR ANEMIA

LOOK:

- Look for palmar pallor. Is it:
 - Severe palmar pallor?
 - Some palmar pallor?

If possible get Hb testing

Classify
ANAEMIA

• Severe palmar pallor	SEVERE ANEMIA	➢ Refer URGENTLY to hospital.
• Some palmar pallor	ANEMIA	<ul style="list-style-type: none"> ➢ Give iron folic acid therapy for 60 days. ➢ Assess the child's feeding & development support care and counsel the mother. <ul style="list-style-type: none"> - If feeding problem, follow-up in 5 days. ➢ Advise mother when to return immediately. ➢ Follow-up in 14 days.
• No palmar pallor	NO ANEMIA	➢ Give prophylactic iron folic acid if child 6 months or older

MAKE SURE CHILD WITH ANY GENERAL DANGER SIGN IS REFERRED after first dose of an appropriate antibiotic and other urgent treatments.

Exception: Rehydration of the child according to Plan C may resolve danger signs so that referral is no longer needed

*WFH/L is Weight-for-Height or Weight-for-Length determined by using the WHO growth standards charts

** MUAC is Mid-Upper Arm Circumference measured using MUAC tape in all children 6 months or older

AGE 2 MONTHS UP TO 5 YEARS

THEN CHECK THE CHILD'S IMMUNIZATION *, PROPHYLACTIC VITAMIN A and IRON-FOLIC ACID SUPPLEMENTATION and DEWORMING STATUS

IMMUNIZATION SCHEDULE:	AGE	VACCINE
	Birth	OPV-0 + BCG + HepB 0
	6 weeks	OPV-1 + Penta-1 +Rota Virus [#]
	10 weeks	OPV-2 + Penta-2 +Rota Virus [#]
	14 weeks	OPV-3 + Penta-3 +Rota Virus [#] + IPV [#]
	9 months	Measles-1
	16–24 months	Measles-2+DPT Booster + OPV
	60 months	DPT Booster

PROPHYLACTIC VITAMIN A

Give a single dose of vitamin A:

100,000 IU /1ml at 9 months with measles immunization

200,000 IU/2 ml at 16–18 months with DPT Booster

200,000 IU /2 ml at 24 months, 30 months, 36 months, 42 months, 48 months, 54 months and 60 months

Ask; has the child (> one year) received vitamin A. If not given in 6 months, give vitamin A supplementation.

PROPHYLACTIC IFA

Give to a child after meals iron syrup 1 ml 2 times a week with an auto dispenser containing 20 mg elemental iron + 100 µg folic acid (IFA syrup) after the child has recovered from acute illness if :

➤ The child 6 months of age or older.

DEWORMING STATUS:

➤ Is the child 1 years or older?

If child more than 1 year and has not received de-worming (in last 6 months), give de-worming dose.

* A child who needs to be immunized should be advised to go for immunization the day vaccines are available at AWC/SC/PHC
Wherever included in the immunization schedule.

ASSESS OTHER PROBLEMS

COUNSEL THE MOTHER

Feeding and Development Supportive Recommendations during Sickness and Health

Birth up to 6 months 	6 up to 9 months 	9 up to 12 months 	12 months up to 2 years 	2 years and older 
<ul style="list-style-type: none"> Breastfeed as often as the child wants, day and night at least 8 times in 24 hours Do not give any other foods or fluids not even water <p><i>Remember</i></p> <ul style="list-style-type: none"> Continue breastfeeding if the child is sick 	<ul style="list-style-type: none"> Breastfeed as often as the child wants Start by going 2 to 3 tablespoons of food Gradually increase to ½ cups (1 cup= 250 ml). <ul style="list-style-type: none"> Mashed roti /rice/bread/biscuit mixed in sweetened undiluted milk or thick dal with added ghee/oil or Khichri with added oil/ghee. Add cooked vegetables also in the servings. OR Servian/dalia/halwa/kheer prepared in mild OR Any cereal porridge cooked in milk, OR Mashed boiled/fried potatoes. <p>Give 2 to 3 meals each day. Offer 1 or 2 Snacks each day between meals when the child seems hungry.</p> <p><i>Remember</i></p> <ul style="list-style-type: none"> Keep the child in your lap and feed with your own hands. 	<ul style="list-style-type: none"> Breastfeed as often as the child wants Give at least half cup serving at a time of: <ul style="list-style-type: none"> Mashed roti/rice/bread/biscuit mixed in sweetened undiluted milk OR Mashed roti/rice/bread mixed in thick dal with added ghee/oil or khichri with added oil/ghee. Add cooked vegetables also In the servings OR Sevian/dalia/halwa/kheer prepared in milk OR Any cereal porridge cooked in milk OR Mashed boild/fried potatoes <p>Give 3 to 4 meals each day. Offer 1 or 2 snacks between meals. The child will eat if hungry.</p> <p>For snacks, give small chewable items that the child can hold. Let your child try to eat the snack but provide help if needed.</p> <p><i>Remember</i></p> <ul style="list-style-type: none"> Keep the child in your lap and feed with your own hands. Wash your own hand child's hand with soap and water every time before feeding. 	<ul style="list-style-type: none"> Breastfeed as often as the child wants Offer food from the family pot Give at least 3/4 cup serving at a time of <ul style="list-style-type: none"> Mashed roti/rice/bread mixed in thick dal with added ghee/oil or khichri with added oil/ghee. Add cooked vegetable also in the servings OR Mashed roti/rice/bread/biscuit mixed in sweetened undiluted milk Or Sevian/daliah/halwa/kheer prepared in milk OR Any ceral porridge cooked in milk OR Mashed boiled/fried potatoes Offer banana/biscuit/cheeko/mango/ papaya <p>Give 3 to 4 meals each day. Offer 1 to 2 snacks between meals. Continue to feed your child slowly patiently.</p> <p>Encourage your child to eat.</p> <p><i>Remember</i></p> <ul style="list-style-type: none"> Sit by the side of child and help him to finish the serving Wash your own hand child's hand with soap and water every time before feeding. 	<ul style="list-style-type: none"> Give a variety of family foods to your child including animal source foods and vitamin A-rich fruits and vegetables. Give at least 1 full cup (250ml) at each meal. Give 3 to 4 meals each day. Give 1 or 2 nutritious food between meals, such as; banana/biscuit/cheeko/ mango/papaya as snacks <p><i>Remember</i></p> <ul style="list-style-type: none"> Ensure that the child finishes the serving Teach your child was his hands with soap and water every time before feeding
<ul style="list-style-type: none"> Play have large colourful things for your child to reach for and new things to see Communicate: Talk to and respond to your child. Get a conversation going with sounds or gestures (copy your child) 	<ul style="list-style-type: none"> Wash your own hand child's hand with soap and water every time before feeding. Play: Actively play with your child. Give your child clean, safe household things to handle, bang and drop. Communicate: Respond to your child's sounds and interests. Tell the child the names of things and people. 	<ul style="list-style-type: none"> Play: Actively play with your child. Give your child clean, safe household things to handle, bang and drop. Communicate: Respond to your child's sounds and interests. Toll the child the names of things and people. 	<ul style="list-style-type: none"> Play: Give your child things to stack up, and to put into containers and take out. Communicate: Ask your child simple questions. Respond to your child's attempts to talk. Play games like "bye-bye" and "peek a boo". 	<ul style="list-style-type: none"> Play: Make simple toys for your child. Communicate: Help your child count, name and compare things.

* A good daily diet should be adequate iron quantity and include an energy-rich food (for example, thick cereal porridge with added oil); Meat, fish, eggs or pulses; and fruits and vegetables

Rights of Children

Rajeev Sethi

The Constitution of India guarantees equality before the law to all citizens, and has pledged special protection for children. In 1992, India accepted the obligations of the UN Convention on the Rights of the Child and the Government has taken steps towards advancing child rights. These include formation of the National Commission for Protection of Child Rights (2005), National Policy for Children (2013), Right to Education (2009), Protection of Children from Sexual Offences (2012) and amendment to Juvenile Justice Act (2015) to protect, promote and defend child rights.

United Nations Convention of Child Rights and Child Health Care

The UN Convention has implications at policy and decision-making level and for practice or health care provision. It has positively influenced child rights pertaining to health and well-being. Physicians should have adequate knowledge of rights of every child in the area of child survival, identity, development, protection and participation. Pediatricians should understand the social determinants of child health and align themselves with child right organizations in advocacy efforts and lobby their local, state and national elected representatives to advance child rights (Table 32.1).

The 2030 Agenda for Sustainable Development Goals (SDG)

The UN General Assembly adopted the 2030 Agenda for SDG in September 2015. The SDG are for universal, integrated and transformative vision for a better world. They comprise 17 goals and 169 targets to wipe out poverty, fight inequality and tackle climate change over the next 15 years. The SDG aims to build on work of the millennium development goals (MDG) which, in September 2000, rallied the world on a 15-year agenda to tackle the indignity of poverty.

India's Approach to Promotion and Protection of Child Rights

The Government of India upgraded an independent Ministry of Women and Child Development (2006) in

Table 32.1: Articles of the UN Child Rights Convention that apply to child health

Article	Purpose
Article 2	Protection from discrimination
Article 3	Best interests of the child a primary consideration: institutions, services and facilities responsible for the care or protection of children shall conform to the standards established by competent authorities
Article 5	Parents responsible for ensuring that child rights are protected
Article 6	Right to survival and development
Article 9	Right of the child who is separated from one or both parents to maintain personal relations and direct contact with both parents on a regular basis
Article 12	Right of a child to express their views, considering the maturity of the child
Article 14	Freedom of expression including seeking, receiving and imparting information
Article 16	Protection of privacy
Article 17	Access to information from mass media, with protection material injurious to child well being
Article 18	Assistance to parents with child rearing responsibilities
Article 19	Protection from physical and mental violence, abuse or neglect
Article 20	Special protection to children deprived of their families
Article 22	Protection of children seeking refugee status
Article 23	Rights of disabled children to special care
Article 24	Right to health and access to health care
Article 27	Right to an adequate standard of living
Article 28	Right to education
Article 30	Right to own culture and religion
Article 31	Participation in leisure and play
Article 34	Protection from sexual exploitation

order to provide focus to the issues of women and children. The National Commission for Protection of Child Rights was constituted in 2007, which also provides for setting up state level commissions, meant for protection and promotion of child rights in the country. Besides the institutional, administrative and legislative framework, India has a strong presence of non-governmental organizations (NGO), a network of community-based people groups, which, along with media, act as watchdogs to protect human and child rights. The Government of India released a third and fourth combined periodic report (2011), which analysis the overall implementations of the UN Convention on Child Rights and challenges that impede the realization of these rights.

General Measures of Implementation

To implement the commitment to child rights, several policies, laws and programs have been introduced:

National Plan of Action for Children (2016): The charter commits to rights of all children by creating an enabling environment for their survival, growth, development and protection.

National Charter for Children (2003): This emphasizes the Government commitment to child rights, while enumerating children's duties towards their families, society and the nation.

National Policy for Persons with Disabilities (2006): The policy recognizes that majority of persons with disabilities can lead a better quality of life if they have access to equal opportunities and effective rehabilitation.

Policy Framework for Children and AIDS in India (2007): This policy seeks to address needs of children affected by HIV/AIDS by integrated services within existing development and poverty reduction programs.

National Rehabilitation and Resettlement Policy (2007): Under this policy, no project involving displacement of families can be undertaken without detailed social impact assessment on lives of children.

National Urban Housing and Habitat Policy (2007): The policy seeks to promote sustainable development of habitat and services at affordable prices and provide shelter to children from disadvantaged families.

National Policy for Children (2013): The Government adopted this policy to reiterate its commitment to rights based approach to children.

National Legislations

The legislative framework for children's rights is being strengthened with the formulations of new laws and amendments in old laws. These include the Food Security Bill (2011), Right to Free and Compulsory Education Act (2009), Prohibition of Child Marriage Act (2006), Commissions for Protection of Child Rights Act (2005), Right to Information (RTI) Act (2005), Goa Children Act

(2005), Child Labor (Prohibition & Regulation) Act (1986; notifications in 2006 & 2008 expanded the list of banned and hazardous processes and occupations) and Information and Technology (Amendment) Act (2008).

Protection of Children from Sexual Offences Act (POCSO) 2012: India has recently adopted the Protection of Children from Sexual Offences Act (2012). This is the first comprehensive law on sexual abuse in India which expands the scope and range of forms of sexual offences, makes reporting of abuse mandatory and defines guidelines for child-friendly police and procedures. Together with the Juvenile Justice Act (2000), this act has created an opportunity to ensure greater protection to children who have suffered abuse. Doctors are obliged to promptly and adequately respond to child victims. POCSO provides safeguards to the best interest and well-being of the child at every stage of the judicial process, in collection of evidence, investigation and trial of the offender. It provides protection of children from sexual offences (penetrative, non-penetrative), sexual harassment and pornography. The Act defines sexual assault to be aggravated when the abuse is committed by police, army personnel, doctor, management or staff of a hospital/ educational institution or if the abused child is mentally ill or disabled. Since the act defines child as anyone below 18 years of age, adolescents are also included.

Juvenile Justice (Care and Protection of Children) Act (2015): This Act replaces the existing Indian juvenile delinquency law and Juvenile Justice Act, so that juveniles in conflict with the law in the age group of 16–18 years, involved in heinous offences, can be tried as adults. The Act came into force from 15 January 2016.

National Programs

The Government of India is implementing several programs on social inclusion, gender sensitivity, child rights, participation and protection. These programs include: Integrated Child Development Services (ICDS), *Kishori Shakti Yojana* and Nutrition Programme for Adolescent Girls, Rajiv Gandhi Crèche Scheme for children of working mother, scheme of assistance to home for children (*Sishu Greh*) to promote in-country adoption, *Dhanalakshmi* or conditional cash transfer schemes for girl child, Program for Juvenile Justice, Child Line (24 hours toll free number 1098 with outreach services for children in need of care and protection), Integrated Child Protection Scheme (ICPS), Integrated Program for Street Children, *Ujjawala* (scheme for prevention of trafficking and rescue, rehabilitation, reintegration and repatriation), *Sarva Shiksha Abhiyan* that addresses educational needs of 6–14-year-old and bridges social, gender and regional gaps with active participation of community, National Program for education of girls at elementary level or *Kasturba Gandhi Balika Vidyalyaya*, National Rural Health Mission (NRHM), Mid Day Meal scheme, Jawaharlal Nehru National Urban Renewal Mission, Universal Immunization Program and Integrated Management of Neonatal and Childhood Illness (IMNCI).

Role of Pediatricians in Realizing Child Rights

The status and condition of children is the clearest indicator of whether nations and societies understand and respect human rights. Survival, early childhood care including health care, nutrition, education, growth and development, are crucial child rights and must be prioritized. Prevention of child abuse, neglect, protection and exploitation (street children, child labor, trafficking) are intimately linked to poor socioeconomic conditions and cultural attitudes. Parents who are illiterate and often ignorant of rights of children, must be made aware to demand these rights. Pediatricians should join hands with professionals, government, elected representatives, policy makers and administrators to ensure implementation of programs.

CHILD ABUSE AND NEGLECT

The WHO defines 'child abuse or maltreatment as forms of physical and/or emotional ill-treatment, sexual abuse, neglect or negligent treatment or commercial or other exploitation, resulting in actual or potential harm to the child's health, survival, development or dignity. The term child abuse has different connotations in different cultural and socioeconomic situations. In the Indian context, it is important to include children who are deprived of education, early development, basic health care or nutrition. Child labor and trafficking are the worst kind of child abuse.

Major types of child abuse include: (i) *Physical abuse*: Acts of commission by a caregiver that cause actual physical harm or have the potential for harm; (ii) *Sexual abuse*: Acts where a caregiver uses a child for sexual gratification; (iii) *Emotional abuse*: Failure of a caregiver to provide an appropriate and supportive environment, and includes acts that have an adverse effect on the emotional health and development; and (iv) *Neglect*: Failure of a parent or guardian to provide for the development of the child, in one or more of the following: Health, education, emotional development, nutrition, shelter and safe living conditions. Neglect is distinguished from circumstances of poverty in that neglect can occur only in cases where reasonable resources are available to the caregiver.

Features of Child Abuse and Neglect

Injuries inflicted by a caregiver on a child can take many forms. Death in abused children is most often the consequence of a head injury or injury to the internal organs. Patterns of injury to the skin and skeletal manifestations of abuse include multiple fractures at different stages of healing. There is evidence that about one-third of severely shaken infants die and that the majority of the survivors suffer long-term consequences such as mental retardation, cerebral palsy or blindness. Children who have been sexually abused exhibit symptoms of infection, genital injury, abdominal pain, constipation, chronic or recurrent urinary tract infections

or behavioral problems. To be able to detect child sexual abuse requires a high index of suspicion and familiarity with the verbal, behavioral and physical indicators of abuse. Many children will disclose abuse to caregivers or others spontaneously, though there may also be indirect physical or behavioral signs. Emotional and psychological abuse has received less attention globally due to cultural variations in different countries. Moreover, corporal punishment of children, i.e. slapping, punching, kicking or beating is a significant phenomenon in schools and other institutions. Child neglect can manifest as failure to thrive, failure to seek basic health care, immunizations, deprivation of education and basic nutrition needs.

Strategies to Reduce Child Abuse and Neglect

Child abuse and neglect should be placed on the national agenda, both as a social and a public health problem. The problems of socially marginalized and economically backward groups are immense, particularly amongst children in urban slums, street and working children and children of construction workers. Child labor cannot be abolished in the presence of abject poverty. However, the Government should make sure that working child is not exploited. The child must get time for education and must receive health care. The employer must provide care for children. The belief behind the legislation is that protection of the children against all forms of abuse and exploitation is a basic child right. Laws should be enforced.

Child Protection services should also reach the rural areas. *Panchayat* officials should be given responsibility to ensure that basic education, nutrition, health care and sanitation is available for proper development of every child in their village. The *panchayat* should be duty bound to ensure that every child is in school and protected from agrarian and allied rural occupations as a part of family or individual child labor.

Pediatricians can do a great deal in recognizing, responding to and reporting child abuse. They are often the first point of contact of a child with abuse and best advocates for protection of their rights. They should be sensitized on how to use Protection of Children from Sexual Offences Act. Pediatricians should seek assistance from special juvenile police units, child welfare committees, toll-free phone service for children in distress (child line 1098), national and state commissions for protection of child rights and NGOs and direct families to these services. The Indian Academy of Pediatrics and the Indian Child Abuse Neglect and Child Labor group have brought out guidelines for pediatricians to respond to child abuse and neglect.

Suggested Reading

- Convention on the Rights of the Child, available from www.unicef.org/crc.
- Seth R. Child abuse and neglect in India. *Indian J Pediatr* 2015; 82:707-14.
- Srivastava RN. Child abuse and neglect: Asia Pacific Conference and the Delhi Declaration. *Indian Pediatr* 2011; 49:11-12.

- Sustainable Developmental Goals(SDG); www.un.org/sustainabledevelopment/sustainable-development-goals.
- The Protection of Children from Sexual Offences Act, 2012; wcd.nic.in/child_act/childprotection31072012.pdf.

ADOPTION

Adoption is an important alternative for the rehabilitation of children who are destitute and abandoned or, for social reasons, cannot be brought up by their parents. Medical practitioners and pediatricians play a vital role in influencing health and social decisions of their adoptive patients and should work closely with counselors and allied health professionals. 'Right to a family' is proposed as a fundamental right by the United Nations. Adoption agencies need to ensure that these rights are protected.

Legal Aspects

In India, only specialized adoption agencies recognized by the State Government can deal with adoption placement. Direct adoption placement by hospitals, maternity and nursing homes is not permitted. Central Adoption Resource Authority is an autonomous body under the Ministry of Women and Child Development, Government of India. It functions as a nodal body for adoption of Indian children and is mandated to monitor and regulate in-country and inter-country adoption. Prospective parents should be advised to read the guidelines from its website and follow the due procedures. The Government has notified guidelines, in pursuance of the Juvenile Justice Act (2000), that enables citizens of all religions the freedom to adopt a minor child, irrespective of whether he/she is a single parent and/or such adoptive parent/s adopt a child of the same sex, irrespective of whether he/she is a single parent and/or such adoptive parent/s adopt a child of the same sex, irrespective of the number of living biological son or daughters. Prior to 2000, adoption was allowed to Hindus under the Hindu Adoption and Maintenance Act; other religious groups were governed by the Guardianship and Wards Act.

Adoption Procedures

A child, who has been relinquished by his/her biological parents or found abandoned, must first be presented to the Child Welfare Committee. This committee has the sole authority to declare the child free for adoption under the current law. In case of an abandoned child, the committee, after due investigations, declares the child as destitute and free for adoption. In case the biological parents want to relinquish a child, they have to execute a document in favor

of the adoption agency, duly witnessed by any authority of the hospital and a relative. A waiting period of two months is given to the biological parents to reconsider the decision, following which the child is free for adoption.

Prospective Adoptive Parents

A child can be adopted by a married couple having infertility or voluntarily opting for adoption. Even single persons are eligible to adopt. Couples who have taken a decision to adopt should go to a registered agency, that is licensed to process adoption by both state government and the Central Adoption Resource Authority, Ministry of Women and Child Development, Government of India. Applications for inter-country adoption, of a child born in India, require to be forwarded by an accredited agency of the country of the adoptive parents, to a recognized placement agency in India and the Central Adoption Resource Authority.

Social workers from the adoption agency provide guidelines and support to pre-adoptive parents, and help make informed decisions (pre-adoption counseling). A home study is conducted by the professional social worker. Additionally, parents are required to submit a document regarding their health and financial status. Once their application is approved, a suitable child is shown to them. After they accept the child, placement is legalized. The placement is followed for 3 years or until legal adoption is complete. The adoptive parents are assured confidentiality and provided support as needed.

Role of a Pediatrician

Pediatricians are often asked for advice prior to adoption; their role consists of the following:

- Counsel and teach adoptive parents about the process of adoption
- Teach parents who wish to relinquish their child due to any reason, the correct procedure and to not leave children in public places or in unhealthy surroundings as this is unsafe and traumatizing
- Discourage private adoptions, since these are illegal
- Examine carefully babies brought from placement agencies, and explain a realistic diagnosis and prognosis to the adoptive parents
- Repeat all essential tests that have a window period (HIV, hepatitis B) after 3–6 months, before placement
- Provide a supportive attitude to encourage adoptive parents to overcome their fears.

Suggested Reading

- Central Adoption Resource Agency; <http://www.cara.nic.in>.

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