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Principles in Paediatric Anaesthesia

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History of Paediatric Anaesthesiology

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History of paediatric anaesthesiology cannot be dissected from general historic development in anaesthesiology, historic developments in paediatrics, historic development of general surgery, historic development of paediatric surgery, historic developments in pharmacology and general historic developments and increased understanding of medical science and technology.

History in General

Many surgeons had strong notions that average men should tolerate pain caused by surgery and thus kept patients away from administering anaesthesia during surgery. Humans have inhabited the Earth for 200,000 years, yet the public demonstration of surgical general anaesthesia happened in 1846. The conviction that small infants did not need anaesthesia. The "whiskey nipple" had been used widely as a sedative supplement to local anaesthesia in infants undergoing abdominal procedures. Giving wine for pain relief became a ritual for doing circumcision surgery for millennia.

History in Specific

Among advances in medicine during the past more than 170 years, certainly the introduction of surgical anaesthesia must be considered the greatest gifts of medical profession to mankind, especially to children. Anaesthesia for children was considered a bit risky endeavour, in India as well as abroad before 1980. Before 1980s, anaesthesiologists preferred open drop ether method for anaesthesia in children in India. Soon later intravenous sodium pentothal was used for short procedures for children. In a short span of less than a quarter of century, paediatric anaesthesiology which started as a subspecialty branch of anaesthesiology has become a superspecialty branch of medicine. Millions of *paediatric* patients receive *anaesthetics* every *year*, (Gregory's Paediatric Anaesthesia by George A Gregory, Dean B. Andropoulos, 5th edn., 2012) but it has been established that those under one year of age require higher standard of care. It is now clear that paediatric anaesthesiology is a well-established and well-recognized subspecialty in its own right.

HISTORY OF PAEDIATRIC ANAESTHESIOLOGY IN INDIA

Overview

In the year 1944, the anaesthesiologists attending a surgical conference at Mumbai (Bombay) thought of forming a common platform for exchange of scientific views, which was consolidated in 1946 following "Ether Day" celebrations in October of that year. With the continued efforts of leading anaesthesiologists of India, the Indian Society of Anaesthesiologists was born on 30th December 1947 with its logo (www.isa.web.in).

In India, paediatric anaesthesiology has evolved slowly over the past 20 years, as both a viable clinical and academic subspecialty of anaesthesiology in medical colleges, where paediatric surgery is done on a large scale and dedicated basis.

PERIOD BEFORE 2005

Anaesthesiologists, who would administer anaesthesia to adult patients, would generally take roles of paediatric anaesthesiologists in various medical colleges. Paediatric anaesthesia has advanced enormously from

the days when anaesthesiologists and surgeons adapted adult techniques and equipment to small children.

In the city of Mumbai paediatric anaesthesia was practiced mainly at teaching institutes like BJ Wadia Children's Hospital and Research Centre, GS Medical College and TN Medical College, where paediatric surgery departments were set. Hence it was found necessary to create a platform to share, discuss and do constructive work in paediatric anaesthesia.

PERIOD AFTER 2005

The Indian Association of Paediatric Anaesthesiologists (IAPA) (http://www.iapa-india.org) was formed in March 2006 by a small group of Mumbai based paediatric anaesthesiologists. Constitution of IAPA was formed, approved and was officially registered in March 2006. Its main aim was to promote safety and higher standard of care in the specialty through education and research. It also advises other professional bodies on anaesthesia for children. It has completed six successful national conferences on paediatric anaesthesia. It is one of the most popular fields to pursue for further training after the basic anaesthesia residency, and its practitioners are desired by surgeons, paediatricians, and parents alike. Hence Paediatric Anaesthesia is fast getting recognition as a superspeciality branch in India. Several institutes have started fellowship programmes of Paediatric Anaesthesia. The paediatric anaesthesiologist must be facile in providing empathetic, efficient care for a wide gamut of special paediatric procedures. There are a tremendous number of technical skills and a body of knowledge to be mastered about the totality of paediatric anaesthesia. Challenges are ongoing as more complex surgical and diagnostic techniques are performed on younger and younger patients.

This maturation of the superspecialty includes better understanding of clinical care in line with advances in paediatrics and paediatric surgery along with increased sophistication in anaesthesia automation and clinical research. DM course in the branch of paediatric anaesthesia has been for the first time granted and recognized in India by Maharashtra University of Health Sciences (MUHS), Nashik and Medical Council of India (MCI) at Seth, GS Medical College and KEM Hospital, Mumbai in the year 2014.

HISTORY OF PAEDIATRIC ANAESTHESIOLOGY IN ASIA

The main aim of Asian Society of Paediatric Anaesthesiologists (ASPA) is to create a platform for interaction between anaesthesiologists from different Asian countries with different health care needs and capabilities. Its official website: http://www.aspa-2000.com.

ASPA was launched in 1999 at the KK Women's and Children's Hospital in Singapore with the goal to foster the growth of safe and quality paediatric anaesthetic care and assist with professional development of its members through high quality academic meetings.

ASPA meetings have now been held in Singapore, Cebu—Philippines, New Delhi—India, Vellore—India, Pattaya—Thailand and Ho Chi Min City—Vietnam. Apart from providing state of the art knowledge on current developments in paediatric anaesthesia the ASPA meetings are also a forum to share experience in providing anaesthesia to children under diverse circumstances that are unique to Asia.

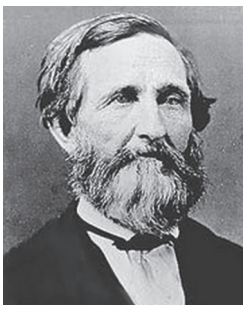
PRIMITIVE PERIOD OF PAEDIATRIC ANAESTHESIA ACROSS THE WORLD

Before the era of ether, circumcisions, amputations, excisions of tumors, cleft lip/harelip repair and correction of gross deformities performed on infants and children without any relief of pain for hundreds of years. Child crying and struggling with pain was controlled manual force. Pain was accepted and unavoidable part of surgery on children. In Japan, general anaesthesia with the herb mixture *tsu san sen* was used in 1837 by Gancho Homma for children over 5 years of age for harelip repair but withheld it from use in younger patients because of its toxicity (Iwai and Satoyoshi, 1992).

PHASE I: INTRODUCTION OF ETHER AS ANAESTHETIC AGENT IN THE USA AND PROGRESS OF PAEDIATRIC ANAESTHESIA UP TO 1940

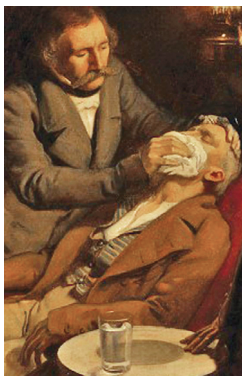
Early successful experiments with ether

1. **Dr Crawford Williamson Long** (November 3, 1815–1878) on March 30, 1842, when he extirpated a small glandular tumour out of the two from the neck of James M Venable, a boy in Jefferson, Georgia. Next on July 3, 1842, in the amputation of the toe of a negro boy belonging to Mrs Hemphill, of Jackson, Ga. Later on Sept. 9, 1843, did extirpation of a tumour from the head of Mary Vincent, of Jackson, Ga. Followed by on January 8, 1845, in the amputation of a finger of a Negro boy belonging to Ralph Bailey, of Jackson, Ga (Long, 1849).[1]



Dr Crawford W Long

2. **William Thomas Green Morton** (August 9, 1819–July 15, 1868), Morton was an USA dentist who first publicly demonstrated the use of inhaled ether as a surgical anaesthetic in Massachusetts General Hospital in Boston in 1846.[2,3]



William Thomas G Morton

Children and women were considered to be **more sensitive to pain** hence anaesthesia was considered appropriate.[4,5] Morton was reluctant to administer ether anaesthesia to children because of the high incidence of nausea and vomiting.[6]

Initial short general anaesthesia with ether

The introduction of ether was the first giant step in the history of anaesthesia. Ether drenched small cloth was applied to the child patient's face until the child was quiet and limp. The surgeon could get 3 or 4 minutes to operate on such patient as the child regained consciousness after that.

Initial use of ether as continuous method of anaesthesia

The use of continuous administration of ether was slowly learnt over a period of time and soon use of ether for anaesthesia became a trivial routine that it was relegated to any inexperienced (non-medical) person by surgeon, while performing surgery.

Nurse anaesthetists

The administration of anaesthesia with ether was such a trivial medical activity; hence qualified physicians never took any special interest in the field of anaesthesia. For patients safety reasons nurses eventually began to assume increasing responsibilities for providing anaesthesia care. In the USA, as late as 1940, a physician, in the lead article published in the first edition of the new journal Anaesthesiology, commented, "During my internship I was trained by a nurse. I was given a cone, a can of ether and a few empirical tricks".[7]

Stagnancy in field of anaesthesia in the USA

Because of anaesthesia was considered a trivial procedure adjunct to surgery, hence the medical field of anaesthesia could not develop in the USA for several decades harming development of anaesthesia in the USA, leave aside development of paediatric anaesthesia.

Surgeons did not differentiate between adult and child in the USA

For many years in the USA, the child was treated as "a little man," surgeons operated with large instruments, and all equipment which was adult sized. Ether remained the principal agent. Use of chloroform was criticized in children.[8] Use of chloroform was advocated in the USA in 1957.[9] Progress was by trial and error. Before 1900, most of the medical literature in the USA related to anaesthesia for children was authored by surgeons.

Increase in initial interest in child anaesthesia

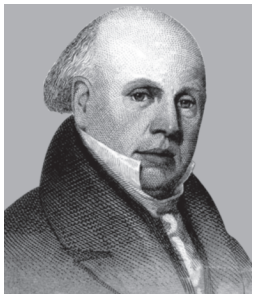
Interest grew in child anaesthesia slowly. Children were given anaesthesia for longer period and for more difficult procedures. Tonsillectomy operation grew to thousands in number between 1887 and 1900. Although often considered dangerous appendectomy surgery slowly became an accepted surgical procedure. The most common type of paediatric surgery done under ether anaesthesia was orthopedic surgery from year 1900 onwards.

Beginning of recognition of preoperative anxiety

One of the first signs of concern for the child's anxiety when undergoing anaesthesia was voiced by James Gwathmey (1907).[10] When he recommended that one should "add a few drops of the mother's cologne to the ether mask and induce the child in the mother's arms." Another step toward easing induction came in 1928 with the entry of tribromoethanol, the German Avertin,

which was used widely as a rectal agent. It provided almost certain sleep in 7 to 8 minutes and was of special value prior to ether induction because, unlike the barbiturates used later, it had a bronchodilating effect and facilitated rather than retarded induction.

James Gwathmey



William Ladd

Development of paediatric surgery and anaesthesia

William Ladd, whose interest stemmed from his experience in caring for children injured in a massive explosion in Halifax, Nova Scotia in 1917, led the development of paediatric surgery in the USA.[11,12] Between 1925 and 1940, activity in both paediatric surgery and anaesthesia began to accelerate. Ladd at Children's Hospital Boston corrected harelip and other neonatal defects under ether anaesthesia. Both Leven and Ladd performed secondary multi-procedure repair of trecho-oesophageal fistula in 1939.

Cyclopropane in 1930 for cardiovascular surgery

In 1930 cyclopropane by closed-system apparatus proved particularly helpful for paediatric anaesthetists Lamont and Harmel developed a miniaturization of the to-and-fro canisters. Waters described in Wisconsin and used this technique for Blalock's "blue baby" (tetralogy of Fallot) operations at Johns Hopkins Hospital. Betty Lank, nurse anaesthetist provided anaesthesia, relaxation, and controlled respiration for Ladd's infants as well as for Robert Gross for surgery of patent ductus arteriosus in 1938 without using endotracheal intubation. She used miniature to-and-fro apparatus with less dead space by using infant size masks.

Fresh initial beginnings in paediatric anaesthesia

By 1940, considerable progress had been made in the ability of minimally trained anaesthetists to provide quite satisfactory operating conditions for the surgeons of that time. By 1940, Ladd with great difficulty corrected the established dictum of "the child is not a little man" He also emphasized on supportive warming, preoperative correction of electrolyte balance, and intraoperative charting of Clinical signs of anaesthetic depth of anaesthesia described by Guedel in 1937. Ladd had used local infiltration for abdominal procedures in premature infants in the late 1930s, and Leigh wrote of spinal anaesthesia for open chest work in the 1940s, but improved inhalation anaesthesia methods phased out both. Robson of Toronto had described intubation of children using digital guidance rather than a laryngoscope[13] did not receive much attention.

Introduction of Chloroform in UK and Progress of Paediatric Anaesthesia up to 1940 of PHASE I

Initial use of chloroform for general anaesthesia

Chloroform was used in England because of smoother and more rapid action. The incidence of deaths after chloroform was very high hence specialized care was recommended. Hence in the UK only physicians were allowed to administer anaesthesia.[14] Hence throughout the UK Empire including India anaesthesiology became a medical specialty, its physicians trained in anaesthesia got equal status with other physicians, and establishing early leadership in this field of anaesthesia for several decades. This helped in early development of paediatric anaesthesia in the UK.

John Snow era of experimentation with chloroform

John Snow (1813–1858), kept notes on hundreds of anaesthetic experiences and research experiments, between the period of 1846 to1958.[15] Snow formulated the first description of signs by which one could monitor and control the depth of anaesthesia in patients of all ages.[16] Guedel's guide to Inhalation Anaesthesia (A Fundamental Guide to Inhalation Anaesthesia by Arthur E. Guedel published in 1937) was used by Snow to describe five stages of anaesthesia, based on excitement, loss of consciousness, relaxation, eye movement, and depth of respiration, served as guidelines throughout the remainder of the century. Snow experimented with ether and chloroform for giving anaesthesia in children. Snow preferred chloroform for infants and children. He warned of its danger with excessive depth in children.[17] His record of successfully anaesthetizing 147 infants for harelip repair in light of high mortality during this operation in that era and later on also, is considered a great paediatric anaesthesia feat.

Era of chloroform mixtures with ether and alcohol

Despite recognized dangers, for next 20 years, chloroform and ether remained the only anaesthetic agents after the remarkable progress made in anaesthesia in England and throughout Europe by Snow. Chloroform remained the principal agent in England and Europe and efforts were made to reduce the complications of

chloroform by diluting it with ether [Chloroform + Ether (CE)] and with alcohol and ether [Alcohol + Chloroform + Ether (ACE)].

Initial use of nitrous oxide

The introductions of nitrous oxide into general use by 1870 and ethyl chloride shortly after 1900 were important advances, reducing or replacing the use of chloroform in many operations not requiring muscular relaxation. They were nonirritating made them particularly acceptable for induction. Between 1888 and 1912, the UK physician anaesthetists Buxton alone published five consecutive editions of Anaesthetics: Their Uses and Administration by Dudley Wilmot Buxton. More anaesthetists contributed more number of articles and texts to medical journals. The first text on paediatric anaesthesia was published in 1923 by C Langton Hewer in "The Lancet" about Anaesthesia for Children.

Following World War I, Magill and Rowbotham popularized tracheal intubation for adult procedures, and in 1937, Philip Ayre of Newcastle-Upon-Tyne reported endotracheal intubation with a T-tube device for harelip repair in neonates (Ayre, 1937). In England, there had been more progress in airway control during anaesthesia.

Magill

PHASE II: EMERGENCE OF PAEDIATRIC ANAESTHESIA (1940–1960)

The practice of adult anaesthesia become established. It expanded by understanding children through Textbook of Paediatrics. Clement Smith's *The Physiology of the Newborn Infant* (1945), Taussig's *Congenital Malformations of the Heart* (1947), and Nelson's *Textbook of Paediatrics* (1950) defined normal and abnormal infants. Charles Robson, in Toronto used fresh information on new agents and techniques adaptable to children and established paediatric anaesthesiology in USA. Robert Cope, at London's Hospital for sick children established paediatric anaesthesiology in England.

M Digby Leigh

First USA Canadian author M Digby Leigh authored *Paediatric Anaesthesia* (1948). He was trained by Waters in Wisconsin. He was appointed head of anaesthesia at Montreal Children's Hospital, where he taught and innovated with Kathleen Belton. They described the use of spinal anaesthesia for intrathoracic procedures. They innovated original paediatric circle absorption apparatus, and a non-re-breathing valve. Leigh moved to Vancouver, UK Columbia in 1947 and to Los Angeles in 1954, where he started the yearly paediatric anaesthesia teaching conference in the USA. He attempted to monitor exhaled carbon dioxide in 1952.

G Jackson Rees

G Jackson Rees anaesthetist at the Alder Hey Children's Hospital Liverpool, worked with mentor and teacher Cecil Grey. Together, they conceived the idea that practically all surgery could be performed under the simple and non-explosive combination of nitrous oxide and curare. Rees, adapting the Ayre T-tube system by adding an expiratory limb and breathing bag (the well-known Jackson Rees system), proceeded to carry-out this concept with astounding success. Rees' foresighted that respiration be controlled in infants with reduced tidal volumes and rates of 60 to 80 times per minute were widely criticized but proved to be rational when increased tidal volumes were found to cause surfactant washout and barotrauma.

Historical Pearl

Children were rarely intubated before 1940 because Jackson Rees ruled intubation in children to be avoided. In the subsequent 30 years saw a proliferation of paediatric laryngoscopes a change in airway management philosophy slowly happened.

New field of paediatric anaesthesia

The new field of paediatric anaesthesia got established by:

1. McQuiston of Children's Hospitals in Chicago
2. Smith of Children's Hospitals Boston
3. Rackow worked at Columbia Presbyterian Hospital in New York.

Foundations of Clinical Control and Support

Progress in Neonatal Surgery and Anaesthesia

1. Primary surgical repair was a challenge but achievable with progress in neonatal surgery and anaesthesia for three difficult congenital defects:
   a. Tracheoesophageal fistula (TEF),
   b. Omphalocele, and
   c. Congenital diaphragmatic hernia (CDH).[3]
2. Open-drop divinyl ether (Vinethene)—ether was preferable over local anaesthesia by the average surgeon for herniorrhaphy and pyloromyotomy

3. Before 1912, pyloric stenosis operation by gastroenterostomy resulted in 50% mortality. Pyloromyotomy replaced gastroenterostomy by Ramstedt where prevention of aspiration during anaesthesia was main aim to reduce mortality to near zero if diagnosed early.

Early attempts to control fear

Fear of needles and the horrors of anaesthetic induction was voiced by psychologists,[20] paediatricians[21] and anaesthesiologists.[22]

Premedication

Morphine, scopolamine, atropine and barbiturates

In this article recommended[23] morphine and promoted[24] the combination of morphine and scopolamine premedication. Intramuscular barbiturates plus morphine mixed with either atropine or scopolamine resulted in severe horror of needles, an uncomfortable dry mouth, and an unpredictable degree of sedation. With the repeated failure of sedative agents, greater skills were developed by caring anaesthetists to gain the confidence of children in preoperative visits and then to divert their attention at induction by telling them stories or by simply lulling them to sleep.

Hypnosis

Limited acceptance could not make hypnosis routine procedure for induction. It was used by Betcher (1958)[25] and Marmer (1959)[26] also favoured hypnosis. Hypnosis used for repair of facial lacerations in small children who were full stomach.

Methods of Induction

Thiopental replaced rectal Avertin, providing greater ease of administration via either the intravenous or the rectal route.[27] Nitrous oxide, cyclopropane, or divinyl ether eliminated use of the dreaded ether.

Control of the Airway

Tongue fall

Simple blockage by the tongue has been an ever-present danger. To prevent obstruction by the tongue, metal and rubber oral airways, often fitted with a metal nipple for insufflation of vaporized ether.

Hypoxia due to secretions

In harelip procedures and tonsillectomy, the complications of hypoxia and death were due to laryngospasm caused by oral secretions, blood, drained pus, aspiration of vomitus. To prevent this suction apparatus was first available in the form of bulb syringes used alone or fitted with rubber catheters and then later as portable motorized pumps

Endotracheal Intubation

Tracheal intubation was outstanding advance in paediatric anaesthesia between 1940 and 1960 to control the airway. It was the efforts of Rees in England and Leigh. Similar efforts were made by various people in Canada, UK, USA (Gillespie, 1939)[28]; Zindler and Deming (1953)[29] and Pender (1954)[30] helped acceptance of tracheal intubation of infants and children in the USA in the 1940s and 1950s.The ongoing development of tracheal intubation led to an increased understanding of laryngeal anatomy.[31]

1. Replacement of the "classic" hyperextension of the head by use of the "sniffing" position for intubation in children.
2. Different types of tracheal tubes made of different materials.
3. Laryngoscopes of several types and sizes.

Medical literature on complications of tracheal intubation,[32] included subglottic stenosis[33] laryngeal irritation from large tubes,[34] and tracheitis caused by contamination.[35]

"Total Control" of Respiration: The Muscle Relaxants

Griffith and Mitchell in Canada in 1942 clinically first used *d*-tubocurarine. Canadians and UK readily accepted it for both children and adults.[36–39] Use of *d*-tubocurarine in the USA had much opposition to "controlled" respiration. But by 1960, the terms "controlled" and "assisted" respiration had gained widespread use in the USA.

Paediatric Breathing Systems: Assisted and Controlled Respiration

With the stimulating effect of ether on respiration in light surgical planes, assisted respiration was not needed. Open chest surgery with cyclopropane and muscle relaxants definitely changed this picture. Special interest was taken in infant circle absorption systems to eliminate problems of carbon dioxide accumulation, several non-rebreathing valves were designed by Leigh and Belton, 1948.[40,41] Over a period of 30 years, apparatus variously called re-breathing (UK), non-re-breathing (USA), and partial re-breathing (general) involved numerous studies and modifications of the basic Ayre T-system.[42] Rees added expiratory limb by attaching breathing bag. At exhaust valves were placed. Valves proximal to face (Mapleson A). Exhaust Valves distal to face (Mapleson D).

Cardiovascular and Thermal Control

Intentional reduction of arterial blood pressure

Reduced blood pressure is reasonably safe and used as initial step for "induced hypotension" to reduce surgical blood loss in major paediatric surgery and to prevent excessive loss due to blood pressure elevation during correction of coarctation of the aorta.

Controlled Reduction of Body Temperature and Cardiopulmonary Arrest

In 1938 following 'Gross' ligation patent ductus arteriosus, did correction of coarctation of the aorta, did repair of vascular rings, and shunt procedures for tetralogy of Fallot under closed or semi-closed inhalation anaesthesia, usually with cyclopropane.[43–45] Introduction of hypothermic control of body metabolism into paediatric anaesthesia to reduce the oxygen requirement by cooling to 3–4ºC by simple ice-water mattress[46] for intracardiac aortic or pulmonary valvotomy[47] and Virtue RW: *Hypothermic anaesthesia*, Springfield, IL, Charles C Thomas, 1955. The drive to bypass both heart and lungs initiated by Gibbon in 1937 became exciting in the early years of 1950s, with competing surgeons Lillihei, Kirklin, and Kay and their respective anaesthesiologists.[48–50] All of them contributing toward the first practical use of the pump oxygenator in 1955, 2 years before publication of the articles cited. Mild and moderate hypothermia techniques were also used in this period for neurosurgery, orthopedic surgery, and harelip repair.[51]

Control during Maintenance of Anaesthesia

Surgeons preferred accuracy rather than speed. The methods of maintenance and support of anaesthesia became more demanding. A precordial or esophageal stethoscope[52] served, first, to keep the anaesthetist in direct contact of strength of breath sounds and the rate, rhythm, and strength of heart sounds. Strength of heart sounds was an important guide to the degree of blood loss at that time. Arterial blood pressure obtained by BP apparatus specially constructed Smith cuff or latex cuff for infants. The electrocardiographs machine was occasionally brought into operating rooms. Body temperature measured intermittently at oral, nasal, or rectal sites. The anaesthesia chart gained importance when legal suits became more frequent.

Control of Blood Loss

Methods of estimating blood loss consisted of assessing blanching of conjunctivae, evaluating the strength of heart sounds, measuring arterial blood pressure, and weighing blood soaked sponges. While speed was still considered essential in paediatric surgery during the excision of Wilms' tumour surgery, it may cause massive hemorrhage and may exsanguinate small infants. Attempts were made to restore the loss with cold, acidified blood brought failing hearts to irreversible arrest. The cautery soon reduced blood loss drastically but inflammable inhalational anaesthetics prevented their use.

Poor Progress in Local Anaesthesia

Local anaesthesia worked well in brachial plexus block[53,54] a little attention was paid to local anaesthesia in the USA. In many other countries, however, where inhalation anaesthesia was less advanced stages, there was routine use of regional and spinal anaesthesia for both infants and children.

Halothane paves way for cautery to control blood loss and electrical gadgets for monitoring in OT

Nitrous oxide anaesthesia with relaxants allowed use of electrical instruments in the operating room. Halothane slowly replaced popular explosive gases used as anaesthetics. Johnstone in 1956 in England first used in Halothane in 10% concentration (nonflammable, nonirritating, and potent anaesthetic agent),which was described by Junkin et al (1957).[55]

Immediately thereafter used in Canada and Stephen, Lawrence, Fabian (1958) in the USA. Flammable anaesthetic agents were replaced by Halothane in the USA allowing cautery to control loss of blood loss. Halothane paved way for development of electronic devices for monitoring and physiologic control of patient during anaesthesia.

Supportive Care

Oxygen Therapy

All pros and cons evaluated for oxygen therapy concentration, pressure and duration.

Fluid Therapy

The time-honored rule developed by Holliday et al (1957)[56] was used for paediatric fluid administration based on metabolic requirements is used even today.

Antibiotic Therapy

Antibiotic agents reduced the morbidity and mortality of small infants by control of infection perioperatively.

Baby Incubators for Temperature Control

Development of enclosed incubators with regulated oxygen, warmth, and humidification for infants with respiratory distress syndrome along with improved oxygen tents were developed for older children including those with cystic fibrosis to help survival.

Teamwork

Paediatric anaesthesiologists and paediatricians along with paediatric surgeon shared responsibility for perioperative care.

Paediatric Intensive Care Unit

The first paediatric intensive care unit was established in Goteburg, Sweden, in 1955. Similar paediatric intensive units were established in Stockholm (Hans Feychtung), Liverpool (Rees), and Melbourne (MacDonald and Stocks) between 1960 and 1964. In USA, the first paediatric intensive care unit was established by John J. Downes at the Children's Hospital of Philadelphia in 1967, followed by Children's Hospital of Pittsburgh (Kampschulte), Yale—New Haven Hospital (Gilman), Massachusetts General Hospital (Todres and Shannon), and the Hospital for Sick Children in Toronto (Conn) in next 4 years.[57]

PHASE III: ERA OF NONFLAMMABLE ANAESTHETICS (1960–1980)

With elimination of flammable agents eliminated, the way was cleared for rapid and extensive advances in each and every areas of paediatric anaesthesia ketamine (Ketalar) by Domino et al (1965)[58] They found a place in paediatric use for uncontrollable patients and to accomplish minor but painful procedures. A major change in the methods for controlling fear in children and their parents was in giving permission to parents, admission next to the child's bedside at all times, including "sleep-in" privileges, and later, to preinduction and induction areas. While many parents felt the unpleasant feeling of ordeal by these human moves were comforting but statistics failed to show that it helped the children undergoing surgical procedure.[59]

Increasing Clinical Precision

Airway Systems

Major evolution of airway systems for paediatric anaesthesia was done by Bain et al (1972).[60] In this article, they modified the partial re-breathing systems. They made exhalation tube pass inside the inhalation arm. This provided for scavenging expired gases.

Monitoring

"Control by the numbers" gained predominance over the unreliable art of anaesthesia. Greater precision in monitoring were taken in the measurement of infant blood pressure by Doppler sonography and by oscillotonometry (Dinamap).[61] The transcutaneous electrode (ear oximetry) for determination of arterial oxygen saturation with limited success.[62]

Serial ABG and Electrolytes

Led by Downes of Philadelphia, arterial blood gas determinations, blood sugar, haemoglobin, electrolytes, and other measurements were serially evaluated intraoperatively in adjacent laboratories.

Catheters

Insertion of arterial and central venous catheters became commonplace, and urinary catheterization became an important guide to fluid and electrolyte replacement. Progress in controlling fluid balance included the recognition of the importance of electrolytes in all intravenous solutions.[63,64]

Blood Replacement

New concepts concerning blood replacement included Davenport's practical recommendation to give blood when loss reached 10% of blood volume,[65] followed later by Furman's more precise suggestion to maintain the haematocrit level above 28 to 30% in children and 40% in the newborn.[66]

Prevention of Food Aspiration

The Sellick maneuver[67] and Salem's many warnings about "the full stomach"[68] were forever fixed in the mind of each new resident doctor. Great emphasis was placed on the prevention of food aspiration and the damaging effects of hypoxia.

Postoperative Patient Management: Ventilation, Resuscitation and Intensive Care

Apart from preoperative and operative anaesthesia techniques a third dimension was added with advent of extensive operation where survival of patients depended on their supportive control during recovery room period. Recovery rooms or post-anaesthesia care units (PACUs) for routine postoperative care had been established in many hospitals over previous decades.

"Cardiac arrest"

When it became evident that the patients occasionally did not survive both the original insult and the

therapeutic assault, the term "cardiac arrest" was coined.[69] Because the exact cause of these mishaps frequently was uncertain, each was considered "an act of God" and successful resuscitation was considered a feather in the cap of any anaesthesiologist who had been associated with one. Intelligent procedures of ventilation and closed-chest cardiac compression, combined with electric and pharmacologic stimulation, brought far greater reason, order, and success.

Twin tenets of anaesthesia

Among many well-known tenets established, two more tenets were added. ***First*** was the danger of succinylcholine in patients with elevated serum potassium levels[70] and ***second*** was poor tolerance to anaesthesia in patients with haemoglobin levels as lower than as 6 g/dL.

Organized Teaching

Accreditation for residency training in paediatric centres was established in Boston in 1970, followed by several other hospitals by 1980. This period marked the definite establishment of teaching facilities for the specialized training of paediatric anaesthesiologists. With markedly enlarged departmental staffs, didactic and clinical instruction became available in numerous institutions. Residents became capable of managing most types of cases and also received instruction in ancillary services. Annual symposia on paediatric anaesthesia initiated by Leigh in 1962 were followed by those organized by Conn in Toronto, Downes in Philadelphia, Salem in Chicago, Ryan in Boston. New texts were written by Davenport (1967) of Canada,[71] Brown et al (1979) in Australia.[72]

International Progress

In France

M. Delegue pioneered the modern paediatric anaesthesia stage, her text *Memento a l 'Uusage de l' Anaesthesiologiste-Reanimateur Paediatrique* celebrated many editions. A marked difference in their approach appeared with their use of combinations of intravenous phenothiazines, antihistamines, and barbiturates in place of inhalation agents, with remarkable success in regional anaesthesia and pharmacology has also been outstanding (Saint Maurice et al. 1986; Murat et al. 1988).

In Europe

Other early leaders in paediatric anaesthesia in Europe include Suuterinen of Finland, Swensson, Feyting, and Ekstrom-Jodal of Sweden, and Rondio and Wezyk of Poland.

In Australia

Douglas Wilson has been called the real pioneer of paediatric anaesthesia in Western Australia, and Margaret McLellan, John Stocks, Ian McDonald, MA Denborough.

In Japan

Japanese interest in paediatric anaesthesia began later but proceeded vigorously beginning in 1958,[73] the publication of *Paediatric Anaesthesia* in 1958 by Onchi and Fujita served as a valuable guide.

In Latin America

Throughout Latin America, Brazilian physicians[74] and others followed USA type of anaesthesia methods to some extent, but in these countries, and especially in Mexico, local and regional anaesthetic techniques were depended on and consequently more highly developed than inhalation anaesthesia.[75]

PHASE IV: PROGRESS AND SOPHISTICATION (1980 TO PRESENT)

Paediatric anaesthesiologists setting computerized monitors and infusion pumps, with syringes loaded and coded with a large cabinet within arm's reach, holding drugs and other equipment for all possible situations. Anaesthesia was induced with minimal resistance from patient. Surgeons waited for fixation of monitors, endotracheal tubes, and catheters. Multiple medications are delivered by the intravenous route, drugs were frequently measured in micrograms per kilogram. The ventilator was set at a prescribed rate and tidal volume. Then surgeons are allowed to drape the patient. Anaesthesiologist uses automated Charting to keep watch on monitors. Now premature infant can receive spinal anaesthesia for herniorrhaphy. Long numbers of hours are required for liver transplantation withstood anaesthesia.

Recognition of Risk

Paediatric anaesthesiologists appreciate that infants and very small children have at increased risk of complications from both anaesthesia and surgery. Previous reports (Salem, 1975) had shown that these were frequently related to cardiovascular factors (including hypovolemia, anaemia), respiratory difficulties (airway obstruction, hypoxia, inadequate ventilation), or electrolyte imbalance (hyperkalemia, hyponatremia, hypoglycemia). In particular, postoperative apnoea, especially in very premature infants, was noted by several doctors[76–78] and overnight hospitalization in

these situations was widely recommended. Risk in small children could be decreased if doctors specially trained and experienced in paediatric anaesthesia provided the anaesthesia care.[79–82]

Changing Patterns of Care

Several areas of surgery have shown that corrective procedures performed in infancy, rather than palliative procedures done initially followed by full repair later in life, lead to improved long-term results. The vast majority of paediatric surgical procedures currently are done in ambulatory patients who never remain overnight in the hospital. Paediatric anaesthesiologists have become increasingly involved in caring for children outside the operating rooms for analgesia required for nonsurgical procedures. This has largely occurred in the radiology departments, where increasingly sophisticated equipment and techniques have led to major advances in diagnosis (computed tomography, magnetic resonance imaging, positron emission tomography, etc.) and new, less-invasive treatment options (cardiac catheterization laboratory, radiation therapy). Anaesthesiologists are being requested to provide care for patients in several other areas like gastrointestinal endoscopy, oncology unit for lumbar punctures and bone marrow aspirations. While children clearly benefit from relief of pain and anxiety in these situations, this has greatly increased demands for anaesthesia services.

NEW DEVELOPMENTS IN ANAESTHESIA

The age-old, frequently used restriction of preoperative intake ultimately underwent scrutiny several times which resulted in concept and reduction of fasting time.[83,84] New, potent, inhalational anaesthetic agents have been developed, virtually replacing halothane as the "standard" for the previous generation. To induce anaesthesia via mask, sevoflurane is used almost exclusively because it acts faster and results in less bradycardia and hypotension.[85,86] This has been especially important in infants. Isoflurane is frequently used for maintenance of anaesthesia, in part because it is currently less expensive; desflurane may be used when particularly rapid awaking is desired. None of these newer agents, however, have the smooth induction properties of sevoflurane. Concerns have been raised about breakdown products that may develop when sevoflurane interacts with some carbon dioxide absorbents, especially when dessicated, leading to overheating of the absorbent system, carbon monoxide production, or both.[87] The clinical significance of this remains to be determined. A new, major feature in airway management has been the promotion of the laryngeal mask airway to eliminate tracheal intubation for many simple procedures, as well as provide airway access in emergency situations when intubation is difficult.[88] Mason and Bingham (1990),[89] Pennant and White (1993)[90] endoscopes have also been developed that permit fiberoptic intubation even in small children. Several "descendents" of fentanyl have been developed, with remifentanil capable of providing very potent and transient analgesia when administered via constant intravenous infusion.[91–93] Fentanyl trans-cutaneous "patches" have also been developed, largely to provide analgesia for chronic pain, and fentanyl is sometimes administered trans-nasally or trans-orally.[94,95] Potent opioids have been particularly useful for cardiac procedures when inhaled anaesthetic agents are not well tolerated[96,97] produced evidence of physiologic stress in infants under light anaesthesia. This brought general agreement that all infants should receive anaesthesia during surgery. Propofol has become the most common intravenous induction agent for adults but has not completely replaced thiopental in children because propofol causes some discomfort when injected into small peripheral veins. Midazolam has replaced diazepam as the intravenous benzodiazepine of choice for sedation in children; midazolam is also the most popular oral sedative in the preoperative setting[98] Midazolam can also be administered via several other routes (including intranasal). The use of lidocaine-prilocaine creams[99] for skin desensitization eases the discomfort of venipuncture for intravenous induction but requires advance application to become effective. Intramuscular injections are rarely necessary now in paediatric anaesthesia practice. Several new, non-depolarizing muscle relaxants have replaced curare. Although pancuronium is commonly used for lengthy procedures, several shorter-acting agents (especially cisatracurium and vecuronium) are frequently administered for brief procedures and have fewer side effects. Rocuronium is often used to facilitate emergency endotracheal intubation, and succinylcholine is no longer administered without good cause, because masseter spasm, malignant hyperthermia, or both occasionally develop after its administration, especially in the presence of potent inhaled Halothane.[100] In addition, the Food and Drug Administration (1997)[101] issued a "black box" warning due to serious complications (including cardiac arrest resulting from acute hyperkalemia) associated with its use, particularly in

young males with unrecognized muscular dystrophy. Regional anaesthesia has become more commonplace in children, beginning in Europe, with "single-shot" techniques (spinal, caudal, peripheral nerve block) reducing the requirements for general anaesthesia and providing postoperative analgesia.[102,103] Continuous infusions of local anaesthetics with or without fentanyl are often delivered intra-operatively and postoperatively via catheters placed during surgery, especially via the epidural route. This is a reflection of the much greater emphasis being devoted to the need of the reducing pain in the postoperative period. Pain control following surgery has been a major focus of paediatric anaesthesiologists with patient-, parent-, or nurse-controlled analgesia available via computer-controlled infusion pumps for delivery of medications by the intravenous or epidural route. Pain treatment services have become more important aspects of the mission of most departments of paediatric anaesthesia; they provide care for children with medical, as well as surgical, pain.[104,105] Preoperative clinics are used to evaluate many patients in advance of their procedures, and significant attention has been devoted to methods of easing induction of anaesthesia, especially the use of oral premedicants and parental presence during mask induction.[106] In all instances, kindness remains the essential feature in preoperative management.

Progress in Monitoring

Electronic, engineering and technical advances have also greatly enhanced patient monitoring. Smaller equipment are now readily available so that very young patients can be monitored carefully and critically. Percutaneous catheters can be inserted directly into any peripheral vein or artery; the Seldinger technique (if necessary with ultrasound guidance) can be used to insert central catheters. Echocardiography can be performed transthoracically or transesophageally in small children. Its use has greatly facilitated the ability of cardiac surgeons to assess the repair of congenital heart lesions intraoperatively.[107] "Standard" monitoring is now quite extensive and sophisticated as promulgated by the American Society of Anaesthesiologists in 1986 and includes continuous pulse oximetry and capnography.

Advances in Surgery

Laparoscopic techniques, robotics, and intraoperative imaging have progressed so extensively and so rapidly into paediatric practice that anaesthesiologists have had to accommodate the special problems and challenges presented by these situations. In field of foetal surgery, where surgeons, obstetricians, anaesthesiologists, and neonatologists must collaborate to care for mother and foetus simultaneously during surgical repair of prenatal anomalies are developed and assessed.[108–111]

Research Efforts

Physiologic studies of cerebral circulation in the neonate by Rogers et al. (1980),[112] gas exchange in cardiac patients,[113,114] pharmacologic biotransformation of sedatives[115] the infant and the myoneural junction[116] and hypoxia in children following anaesthesia.[117] The report by Lerman et al (1986)[118] which was concerning post-anaesthetic vomiting after strabismus surgery is another illustration of one of the problems of the conscious child that remains particularly difficult to control during anaesthesia.

SUMMARY

Paediatric anaesthesia has advanced enormously. Times of anaesthesiologists adapting adult anaesthesia techniques are things of past. There are dedicated anaesthesia equipment to small children. It is clear that paediatric anaesthesiology is a well-established and well-recognized super specialty at postgraduate level. Anaesthetists accept challenges of undertaking more complex surgical techniques being performed on younger and younger patients for longer and longer duration.

Landmark Years in History of Anaesthesia

1846 The discovery of ether as a general anaesthetic.
1885 The discovery of injectable cocaine and local anaesthesia.
1896 The discovery of the hypodermic needle, the syringe, and the injection of morphine.
1905 Discovery of the measurement of blood pressure by blood pressure cuff.
1913 Discovery of the cuffed endotracheal breathing tube.
1934 The discover of thiopental and injectable barbiturates.
1940 The discovery of curare and injectable muscle relaxants.
1950s The development of the post-anaesthesia care unit (PACU) and the intensive care unit (ICU)
1956 The discovery of halothane, the first modern inhaled anaesthetic.
1983 The discovery of pulse oximetry monitoring.

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2

Anatomical Considerations in Paediatric Anaesthesia

Amit Padvi, Namita Padvi and Bhvya Baldwa

INTRODUCTION

For the study of paediatric anaesthesia, a clear understanding of the anatomical, physiological, pharmacological and psychological differences across various age groups is essential. Amongst paediatric patients, neonates and infants require special consideration as they are at higher risk of morbidity and mortality. The risk is generally inversely proportional to age. The most striking contrast between adults and children is obviously the body size. Several anatomical features of the neonatal and infant airway differ from that of adults and are important to the anaesthesiologist. Anatomic relationships and landmarks are constantly changing throughout infancy and childhood, which interferes with regional procedures and requires quite a good knowledge of developmental anatomy.

The key differences between the anatomical features of children and adults are highlighted in the chapter.

BODY SIZE

As previously mentioned, the most obvious difference between children and adults pertains to body size. But

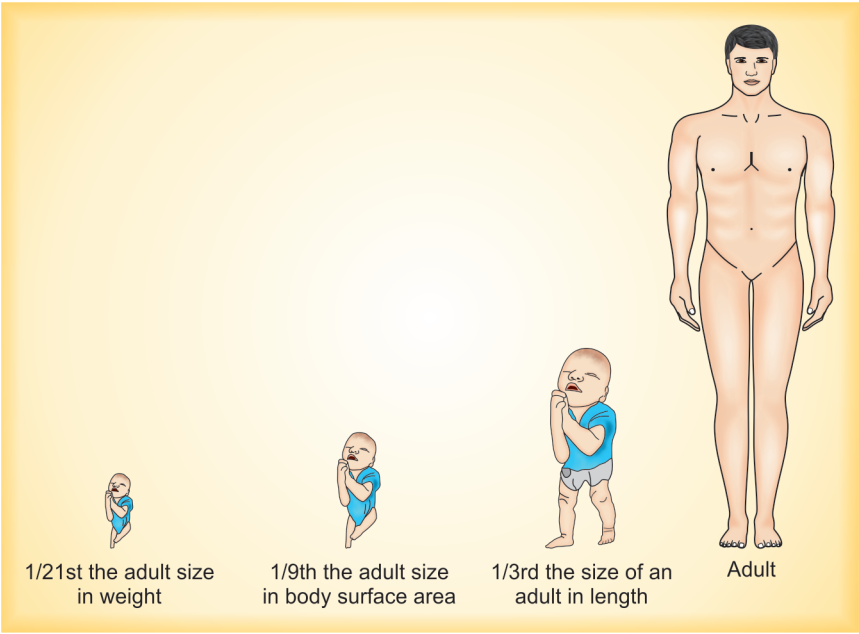

Fig. 2.1 As per Harris (1957), a normal full term, a normal newborn infant weighing 3 kg is 1/3rd the size of an adult in length, but 1/9th the adult size in body surface area and 1/21st the adult size in weight

at the same time, children are not small adults. The paediatric population as per age group can be divided as:

1. Neonates—refers to an infant in the first 28 days after birth.
2. Infants—a child of up to 12 months of age
3. Toddler child—1 to 4 years
4. Schoolgoing child—4 to 12 years
5. Adolescent and teenage—13 to 18 years

"Normal" full-term neonate weighs 3 to 3.5 kg with a height of approximately 50 cm, and within 10 to 15 years they will multiply their weight by more than 12 (>1200%) and their height by more than 3 (>300%).[1]

Amongst these various parameters, body surface area (BSA) is the most important as it closely matches variations in basal metabolic rate measured in kilocalories per hour per square meter. It is for this reason, BSA is considered to be a superior standard than age or weight in judging basal fluid and nutritional requirements. Nomograms, as that of Talbot and associates (1952), are available for clinical calculation of BSA. To calculate BSA, the following formula can be used:

Formula of Gehan and George (1970)

$BSA(m^2) = 0.0235 * Height^{0.42246} * Weight^{0.515456}$.[2]

Table 2.1 Relation of age, height, and weight to body surface area (BSA)

Age (y)	Height (cm)	Weight (kg)	BSA (m^2)
Premature	40	1	0.1
Newborn	50	3	0.2
1	75	10	0.47
2	87	12	0.57
3	96	14	0.63
5	109	18	0.74
10	138	32	1.10
13	157	46	1.42
16 (Female)	163	50	1.59
16 (Male)	173	62	1.74

Based on standard growth chart and the formula of DuBois and DuBois (1916): $BSA\ (m^2) = 0.007184 \times Height^{0.725} \times Weight^{0.425}$.[3]

There is a difference in the relative size of body structures in infants and children. Neonates have a large head (35 cm in circumference), which is larger than chest circumference. Head circumference increases by 10 cm during the first year of life and then 2 to 3 cm during the second year, when it reaches three-fourths the adult size.

AIRWAY

The anatomy of the airway of neonates and infants is different and difficult from that of adults. From about 4 years of age the airway anatomy becomes more like an adult and the airway problems associated with anaesthetizing children become less frequent. The important features of the airway of neonates and infants are listed.

Upper Airway

1. Relatively large head.
2. Prominent occiput.
3. Short neck: In a full-term neonate, the chin often meets the chest at the level of the second rib, making them prone to upper airway obstruction during sleep. In an infant with a tracheostomy, the orifice is often buried under the chin unless the head is extended with a roll under the neck.
4. Relatively small mandible.
5. Relatively large tongue.
   a. The size of the tongue means that there is relatively less space in the infant airway and that they are prone to upper airway obstruction.
   b. The tongue may also complicate direct laryngoscopy. It may be difficult to displace anteriorly with the laryngoscope.
   c. For the first few weeks of life, as a result of the large tongue, neonates and infants preferentially breathe through the nose rather than the mouth. This imposes a resistance to ventilation that is increased in the presence of nasal congestion from infection or the presence of a foreign body such as a nasogastric tube, oxygen prongs, or an endotracheal tube.
6. Abundant lymphoid tissue.
7. The pharynx tends to easily collapse by posterior displacement of the mandible, or external compression of the hyoid. Infants are more prone to upper airway obstruction under anaesthesia or sedation because upper airway muscles, which normally support the airway patency, are extremely sensitive to the depressant effect of anaesthesia and sedation, resulting in pharyngeal airway collapse and obstruction.
8. Relatively large omega or U-shaped epiglottis. It may fall backwards over the laryngeal inlet, if the tip of the laryngoscope blade is in the vallecula. A better view is usually obtained if the tip of the

laryngoscope is positioned on the laryngeal surface of the epiglottis.

9. Larynx is higher up and lies at the level of C_{3-4}.
10. Angled vocal cords: The orientation of the vocal cords directs the tip of an endotracheal tube against the anterior wall of the trachea, where it may hold up and can create the impression that the endotracheal tube is too wide to enter the cricoid ring.
11. Cricoid ring is the narrowest part of the upper airway.
12. Neonates preferentially breathe through the nose. Their narrow nasal passages are easily blocked by secretions and may be damaged by a nasogastric tube or a nasally placed endotracheal tube. Nasal passage contributes to 50% of airway resistance. There might be difficulty in nasal intubation as a "blindly" placed endotracheal tube may easily lodge in anterior commissure of the larynx rather than in trachea.
13. The large head, prominent occiput, and cephalad larynx combine to produce a view of the larynx which is often described as 'anterior' but is actually cephalad compared with adults.[4]
14. The 'sniffing' position does not help in bag mask ventilation or to visualize the glottis. The head needs to be in a neutral position.
15. Endotracheal tube (ETT): The diameter of the ETT must be narrow enough not to exert pressure on the mucosa of the cricoid cartilage. It should also allow a seal adequate for positive pressure ventilation with a minimal leak, at a peak inflation pressure of 20 cm of H_2O.
16. Trauma to the airway can easily result in oedema. One millimetre of oedema can narrow a baby's airway by 60% (Resistance $\propto 1/\text{radius}$). Therefore it is suggested that a leak be present around the endotracheal tube to prevent trauma resulting in subglottic oedema and subsequent post-extubation stridor.
17. Relatively more salivary secretions.

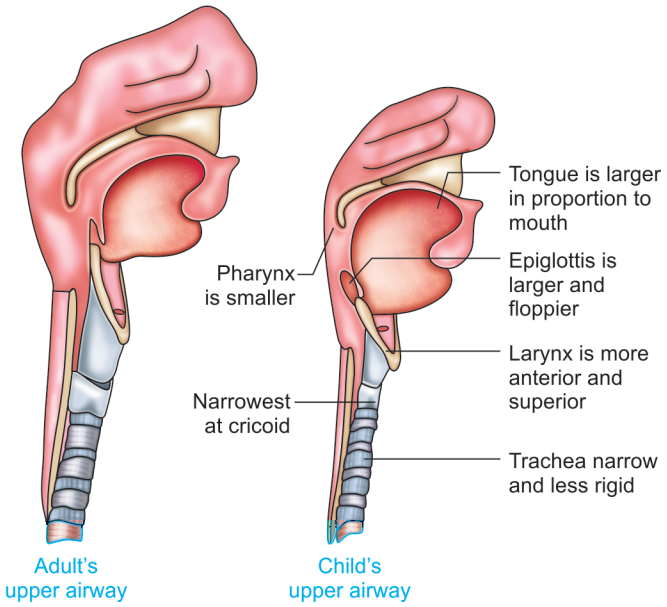

Fig. 2.3 Comparison of upper airway in child and adult

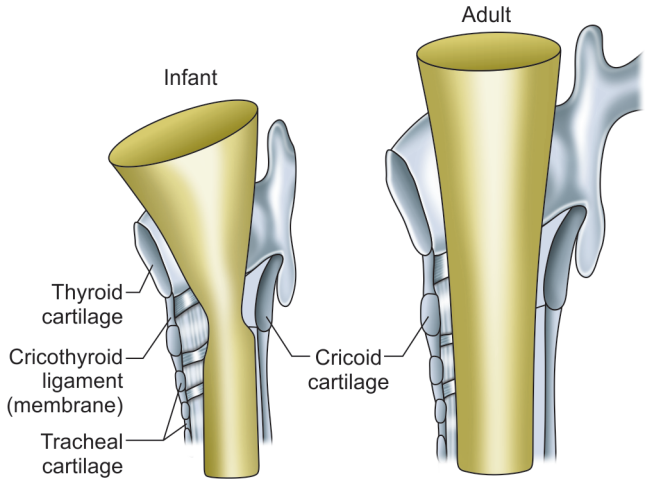

Fig. 2.2 Comparison of infant and adult airway

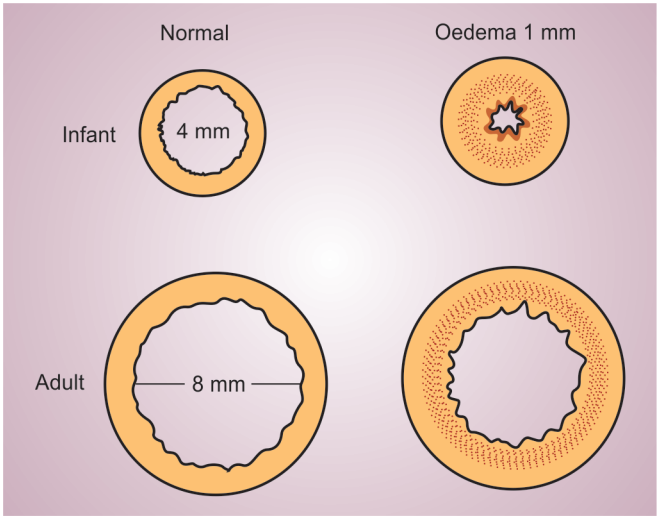

Fig. 2.4 Airway oedema in infant and adult

Table 2.2 Relation of airway oedema, resistance and cross sectional area of infant and adult trachea

	Oedema	
	Resistance ($R \propto 1/r^4$)	Cross section area
Infant	Increase by 16 times	Decreased by 75%
Adult	Increase by 3 times	Decreased by 44%

Lower Airway

1. The tracheal length may be as little as 3 cm and diameter may be 6 mm. Tracheal length is shorter resulting in increased chances of endobronchial intubation. Conversely, short endotracheal tubes are prone to unintentional displacement.
2. At the carina left and right main bronchi bifurcate at the same angle and hence endobronchial intubation is as likely to be left-sided as right-sided.
3. The total number of alveoli is only 10% of that of an adult and is thick-walled. A single terminal bronchiole opens into a single alveolus instead of a fully developed clustering.
4. Horizontal alignment of the soft and pliable ribs prevents the 'bucket-handle' action of the adult thoracic cage. There is less efficient ventilation than in adults because of:
   i. Weak intercostal and diaphragmatic muscles (due to a lack of type I fibres)
   ii. More horizontal attachment of intercostal muscles
   iii. Protuberant abdomen

   Limited respiratory reserve results in earlier onset of fatigue if the work of ventilation increases during anaesthesia or illness.
5. The chest is relatively small in relation to the abdomen, which is protuberant with weak abdominal muscles. The thorax is too compliant to resist inward recoil of the lungs. In the awake state, the chest wall is maintained relatively rigid with sustained inspiratory muscle tension, which maintains the end-expiratory lung volume (functional residual capacity [FRC]). However, under general anaesthesia, the muscle tension is abolished and FRC collapses, resulting in airway closure, atelectasis, and venous admixture unless positive airway pressure (CPAP) or positive end-expiratory pressure (PEEP) is maintained.
6. Chest wall compliance is higher in neonates and infants (0.06 mL/cm H_2O) compared with (0.04 mL/cm H_2O) in adults, because of the cartilaginous ribs and lack of chest wall musculature. This explains why intercostal and sternal retractions occur early in neonates and young infants during respiratory distress and airway obstruction.
7. Upper and lower airways are susceptible to a large increase in airway resistance (and the work of breathing) in the event of laryngeal or bronchial spasm.
8. Muscles of ventilation are easily subject to fatigue due to low percentage of Type I muscle fibres in the diaphragm. This number increases to the adult level over the first year of life.
9. The alveoli are thick walled at birth. There is only 10% of the total number of alveoli found in adults. The alveoli clusters develop over the first 8 years of life.

Toddlers

1. Head is more proportional to body size.
2. Teeth are formed.
3. Jaw becomes larger.
4. Epiglottis becomes less floppy.
5. Diaphragm remains the main muscle of respiration till 7 years of age.
6. Tracheal length on an average in the newborn is 3 cm, in a five year old child 6 cm, at the age of ten 7 cm and at the age of 15 years it is 8.5 cm.[5]

CENTRAL AND AUTONOMIC NERVOUS SYSTEM

1. Neonates have a relatively large brain, weighing about 1/10 of its body weight compared with about 1/50 in the adult. In a child, there is rapid development of the brain; its weight doubles by 6 months of age and triples by 1 year. At birth the brain weighs approximately 330–350 g (10–15% of body weight). Adult proportions (1200–1400 g—2% of body weight) are reached around 12 years of age.
2. The cerebral cortex is not fully developed and synaptic connections are not mature. Myelination and dendritic proliferation progress in the last 3 months of pregnancy and during the first year of life.
3. Approximately one-fourth of the neuronal cells are present at birth. By 1 year of age, the development of cells in the cortex and brain-stem is nearly complete. Myelinization and elaboration of dendritic processes continues till the end of third year. Incomplete myelinization is associated with primitive reflexes, such as the Moro and grasp reflexes, in the neonate.

4. The sutures are open and there is a large anterior fontanelle. Palpation of the anterior fontanelle can be used to evaluate intracranial pressure in neonates and infants. Increasing intracranial pressure is partly relieved by expansion of the fontanelles and separation of the suture lines so that head size increases before intracranial pressure rises.
5. In the preterm neonate cerebral vessels are at risk of rupture especially in the region of the germinal matrix close to the nucleus caudatus. The germinal matrix has a rich blood supply, scarce vascular supporting tissue, and thin vessel walls leading to a high chance of intracerebral and intraventricular haemorrhage. With increasing gestational age the germinal matrix involutes and the risk of bleeding decreases.
6. The volume of CSF is proportionately greater than in adults (4 mL/kg compared with 2 mL/kg) and this partly explains the relatively higher dose requirements for local anaesthetic (LA) solution and shorter duration of subarachnoid analgesia. The sacral hiatus is relatively large compared with later life and is not ossified. For these reasons it provides easy access to the lower epidural space.
7. The blood–brain barrier is not fully developed and it is anatomically and functionally incomplete. Bilirubin, opioids, and barbiturates all cross freely into the CNS through this blood–brain barrier.
8. At birth the spinal cord ends at the third lumbar vertebra. At 1 year of age, the cord assumes its permanent position, ending at the first lumbar vertebra.[6] The spinal cord of the foetus initially occupies the entire length of the spinal canal. Differential growth of the canal and spinal cord causes the termination of the cord to move cephalad relative to the vertebral canal. It is at the level of S1 at 28 weeks' gestation, L3 at term, L2/3 at 1 year, and the adult level of L1/L2 around the age of 8 years. The intercristal line in neonates is at the level of L5–S1 compared with L4 in adults and lumbar puncture is performed below this line. Ossification of the sacral vertebrae is not complete and sacral intervertebral epidural analgesia is feasible.
9. The epidural space in the infant contains fat that is loculated with distinct spaces between individual lobules. This means that a catheter introduced into the epidural space via the sacral hiatus can often be threaded to thoracic level to provide epidural analgesia for thoracic dermatomes.
10. In contrast to the central nervous system, the autonomic nervous system is relatively well developed in the neonate. The parasympathetic components of the cardiovascular system are function optimally at birth. However, the sympathetic components, are not fully developed until 4 to 6 months of age.[7] Baroreflexes to maintain blood pressure and heart rate, which involve medullary vasomotor centres (pressor and depressor areas), are functional at birth in awake newborn infants.[8]

The laryngeal reflex is activated by the stimulation of receptors on the face, nose, and upper airways of the newborn resulting in reflex apnoea, bradycardia, or laryngospasm. Various mechanical and chemical stimuli, like water, foreign bodies, and noxious gases, can trigger this response. This protective response is so potent that it can cause death in the newborn.

RESPIRATORY SYSTEM

At full-term birth, the lungs are still in the stage of active development. The formation of adult-type alveoli begins at 36 weeks post conception but represents only a fraction of the terminal air sacs with thick septa at full-term birth. It takes more than several years for functional and morphologic development to be completed. Similarly, control of breathing during the first several weeks of extrauterine life differs notably from control in older children and adults. Of particular importance is the fact that hypoxemia depresses, rather than stimulates, respiration. The development of the respiratory system and its physiology are detailed in Chapter 4, Essentials of Respiratory System.

CARDIOVASCULAR SYSTEM

During the first minutes after birth, the newborn infant must change his or her circulatory pattern dramatically from foetal to adult type to survive in the extrauterine environment. Even for several months after initial adaptation, the pulmonary vascular bed remains exceptionally reactive to hypoxia and acidosis. The heart remains extremely sensitive to volatile anaesthetics during early infancy, whereas the central nervous system is relatively insensitive to these anaesthetics. Cardiovascular physiology in infants and children is discussed in Chapter 3.

FLUID AND ELECTROLYTE METABOLISM

Like the lungs, the kidneys are not fully mature at birth, although the formation of nephrons is complete by

36 weeks—gestation. Maturation continues for about 6 months after full-term birth. The glomerular filtration rate (GFR) is lower in the neonate because of the high renal vascular resistance associated with the relatively small surface area for filtration. Despite a low GFR and limited tubular function, the full-term newborn can conserve sodium. Premature infants, however, experience prolonged glomerulotubular imbalance, resulting in sodium wastage and hyponatremia (Spitzer, 1982). On the other hand, both full-term and premature infants are limited in their ability to handle excessive sodium loads. Even following water deprivation, concentrating ability is limited at birth, especially in premature infants. After several days, neonates can produce dilute urine; however, diluting capacity does not mature fully until 3 to 5 weeks of life (Spitzer, 1978). The premature infant is prone to hyponatremia when sodium supplementation is inadequate or with overhydration. Furthermore, dehydration is detrimental in the neonate regardless of gestational age.

SUMMARY

1. Neonates have relatively large head and tongue with short neck and small mandible.
2. Neonates are obligate nasal breathers.
3. Epiglottis is large, floppy and omega shaped.
4. Cricoid ring is the narrowest part of the upper airway hence easily prone to.
5. Short length of trachea leads to higher chances of endobronchial intubations.
6. Soft, pliable ribs prevent bucket handle movement of thoracic cage.

Four differences between the adult and paediatric airway

1. Infant tongue is proportionally large.
2. The infants larynx is higher (rostral) in the neck (C3–4) than an adult (C4–5).
3. The infants epiglottis is omega shaped (W) and angled away from the trachea.
4. The narrowest part of the larynx is the cricoid cartilage below the vocal cords.

Positioning

Use of the chin lift and jaw thrust can help restore flow through an obstructed upper airway by separating the tongue from posterior pharyngeal structures.

The goal is to line up three divergent axes: Oral, pharyngeal and tracheal.

1. Aligning the axes (initial)
2. Aligning the axis (occiput roll)
3. Aligning the axis (extension)

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3

Essentials of Cardiovascular System in Infants and Children

Chinmayi S Patkar and Namita Padvi

INTRODUCTION

Paediatric anaesthesia poses a challenge to the anaesthesiologist in view of the ongoing development and maturation of the organ systems, especially the cardiopulmonary system. The stage of organ maturation varies with age in each individual child, thus making it essential for the anaesthesiologist to be familiar with each and every age group ranging from neonates to young adolescents. In addition to age and development, the congenital heart diseases have a profound impact on the pharmacodynamics of anaesthetic agents.

The objective of this discussion is to focus on normal cardiovascular physiology in paediatric population in the context of continual organ maturation, which will aid the anaesthesiologist to deal with any paediatric patient on a routine basis.

FOETAL CIRCULATION (Fig. 3.1)

The chief function of the cardiovascular system is to provide oxygen delivery and metabolic nutrition to all the organ systems of the body. The foetal circulation differs from its adult counterpart in numerous ways. Firstly it encompasses the entire maternal fetoplacental unit comprising of the placenta and umbilical vessels. Secondly unlike in adults, the lungs do not participate in gas exchange but require only nutrient flow. This necessitates the presence of foetal intracardiac and extracardiac shunts to allow minimal blood flow to the lungs while simultaneously ensuring oxygenation to all the tissues. With the first cry at birth, respiratory exchange is initiated in the neonatal lungs and the placenta is soon after eliminated from circulation. The formerly 'shunt dependent' foetal circulation now has to function independently in order to allow a smooth transition to a neonatal circulation. Transitional circulation is an orderly process embracing all adaptive changes in the foetal circulation till it establishes a neonatal circulation. The presence and persistence of transitional circulation can cause adverse effects on the cardiovascular function of the neonate.

Deoxygenated blood is carried down the descending aorta to the umbilical arteries which then enter into the placenta. The umbilical arteries branch out to form the chorionic vessels ultimately ending into an extensive

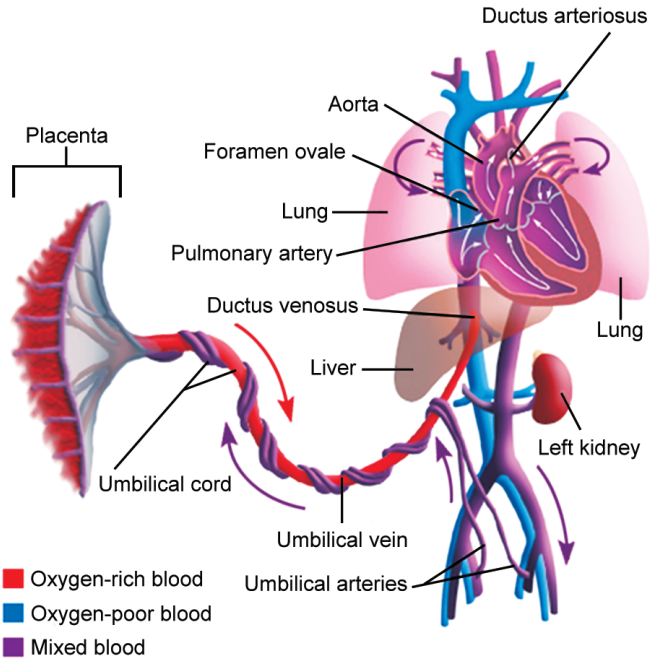

Fig. 3.1 Foetal circulation

arterio-capillary-venous network, namely the inter-villous system. This chorionic villus is the site of oxygen and nutrient exchange, thus representing the functional unit of the placenta. Oxygenated blood from the placenta is then carried by the umbilical vein to the foetal organ systems.

50 to 60% of the highly oxygenated umbilical venous blood is bypassed by the ductus venosus to enter the inferior vena cava (IVC) directly. The foramen ovale (FO) preferentially carries the oxygenated blood from the IVC into the left atrium (LA) and left ventricle (LV). The LV carries this relatively highly oxygenated blood to the brain and coronary vessels via the ascending aorta. Also, some portion of blood from the right atrium (RA) coming via the superior vena cava (SVC), coronary sinus and part of IVC enters the right ventricle (RV). Due to high resistance of the pulmonary vasculature and relatively lower systemic vascular resistance of the placental unit, major portion of blood ejected from the RV goes to the descending aorta and placenta via the ductus arteriosus. Thus the foetal blood flow circuit demonstrates that both the ventricles function in 'parallel' to provide a mixed blood supply to the body organs as opposed to that in adults, where we observe the LV and RV working in 'series'. The presence of various intracardiac and extracardiac shunts allows the preferential streaming of oxygenated blood to the vital organs, namely brain and myocardium while bypassing the lungs and liver.

Clinical Pearl

Foetal circulation is shunt dependent and in 'parallel'; adult circulation is in 'series'.

In the foetus, the cardiac output of the left and right ventricles together comprises the total cardiac output, described as the combined ventricular output (CVO) (Table 3.1). About 45% of the CVO is directed to the placental circulation and only 8% of CVO enters the pulmonary circulation.[1] The RV has a cardiac output of approximately 330 mL/kg/min, whereas the LV output measures at about 170 mL/kg/min.[2] At birth, both RV and LV eject an output of 350 mL/kg/min. The reported ratio of right to left cardiac output ranges from 1.0 to 1.5 but most studies have agreed upon the right-sided dominance of foetal cardiac output.[3] Various poorly understood complex mechanisms involving circulating catecholamines and locally mediated vasoactive substances are believed to play a role in the control of foetal circulation.[1]

Clinical Pearl

Cardiac output in foetus is right-sided dominant.

The foetus survives in a relatively hypoxemic environment in-utero and yet has to perform the task of providing optimum oxygenation to the developing organ systems. The highest partial pressure of oxygen (PO_2) in the foetal circulation is observed in the umbilical vein being around 4.7 kPa, i.e. 30–35 mmHg and foetal blood is 80–90% saturated.[1] Optimum tissue oxygen delivery is ensured by adaptive mechanisms such as foetal haemoglobin (HbF) and 2,3-diphosphoglycerate (2,3-DPG). Oxygen delivery to a foetal organ is the product of blood flow to that organ and the oxygen content of foetal arterial blood; which in turn depends upon the haemoglobin (Hb) and its oxygen saturation (SaO_2).[1] Intraerythrocyte 2,3-diphosphoglycerate (DPG) is a product of glycolysis which normally acts to lower oxygen affinity and improve oxygen delivery to tissues. The gamma chains of foetal haemoglobin HbF do not bind as readily to 2,3-DPG thus resulting in higher affinity for oxygen as compared to adult form of haemoglobin (HbA). The high concentration of HbF (~ 80% at term) and low levels of 2,3-DPG permit efficient oxygen uptake in the placenta. Also the P_{50}, i.e. the oxygen tension at which 50% blood is saturated with oxygen is lower in the foetus at 3.6 kPa than in the

Table 3.1 Combined cardiac output and distribution in human foetus during the second half of pregnancy according to Rasanen et al.[4]

% of combined cardiac output at gestational age			
	20 weeks	**30 weeks**	**38 weeks**
Combined cardiac output	210 (mL/min)	960 (mL/min)	1900 (mL/min)
Left ventricle	47	43	40
Right ventricle	53	57	60
Foramen ovale	34	18	19
Lungs	13	25	21
Ductus arteriosus	40	32	39

adult (4.8 kPa). These factors enable to maintain the oxygen saturation in the umbilical venous blood greater than the uterine venous blood.

TRANSITIONAL CIRCULATION

Several changes occur in the foetal circulation at birth to facilitate its efficient transition into neonatal circulation. The separation of placenta, clamping of umbilical vessels and the neonate's respiratory efforts are the initiating events leading to these alterations. The first cry of the baby heralds the entry of blood into the pulmonary circulation with an increase in oxygen saturation. The placenta is eliminated from circulation altogether thus converting the low resistance circulatory system into a high resistance one. The intracardiac and extracardiac shunts cease to function immediately and permanently close over the course of time. Various neurohumoral and chemical mediators such as prostaglandins, kinins and nitric oxide (NO) contribute to these circulatory changes.

At birth, the first breath initiates entry of blood into the pulmonary circulation with reduction in pulmonary vascular resistance (PVR). Thereafter, there is a gradual decline in PVR over the ensuing years due to structural remodeling of the pulmonary vascular musculature. The placenta detaches from the uterine wall to cause constriction of the placental blood vessels. This event combined with clamping of the umbilical vessels leads to a consequent rise in systemic vascular resistance (SVR). With a fall in PVR and rise in SVR, the left atrial pressures increase above that of the right atrium causing the flap valve of the foramen ovale to close functionally. The prostaglandins [prostacyclin (PGI_2) and prostaglandin PGE_2] play a significant role in-utero to maintain the patency of the ductus arteriosus. The reduction in circulating prostaglandin levels with the separation of placenta and increased arterial oxygen tension cause the functional closure of the ductus arteriosus within 24 to 48 hours of birth. The anatomical closure occurs within 2 to 3 weeks by ductal fibrosis to become the vestigial remnant, namely ligamentum arteriosum. The ligation of the umbilical veins leads to a fall in the portal pressure relative to the inferior vena cava pressure which prompts functional obliteration of the ductus venosus within the first week of life. Its anatomical closure follows in the ensuing period to form the ligamentum venosum by the end of three months of birth.

Under certain adverse circumstances, the neonatal circulation can revert back to foetal circulation as the anatomical closure of shunts does not occur immediately after birth. Hypoxemia and acidosis are potent stimuli which are known to cause reversal of shunt patency. Persistence of foetal circulation (PFC) happens when shunting is present in the neonates beyond the transitional period without any evidence of underlying congenital heart disease.

Clinical Pearls

	Functional closure	Anatomical closure	Remnant structure
Foramen ovale	At birth	0–1 week	Fossa ovalis
Ductus arteriosus	24–48 hrs	2–3 weeks	Ligamentum arteriosum
Ductus venosus	0–1 week	2–3 months	Ligamentum venosum

BASIC PRINCIPLES OF CARDIAC FUNCTION

Preload is defined as the ventricular load at the end of diastole and before contraction has begun. In the intact heart, preload represents the diastolic stress caused by distension of the ventricular wall by blood volume. It is a reflection of the atrial filling pressures which then empty into the right ventricle (RV) or left ventricle (LV) during diastole. Clinically, we use indirect measurements of LV volume such as pulmonary wedge pressure or central venous pressure as surrogate markers of preload assessment.

Afterload is defined as systolic load on the LV after contraction has started. In other words, it is the stress developed in the left ventricular wall during ejection. The concept of afterload is more complex as LV ejection is a dynamic process. Preload is considered to be the wall stress at the end of diastole, whereas afterload is the wall stress experienced during LV ejection. To improve our understanding of afterload, we need to elucidate the concept of wall stress. The law of Laplace states that wall stress (σ) is proportional to the product of pressure (P) and radius (R) divided by wall thickness (h) in thin-walled spheres or cylinders:

$$\sigma \propto \frac{P \times R}{2\,h}$$

In accordance with the law of Laplace, wall stress is directly related to intraventricular pressure and inversely related to its wall thickness.

Afterload is often linked to vascular resistance, although impedance offers a more precise measurement. Aortic impedance is described as aortic pressure

divided by aortic flow. However, in clinical practice, echocardiography alone can measure aortic impedance noninvasively. Routinely we approximate systolic blood pressure measurement with afterload, provided there is no aortic stenosis.

The sarcomere is the functional unit of the myocardium. The relation between resting sarcomere length and the amount of built-up tension was originally defined in isolated skeletal muscle fibers. The increase in length of the resting sarcomere caused by a rise in venous filling leads to greater force of contraction and ultimately greater stroke volume and cardiac output (Fig. 3.2). This intrinsic ability of the heart to adapt to changing volumes of inflowing blood within physiologic limits is known as the Frank-Starling law.[5] Thus an increased preload initiates myocardial stretching which increases the end-diastolic volume (EDV) generating a positive inotropic effect which translates into a rise in stroke volume.

Contractility represents the intrinsic ability of the myocardium to contract and perform mechanical work at a given preload. Changes in contractility can bear either a positive inotropic effect which enhances cardiac performance or a negative inotropic effect which diminishes performance. Sympathetic input to the heart via $\beta_1$receptors on cardiac membrane increases contractility by release of norepinephrine, thereby exerting positive inotropic effect. Severe hypoxia, acidosis and myocardial depressants like anaesthetic agents are a few examples causing negative inotropic effect.

Stroke volume is the amount of blood ejected by the ventricles per heart beat. This volume is determined by the preload, afterload and myocardial contractility acting in tandem. Cardiac output is the product of stroke volume and heart rate. As the immature myocardium displays limited ability to increase stroke volume in an attempt to improve cardiac performance, the paediatric heart is more dependent on heart rate.

Clinical Pearls

- Frank-Starling mechanism is poorly developed
- Cardiac output is heart rate dependent

STRUCTURAL AND FUNCTIONAL DEVELOPMENT

The cardiovascular system is one of the first organ systems in the foetal body to become operational. As early as five weeks postconception, the basic circulatory parameter, namely heart rate is identifiable. The external heart formation is completed by six weeks of gestation. However, it is still undeveloped in terms of constitution, function and innervation.

Structurally, the neonatal myocardium is immature with lesser proportion of cellular matter (mitochondria, DNA) and lesser contractile proteins, namely actin and

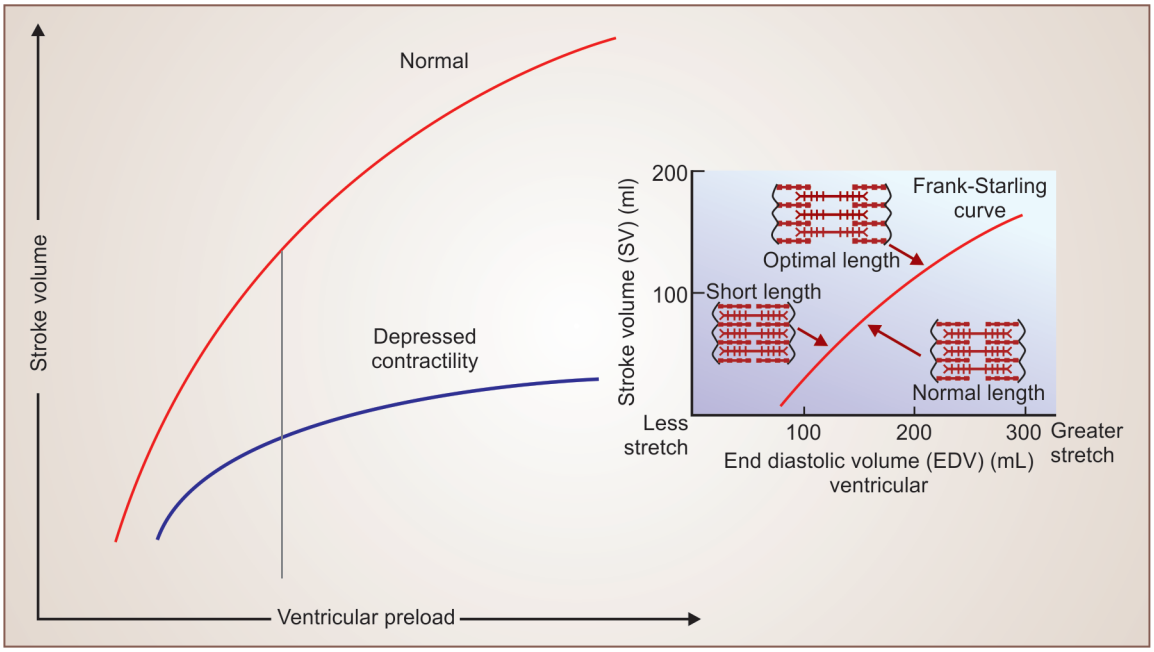

Fig. 3.2 Frank-Starling mechanism and sarcomere length (inset)

myosin. The myofibrils are scanty, poorly defined and aligned peripherally with limited capacity of protein synthesis. The myocardium is composed of higher proportion of non-elastic and non-contractile proteins (60% versus 30% in the adult myocardium) which renders it less compliant as compared to the adult heart. There is a greater extent of Type I collagen in the newborn's myocardium which is more rigid as compared to the adult Type III collagen. The neonatal myocytes contain higher proportion of water than contractile elements accounting for their decreased contractility.

The cell replication process varies in the foetus as compared to the adult. Foetal cardiomyocytes demonstrate the ability to undergo hyperplasia in addition to hypertrophy while the adult mature myocytes can divide only by hypertrophy, i.e. increase in size. The cell dimensions and surface area of the myocytes rapidly increase in the postnatal life.

The functional limitations of the neonatal heart are largely attributed to its structural immaturity. The poor compliance of the myocardium leads to its limited cardiac reserve. The heart is unable to respond to an increase in volume on the Frank-Starling curve to an extent the adult heart would. This results in the cardiac output being dependent upon heart rate more than stroke volume. The adult mechanism of increasing stroke volume to cause a proportionate rise in cardiac output is more resourceful. But infants and children, on the other hand, expend more energy in the process of increasing cardiac output by increasing their heart rate during stressful situations.

The changes in ventricular pressure are more easily transmitted to the opposite ventricle in the immature myocardium. Also, the LV and RV diastolic filling is severely impaired. Limited compliance and equal masses of both the ventricles contribute to their interdependence. The pressure and volume overload experienced by both the ventricles at birth lead to their hypertrophy. The adult ratio of LV to RV mass of 2:1 is attained several months after birth. Also, the biventricular interdependence makes the heart more susceptible to myocardial depression when faced with adverse events such as hypoxia, acidosis or anaesthetic agents. The stiffer nature of the myocardium restricts it potential to respond adequately to fluid overload. Thus, the neonates poorly withstand any increase in preload, afterload or depressed myocardial contractility.

Another important point pertaining to calcium ions is worthy of mention here. Calcium ions are essential for the excitation-contraction coupling resulting in myocardial contraction. These ions diffuse into the t-tubules and are released when required to enhance contractility. The earliest evidence of longitudinal sarcoplasmic reticulum is seen by the beginning of second trimester, but t-tubules are visible only after birth. Due to this underdeveloped sarcoplasmic reticulum in the neonatal heart, there is a limited storage capacity of calcium. Thus the neonatal myocardium is more dependent on sodium calcium channels for calcium influx from the extracellular space. This explains the increased sensitivity of neonatal heart to hypocalcemia and drugs like digitalis, calcium channel blockers, etc. and its dependence on extraneous calcium sources. Also, the reduced Ca-ATPase enzyme activity on the sarcoplasmic reticulum results in a decreased calcium release and reuptake.

Lastly, the source of energy for myocyte metabolism in the neonate is lactate while in adults long chain fatty acids are favored. This difference is due to deficiency of enzyme carnitine palmitoyl transferase-1 which transports long-chain fatty acids into the mitochondria. The relative dependence of the neonatal myocardium on anaerobic metabolism offers a somewhat protective role against hypoxia. The fundamental differences in the cardiovascular functioning of the neonate and adult are summarized in Table 3.2.

AUTONOMIC REGULATION OF CARDIAC FUNCTION

The cardiovascular functioning is regulated by the nervous system so as to ensure its optimum performance under different physiological circumstances. The autonomic system plays a crucial role in the control of cardiovascular homeostasis. During foetal period, this autonomic regulation of the heart is undeveloped

Table 3.2 Functional differences in the neonatal and adult cardiovascular parameters

	Neonate	Adult
Cardiac output	HR dependent	SV and HR dependent
Compliance	Less	Normal
Starling response	Limited	Normal
Preload reserve	Limited	Normal
Afterload compensation	Limited	Effective
Ventricular inter-dependence	High	Relatively low
Myocardial metabolism Chief substrate	Anaerobic Lactate	Aerobic Long chain fatty acids

and continues to remain immature throughout the neonatal life.

At birth, the heart is innervated by both sympathetic and parasympathetic systems. Both α and β-adrenergic receptors have been detected in the neonatal myocytes. However, it has been demonstrated that the sympathetic nervous system is incomplete at both the postganglionic receptor site and the receptor-effector level.[6] Furthermore, the sympathetic and parasympathetic systems attain maturity at a differential rate; the former being adequately functional by early infancy and the latter in the early neonatal period. This leads to parasympathetic dominance in the neonatal life which is clinically observed as marked bradycardia in response to adverse stimuli such as hypoxia, acidosis or anaesthetic agents.

The two prime functions of the autonomic nervous system are regulation of the distribution of cardiac output to each organ system and maintenance of blood pressure. These functions are determined by equilibrating the arteriolar and venular tone mediated by sympathetic and parasympathetic innervation.

The intrinsic and extrinsic cardiovascular reflexes serve to buffer sudden acute changes in blood pressure. Studies in humans and experimental animals suggest that arterial baroreceptors are present in the foetus, incompletely developed at term and undergo postnatal maturation. The baroreceptor reflex arc consists of an afferent limb located in the carotid body and aortic arch, a central medullary cardiovascular centre and an efferent limb composed of sympathetic and parasympathetic nerves to the heart and blood vessels. The foetal life demonstrates an enhanced sensitivity of the efferent limb of this reflex. In preterm infants, postural changes elicit no change in heart rate, but there is an increase in peripheral vascular resistance, illustrating an incomplete and attenuated baroreceptor response.[7] The chemoreceptor reflex in utero is presumed to be well developed as manifested by foetal bradycardia in response to hypoxia.

The salient features of the major cardiovascular reflexes are presented in Table 3.3.

The autonomic system displays its maximal profound impact on heart rate and contractility. The sympathetic and parasympathetic systems have a complementary action on heart rate. Cardiac output in the paediatric age group is more dependent on heart rate rather than on stroke volume. The resting normal sympathetic tone maintains contractility 20% greater than that in the denervated heart.[7] Heart rate and contractile force both can be raised to about 100% by increasing the sympathetic flow to heart. However, a higher heart rate translates into greater myocardial energy consumption. Thus infants and children tend to expend more energy while increasing their cardiac output especially when subjected to stress.

Circulating catecholamines released from adrenal gland and para-aortic chromaffin tissue also mediate autonomic control over heart much before direct innervation matures completely. An indirect evidence of immature innervation at birth is the lower levels of neurotransmitters as compared to that in adults. Catecholamine secretion is vital at birth to assist the foetus in adapting to the newly acquired external environment.

Clinical Pearls

- Parasympathetic system dominates over sympathetic system in neonates and infants.
- Vagal bradycardia observed in response to hypoxia, acidosis and myocardial depressant anaesthetic agents.

Table 3.3 Major cardiovascular reflexes. The Bainbridge and the "reverse" Bainbridge reflexes: History, physiology, and clinical relevance[8]

Reflex	Receptors and location	Afferent limb	Efferent limb and response
Arterial baroreceptor reflex	Stretch receptors in vessel wall of carotid sinus and aortic arch respond to changes in arterial blood pressure	Fibers in glossopharyngeal and vagus nerves to medulla	Homeostatic control of arterial blood pressure via changes in cardiac output and systemic vascular resistance mediated by the autonomic nervous system
Bezold-Jarisch reflex	Mechanical and chemosensitive receptors in ventricular walls	Nonmyelinated vagal C-fibres to medulla	Inhibition of sympathetic outflow resulting in bradycardia, peripheral vasodilation and hypotension
Bainbridge reflex	Stretch receptors at junction of the vena cava and right atrium and at junction of the pulmonary vein and left atrium respond to changes in volume in central thoracic compartment	Fibers in vagus nerve to medulla	Inhibition of vagal outflow and enhancement of sympathetic outflow to sino-atrial node causing tachycardia

PREOPERATIVE ASSESSMENT OF CARDIOVASCULAR SYSTEM

The cardiovascular system is continually in a state of dynamic transformation as it undergoes physiological development and maturation. The anaesthesiologist should be accustomed to the age related physiological variations while evaluating the patient prior to surgery. The objectives of a scheduled preoperative assessment should be to allay anxiety of parents, establish a friendly rapport with the child and form an individualised plan of anaesthetic management.

History

The skill of eliciting history is an essential prerequisite in the preoperative assessment of paediatric patients posted for surgery. The initial assessment of the cardiovascular system involves the general well-being of the child in terms of ability to 'thrive'. Feeding difficulty is an early indicator of cardiovascular disease in neonates and young infants. Inadequate growth and developmental delays reflect poorly on the overall health of the patient.

It is imperative to review the growth charts in the younger age group to follow the development of the patient over a period of time and compare it with the acceptable standard for age. Acute and chronic illnesses affect growth and development negatively; with loss of weight being the first sign of impairment followed by a lag in height and head circumference. In older age group, we can gauge the child's development by asking the parents to compare his overall growth and activity with that of his peers.

Cardiovascular disease is implied by more specific symptoms such as shortness of breath, cyanotic spells and palpitations. Chest pain and syncope are uncommon in children as compared to adults and signify an underlying cardiac pathology when present. Maternal exposure to drugs such as lithium, phenytoin or alcohol and diseases such as rubella, diabetes mellitus; to name a few are known to be associated with congenital cardiac lesions. Likewise, prematurely born neonates are placed at a higher risk of having patent ductus arteriosus. Hence, prenatal and birth history must be elicited precisely. Family history and enquiry about health of other siblings is also necessary.

Examination

General examination includes a thorough inspection of the child for central cyanosis, clubbing, splinter hemorrhages, pallor or icterus. Features of facial dysmorphism or other associated congenital anomalies such as syndactyly, polydactyly, cleft lip or palate can act as markers of a syndrome and warrant a detailed cardiac examination to rule out heart defects. Assessment of jugular venous pressure is not much relied upon in children less than eight years of age. Inspection of precordium for any obvious bulge or chest deformity like pectus carinatum or excavatum forms an integral part of systemic examination. Palpation of peripheral and central pulses helps to evaluate rate, rhythm, volume status of heart and to identify specific signs such as brachiofemoral delay classically seen in coarctation of aorta. Precordial palpation allows localization of the apex beat which lies in the 4th intercostal space from birth to three years of age and gradually migrates to lie in the 5th intercostal space with increasing age.[9] It also aids in detection of thrills associated with murmurs, if any.

Auscultation of the chest becomes the most significant part of cardiovascular examination. It is mandatory to perform a detailed auscultation of all the components of the cardiac cycle in all the auscultatory areas with both the bell and diaphragm of stethoscope.[10] Innocent, functional or benign murmurs are quite common in childhood and should be distinguished from pathological murmurs which denote an underlying cardiac disease.

These physiological murmurs are soft, systolic in nature and recede with change in position, exercise or hemodynamic status of the child. On the contrary, diastolic or continuous murmurs and those associated with a palpable thrill are always pathological. A notable exception is a venous hum which is a benign continuous murmur best heard at the base of the neck due to turbulent venous flow in the superior vena cava and jugular veins. The benign or innocent murmurs of childhood are enlisted in Box 3.1.[10]

Box 3.1: Innocent murmurs of childhood[10]

Systolic murmurs	Continuous murmurs
Vibratory Still's murmur	Venous hum
Pulmonary flow murmur	Mammary arterial soufflé
Peripheral pulmonary arterial stenosis murmur	
Supraclavicular systolic murmur	
Aortic systolic murmur	

Chest X-ray and ECG

The specific age-related changes in the cardiovascular system add to individual variations in the paediatric

chest X-ray and ECG which need to be interpreted correctly.

The heart shadow is relatively large in infants with the cardiac silhouette occupying almost 50–55% of the thoracic width on anteroposterior view. In neonates and infants, the thymus may contribute to apparent cardiomegaly and this should be distinguished by a lateral view X-ray. Apart from size, one should also pay attention to the cardiac shape and pulmonary vasculature for signs suggestive of congenital heart disease.

It is not routine to advise ECG in paediatric patients, except when history and physical examination particularly raise a suspicion of an underlying cardiovascular disorder. Age-specific changes occurring in the cardiovascular system during development are reflected in the ECG. For example, in early neonatal period the right ventricle dominates over the left ventricle in both size and function. This is reflected in the ECG as right ventricular dominance and right QRS axis deviation. Over the early months of postnatal life, the left ventricle grows in size and gradually demonstrates its dominance on ECG. The ECG values which change rapidly in the first year of life evolve more gradually after infancy to mature completely by late adolescence and early adulthood. The normal ranges as per age are represented in Table 3.4 for heart rate, QRS axis, PR and QRS complex intervals and R- and S-wave amplitudes.[11]

Apart from chest X-ray and ECG, 2D-echocardiography forms an important tool of assessment of cardiac function. The non-invasive nature of this investigation goes a long way in predicting the effects of anaesthetic agents in a patient with cardiovascular abnormality. Cardiac catheterization is an invasive method of definitive assessment in paediatric patients having cardiac disorder.

EFFECTS OF ANAESTHETIC AGENTS ON CARDIOVASCULAR SYSTEM

The cardiovascular system is susceptible to the effects of anaesthetic agents in myriad ways depending upon the age-related physiological development. It is necessary to consider physiological evolution while administering anaesthesia to the paediatric patient. One should pay due attention to the type of anaesthetic agent selected for a particular patient as per the nature and duration of surgery. The cardiopulmonary and drug interactions should also be taken into account while applying a tailor-made approach for each individual. The anaesthetic goals relevant to the cardiovascular system are maintenance of optimum oxygen delivery and adequate ventricular output.

Premedication

The need for premedication can be validated by the fact that a calm and composed child offers an opportunity of a smooth and safe induction while maintaining hemodynamic stability. Premedication is unwarranted in the neonates and infants up to eight months age. However, infants start developing stranger anxiety from 8 to 9 months of age, thus necessitating premedication. Elder children above the age of six years can be dealt with reasoning and psychological counseling, again depending upon the emotional and mental make-up of the individual.

Benzodiazepines and opioids administered orally or intravenously are the frequently employed

Table 3.4 ECG variables—normal range values for age[11]

Age	HR (bpm)	QRS axis (degree)	PR interval (sec)	QRS interval (sec)	R in V_1 (mm)	S in V_1 (mm)	R in V_6 (mm)	S in V_6 (mm)
1st week	90–160	60–180	0.08–0.15	0.03–0.08	5–26	0–23	0–12	0–10
1–3 weeks	100–180	45–160	0.08–0.15	0.03–0.08	3–21	0–16	2–16	0–10
1–2 months	120–180	30–135	0.08–0.15	0.03–0.08	3–18	0–15	5–21	0–10
3–5 months	105–185	0–135	0.08–0.15	0.03–0.08	3–20	0–15	6–22	0–10
6–11 months	110–170	0–135	0.07–0.16	0.03–0.08	2–20	0.5–20	6–23	0–7
1–2 years	90–165	0–110	0.08–0.16	0.03–0.08	2–18	0.5–21	6–23	0–7
3–4 years	70–140	0–110	0.09–0.17	0.04–0.08	1–18	0.5–21	4–24	0–5
5–7 years	65–140	0–110	0.09–0.17	0.04–0.08	0.5–14	0.5–24	4–26	0–4
8–11 years	60–130	–15–110	0.09–0.17	0.04–0.09	0–14	0.5–25	4–25	0–4
12–15 years	65–130	–15–110	0.09–0.18	0.04–0.09	0–14	0.5–21	4–25	0–4
>16 years	50–120	–15–110	0.12–0.20	0.05–0.10	0–14	0.5–23	4–21	0–4

premedicants. Alternative routes of drug administration include intramuscular, rectal (methohexital) or intranasal (midazolam) which are less commonly preferred. Sedative doses which can compromise the airway patency should be avoided in patients with decompensated hemodynamics.

1. **Methohexital:** Rectal methohexital 25–30 mg/kg induces sleep in healthy paediatric patients with minimal cardiovascular side effects. The primary effects are increased HR and decreased SV.[12]
2. **Midazolam:** Midazolam is the most widely used benzodiazepine in children for causing amnesia and sedation in short procedures and in the ICU. It has been used as a premedication via intravenous, oral or intranasal route; with the latter two routes being favorable in the paediatric population. It is preferred over diazepam and lorazepam due to its water-soluble properties and faster elimination. Previous studies have confirmed a fall in blood pressure and cardiac output by a bolus dose of midazolam.[13] Continuous infusions have been found to be more cardiostable than intermittent boluses.
3. **Opioids:** Opioids are μ-receptor agonists which attenuate the sympathetic and neuroendocrine response to laryngoscopy and surgical stress. They have a limited direct effect on the hemodynamic stability and are required to be administered with caution in view of major respiratory depression. High-dose opioid induction technique is hence preferred in paediatric patients posted for cardiac surgeries. There exists a wide range of opioids available to select from based on their pharmacological properties such as the long acting (elimination half life 120 minutes), less potent morphine to the ultra-short acting (context sensitivity half-time of 4 min. after 4 hour infusion), highly potent remifentanil (100–200 times more potent than morphine).

Induction Agents

1. **Volatile agents:** Inhalational induction and maintenance holds a pivotal place in paediatric anaesthesia due to numerous reasons. Firstly, the ease of administration by simple mask holding precludes the need of pricking the child, thereby making him uncomfortable or cranky. Secondly, the rapid wash-in and wash-out of the volatile agents guarantee a rapid induction and recovery respectively. All volatile anaesthetics affect the cardiovascular system by their direct myocardial depressive action along with peripheral vasodilation. This is clinically manifested by as a dose-dependent reduction in heart rate, mean arterial pressure, systemic vascular resistance (SVR) and cardiac index. Neonates and infants are more vulnerable to episodes of bradycardia, hypotension, and cardiac arrest than older children when under inhalational anaesthesia.

   Halothane was the inhalational induction agent of choice for paediatric patients in the past decades. Halothane is known to cause dose-dependent direct myocardial depression and sensitization of the heart to the effects of adrenaline. Ever since the introduction of sevoflurane into clinical practice, the use of halothane has considerably declined. Sevoflurane with its low blood gas partition co-efficient and trivial airway irritability, is the inhalational agent of choice for a smooth, stable and rapid induction. It is also preferred for maintenance anaesthesia owing to rapid recovery profile.

   Isoflurane and desflurane both are known to cause a dose-dependent reduction in myocardial contractility and reflex increase in sympathetic tone. However, they do not sensitize the myocardium to effects of adrenaline.
2. **Intravenous drugs**
   a. ***Thiopentone:*** Barbiturates cause a dose-dependent negative inotropic effect on the heart which is mediated through the calcium channels and the medullary vasomotor centre. The recommended dose of thiopentone for induction in children (5–6 mg/kg) and infants (7–8 mg/kg) is higher than that in adults (3–4 mg/kg). In healthy neonates, the dose requirement is 4 to 5 mg/kg which can be explained by a decreased plasma protein binding, underdeveloped blood–brain barrier and higher sensitivity of neonatal receptors.

      Thiopentone causes a reduction in the mean arterial pressure by decreasing the sympathetic tone, preload and cardiac index. Heart rate increases in response to hypotension via baroreceptor reflex mediated sympathetic stimulation. These cardiovascular effects of thiopentone are more prominent with associated hypovolemia, hypertension and sympathetic stimulation as seen in sepsis; and may be exacerbated by accompanying histamine release. Sodium thiopentone being antalgesic, cannot prevent significant hemodynamic responses to noxious stimulation when administered alone.

b. ***Propofol:*** The most profound effect of propofol as an induction agent on the cardiovascular system is a fall in mean arterial pressure by 15–30% in healthy children. This is attributed to a reduction in SVR caused by peripheral smooth muscle relaxation and inhibition of sympathetic activity. Arteriolar smooth muscle relaxation is mediated by closure of voltage gated calcium channels and an enhanced release of local nitric oxide (NO). However, it does not affect the pulmonary vasculature with no reduction of pulmonary vascular resistance (PVR) or mean pulmonary artery pressure. This fact may influence the direction and extent of intracardiac shunting in patients with congential heart defects.

Propofol does not cause a tachycardic response to hypotension on induction by either inhibiting or resetting the baroreflex response. In fact, a fall in heart rate of up to 20% may be observed on induction with propofol. Significant bradycardia can occur in children less than two years age, poor American Society of Anaesthesiologist' Society (ASA) status, strabismus surgery and simultaneous administration of opioid. It may rarely cause rhythm disturbances such as a systole, complete heart block, junctional rhythm and atrial premature beats.

Prolonged infusions of propofol at a dose of more than 4 mg/kg/hour for duration longer than 48 hours are associated with a rare but potentially fatal propofol infusion syndrome. Initially it was reported in critically ill paediatric patients but later was documented in adults as well. It is a constellation of metabolic disturbances such as metabolic acidosis, rhabdomyolysis and hypertriglyceridemia, clinically manifesting as refractory bradydysrhythmias and ultimately resulting in multiorgan failure. The pathophysiological mechanism is propofol mediated impaired mitochondrial fatty acid chain oxidation and respiratory chain inhibition mimicking mitochondrial myopathies.

Previous studies comparing the cardiovascular effects of intravenous induction in children found the reduction in mean arterial pressure to be significantly greater after propofol (28–31%) than after thiopentone (14–21%), whereas the reduction in cardiac index was not significantly different.[14] Baroreflex mediated increases in heart rate and systemic vascular resistance were less after propofol than after thiopentone. The baroreceptor reflex was more attenuated in children aged less than 2 years than in older children.[14] Pain on injection caused by propofol becomes a deterrent for its use in intravenous induction in children.

c. ***Ketamine:*** Ketamine produces dissociative anaesthesia and displays its unique properties in terms of cardiovascular stimulant effects. Routine induction dose of ketamine causes an increase in heart rate, cardiac index, systemic and pulmonary blood pressures as well as SVR and PVR. The increase in these hemodynamic variables translates into a rise in myocardial oxygen consumption and cardiac work. Cardiovascular stimulant actions are probably related to its sympathomimetic effects mediated by the central nervous system and peripheral sympathoneural release of norepinephrine.

Ketamine remains the induction agent of choice in cyanotic congenital heart disease, namely tetralogy of Fallot where maintenance of SVR is of prime importance for the right to left shunt fraction. The incidence of emergence reactions seen after ketamine anaesthesia is lower in the paediatric age group as compared to the adults (10–30%). Another advantage of this drug is the variety of routes of administration such as intravenous, intramuscular, nasal, oral and rectal; making it suitable for use in children.

d. ***Etomidate:*** Among all the intravenous induction agents available, etomidate is the most cardiostable drug with minimal effects on hemodynamics. It has negligible effect on sympathetic stimulation, baroreceptor reflex response and histamine release. However, it is not routinely used in clinical practice due to direct adrenocortical suppression.

The cardiovascular effects of intravenous induction agents are mentioned in Table 3.5.

Table 3.5 Cardiovascular effects of intravenous induction agents

	HR	MAP	CO	Contractility	SVR	Vasodilation
Thiopentone	+	–	–	–	±	++
Propofol	–	– –	–	– –	– –	++
Ketamine	++	++	+	±	±	0
Etomidate	0	0	0	0	0	0

Local Anaesthetics

The use of local anaesthetics, namely lignocaine and bupivacaine has been widely practiced in paediatric anaesthesia for topical as well as regional anaesthesia and analgesia. The low levels of pseudocholinesterase in children and limited protein binding alter the pharmacokinetics of these local anaesthetics. Hence the total cumulative dose needs to be taken into consideration while injecting local anaesthetics.

The effect of sympathetic blockade by local anaesthetics on the cardiovascular hemodynamics is minimal in young children. Caudal and epidural anaesthesia have limited hemodynamic alterations and are well tolerated by children of all ages.

FAQs

Q. Describe the foetal circulation in detail and the changes taking place at birth. State the anaesthetic implications of transitional circulation and persistence of foetal circulation.

Q. Describe the physiological differences between the neonatal and adult cardiovascular system.

Q. Describe the anaesthetic management of a 6-year old child with unrepaired and unpalliated Tetralogy of Fallot posted for total intracardiac repair.

Q. Mention the cardiovascular effects of standard intravenous induction agents in paediatric patients. Mention the rationale of using intravenous induction agents in congenital cardiac defect with L → R shunt.

SUMMARY

Foetal circulation differs from the adult one in being shunt dependent and in parallel due to the presence of low resistance type placental circuit. At birth, the placenta is eliminated from circulation and SVR increases while PVR falls and pulmonary blood flow rises.

It is vital to understand the basic principles of cardiac physiology as well as the structural and functional immaturities in the paediatric age group. The age related circulatory variables need to be borne in mind while administering anaesthesia to these patients. The parasympathetic overdominance results in a bradycardic response to adverse stimuli such as hypoxia, acidosis and anaesthetic agents. A thorough preoperative assessment and examination of the child enables the anaesthesiologist to formulate a safe and effective plan. A detailed understanding of the clinical pharmacology of anaesthetic agents and their application in the paediatric patients is central to the anaesthetic management.

Take Home Message

A precise knowledge of the cardiovascular physiology, structural and functional development and interactions of anaesthetic agents with the cardiopulmonary system is essential to provide safe and effective anaesthesia to paediatric patients.

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4

Essentials of Respiratory System in Infants and Children

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INTRODUCTION

The most common critical incidents related to respiratory system are seen in paediatric age group. There are anatomical and physiological differences between neonates, infants and child. Again they differ from adult respiratory system. The knowledge about development in respiratory system helps to provide appropriate anaesthesia to paediatric group and to reduce complication rates. The chapter will provide appropriate informations and also anaesthetic considerations in detail.

Key Points

1. At birth, control of ventilation is immature. This maturity occurs at 3 weeks of age in term baby.
2. Neonates and preterm babies are more prone for post operative apnoea episodes. Risk of postoperative apnoea is less after 1 month of age in term and 60 weeks PCA in preterm babies.
3. In first few weeks, response to hypercapnia is blunted.
4. In hypoxia, neonate responds with hyperventilation followed by apnoea. But the apnoeic response to hypoxia is suggestive of respiratory muscle fatigue or upper airway obstruction.

Developmental Changes

Developmental changes in all systems should be so sufficient to withstand drastic changes at the time of birth. All systems adapt the changes from gestational age and makes foetus to survive in external environment too. Cardiorespiratory adaptation is one of the very crucial adaptations. After the birth, within few minutes, neuronal drive and respiratory muscles must replace all liquid filled in lungs by sufficient amount of air. Therefore, gas exchange will take place. This chapter will provide a clear view of developmental and relevant aspects of respiratory systems and will also discuss about anaesthetic considerations in detail.

DEVELOPMENT OF LUNGS

Development of lungs (Fig. 4.1) starts in prenatal period and changes are as follows:[1,2]

1. Embryonic phase: Groove in ventral foregut, endoderm surrounding mesenchymal tissue to form lung buds.
2. Pseudoglandular phase: [Till 17 weeks of gestation (WOG)]—rapid budding of bronchi and lung growth, preacinar branching is complete. During this phase, any disturbance to free expansion leads to hypoplasia as occurs with *diaphragmatic hernia*.
3. Canalicular phase: (Till 24 WOG), development of respiratory bronchiole, and capillaries surrounding it.
4. Terminal sac period: (After 24 WOG)—appearance of clusters of air spaces (saccules), with thick and irregular septa.
5. (At 26–28 WOG) Capillary proliferation around saccules. In premature infants, it may be seen earlier at 24 WOG, hence they can survive in neonatal intensive care.
6. At 28 WOG: Thinning of saccular walls, lengthening of saccules with additional generation.
7. At 32 WOG: Alveolar formation starts from saccules. Most of alveolar formation occurs in 12–18 months of postnatal life.

However, morphologic and physiologic development of lungs continues during the first decade of life.

1. **Lung volume** in early postnatal period, is disproportionately small compared to body size (Fig. 4.2).

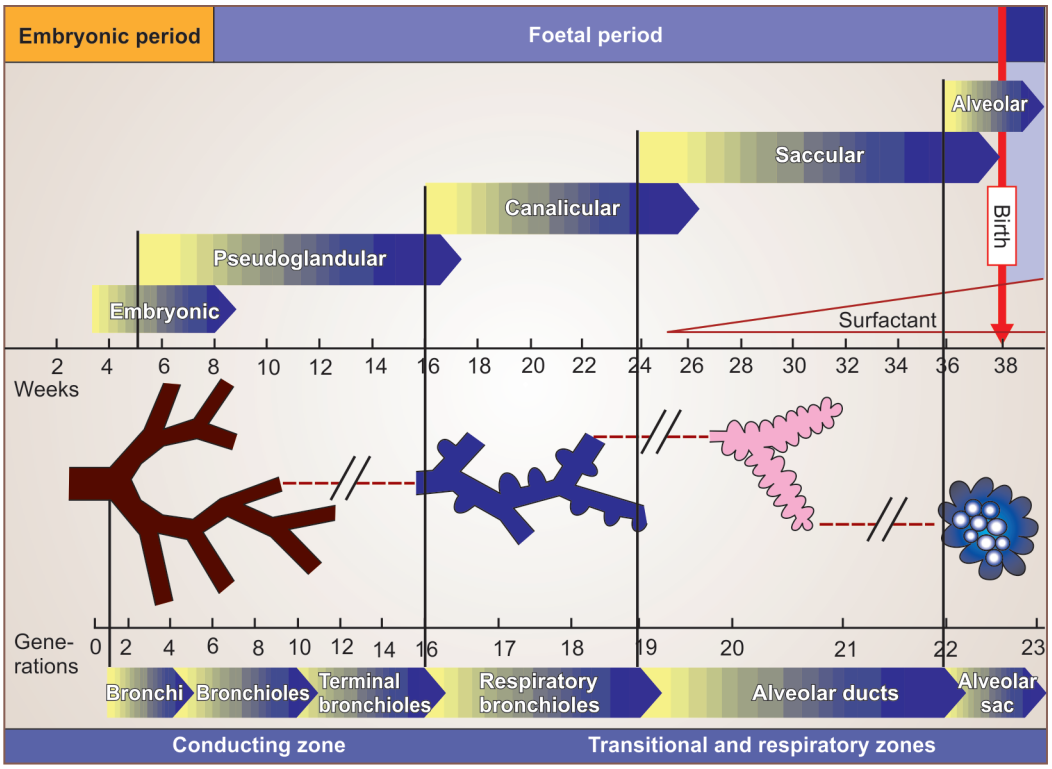

Fig. 4.1 Development of Lungs

High metabolic rate due to higher oxygen consumption markedly increases ventilatory requirement per unit lung volume. Hence infants have less reserve of lung volume and surface area for gas exchange. Therefore, they are prone to **early desaturation** in case of hypoventilation or apnoea for short duration.

2. **Foetal lung fluid**: It is produced in large quantity by lung to expands the airways against closed larynx. This fluid contains growth factor, **human bombesin**, which stimulates lung growth and development. This fluid is periodically expelled into uterine cavity and contributes about one-third of total amniotic fluid. Hence prenatal ligation or occlusion of trachea was tried with some success in **congenital diaphragmatic hernia**, to expand growth of airway and hypoplastic lung.[1,2]
3. **Type II pneumocytes**: It forms alveolar lining and produces pulmonary surfactant. These cells appear as early as 20 WOG or in 24–26 WOG. The pulmonary surfactant helps to reduce surface tension and stabilizes air spaces after air breathing.
4. **IRDS or HMD in premature patients**, leads to immaturity of lungs and hence inefficient production of pulmonary surfactant. Corticosteroids helps to accelerate the growth and maturation of lungs resulting in early appearance of above cells and

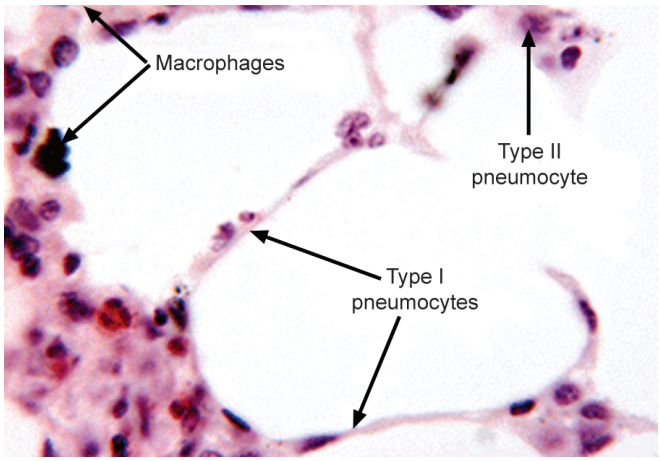

Fig. 4.2 Type II pneumocytes

hence surfactant production. **Prenatal glucocorticoid therapy** has been used widely to induce lung maturation and surfactant synthesis in mothers at risk of premature delivery. It should be given 24–48 hrs before delivery of premature baby.

CONTROL OF BREATHING[2,3]

1. **Central chemoreceptors:** Response depends on changes in H^+ ions conc. in CSF

a. Dorsomedial respiratory group: Inspiratory
b. Ventrolateral respiratory group: Expiratory
c. Pontine group: Rapid breathing
d. PreBotzinger complex: Rhythmic breathing

2. **Peripheral chemoreceptors:** Present at Bifurcation of common carotid artery—response depends on changes in arterial oxygen.
3. **Upper airway receptors:** Stimulation of receptors in the nose produces sneezing, apnoea, changes in the bronchomotor tone and diving reflex.

   During swallowing, there is inhibition of breathing, closure of larynx. Co-ordination between laryngeal and pharyngeal muscles are hence maintained.
4. **Tracheobronchial and pulmonary receptors**
   a. Slowly adapting (pulmonary stretch receptors): Membranous posterior wall of trachea and central airways. Hering-Breuer inflation reflex—apnoea due to inflated ETT cuff.
   b. **Rapidly adapting (irritant or deflation):** Situated in carina and large airways Hering-Breuer deflation reflex—increase in respiratory drive at low lung volumes as in IRDS and pneumothorax. It also mediate paradoxical reflex of Head—deep inspiration instead of inspiratory inhibition and it helps to inflate the unaerated portion of newborn lung.
   c. **C fibre endings:** Near the pulmonary capillaries. It is stimulated by pulmonary congestion, microemboli, pulmonary oedema, anaesthetic gases. Such stimulation leads to apnoea followed by rapid shallow breathing, hypotension and bradycardia. Reflex contraction of the laryngeal muscles responsible for laryngospasm.

Key Points

Maturation of control of breathing depends on postconceptional age than the postnatal age. The hypoxic and hypercapnia response drive is not well developed in newborns and infants. Hence they are more prone to respiratory depression due to immaturity as well as increased respiratory muscle fatigue. This risk is more in preterm infants.

Regulation of Breathing[2,3]

As in adult, infant responds to an increase in **$PaCO_2$** by increasing alveolar ventilation. This strength is totally dependent on gestational age and postnatal age. And hypoxia in infants, may depress the hypercapnic ventilatory response.

High concentration of **oxygen** depresses the respiration in newborn while low concentration stimulates it. But sustained hypoxia leads to ventilatory depression.

Nonspecific factors are blood glucose; anaemia affects breathing due to inadequate substrate availability. Cold stress also depresses ventilator drive.

Periodic breathing common in newborns. It is characterized by recurrent pauses in ventilation lasting more than 5–10 seconds, alternating with bursts of respiratory activity. Periodic breathing is more commonly seen in preterm infants and it is related to gestational age. Periodic breathing and apnoea of prematurity should be diagnosed appropriately.

Apnoea of prematurity may be life threatening event. In this ventilator pauses are prolonged and are associated with desaturation, bradycardia and loss of muscle tone. Factors contributing these events are

i. **Brainstem immaturity:** Blunted response to hypercarbia and hypoxia and **delay** in response conduction through brainstem.
ii. **Respiratory fatigue:** Chest wall deformity.

Treatment: Give tactile stimulation, in mild to moderate cases.

In severe cases:

1. Theophylline or caffeine to increase respiratory drive.
2. Positive pressure ventilation to stabilize respiratory function.

Anaesthesia Pearls

Prematurity is risk factor for postanaesthetic respiratory depression.

This can be life threatening and inversely related to gestational age and postconceptional age at the time of anaesthesia. The greatest risk is up to 60 weeks after conception.

MECHANICS OF BREATHING[1–3]

In infancy, rib grows horizontally from vertebral column and moves a little with inspiration. This anatomic configuration of ribs makes accessory muscles ineffective in infants (Fig. 4.3).

The chest wall consists of mainly cartilages calcification, poorly developed musculature and incomplete calcification of ribs. This results in floppy chest wall. As age grows, chest wall becomes stiff. In preterm, chest wall is more retractile.

The paradoxical chest wall movement commonly occurs in younger children and infancy due to increased

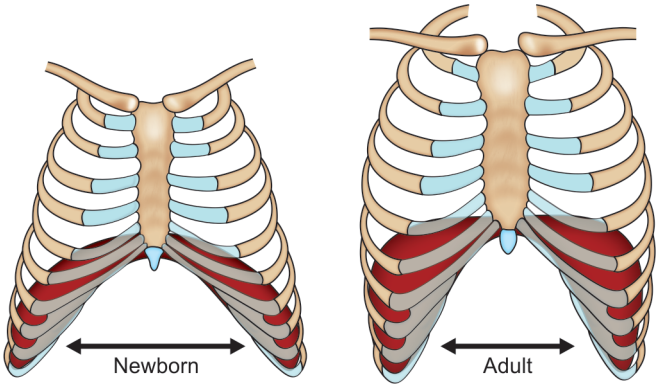

Fig. 4.3 Small lung volume of neonate compared to adult

respiratory effort. It is mainly seen under general anaesthesia with upper airway obstruction or it could be because of decreased intercostals muscles tone. In paradoxical respiration, inward movement of rib cage opposes inspiration of diaphragm. Diaphragmatic displacement may increase as the severity increases to maintain tidal volume. Due to increase workload, there will be respiratory muscle fatigue and hence respiratory failure.

Diaphragmatic fatigue is due to low content of type I muscle fibres. Type I muscle fibre has slow twich and high oxidative capacity. These fatigue resistant fibres make up <10% total muscle fibres before 37 weeks of gestation. A higher content of it confers fatigue resistance as the age advances. In adult diaphragm, Type I fibres is about 50% while those are 25% in term infant.

Lung compliance depends on lung volume which is more in childhood. Specific compliance of the lung does not depend on size. It mainly depends on FRC or TLC. It remains constant while specific compliance of chest declines due to progressive calcification and increasing thoracic muscle mass. Therefore, specific compliance of entire respiratory system declines in the childhood due to changes in the chest wall. Elastic recoil increases as the age advances.

LUNG VOLUME[1,2,4]

Development of airways up to terminal bronchiole completes by 16th weeks of gestation. Full term new born has 20–50 millions terminal primitive air saccules. Later it develops into alveoli. At 12–18 months of age alveoli number reaches to adult value which is 400 million or more.

In early postnatal period, lung volume of infant is disproportionate and smaller in relation to size (Fig. 4.4). Infants metabolic rate is twice as that of the adult. Hence, venitilatory requirement is more in infants. Hence minute ventilation approximately 200 mL/kg/min and oxygen consumption 7 mL/kg/min are twice that of the adult. Less reserve in lung surface area for the gas exchange. Tidal volume remains constant 7–10 mL/kg throughout life. Ventilator need is achieved by increase in respiratory rate in newborns, infants and children. General anaesthesia markedly diminishes FRC, which further reduces oxygen reserve in infants.

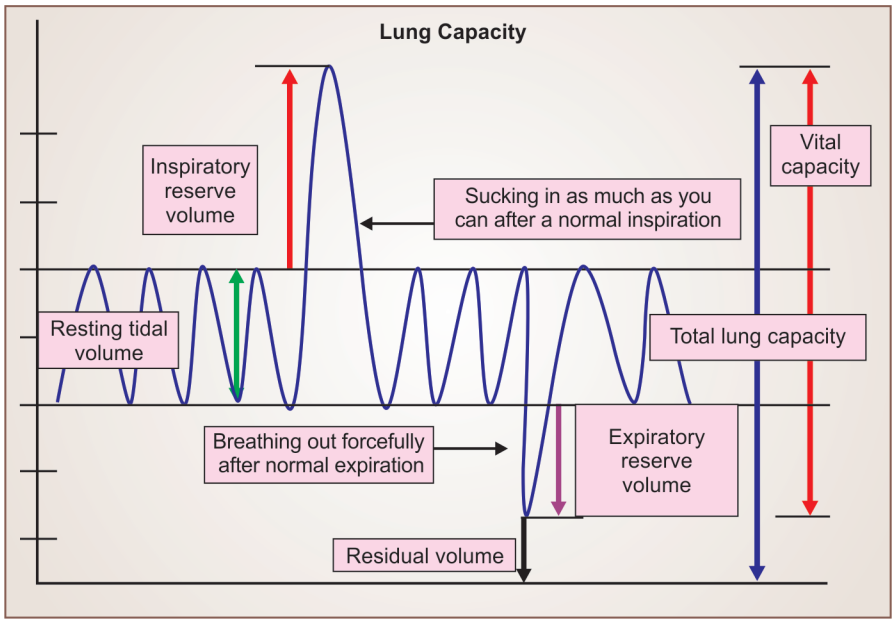

Fig. 4.4 Lung volumes

Total lung capacity: Maximum lung volume allowed by stretching of thorax and lungs. In infant, 60 mL/kg and that in adult 90 mL/kg.

Residual volume: Volume of air remains in lung after deep expiration. It is of 25% of TLC.

Functional residual capacity: It depends on balance between outword stretch of thorax and inward recoil of the lungs. 25% TLC normal in upright position, 40% TLC in supine position. It is 30 mL/kg throughout.

Pleural pressure in older children and adult is –5 cm of water but in neonates and infants, it is slightly negative. In Infants outward recoil of chest wall is very less while lung recoil is slightly less. Hence FRC further reduces 10–15% more in anaesthesia, apnoea and paralysis. In awake patient, FRC is maintained by sustained tonic activity of the inspiratory muscle. In infants, there is no fixed level of FRC.

Closing Capacity [2,3]

$$CC = CV + RV$$

Closing volume: Volume of lung above the RV at which airflow ceases during expiration from dependent lung zones. Closing capacity as percentage of TLC is relatively high in children, while it is very high in infants. The closing capacity is more than the FRC in infants and children leads to early airway closure.

Compliance of the lung decreases in the conditions associated with decreased lung volume such as atelectasis, intrapulmonary tumor. It is also decreased in IRDS due to increased surface tension. Compliance of the chest wall decreases in kyphoscoliosis, scleroderma and abnormal thoracic contour.

Airway Resistance

It consists of upper and lower airway resistance.

Upper Airway Resistance

It consists of 65% of total airway resistance. It starts from the mouth, oral cavity, pharynx, larynx up to the upper thoracic part of trachea. Newborns and infants are obligate nose breather because of cephalad epiglottis and the close approximation of the soft palate to the tongue and the epiglottis. If any occlusion or obstruction to the nasal airway occurs, it increases airway resistance by 50% which leads to obstructive apnoea.

Lower Airway Resistance

It consists of 35% of total airway resistance while smaller peripheral airways consist of 10% of it. This starts from lower thoracic part of trachea, bronchi, bronchioli and alveolar ducts as the gas flows to small airways, flow resistance should increase due to small caliber, but cross sectional area of the airway towards the peripheries and the number of airways are more and hence the flow resistance of the airways decreases towards the periphery. Lung conditions like BPD, cystic fibrosis would not change total airway resistance

GAS DIFFUSION [1–3]

Pulmonary gas exchange occurs by diffusion at all ages. Pulmonary diffusion in childhood is mainly affected by changes in surface area of alveolar capillary membrane.

Total diffusion capacity is similar as that of the adult **with relation to** alveolar ventilation and oxygen consumption. It is more flow limited than the diffusion limited. Total gas exchange surface area is smaller in relation to body size in infancy. This is suggestive of reduce physiological reserve.

As the child grows, diffusion capacity increases linearly with height. This is closely related to lung growth. Thickness of blood gas barrier for diffusion declines in early gestational ages. Therefore, alvoeloar arterial oxygen difference is higher in term neonates and even higher in preterm. Venous admixture is higher in infants than in adult. It is at 10–20% of cardiac output. While in adult, it is 2–5% of cardiac output. Intrapulmonary anatomic shunting is the major factor for venous admixture mainly at the opening of developing alveoli. Ventilation perfusion imbalance is different than that of the adult. It mainly arises from opening and closing of lung units.

Extrapulmonary right to left shunting contributes to alveolar arterial oxygen difference in the first few hours of life.

Surfactant and Surface Tension [5]

Surface tension principle: When water forms a surface with air, the water molecules on the surface of the water have an especially strong attraction for one another. As a result, the water surface is always attempting to contract. This is what holds raindrops together, that is, there is a tight contractile membrane of water molecules around the entire surface of the raindrop. On the inner surfaces of the alveoli, the water surface is also attempting to contract. This results in an attempt to force the air out of the alveoli through the bronchi and, in doing so, causes the alveoli to try to collapse. The net effect is to cause an elastic contractile force of the entire lungs, which is called the surface tension elastic force.

The alveolar surfaces of human lungs are lined with surface active materials with unique properties that are responsible for the stability of air spaces.[6] These materials, which contain specific phospholipids and proteins (discussed later), are collectively called pulmonary surfactant.

Pressure in Occluded Alveoli Caused by Surface Tension[5]

If the air passages leading from the alveoli of the lungs are blocked, the surface tension in the alveoli tends to collapse the alveoli. This creates positive pressure in the alveoli, attempting to push the air out. The amount of pressure generated in this way in an alveolus can be calculated from the following formula:

Pressure = 2 × Surface tension/Radius of alveolus

For the average-sized alveolus with a radius of about 100 µm and lined with *normal surfactant*, this calculates to be about 4 cm of water pressure (3 mmHg). If the alveoli were lined with pure water without any surfactant, the pressure would calculate to be about 18 cm of water pressure, 4.5 times as great. Thus, one sees how important surfactant is in reducing alveolar surface tension and therefore also reducing the effort required by the respiratory muscles to expand the lungs. Note from the preceding formula that the pressure generated as a result of surface tension in the alveoli is *inversely* affected by the radius of the alveolus, which means that the smaller the alveolus, the greater the alveolar pressure caused by the surface tension. Thus, when the alveoli have half the normal radius (50 instead of 100 µm), the pressures noted earlier are doubled. This is especially significant in small premature babies, many of whom have alveoli with radii less than one quarter that of an adult person. Further, surfactant does not normally begin to be secreted into the alveoli until between the sixth and seventh months of gestation, and in some cases, even later than that. Therefore, many premature babies have a little or no surfactant in the alveoli when they are born, and their lungs have an extreme tendency to collapse, sometimes as great as six to eight times that in a normal adult person. This causes the condition called respiratory distress syndrome of the newborn. It is fatal if not treated with strong measures, especially properly applied continuous positive pressure breathing.[5]

The airways contain different types of cells. The walls of the alveoli contain type I cells, which cover 95% of the alveolar surface, and type II cells which produce surfactant.[2] Chemical composition of surfactant is approximately 10% lipoprotein and 90% phospholipid. Of the phospholipid fraction of surfactant, phosphatidylcholine constitutes about 70%, which is mainly surface active.[6] Phosphatidylglycerol, another surface active phospholipid, was subsequently identified in the lung extract and comprises about 10% of surfactant fraction.[7] Phosphatidylglycerol appears late during the development; its appearance or reappearance coincide with the recovery from IRDS and acute respiratory distress syndrome (ARDS) in adults and with the loss of surfactant.[8] Other phospholipids include sphingomyelin (also surface active), phosphatidylethanolamine and phosphatidylinositol, which are not surface active.[9] The production of phosphatidylcholine increases towards term, whereas that of sphingomyelin decreases. The ratio of these phospholipids (L/S ratio) in the amniotic fluid has been used as an index of foetal lung maturity.[10]

There are four surfactant proteins (SP) that have been identified (SP-A, SP-B, SP-C, and SP-D), which comprise about 10% of surfactant on the mature alveolar surface. SP-B and SP-C are intimately linked to the stability of surface active monolayer at the alveolar surface. SP-B is essential for myelin formation of the lamellar inclusions in type II cells and promotes surface adsorption of dipalmitoylphosphatidylcholine in the lipid mixtures and an addition of the mixture of surface active phospholipids, and SP-B restores the normal pressure-volume curves of the lungs in the animal model of IRDS.[11,12] Surfactant proteins SP-A and SP-D are similar in structure, containing proline-rich collagen domain in addition to carbohydrate domain (called collectins). SP-A and SP-D seems to function primarily as innate host defense molecules in the airways and alveoli.[13] A decrease in SP-A is probably common in patients with severe lung injury. Infants born with decreased SP-A/dipalmitoylphosphatidylcholine ratio are at increased risk of developing BPD and dying.[14]

Surfactant phospholipids and proteins are produced within the type II pneumocytes, stored in the osmiophilic lamellar inclusions within these cells, and excreted into the alveolar surface, forming tubular myelins and subsequently spreading to form surface-active alveolar lining layers.[15]

Surfactant replacement therapy using human, bovine, or synthetic surfactant in premature infants with IRDS has been established as an important and essential form of therapy, reducing morbidity and mortality.[16–19]

Surfactant replacement therapy has been extended to cover other clinical conditions with surfactant

deficiency or inactivation not only in premature infants but also in full-term infants, children, and adults. These conditions include neonates with persistent pulmonary hypertension (PPHN) in whom surfactant production by type II pneumocytes is depressed because of severe pulmonary hypoperfusion and hypoxia; neonates with severe congenital diaphragmatic hernia (CDH) whose immature lungs are damaged by ventilator-induced lung injury and surfactant inactivation by plasma protein leak on the alveolar surface; meconium aspiration syndrome caused by pulmonary hypoperfusion, inflammation, and inactivation of surfactant by protein leak; and ARDS in children and adults.[20,21]

CILIARY ACTIVITY

The tracheal and bronchial walls have pseudostratified epithelium that consists of ciliated cells, non-ciliated serous and brush cells, and abundant mucus-secreting goblet cells. Goblet cells and mucus-secreting glands diminish in number toward the periphery of the airway system. The mucous of respiratory tract is produced by numerous serous and mucous cell glands present in submucosal area. The mucosal surface is covered by a serous fluid layer, in which the cilia beat. Above this periciliary layer of serous fluid lie discontinuous flakes of mucus which are moved cephalad by the cilia (Fig. 4.5).[22]

Functions of Cilia

The cilia in the respiratory tract play an important role in the removal of mucoid secretions, foreign particles, and cell debris and are an essential defense mechanism of the airway system. These cilia move in a synchronous, whip-like fashion at a rate of 600 to 1300 times per minute. They can move particles toward the mouth at the rate of about 1.5 to 2 cm/min.[19] Ciliary function is influenced by the thickness of the mucous layer and other factors that can occur with dehydration or infection. In tissue culture, some viral infections reduce ciliary motion as much as 50%, and repeated infections in vivo can destroy the cilia completely.[20] Inhalation of warm air with 50% humidity maintains normal ciliary activity, whereas breathing dry air for 3 hours results in a complete cessation of mucus movement. Ciliary activity can be restored by breathing warm, saturated air.[23–25] Breathing 100% oxygen and controlled positive pressure ventilation also affect ciliary function.[26–29]

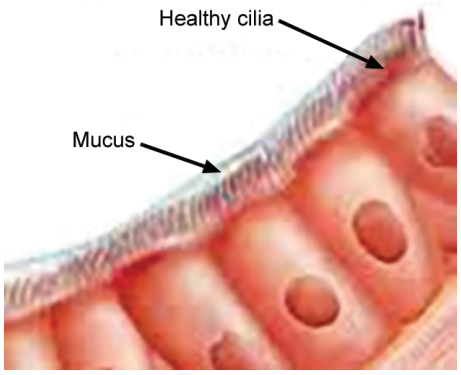

Fig. 4.5 Tracheal epithelium

Inhaled anaesthetics seem to decrease ciliary function in both animals and humans. Forbes and Horrigan observed a dose-related depression of ciliary activity during halothane and enflurane anaesthesia.[30] The same group of investigators found delayed mucus clearance during and 6 hours after discontinuation of halothane or diethyl ether anaesthesia.[29] These findings suggest that inhaled anaesthesia has adverse effects on mucociliary clearance, especially in patients with pulmonary disease. The effect of anaesthetics on mucociliary clearance in infants and children has not been reported.

OXYGEN TRANSPORT

Oxygen is required by almost every tissue metabolism. Continuous supply of oxygen is mainly dependent on three factors—pulmonary ventilation, cardiac output and blood haemoglobin concentration and characteristics. Oxygen is mainly carried in blood in two forms, dissolved in plasma and as oxyhaemoglobin. The amount of oxygen carried by the plasma depends on its solubility and is small (0.31 mL/dL per 100 mmHg). Most oxygen molecules in blood combine reversibly with haemoglobin to form oxyhaemoglobin. Each molecule of haemoglobin combines with four molecules of oxygen; 1 g of oxyhaemoglobin combines with 1.34 mL of oxygen.

Oxygen Haemoglobin Dissociation Curve (Fig. 4.6)

It reflects the affinity of haemoglobin for oxygen. As blood circulates through the normal lungs, oxygen tension increases from the mixed-venous PO_2 of around 40 mmHg to pulmonary capillary PO_2 of above 105 mmHg, and haemoglobin is saturated to about 97% in arterial blood. The shape of the dissociation curve is such that further increase in PO_2 result in a very small increase in oxygen saturation (SO_2) of haemoglobin. The blood of normal adults has SO_2 of 50% when PO_2 is 27 mmHg at 37°C and a pH of 7.4. The P50, which is the PO_2 of whole blood at 50% SO_2, indicates the affinity of haemoglobin for oxygen. An increase in blood pH

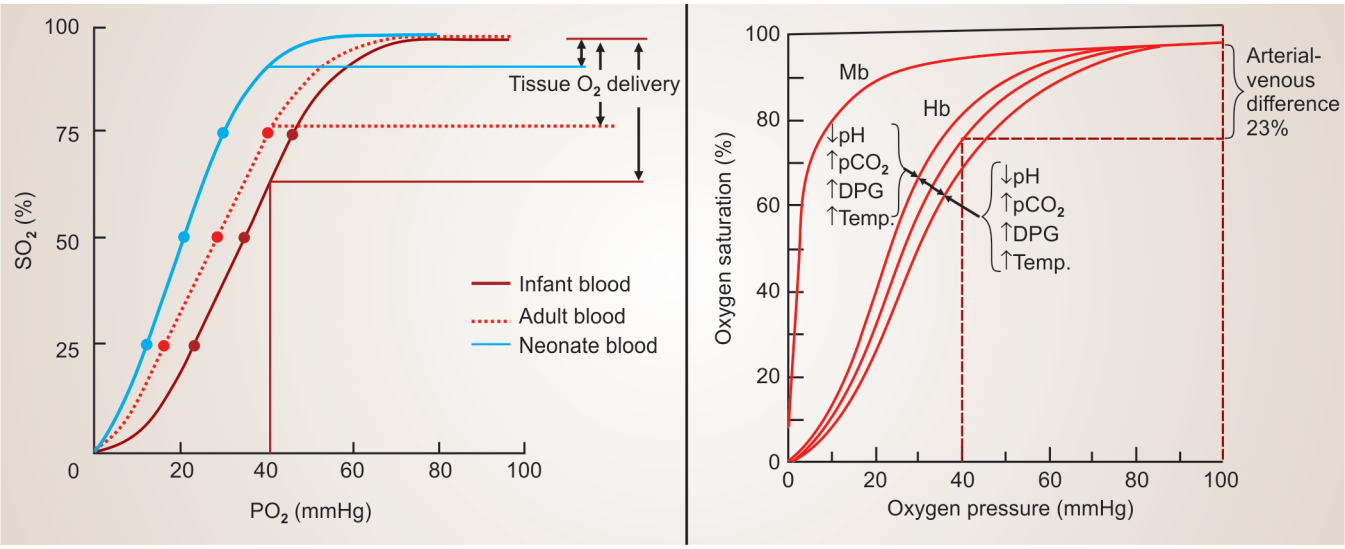

Fig. 4.6 Oxygen haemoglobin dissociation curve

increases the oxygen affinity of haemoglobin (Bohr effect) and shifts the oxygen-haemoglobin (O_2-Hb) dissociation curve to the left. Similarly, a decrease in temperature also increases oxygen affinity and shifts the O_2-Hb dissociation curve to the left; a decrease in pH or an increase in temperature has the opposite effect and the O_2-Hb curve shifts to the right.[33] Human erythrocytes contain an extremely high concentration of 2,3-DPG, averaging about 4.5 mol/mL, compared with ATP (1 mol/mL) and other organic phosphates.[33,34] Thus, an increase in red cell 2,3-DPG decreases the oxygen affinity of haemoglobin, increases P50 (shifts the dissociation curve to the right), and increases the unloading of oxygen at the tissue level. Increase in 2,3-DPG and P50 have been found in chronic hypoxemia.

In the newborn, blood oxygen affinity is extremely high and P50 is low (18 to 19 mmHg), because 2,3-DPG is low and foetal haemoglobin (HbF) reacts poorly with 2,3-DPG. Oxygen delivery at the tissue level is low despite high red blood cell mass and haemoglobin level. After birth, the total haemoglobin level decreases rapidly as the proportion of HbF diminishes, reaching its lowest level by 2 to 3 months of age (physiologic anaemia of infancy). During the same early postnatal period, P50 increases rapidly; it exceeds the normal adult value by 4 to 6 months of age and reaches the highest value (P50 = 30) by 10 months and remains high during the first decade of life.[28–30] This high P50 is associated with a relatively low haemoglobin level (10 to 11 g/dL) and an increased level of 2,3-DPG, probably related to the process of general growth and development and high plasma levels of inorganic phosphate.[34,35] These observations engendered a hypothesis to explain why haemoglobin levels are relatively lower in children than in adults (physiologic "anaemia" of childhood).[35] Because children have a lower oxygen affinity for haemoglobin, oxygen unloading at the tissue level is increased.

SUMMARY

1. Neonates and preterm babies are more prone for postoperative apnoea episodes. Risk of postoperative apnoea is less after 1 month of age in term and 60 weeks PCA in preterm babies.
2. Lung volume in early postnatal period is disproportionately small compared to body size. High metabolic rate due to higher oxygen consumption markedly increases ventilatory requirement per unit lung volume.
3. Type II pnemocytes forms alveolar lining and produces pulmonary surfactant. This cells appear as early as 20 WOG or in 24–26 WOG.
4. Periodic breathing and apnoea of prematurity should be diagnosed appropriately and treat appropriately.
5. Specific compliance of entire respiratory system declines in the childhood due to changes in the chest wall. Elastic recoil increases as the age advances.
6. Upper airway resistance consists of 65% of total airway resistance. If any occlusion or obstruction to the nasal airway increases, airway resistance by 50% leads to obstructive apnoea.

7. FRC further reduces 10–15% more in anaesthesia, apnoea and paralysis. In awake patient, FRC is maintained by sustained tonic activity of the inspiratory muscles.
8. The closing capacity is more than the FRC in infants and children leads to early airway closure.
9. Pulmonary diffusion in childhood is mainly affected by changes in surface area of alveolar capillary membrane. Thickness of blood gas barrier for diffusion declines in early gestational ages. Therefore, alvoeloar arterial oxygen difference is higher in term neonates and even higher in preterm.
10. Venous admixture is higher in infants than in adult. It is at 10–20% of cardiac output. While in adult, it is 2–5% of cardiac output.
11. In the newborn, blood oxygen affinity is extremely high and P50 is low (18 to 19 mmHg), because 2,3-DPG is low and foetal haemoglobin (HbF) reacts poorly with 2,3-DPG. Oxygen delivery at the tissue level is low despite high red blood cell mass and haemoglobin level.
12. Inhalation of warm air with 50% humidity maintains normal ciliary activity, whereas breathing dry air for 3 hours results in a complete cessation of mucus movement.

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5

Essentials of Central Nervous System in Infants and Children

Shrikanta P Oak and Anjana S Wajekar

INTRODUCTION

The central nervous system in the infants is immature and differs from older children and adult in several ways. Normal mental development depends on maturation of the central nervous system.

Embrology

Almost the whole of central nervous system is derived from the ectoderm.[1] The neural tube in the foetus has an enlarged cranial part which forms the brain and a narrow caudal part that becomes the spinal cord. The cranial part divides into:

1. Procencephalon (Forebrain): It forms the cerebral cortices, thalamus, hypothalamus and basal ganglia.
2. Mesencephalon (Midbrain): It develops into the midbrain.
3. Rhombencephalon (Hindbrain): It is a precursor of the cerebellum, pons and medulla.

The rest of the neural tube forms the spinal cord. The ventricles arise from the central canal of the neural tube.

Development occurs in three stages: Cytogenesis, histogenesis and organogenesis. The final composition and shape of the nervous system is determined by organogenesis.

Gross Anatomy

Brain weight:

- At birth: 330 to 350 g (10–15% of body weight).
- >12 years–adult: (1200–1400 g approximately 2% of body weight).

The brain doubles in size in the first year and reaches 80% of adult weight by the age of two.[2]

It is encased in a bony cranium.

Proportion of cranial contents in a child:

1. 80% brain parenchyma—It is made up by the neurons, their supporting glia and the interstitium.
2. 10% cerebrospinal fluid
3. 10% blood

The Monro-Kellie hypothesis states that the sum of the intracranial volumes of blood, brain and CSF is constant.

NEURAL DEVELOPMENT

The nervous system develops over a very long period of time extending from the embryonic period through puberty, with some remodelling continuing throughout lifetime.

There are five steps that make up brain development.

1. **Neurogenesis:** It is the process of differentiation of embryonic cells into neurons. It occurs largely in the foetal period.
2. **Neural migration**: The organization of the brain proceeds with migration of these neurons according to their function in particular areas of the brain. It extends from prenatal period to at least 8 to 10 months post-natally.
3. **Myelination**: It involves encasing the axon of the neuron in myelin, which is an electrically insulating material. Schwann cells supply the myelin for peripheral neurons, whereas oligodendrocytes myelinate the axons of the central nervous system. In humans, myelination begins in the 14th week of foetal development, mainly in brainstem and cerebellum, although a little myelin exists in the

brain at the time of birth.[2] During infancy, myelination occurs quickly and continues through the adolescent stages of life. Developmentally it occurs first in the peripheral nervous system spreading centripetally to spinal cord and lastly the brain with some nerves never getting myelinated. It is the major cause of the increase in a child's brain size.

Myelination is generally finished before major neural pathways become completely functional.

Also composition of the myelin in the immature brain is a transitional form differing from the adult myelin.[3] Myelination doesn't entirely encase a nerve leaving nodes of Ranvier at regular intervals which are the site of sodium channels. Breast feeding increases the speed of myelination in the brain.

Functions:

a. Speed of nerve conductions increases with development of nodes of Ranvier. Myelinated fibres succeed in reducing sodium leakage into the extracellular fluid (ECF) helping in agile communication.

b. The myelin sheath provides a track along which regrowth can occur in the event of nerve severance.

Incomplete myelination of nerve tissue in neonates and infants contribute to shorter onset times of local anaesthetics and allows effective blockade with very low concentrations of local anaesthetic solutions.

It is also responsible for variation in waveform morphology during neurophysiologic monitoring.

While **SSEPs** may show blunted peaks with delayed latencies, D waves of MEPs will not be reliable in children < 2 years of age.[4] Proper adjustment of stimulus is needed in such cases. Also, MEP monitoring can be done only with TIVA.

4. **Synaptogenesis:** Synapses interconnect the various neurons leading to the functional organisation of the brain. Synapses begin forming prenatally continuing throughout life.
5. **Pruning:** It refines existing useful connections and eliminates unused connections. The most rapid pruning occurs between ages 3 and 16, occurring in different areas of brain.

Pruning helps to play a role in synaptic re-modelling throughout life depending on experience and environmental stimuli.

Paediatric Anaesthesia Pearls

- Incomplete myelination of nerve tissue in neonates and infants contribute to shorter onset times of local anaesthetics and allows effective blockade with very low concentrations of local anaesthetic solutions.
- It is also responsible for variation in waveform morphology during neurophysiologic monitoring.

DEVELOPMENT OF BLOOD–BRAIN BARRIER

The blood–brain barrier (BBB) is a highly selective, permeable barrier that separates the circulating blood from the brain extracellular fluid (BECF). Development of blood–brain barrier is incomplete in newborns and infants and continues throughout childhood. It is a functional neurovascular unit composed of the capillary endothelium with basement membrane, astrocytes, pericytes, and extracellular matrix. These are connected by tight junctions (TJ) such as zonula occludens-1 (ZO-1) and claudin-5 (cl 5).

It is deficient in the circumventricular organs, the roof of the third and fourth ventricles, capillaries in the pineal gland, on the roof of the diencephalon and the pineal gland.

Transport Across Blood–brain Barrier[5]

1. Passive diffusion: For example, water, some gases and lipid soluble molecules. Bilirubin, opioids and barbiturates all cross freely into the CNS in infants across blood–brain barrier.
2. Carrier-mediated transporters: e.g. glucose and amino acids.
3. Active efflux transporters such as P-glycoprotein: e.g. some drugs, toxic metabolites, potential neurotoxins
4. Receptor-mediated transcytosis systems.

The blood–brain barrier is unique in that the interstitial osmotic pressure is the determinant of the Starling force in central nervous system.The oncotic pressure is not significant as proteinsand other colloidscannot cross the impermeable blood–brain barrier. According to Pascal's principle, the interstitial fluid pressure in the brain is equal to the intracranial pressure.

Functions of the Blood–brain Barrier

1. To protect the brain from many common bacterial infections
2. Restricts large or hydrophilic molecules into the cerebrospinal fluid (CSF), while allowing the diffusion of small hydrophobic molecules (O_2, CO_2, hormones).

Disruption of the Blood–brain Barrier

A variety of brain insults result in blood–brain barrier disruption including:

1. Traumatic brain injury (TBI),
2. Ischaemic stroke,
3. Intracerebral haemorrhage,
4. Primary and metastatic neoplasms,
5. Infectious diseases (meningitis, ventriculitis, and cerebral abscess),
6. Severe toxic–metabolic derangements (encephalopathy, liver failure).

Although the initial insults to the brain in various pathologies are quite different, there is a common final pathway in the form of disruption of above transport mechanisms resulting in loss of blood–brain barrier integrity.[6]

Pathophysiological Significance of Disruption

1. Blood–brain barrier breakdown endangers the homeostatic control of the cerebral interstitium.
2. Disruption of blood–brain barrier leads to 'vasogenic' oedema in the interstitial space resulting in reduction of the cerebral compliance and increased intracranial pressure.

   This vasogenic oedema from tumour vasculature develops gradually. Tumour oedema leaks from developing vessels that lack some of the typical blood–brain barrier features.
3. With blood–brain barrier disruption, substances present in the plasma come in contact with parenchymal structures. For example, glutamate, a cerebral excitotoxin, has plasma concentration 5–10 times more than found in cerebrospinal fluid. Infusion of amino acid solutions containing glutamate, can double plasma glutamate, and should be used with caution in patients with an open blood–brain barrier.

Almost all general anaesthetic agents can alter the blood–brain barrier function but the degree of the blood–brain barrier disruption is less during isoflurane-anaesthesia as compared to pentobarbital anaesthesia.[5]

Factors Affecting CNS Penetration of Drugs

1. **Lipophilic analogues:** A drug's lipophilicity correlates strongly with BBB permeability. For example, diamorphine, a diacyl derivative of morphine, crosses the blood–brain barrier 100 times more easily than its parent drug just because it is more lipophilic.
2. **Prodrug:** Lipophilic prodrugs may easily cross blood–brain barrier bringing the hydrophilic active form closer to receptor site but it may also increase the systemic tissue absorption, thereby increasing its side effects. For example, steroids and cytotoxic agents.
3. **Carrier and receptor mediated transport:** Non-transportable drugs can be conjugated with carriers for transport across blood–brain barrier by transcytosis at the receptor sites. This technology is being used for peptide based pharmaceuticals such as neurotrophins and small molecules incorporated within liposomes. In spite of this, effectiveness of this technique is under investigation.
4. **Transient disruption** with chemical or hyperosmotic agents (egmannitol, etc.) can be used a route for drug delivery like antineoplastic agents as treatment modalities. This treatment is still investigational.

Paediatric Anaesthesia Pearl

- The interstitial osmotic pressure is the determinant of the Starling force in central nervous system.
- Disruption of blood–brain barrier leads to 'vasogenic' oedema in the interstitial space resulting in reduction of the cerebral compliance and increased intracranial pressure.

Cerebral Oedema

Types

1. **Vasogenic oedema:** It is caused by the breakdown of blood–brain barrier or blood–CSF barrier resulting into an exudative oedema in the interstitium. The spread of this can be quite rapid and extensive. Tumour cells can produce vascular endothelial growth factor (VEGF) which can cause disruption of blood–brain barrier. Dexamethasone helps reduce VEGF secretion, thereby reducing cerebral oedema.
2. **Cytotoxic oedema:** This is the intracellular oedema in the neuronal or glial cells occurring secondary to cerebral ischemia or trauma. The blood–brain barrier is intact but the sodium–potassium pump is impaired in the cell membranes leading to retention of sodium and water intracellularly. It is generally focal but if it spreads, the prognosis is very poor.

Generally, both vasogenic and cytotoxic oedema occur together. Cytotoxic oedema occurs initially after the primary insult followed by the vasogenic oedema which may last for days or longer.

Other classification can be according to cause—osmotic, hyperemic, interstitial, etc.

Resolution of Cerebral Oedema

1. Vasogenic oedema resolves partially by drainage of fluid into CSF depending on pressure gradient between brain tissue and CSF.
2. Brain ECF proteins are cleared by glial uptake, thus helping to reduce oedema.

Central Nervous System Physiology

Specific data on cerebral blood flow (CBF) in human infants and children are rare and hence many anaesthetic principles must be inferred from the data in animals and adult humans.

The cerebral blood flow is 10 to 20% of the cardiac output in the first six months of life, increasing up to 55% from 2nd to 4th year and again reaching the adult levels of 15% by 7 to 8 years.[7]

Cerebral Blood Flow (CBF)

- **Adult:** 50 mL/100 g of brain tissue per min—gray matter–80% and white matter–20%.
- **Premature and newborn infants:** 30–40 mL/100 g per min
- **Infants and older children** 65–85 mL/100 g per min.[8,9]

Cerebral Metabolic Rate of Oxygen ($CMRO_2$) Consumption

- **Adult:** 3–4 mL/100 g per min.
- **Child:** 5 mL/100 g per min

CBF and $CMRO_2$ are directly proportional. Increased $CMRO_2$ (seizures or fever) increases CBF and decrease in $CMRO_2$ (hypothermia and barbiturate) decreases CBF.[10]

CBF also depends on[11]

1. **Cerebral perfusion pressure** (CPP)

$$CPP = MAP - \frac{CVP}{ICP}$$

Cerebral blood vessels dilate at lower MAP and constrict at higher MAP, thus maintaining the cerebral perfusion pressure in the range varying between 50 and 150 mmHg in adults. This is autoregulation. This may take up to 2 minutes to occur. Because MAP in infants are often < 60 mmHg, autoregulatory limits are as low as 20 mmHg and upper limit is not known.[7]

Also, this autoregulation is impaired in premature neonates.

Their cerebral blood vessels are at risk of rupture due to varied reasons, increased blood pressure being commonest, especially in the region of the germinal matrix leading to intracerebral and intraventricular haemorrhage. Due to this low autoregulatory reserve, low blood pressure may cause cerebral ischemia. With increasing gestational age, the germinal matrix involutes and the risk of bleeding decreases. Hence maintenance of blood pressure in this narrow range is essential to prevent cerebral ischaemia and intraventricular haemorrhage.

Autoregulation is attenuated by hypercapnia, hypoxia, high concentrations of volatile agents, nitroprusside and trauma. In local areas around brain tumours and focal cerebral ischaemia, autoregulation is lost and perfusion is pressure dependent.

The lower limit of autoregulation is lower with drug induced hypotension than during hypovolemic hypotension.

2. **$PaCO_2$:** Increase in $PaCO_2$ dilates the cerebral vessels linearly and vice versa between 20 and 80 mmHg so that a 4% change in CBF occurs for each 1 mmHg change in $PaCO_2$ in this range. Outside this range, >80 mmHg vessels are maximally dilated and <20 mmHg causes ischaemia induced metabolic changes which override the changes to $PaCO_2$. These responses are not completely developed at birth.
3. **PaO_2:** In adults, this is less sensitive. Foetal and neonatal circulation responds to small changes in PaO_2 perhaps due to high O_2 affinity of foetal haemoglobin. The age at which this heightened responsiveness decreases is not known.
4. **Haematocrit:** Adult >50% increases viscosity and decreases CBF, <30% increases CBF
5. **Body temperature:** $CMRO_2$ and CBF reduced by hypothermia.

Paediatric Anaesthesia Pearl

- Cerebral perfusion pressure (CPP) = MAP – (Cerebral) CVP/ICP.·
- The MAP in infants is often <60 mmHg, autoregulatory limits are as low as 20 mmHg and upper limit is not known.·
- The premature neonates are at an increased risk of intracerebral and intraventricular haemorrhage.
- Responsiveness of cerebral circulation to $PaCO_2$ is not developed in infants.

Intracranial Pressure (ICP)

The intracranial pressure is determined by the volume of the intracranial contents. According to the Monro-Kellie doctrine, the intracranial volume remains constant. An increase in volume of any one component will result in a decrease in volume of other two components. CSF and cerebrovascular compartment are

the adaptable components. After the intracranial compliance (the change in volume for a given change in pressure) is exhausted, the intracranial pressure (ICP) will rise exponentially. In infants due to open sutures, the rise in intracranial pressure will be further compensated.

Age group	Normal range of ICP (mmHg)
Adult	<10–15
Children	3–7
Term infants	1.5–6

At birth, the sutures are open and there is a large anterior fontanelle, which closes by 9–18 months approximately. Palpation of the anterior fontanelle can be used to evaluate intracranial pressure in neonates and infants. Increasing intracranial pressure is partly relieved by expansion of the fontanelles and separation of the suture lines so that head size increases before intracranial pressure rises. A transducer placed on the anterior fontanelle is a non-invasive technique of intracranial pressure monitoring in infants.

The brain is divided into different compartments by dural projections like falxcerebri and tentorium cerebelli. Rise in intracranial pressure can cause shift in these compartments. The three types of intracranial herniation are transtentorial, tonsillar and subfalcine.[12]

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Increasing intracranial pressure is partly relieved by expansion of the fontanelles and separation of the suture lines so that head size increases before intracranial pressure rises in infants.

DEVELOPMENT OF CSF CIRCULATION AND VOLUME

Cerebrospinal fluid is an ultrafiltrate of plasma. The choroid plexus epithelial cells constitute the blood—CSF barrier.

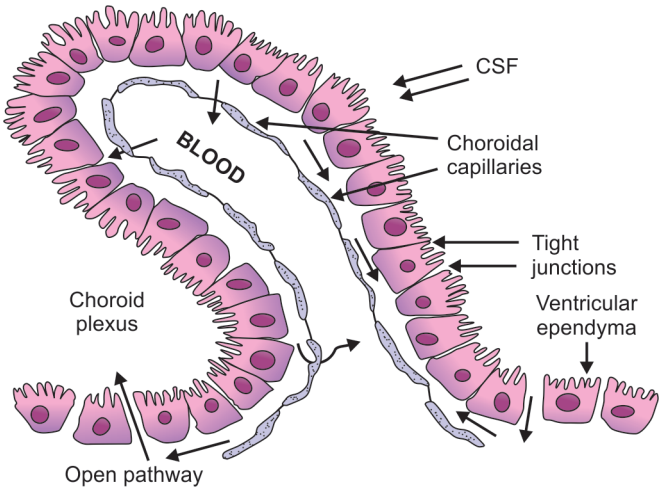
Cerebrospinal fluid aspects

CSF pressure [mm of Hg]	
Child	3–7.5
Adult	4.5–13.5
CSF volume [mL]	
Infants	40–60
Young children	60–100
Older children	80–120
Adults	100–160

CSF Formation and Circulation

Production

CSF is formed in the capillary lining of the choroid plexus in the two lateral cerebral ventricles (2/3rd) and also the capillary endothelial cells of the third and fourth ventricles (1/3rd).



Pathway

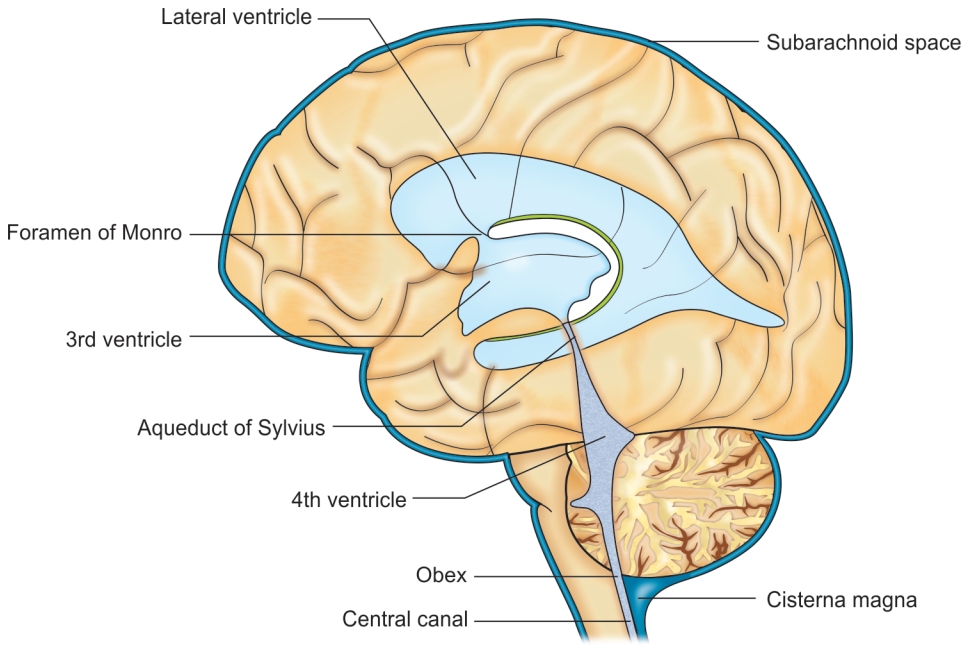
The CSF produced in lateral ventricles drains through the two foramen of Munroe into the third ventricle and through the aqueduct of sylvius into the fourth ventricle. Most of the CSF drains through the two lateral Foramen of Luschka and the central foramen of Magendie into the subarachnoid space surrounding the brain and spinal cord. A small proportion of CSF flows from the 4th ventricle into the central canal of the spinal cord.

Absorption

In adults and older children, CSF absorbed by the arachnoid villi in the dural venous sinuses especially the sagittal dural sinus. In neonates the arachnoid villi are not fully developed and absorption also occurs into the paranasal sinuses, lymphatics along the cranial nerves and lymphatics of the nose.[13]

CSF Formation

1. Rate at 0.35–0.40 mL/min or 500–600 mL/day
2. 0.25% of total volume replaced each minute
3. Turn over time for total CSF volume: 5–7 hours = 4 times/day
4. 40–70% enters macroscopic spaces
5. 30–60% enters across ependyma and pia.



CSF Composition

	Plasma	CSF
Sodium (nM)	140	141
Potassium (nM)	4.6	2.9
Magnesium (nM)	1.7	2.4
Calcium (nM)	5.0	2.5
Chloride (nM)	101	124
Bicarbonate (nM)	23	21
Glucose (nM)	92	61
Amino acids (nM)	2.3	0.8
pH	7.41	7.31
Osmolality (mosm/kg water)	289	289
Protein (mg/dl)	7000	28
Specific gravity	1.025	1.007

Functions of CSF

1. The low specific gravity of CSF (1.007) relative to that of the brain (1.040) reduces the effective mass of a 1400 g brain to only 47 g. It also acts as a shock absorber.
2. It is a source of nutrients, primarily glucose, vitamins, monosaccharides and amino acids.
3. Control of the chemical environment by removal of metabolic products and unwanted drugs.

Paediatric Anaesthesia Pearl

- Rate of CSF production is 0.35–0.40 mL/min or 500–600 mL/day.

Development of Spinal Cord

Anatomic relationships and landmarks are constantly changing throughout infancy and childhood, which requires a good knowledge of developmental anatomy of the spinal cord.[14,15]

Sl. No.	Anatomy and physiology	Anaesthetic implications
1.	Termination of spinal cord. S1 at 28 weeks' gestation, L3 at term, L2/3 at 1 year, and the adult level of L1/L2 around the age of 8 years.	Neuraxial blocks below L3 only in infants.
2.	Dural sac termination S4 at birth and S2 by 12 months	Neuraxial blocks below L3 up to S2 only in infants.
3.	Delayed myelination of nerve fibres	Diluted local anaesthetic to be used. Onset faster but duration shorter.
4.	Curvatures of spinal cord Cervical lordosis: 3–6 months Lumbar lordosis: 6–9 months	Orientation of epidural/spinal needle important

Contd...

Sl. No.	Anatomy and physiology	Anaesthetic implications
5.	Incomplete ossification of sacral vertebra posteriorly	Lower sacral epidural/caudal approaches preferred in children
6.	Intercristal line (line joining two iliac crests) L5–S1 at birth, L5 in young children and L3–4 in adult	Neuraxial blocks below intercristal line in infants.
7.	CSF circulation Volume: 4 mL/kg, double of adult ½ of it in spinal space unlike adult (1/4th)	Pharmacokinetics of intrathecal drugs differ. Short duration of action, e.g. half life of Bupivacaine–45 minutes in neonates and 75–90 minutes till 5 years.
8.	Spinal fluid hydrostatic pressure 30–40 mmH_2O in horizontal position	No need for cervical flexion in lateral position for lumbar puncture. In fact, it may obstruct the airway.
9.	Immature sympathetic system up to 5 years	Fluid preloading and vasopressors drugs unnecessary. Spinal block preferred in critically ill and moribund neonates.
10.	Immature hepatic metabolism and reduced plasma proteins	Increased risk of local anaesthetic toxicity
11.	Loculated epidural fat	Threading of sacral catheter up to thoracic levels difficult.

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- The spinal cord ends at L3 level at term.·
- The volume of cerebrospinal fluid CSF is 4 mL/kg which is double the adult volume.·
- In infants half of this volume is in the spinal space, whereas adults have only one-fourth.
- The spinal fluid hydrostatic pressure of 30–40 mm H_2O in horizontal position is much less than that in adults.

Impact of maternal anaesthesia for non-obstetric surgery and foetal surgeries on foetal neurodevelopment.

Substantial foetal neurodevelopment takes place in the second trimester of pregnancy. The foetal neuroendocrine response to noxious stimuli also develops in the second trimester. Certain important developments occurring in the second trimester include:

1. Development of peripheral nerve receptor: 7 to 20 weeks of gestation.
2. Development of C fibres: 8 to 30 weeks of gestation.
3. Development of spinothalamic tract: 16 to 20 weeks of gestation.
4. Development of thalamocortical fibres: 17 to 24 weeks of gestation.
5. Response to pain and foetal stress: In response to painful stimuli, vigorous movements and breathing efforts with increase in levels of cortisol, norepinehrine and beta endorphinsare seen. Also there is no evidence of placental transfer of norepinephrine to foetus, thus proving that independent stress response exists since 18th week of gestation.[16,17]

In this scenario, foetal anaesthesia and analgesia require an independent and important consideration during maternal and foetal surgeries. In the absence of these there may be a significant modulation in development of foetal nervous system leading to altered pain sensitivity such as hyperalgesia.

Paediatric Anaesthesia Pearl

Foetal anaesthesia and analgesia during maternal surgeries is essential since it has been proved that independent stress response develops in foetus in second trimester.

ANAESTHETIC NEUROTOXICITY

Apoptosis is a normal part of the developmental process in the body responsible for remodelling of the architecture of the entire body including the central nervous system.

All commonly used anaesthetic agents like inhalational agents, diazepam, midazolam, pentobarbital, propofol, ketamine, etc. in vivo and in vitro animal studies have found to dramatically accelerate the physiologic apoptosis in the immature brain, altered synapse formation, mitochondrial dysfunction, altered calcium homeostasis leading to neuronal cell death. Immature neurons have GABA and NMDA receptors, which is one of the paths of neurotoxicity in the developing brain. It may be dose and exposure-time

related. It is unclear whether this neuro-apoptosis translates into permanent cell loss and dysfunction or is compensated by the developing brain's ability to repair. Various animal studies have found differential effects on the neurocognitive outcomes like impaired learning, memory, behaviour, etc. The possibility of these changes also occurring in humans cannot be ignored and further studies are required for their evaluation. Also, different regions of the immature brain are affected depending on the peak time of neurogenesis in that part. Since apoptosis is a lifelong phenomenon, not only neonates but also older children and adults may show this anaesthetic neurotoxicity leading to increased incidences of postoperative cognitive dysfunction.[16,18]

Paediatric Anaesthesia Pearl

There is growing evidence that exposure of general anaesthetic agents to the growing brain of the child can lead to neuronal apoptosis and long term cognitive impairment.

SUMMARY

The practice of paediatric neuro-anaesthesia encompasses understanding and application of these differences in the anatomic and physiologic mechanisms and their effect on anaesthesia management.

FAQ with Answer

Q. What is the impact of chemical sympathectomy after spinal anaesthesia in children and role of preloading with fluid?

A. The physiological impact of sympathectomy is minimal or none in smaller age groups. The fall in blood pressure and a drop in the heart rate are practically not seen in children less than five years. Therefore there is no role of preloading with fluids before a subarachnoid block.[7]

Key Points

1. Children differ from adults in brain and spinal cord development both anatomically and physiologically. They havedelayed myelination, immature neural pathway development and blood–brain barrier, cerebral blood flow and spinal architecture. These changes affect our anaesthesia management.
2. Delayed myelination in infants contributes to shorter onset times of local anaesthetics and variation in waveform morphology during neurophysiologic monitoring.

Contd...

Key Points *(Contd...)*

3. The premature neonates are at an increased risk of intracerebral and intraventricular haemorrhage.
4. Techniques of neuraxial regional anaesthesia in paediatric anaesthesia necessitate understanding the anatomical and physiologic differences between children and adults. The spinal cord ends at L3 at birth.
5. Foetal anaesthesia and analgesia for maternal surgeries for non-obstetric or foetal surgeries are important for foetal neural structural development and cognitive functions.
6. There is a growing evidence that exposure of general anaesthetic agents to the growing brain of the child can lead to neuronal apoptosis and long-term cognitive impairment.

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6

Essentials of Liver Functions, Kidney Functions and GI and Endocrine System

Ashish Mali

RENAL SYSTEM

The renal system deals with water excretion and reabsorption according to body requirements, meeting severe fluid challenges.

Embryological the urinary and genital systems develop very closely as they both develop from common mesodermal ridge.

During the intrauterine life three overlapping kidney systems are formed in cranial to caudal sequence.

1. Pronephros: First system which is rudimentary and non-functional.
2. Mesonephros: Second system which may be functional for short span during early foetal period.
3. Metanephros: Third system which forms the permanent kidney.

Pronephros: This is represented as seven to ten solid cell groups in the cervical region at the fourth gestational weeks. These are vestigial excretory units called nepherotomes and regress before more caudal ones are formed. The pronephric system disappears by the end of fourth week.

Mesonephros: As the pronephric system regresses early in the fourth week of development, the intermediate mesoderm from the upper thoracic and upper lumbar segments forms the mesonephros and mesonephric duct.

During this time there is appearance of the first excretory tubule of the mesonephros. These tubules then lengthen taking S-shaped loop pattern tuft of capillaries is acquired at their medial extremity forming a

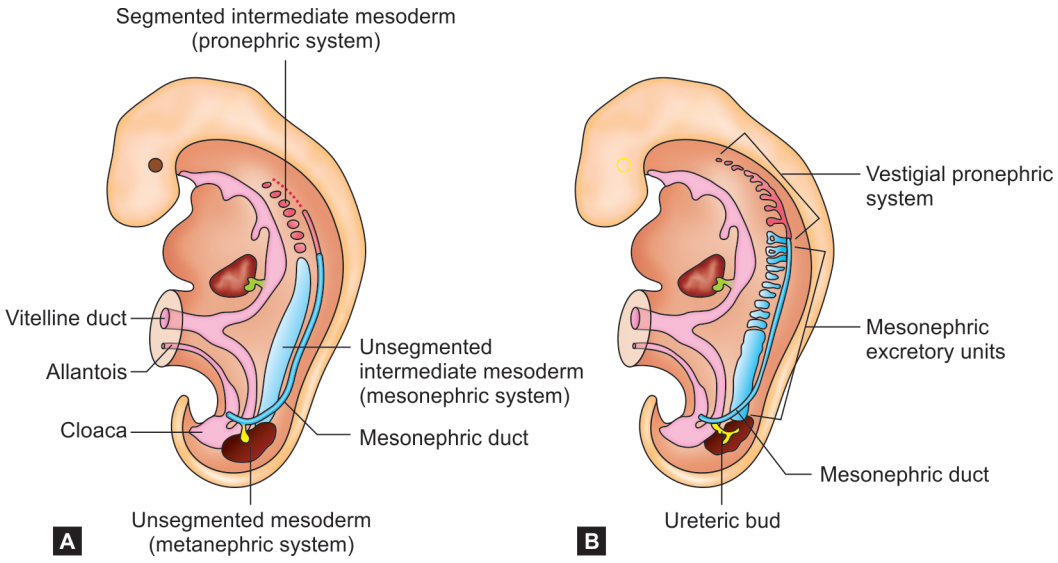

Fig. 6.1A and B Pronephric, Mesonephric and Metanephric system in the initial **(A)** and later stage **(B)**

glomerulus. The tubules then form Bowmen's capsule around the glomerules, these structures collectively constitute the renal corpuscle. The lateral end of the tubule enters the longitudinal collecting ducts called the Wolffian or the Mesonephric duct. Somewhere around the middle of the second month two ovoid shaped organs are developed on each side of the midline by the Mesonephros known as urogenital ridges. As the development proceeds, the differentiation of the tubules start towards the caudal end and degenerative changes starts at the cranial tubules. These changes are so done that by the end of second month majority of these disappears. Some caudal tubules and mesonephric ducts may persists in males but in females they totally disappear.

Metanephos: This is definitive kidney[1] (permanent kidney), which appears in the fifth week. The excretory units of this develop from metanephric mesoderm as it has developed from the mesonephic system.The ureter, pelvic part of ureter and collecting system develops from the ureteric bud as a outgrowth of the mesonephric duct just before it enters the cloacae. The caudal extension of the nephrogenic cords forms the metanephrogenic mass which then forms the excretory system. The ureteric bud penetrates the metanephrogenic tissue that covers the bud as a cap. The ureteric bud differentiates repeatedly to form the ureter, renal pelvis, major calyces, minor calyces, papillary ducts and the collecting tubules which all contribute to make the collecting system.

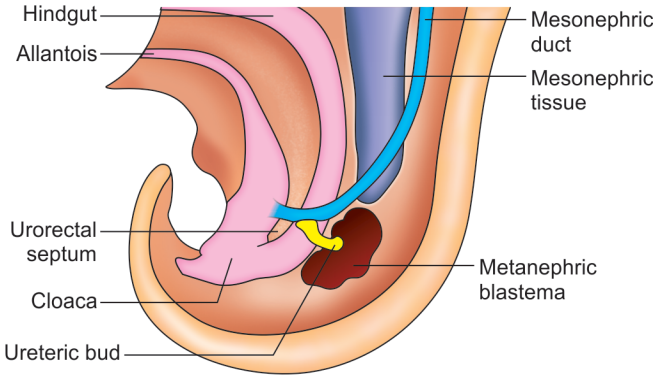

Fig. 6.2 5th week relation of cloaca and hindgut. Note the ureteric bud penetrating the metanephric mesoderm

The collecting tubules induce the metanephic tissue to differentiate and divide so that each tubule is covered by a small tissue of metanephic tissue. This association results in the formation of the renal vesicle which indeed transforms into small tubules that forms the nephon (excreatory unit). The tubule on one end joins a vascular tuft to form the glomerulus, while the other end joins the collecting system.

The end that has the vascular relay forms the Bowman's capsule. The tubule from the Bowman's capsule continues to lengthen and differentiate to form the proximal convoluted tubule, loop of Henle and the distal convoluted tubule. All this continuous till the 34th week of gestation.

The development and distribution is such that the most recently formed nephorns are at the outer cortex

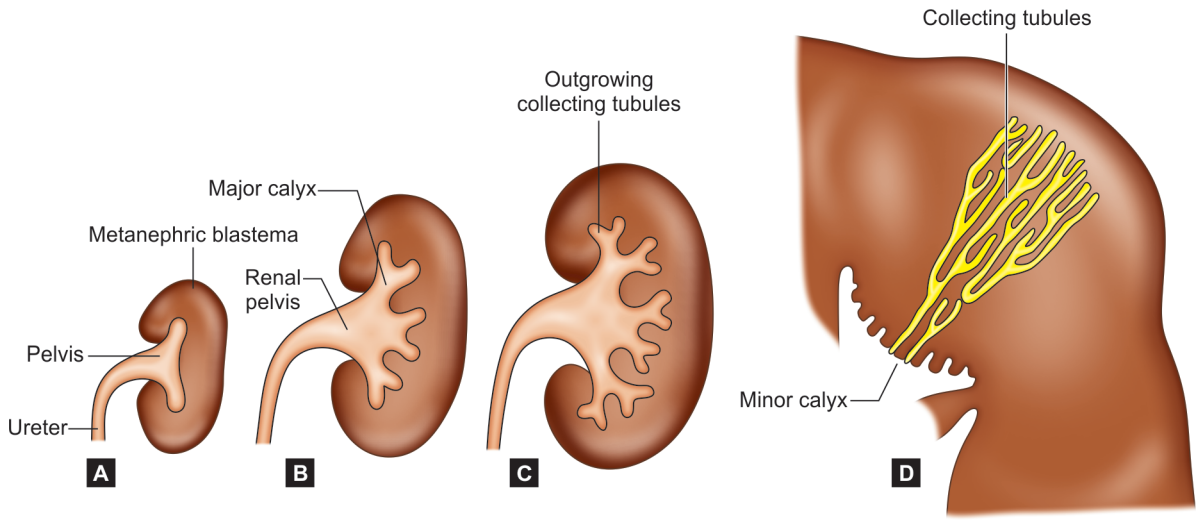

Fig. 6.3A to D Development of pelvic calycial system. **(A)** 6 weeks, **(B)** end of 6th weeks, **(C)** 7th week and **(D)** newborn

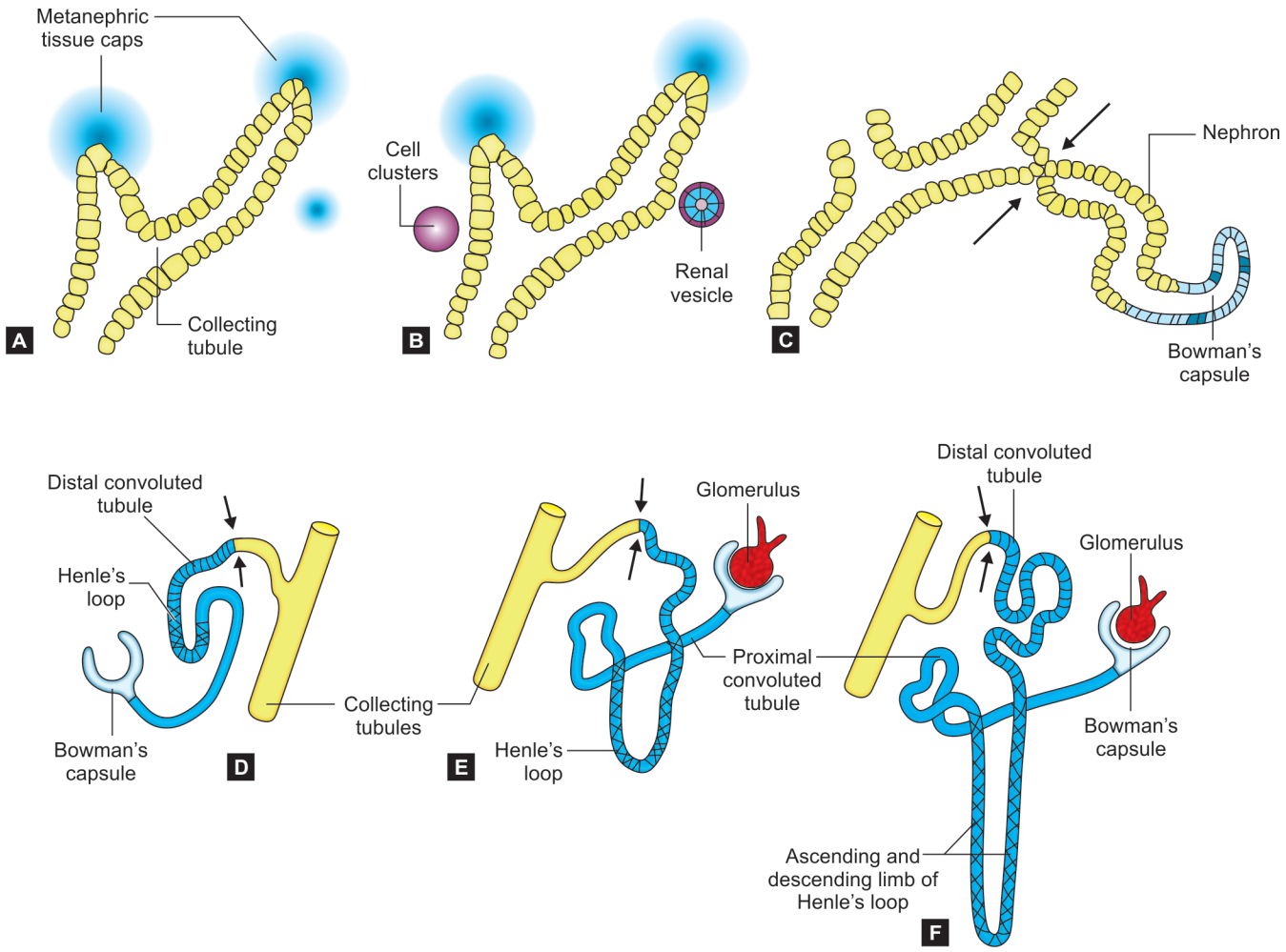

Fig. 6.4A to F Development of excretory unit of the metanephric system

and are called cortical nephorns, while the older nephorns are near the medulla and are called juxtra medullary nephorns, ratio being (8:1). In immature newborns (34th weeks) both these are anatomically and functionally different. Regarding the infant status in the uterus, the formation of nephrons does not accerate and is completed at 34th week.

After 34 weeks the increase in the size of the kidney is more due to enlargement and growth of the nephorns rather than formation of new nephorns. Though the renal system develops in cephalo caudal direction, the permanent kidney migrates in the cepaloid direction due to marked growth and development in the lumbar and sacral region and degree of body curvature of the foetus. At 8 weeks it is at the level of 2nd lumbar vertebra. The kidneys also rotate by 90 degrees so that the initially ventrally facing hilum becomes medially placed.

Key Points

Three renal systems come in the development in sequence: Pronephros, mesonephors and metanephros.

Pearls

Metanephros is permanent and definitive kidney.

Foetal Urine

The permanent kidneys produce urine by the ninth week, the time approximately when the ureter opens in the bladder. The development proceeds so that the loop of Henle and tubular re-absorption is started by 14th week. As contrast to adults in foetal life, the placenta does the work of excretion of waste material. The urine contributing to the amniotic fluid acts as a cushion for the foetus and is also necessary for the normal growth and development of the lung. It is a

hypotonic solution without sugars and proteins. The foetus starts swallowing the amniotic fluid by 20th week which then is absorbed by the GI tract and through it into the vascular system. It is then filtered by the kidneys and excreted in the urine.

ABNORMALITIES[1]

- Wilms' tumor: Cancer of the kidneys
- Renal dysplasia or agenesis: Transplant or dialysis
- Multicystic dysplasias: Numerous ducts surround undiffentiated cells, nephrons fail to develop, collecting ducts are never formed as ureteric bud fails to branch.
- Renal agenesis: Interaction between metanephric mesoderm and ureteric bud fails to occur.
- Congenital polycystic kidney: Kidney contains many cysts. It may be autosomal dominant or autosomal recessive.

There may be bifurcation of the ureter or duplication, ectopic openings.

Kidneys may have abnormal location—pelvic kidney, near the common iliac artery in the pelvis. The lower pole may be fused to form horseshoe shape kidney. Accessory renal arteries are also not uncommon.

SUMMARY

The development of the urinary system is from the mesodermal tissue. Three systems develop in sequence from cranial to caudal part, out of which 1st two are temporary (**Pronephros and Mesonephros**) and the last is permanent (**Metanephros**).

Pronephros: Comparatively small, develops in the cervical region, but is vestigial.

Mesonephros: Comparatively big, develops in the thoracic and lumbar region, forms a type of excretory system and may function briefly.

Metanephros: Big system, develops from two sources. Collection system from mesonephric duct (ureter, renal pelvis, calyces and the collecting system) and metanephrogenic tissue (kidney tissue).

There may be abnormal position or abnormal development of kidney as well as ureter.

FAQs

Q. Which are the three systems during the development of the urinary system? Mention their parts.

Q. Does any system remain as a vestigial organ?

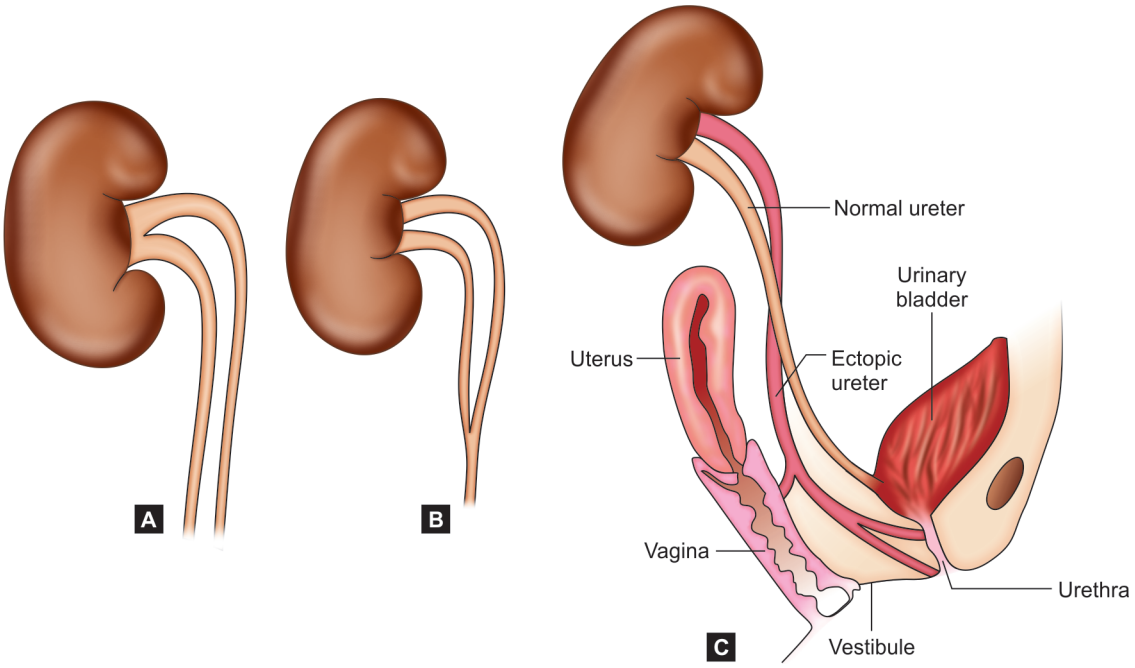

Fig. 6.5A to C Duplication of ureter (A) complete, (B) partial and (C) ectopic openings

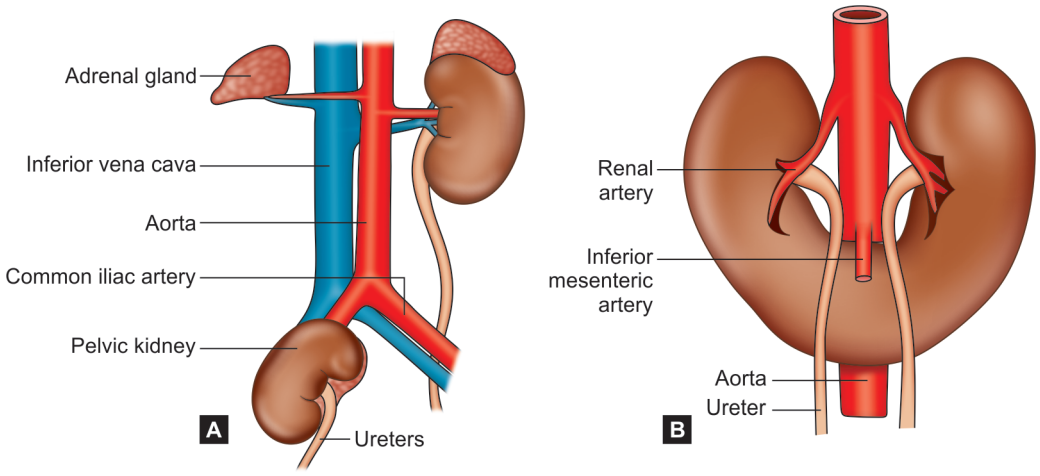

Fig. 6.6A and B Kidneys **(A)** ectopic (pelvic) kidney and **(B)** horseshoe kidney

RENAL PHYSIOLOGY

Before birth the kidney is a silent organ as placenta does its work. However, at birth the kidney takes its role which is of excretion of waste products, metabolites, drugs and maintaining volume, osmotic pressure and chemical composition of CSF.

Though being immature at birth the neonate kidneys perform the same function as that of the adult. Some relief is provided to the kidney as 50% of the dietatary nitrogen is incorporated into new tissue, thus decreasing half of the excretory load.

At birth the tubules are not fully grown and also the glomeruli area of filtration is similar in relation to body weight. As already discussed at term nephrogenesis is completed, while in preterm it is still continuous. Urine starts to come from 9 to 12 weeks. At term kidney produces 20–30 mL/ hr of filtrate.

Glomerular Filtration Rate

It is low and slow than adults in term babies (10 mL/ min/1.73 m^2) and even low in preterm. The neonatal GFR increases with fluid challenge or loading but there is a limit to it hence overzealous infusion of fluids can cause oedema.

Renal Blood Flow

Renal perfusion is dependent in neonates on the renal vascular resistance and arterial blood pressure and blood flow. Before and immediately after birth there is high renal vascular resistance and low renal blood flow (6% of circulation). After that the resistance decreases and arterial blood flow and blood pressure increases in the renal vessels causing increase in the GFR. The GFR increases by 2 times in 2 to 4 weeks.

GFR at 2 weeks is 20 to 30 mL/min/1.73 m^2. Adult values are reached at 1 year of age, hence initially the babies have high creatinine values which eventually decrease and come to normal values. Renal blood flow and GFR are decreased by asphyxia and hypoxia due to decrease in arterial blood pressure and renal and cardiac ischaemia.

Tubular Function

Even though the formation of nephrons is completed at term, the functional ability is still limited. The concentrating ability is still less due to urea concentration in the medullary interstitium, the loop of Henle being short and the sensitivity of ADH is still less. The ability to concentrate the urine is quickly develops so that at the age of 2 months it is 1000 mosmols/L.

This becomes important when fluid administration is insufficient due to some reasons (and in case of insensible loss) as it is difficult to handle dietary solutes. Neonates can concentrate urine to half of that of the adult as medullary concentration of urea in immature kidneys is low causing decrease osmotic gradient. In premature babies this ability is further decreased. The conservation of important solutes is also hampered due to marked immaturity of the tubules.

Sodium: An important solute is sodium, the capacity to absorb sodium is very very less, this leads to high renal losses of sodium, hence they are called obligatory sodium loosers.[4] In pre-terms this is still worse, (approximately three times greater) here it is important

to mention that the renin–angiotensin aldosterone system is intact in infants. Distal tubule even with increase aldosterone cannot efficiently reabsorb sodium. Slowly, then the tubules start to respond to renin–angiotensin aldosterone system. All these cause hyponaetremia. Hence all fluids of neonates should contain sodium 2–4 mmoles/kg/day and in preterms should contain 5–10 mmoles/kg/day.

Pearls

Neonates are obligatory sodium losers.

Potassium: Kidneys manage potassium levels according to serum aldosterone levels. Aldosterone receptors are present on distal nephrons which cause increase secretion of potassium in urine. In neonates this is less efficient, hence they have hyperkalemia. This hyperkalemia is without ECG changes and is well tolerated by the neonates and does not require treatment.

Key Points

Kidneys are immature in view of excretion absorbtion and handling fluids and electrolytes.

pH balance: The mechanism of acid secretion is mature and efficient at term but not in immature babies. As gestational age increases, the excretion also increases.

The renal threshold for bicarbonates is decreased than adults.

16–20 mmols/L in preterm
19–21 mmols/L in term
24–28 mmols/L in childhood.

The limitation in infant's ability to excrete a hydrogen ion load is due to decreased concentration of buffers like ammonia and phosphates in urine.

Glycosuria

It is not in term children, but in preterm there is decreased tubular re-absorption of glucose. This causes osmotic diuresis causing Na^+ and water losses.

Proteinuria

- Normally no proteinuria.
- In premature it is increased by 16–21%.

Take Home Message

Avoid overzealous hydration.

SUMMARY

Kidneys are immature at birth and find difficult to handle stress. GFR is less in neonates and tubules do not necessarily reabsorb or secrete all the substances presented to them. Tubular re-absorption rate of sodium is reduced and proteins, amino acids are poorly dealt. Also there is limited ability to concentrate the urine and the threshold for bicarbonate is also lowered.

FAQ

Q. What should all IV fluids of neonates contains?

LIVER

- Development of liver and relevant metabolism.
- Anatomy and development.

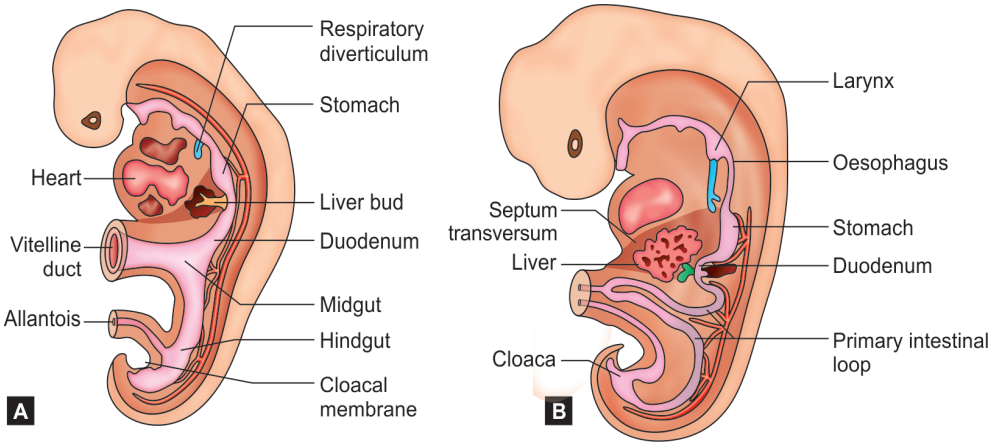

Fig. 6.7A and B (A) 25-day-old embryo showing liver bud formation along with GI in the primitive stage and **(B)** 32-day-old embryo showing epithelial liver cords cells penetrating the mesenchyme of septum transversum

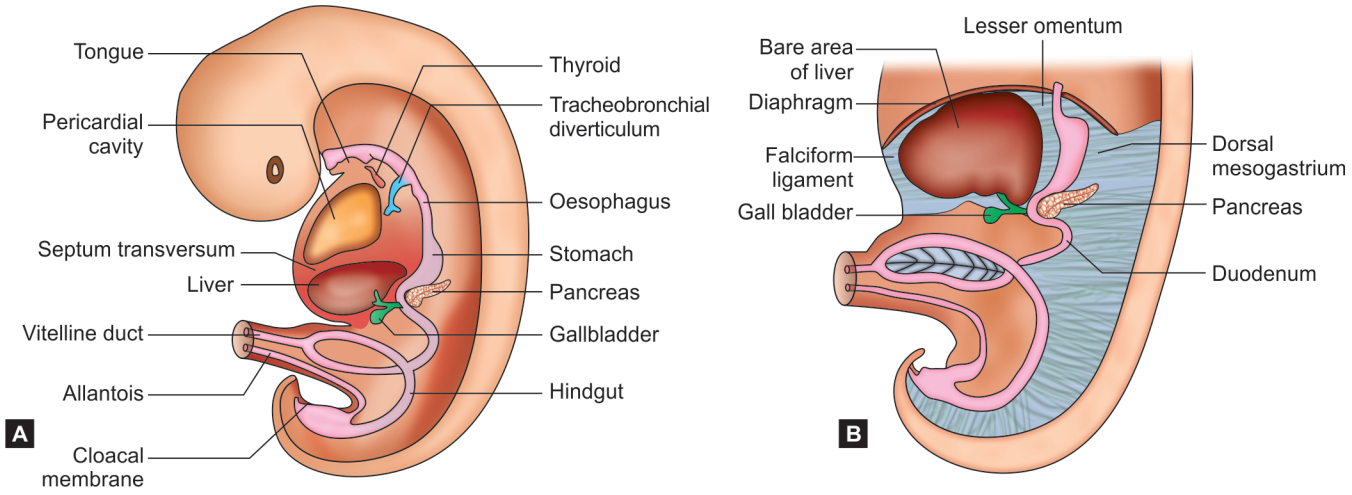

Fig. 6.8A and B Caudally expanding liver pushing the abdominal contents and anterior and posterior attachments of the gut

The liver and biliary tree tract develops in the middle to late of 3rd to 4th week of gestation as a ventral bud from the endodermal epithelium at the distal end of foregut.

The liver bud cells proliferate rapidly which then penetrate the septum transversum (mesoderm connecting pericardial cavity and the stalk of the yolk sac).[1] Three outpouchings then differentiate as liver, gallbladder, and ventral pancreas. By seventh week the morphologic development is completed but not the functional.

At this time bile duct starts to form as the connection between the hepatic diverticuli and the foregut narrows in size.

The bile duct gives small ventral outgrowth which gives rise to the gall bladder and cystic artery. Then the epithelial liver cells intermingle with vitelline and umbilical veins which forms hepatic sinusoids. Later liver cords differentiate into liver cells (parenchyma) and form the lining of the billiary duct. The mesoderm of the septum transversum gives rise to the connective tissue cells, Kupffer cells and haemopoietic cells.

During seventh week only hepatic cannaliculi and the intrahepatic and the extrahepatic bile ducts proliferate. Maternal viruses, drugs and toxins are known to increase the vulnerability of the anomalies at this stage of the hepatic and biliary tract development. Associations include intrahepatic biliary atresia and congenital heart disease.

Weight of the liver at the time of birth is 120–160 gm (nearly 4% of the infant weight). Not yet full structurally mature additional 4 to 8 weeks are required for peripheral branching of intrahepatic biliary tree to develop into proper hepatic portals.

The liver has 2 lobes and 8 structurally independent segments which have hepatic artery, hepatic vein and bile duct.

It has dual blood supply:

1. **Portal vein:** Venous blood from spleen and intestine (70%).
2. **Arterial:** Blood from hepatic artery (30%).

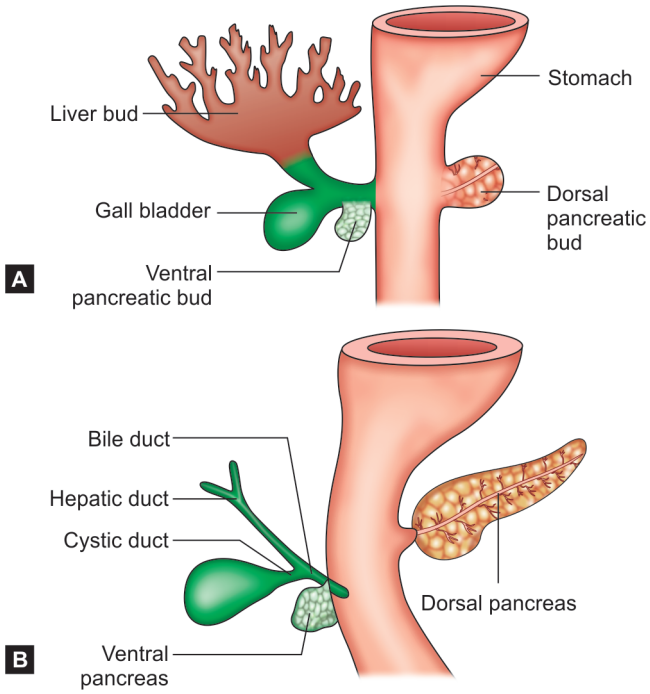

Fig. 6.9A and B Liver, gall bladder, cystic duct, bile duct and pancreatic bud development

Lastly blood from liver goes to heart via right and left hepatic veins through inferior vena cava.

Foetal hepatic circulations differ from adult circulation.

Ductus venosus:[1] Connection between umbilical veins and IVC shunts oxygenated blood around the immature liver to enter the right atrium (an essential shunt). This shunt flow is controlled by a sphincter mechanism.

Ductus venosus closes functionally immediately after birth as the pressure in the umbilical vein decrease immediately after birth. At 2 weeks of age almost 95% of complete functional closure occurs, in others it takes a little longer.

A rare but not a uncommon problem is patent ductus venoses, known as congenital portosystemic venous shunt which may manifest as hepatic dysfunction or encephalopathy. Reversals of the symptoms are seen on closure of the same.

Liver parenchymal structural unit is a lobule,[2] which has central vein at the center of the wheel bordered by portal tracts which has a traid of bile duct, portal vein and hepatic artery, between are the liver cells, kupffer cells, etc. Blood flows from ports towards the central vein bathing the hepatocytes.

Bile has an opposite flow to the portal vein thus forming the hepatic accini to complete.

Key Points

Liver is a mesodermal organ to origin from the foregut.

Pearls

Liver has dual blood supply.

SUMMARY

The liver and the gall bladder develop as out growing of the endoderm epithelium from the upper part of the duodenum (foregut). The parenchyma is formed by the growing biliary system cells and the epithelial liver cord cells in the septum transversum. The hemopoietic cells, Kupffer cells and the connective tissue cells originate in the mesoderm.

FAQs

Q. Liver develops from which primitive gut?

Q. Where do Kupffer cells arise?

LIVER OR HEPATIC PHYSIOLOGY

Lipid solubility is an important factor for passive diffusion across the cellular membrane. These lipid soluble things accumulate in the fat stores of the body and also become protein bound, hence difficult for excretion. Even renal and biliary excretion of these things can cause reabsorption, hence these things are difficult to get off.

The function of major portion of liver is to convert the lipid soluble things into water soluble things which can be excreted by the kidney.

The reactions for the drug biotransformation and metabolism are hydroxylation and conjugation. Hydroxylation prepares the metabolite for conjugation.

Phase 1: Hydroxylation

Phase 2: Conjugation

In neonates the hepatic phase 1 and phase 2 reactions are not fully active and in neonates it is even less causing more problems. They become active at 2 to 3 months of life.

Phase 1 reaction includes:

1. Oxidation
2. Hydrolysis
3. Reduction

Phase 1 reactions[2] are catalyzed by cytochrome P450 enzyme. It is mixed function oxidase system. In neonates its activity is only 28% of that of the adults. Genetic and non genetic factor affect cytochrome P450 activity. The non-genetic factor includes concomitant disease status, diminished nutritional state and exposure to pharmacological and other naturally occurring compounds. Even drugs can inhibit and stimulate the P450 system enzymes.

Stimulants

- Omeprazole
- Ethanole
- Phenytoin
- Carbamazepine

Inhibitors

- Ketaconazole
- Disulfiran
- Quinidine
- Erythromycin

Other system phase 1 reactions such as alcohol dehydrogenase (choral hydrate metabolism), plasma esterase (amino-ester LA metabolism) and N-acetyl transferase (isoniazide and hydralazine metabolism) are also deficient.

Phase 2 reactions[2] is a phase of conjugation to decrease the lipid solubility and increase the water solubility to facilitate excretion by urine or gut. Phase 2 reactions include:

1. Sulfation
2. Glucuronidation
3. Methylation
4. Glutathione
5. Acetylation

Reactions like acetylation, glycination and glucoronidation are very deficient at birth. At the same time sulfation is active which metabolises opiods and in neonate's paracetamol.

During the neonatal period the liver is immature in its ability to metabolise and clear the substance. Size of the liver simply does not matter, as it larger as compared to its body size when compared to adults. Hepatic blood flow, development status of hepatic transport, and enzyme system all affect the drug clearance.

Bilirubin Metabolism

The breakdown of erythrocytes (80%) and ineffective erythropoiesis all together produce bilirubin. Normally this bilirubin is sent to liver where it is conjugated and then excreted.

In neonates the enzyme which catalyzes the transfer of glucuronic acid to bilirubin (urine dephosphoglucuronyl transferase) to form glucuronides and allow the excretion in bile only 1% to that of the adult. It takes 3 to 4 months for it to reach the adult values. Hence increase bilirubin or jaundice is common at term called physiological jaundice. It is more common in pre-term babies due to lower values of the enzyme. This jaundice starts around 2 to 3 days of life and continues till around 10–12 days, when the values of the enzyme start increasing. In adults the production of bilirubin is 50–70 mcg/kg/day but this value is increased to double or triple (100–140 mcg/kg/day) in neonates due to increased production from erythrocyte breakdown, limited metabolism and excretion. In addition there is increased enterohepatic circulation of bilirubin due to limited capacity of urobilinogen and urobilin.

Plasma level of bilirubin can be detrimental when they increase up to or are more than 200 mmmol/L. When level increases it gets deposited and damage basal ganglia 'cerebellum and hippocampus. This condition is called kernicterus with elements of cerebral palsy, mental handicap and deafness.

Factors affecting increase serum bilirubin:

1. Decrease albumin concentration
2. Haemolysis
3. Sepsis
4. Gestational diabetes mellitus
5. Delayed passage of meconium
6. Drugs increase binding to proteins.

The commonest treatment for this is phototherapy which converts bilirubin to photoisomer like lumirubin which is excreted in bile and urine.

Vitamin K

Factors like 2, 7, 9, 10 are less at term, all these factors are vitamin K dependant. Hence as a general measure vitamin K is given to all neonates to prevent the haemorrhagic disease of newborn.

Drug metabolism may be affected and in fact prolonged due to certain circulatory shunt bypasses that bypass the hepatic bed which decrease the clearance of drug metabolism in liver. For example, the ductus venosus a connection between IVC, portal vein and umbilical vein remain patent for 7–10 days of birth.

Glycogen Storage

The liver storage capacity of neonate is less and the activity of the rate limiting enzyme in gluconeogenesis is also less (as low as 10% of adult value), hence the neonates are at risk of developing hypoglycemia if not fed frequently. Hence as a precautious method glucose is added to all infusions till feeding is started, with frequent blood sugar monitoring.

Opiod Metabolism

The conduct of anaesthesia is not much affected due to the liver's limited capacity, but we have to be more watchful and careful in the postoperative period when the drugs are going to be metabolized and excreted. Hence modification of dosage, intervals, infusion are required.

Anaesthetic Drugs

Halothane has been associated with development of severe hepatic injury, hence other drugs like sevoflurane, isoflurane should be preferred.

Muscle Relaxants

Scoline metabolizes by plasma cholinesterase, a protein synthesized by liver by only functional hepatocytes.

SUMMARY

Before birth most of the functions of liver are carried by the placenta. Phase 1 and phase 2 reactions of metabolism are not fully developed or some reactions are developed and some are not. Detoxification and carbohydrate metabolism are not nor developed properly at birth and more so in prematurity. The bilirubin load caused by red blood cells breakdown is also not conjugated, hence causes physiological jaundice which regress slowly. Vitamin K dependant coagulation factors are very low, hence vitamin K has to be supplemented.

Gluconeogenesis is also not optimum hence hypoglycemia is common.

Key Points

They do not have a fully mature enzyme and bilirubin handling system.

Pearl

Add glucose to all IV fluids of neonates.

Take Home Message

Avoid starving and giving drugs which are difficult to metabolise in liver.

FAQs

Q. Should all IV fluids of neonates contain glucose?
Q. Why neonates have jaundice?

GASTROINTESTINAL SYSTEM

Structural and Functional Development of Intestine

The primitive gut is formed by the cephalo-caudal and lateral folding of the embryo which causes the endoderm lined yolk sac to incorporate the embryo.[1] During the third week the primitive gut is separated from the notochord and there are two other endoderm lined cavity which remain outside the embryo, the yolk sac and the allantois.

The primitive gut forms a blind ending tube causing foregut at the cephalic end and hind gut at the caudal end. The middle part forms the midgut and this part temporarily remain connected to the yolk sac by means of vitelline duct.

The primitive gut starts from the mouth and ends at the upper end of the anus. Various organs are derived from primitive gut and their derivation is divided into four sections:

1. Pharyngeal gut is the part that starts from the oropharyngeal membrane to the respiratory diverticulum. This part contributes to the formation of head, neck and other important parts.
2. The parts after this till the liver outgrowths form the foregut. It forms the oesophagus, stomach, first part of the duodenum and second part till the liver diverticulum.
3. The midgut is from the second part of the duodenum caudal to liver bud till the right two-thirds (2/3rd) of the transverse colon. It forms the lower duodenum, jejunum, ileum, ceacum, appendix, ascending colon and first 2/3rd of transverse colon.
4. The hindgut starts from distal 1/3rd of left transverse colon. It forms lateral 1/3rd transverse colon, descending colon, rectum and upper part of anal canal.

The endoderm not only gives internal lining to the digestive tract but also forms specific cells of glands (parenchyma) like hepatocytes, exocrine and endocrine cells of pancreas, etc. The connective tissue (stroma) of the gland is derived from the visceral mesoderm. The visceral mesoderm also forms connective tissue and peritoneal components of the wall of the gut.

Each division of the gut is supplied by branches of the primitive aorta. The celiac artery formed by the

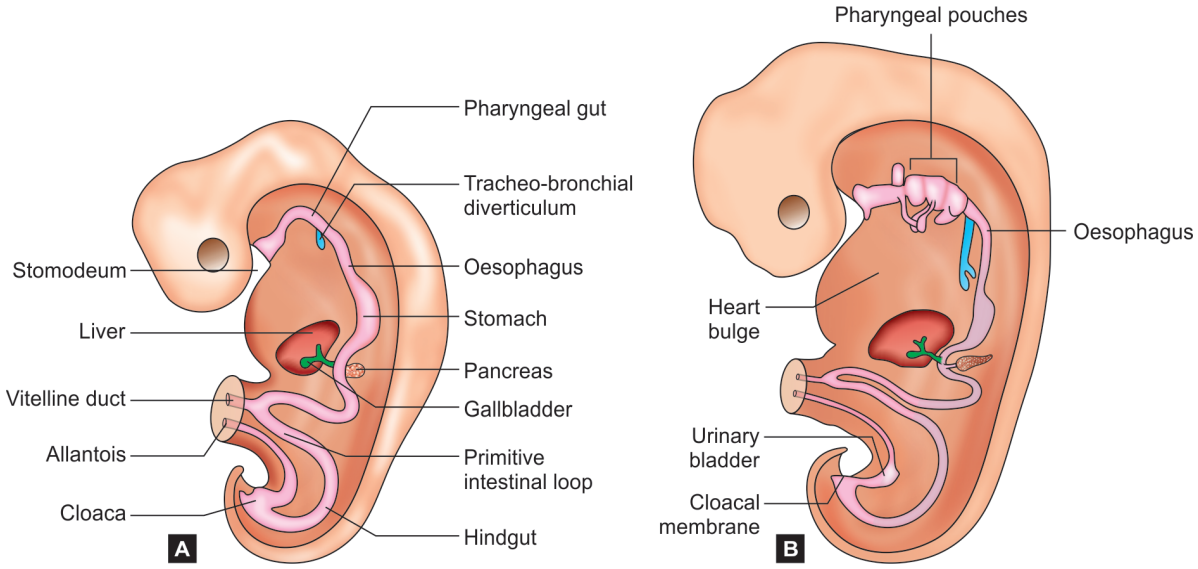

Fig. 6.10A and B (A) 4th week and **(B)** 5th week of development of GI tract along with other derivatives

fusion of paired ventral tributaries of the dorsal aorta supplies the infradiaphragmatic portion of foregut. The superior mesenteric artery supplies the midgut and inferior mesenteric artery supplies the hindgut.

There is a general histology for the gastrointestinal tract in the sequence of mucosa, sub-mucosa, muscular layer and the serosa (from inside to outside in concentric manner). These may vary at various sites for some special purpose.

The Mesenteric Origin

This is a double layer of peritoneum that suspends the gut tube and its various derivatives from the dorsal and ventral body walls. This endorses all organs and the gut and connects them to the body wall. Organs develop inside this are called intraperitoneal organs. There are something called a peritoneal ligaments which are double-layered bands that pass from organ to organ and organ to body wall. The basic intention of the mesentery and ligaments is to provide vascular, neural and lymphatic access to the abdominal viscera.

During the initial phase the mesenchyme of the posterior abdominal wall is connected to foregut, midgut and hindgut with a broad connection. Around the eight week, there is narrowing of the connective tissue bridge such that the latter part of the foregut, midgut and majority of hindgut are suspended from the abdominal wall by the dorsal mesentery.

The mesentery starts from lower end of the oesophagus to the end of hindgut and has various names in various areas, like the region of stomach forms the mesogastrium or greater omentum, the area around duodenum forms dorsal mesoduodenum the colon the dorsal mesocolon. Dorsal mesentery of the jejunum and ileum form the mesentery proper.

The ventral mesentery is not present throughout, it is present only around the terminal oesophagus, stomach, upper duodenum, these are derived from the septum transversum. The liver develops in the septum transversum and divides the ventral mesentery into lesser omentum (extents from the lower portion of the oesophagus, stomach, and upper duodenum to the liver). The falciform ligament extents from the liver to body wall.

Foregut

Oesophagus

At the 4th week of development of the embryo the respiratory diverticuli develops from the ventral part of the foregut near the pharyngeal gut. Slowly the trachea-oesophageal septum develops from the dorsal part of the foregut, thus separating the respiratory system (anteriorly) and GI system (dorsally) of the oesophagus. Initially the oesophagus is short but then it elongates as the heart and lung descends.

Stomach

Around 4th week a fusiform dilatation occurs of the foregut which develops the stomach later. Following this there is a difference in the growth of various walls of the stomach, which causes change in the shape as well as its relations to other organs.

The stomach rotates by 90° in clockwise direction around its longitudinal axis, as a result its left side faces

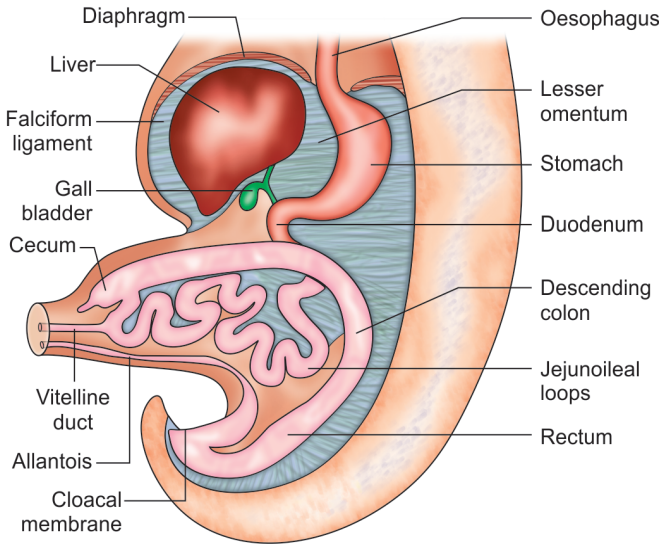

Fig. 6.11 Umbilical herniation of intestinal loops along with formation of caecum. Initially 90 degrees and then 180 degrees

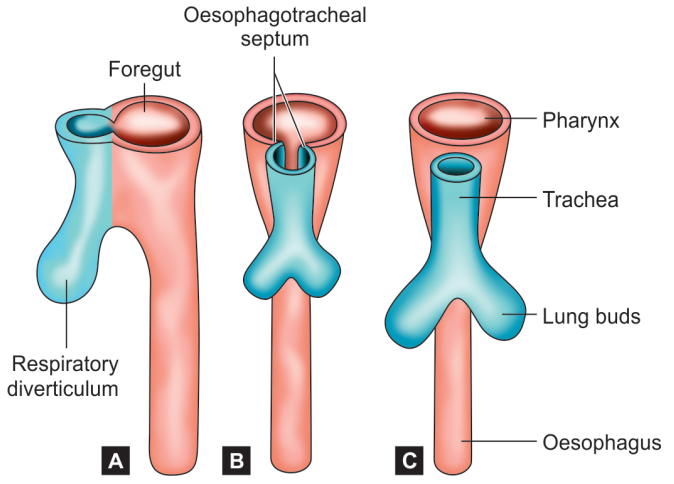

Fig. 6.12A to C Successive development (separation) of respiratory diverticulum and oesophagus from the foregut

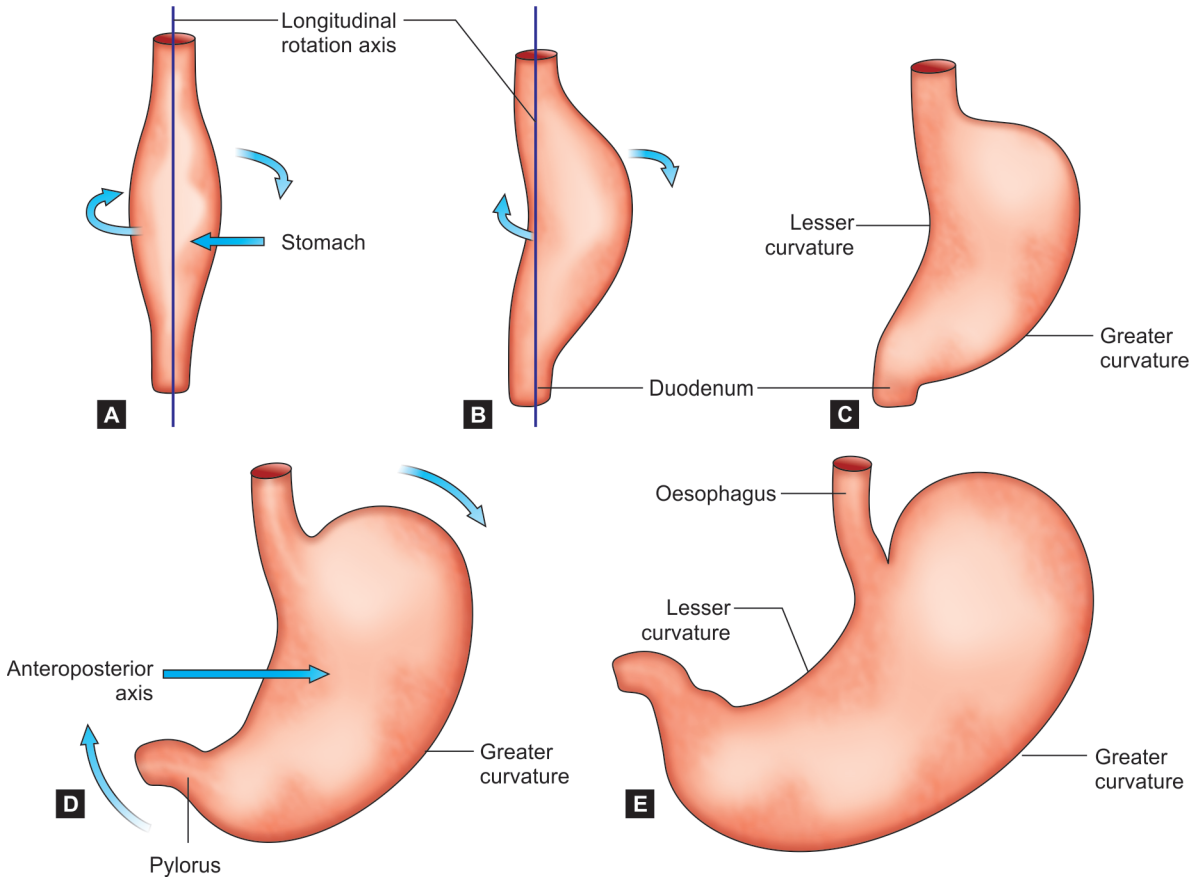

Fig. 6.13A to E Rotation of the stomach in longitudinal and anteroposterior axis

anteriorly and right side faces posteriorly. During this rotation process the original posterior wall of the stomach grows faster than the anterior portion forming greater and lesser curvature.

During the start of the development of stomach the cephalic and caudal end of the stomach are in the midline but due to asymmetrical rotation pyloric part (caudal) moves up and to the right while cardiac part (cephalic) moves to the left and slightly down, thus stomach has an axis of above left to below right.

Due to all of the above the dorsal mesogastrium bulges down and continues to grow down to forms a double layered sac extending over the transverse colon and small intestine called the greater omentum.

Duodenum

Duodenum is formed by terminal foregut and cephalic midgut, junction being the part just distal to the origin of the liver bud. As stomach rotates and shrinks, the duodenum assumes a 'C' shaped loop and rotates to the right. Along with this rotation there is also rapid growth of the head of pancreas, both these factors take the duodenum from the central portion to the right side of the abdominal cavity.

Duodenum and the head of pancreas hit against the dorsal body wall, the two peritoneums fuse with each other so that the later part of the duodenum (except the initial part near the pyloris) and the pancreass becomes retroperitoneal. Initial the duodenum has its lumen obliterated by proliferated cells, but later on its lumen is recannalised. As the duodenum has originated from both foregut and hindgut, its vascular supply is by both celiac and superior mesenteric artery.

Pancreas

The pancreas is formed by fusion of two buds, one dorsal and other ventral; both originate from the endodermal lining of the duodenum.

Dorsal pancreatic bud grows in the dorsal mesentry while the ventral pancreatic bud is near the bile duct. As discussed previously with the rotation of the duodenum and shifting to the right side, there is change

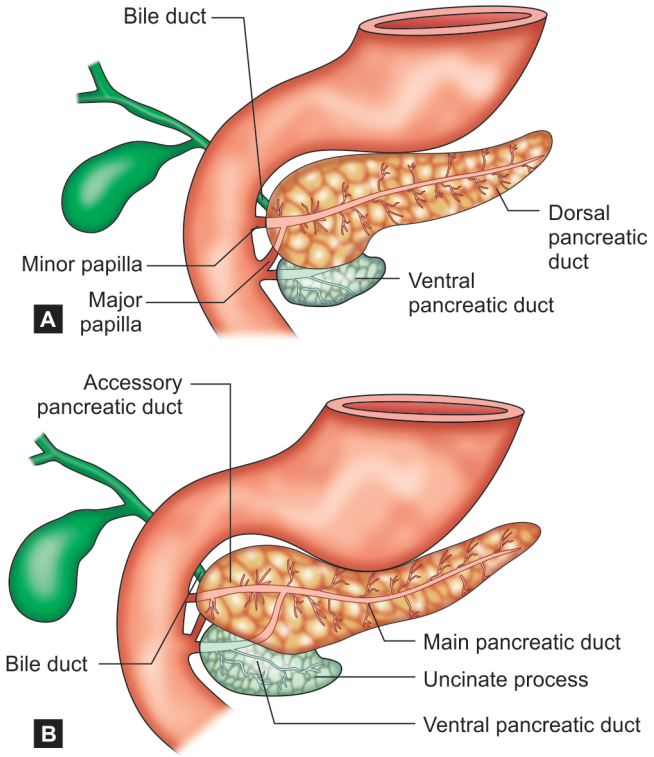

Fig. 6.14A and B Ventral and dorsal pancreatic bud placement and their duct formation

in orientation of the pancreatic ducts such that the ventral bud comes to lie dorsally and immediately below and behind the dorsal bud. Then both these buds fuse to form the parenchyma of the pancreatic tissue. The ventral bud forms the uncinate process and the inferior part of the head of the pancreas. Later the main and the accessory pancreatic duct are formed and open on major and minor papilla on the duodenum respectively.

The 3rd month of the foetal life sees the formation of the islets of the Langerhans from the parenchyma and then distribute in the pancreas. The parenchyma also gives rise to somatostatin and glucagon secreting cells. Insulin secretion starts around 5th month.

Midgut

The midgut in adults starts immediately distal to the bile duct opening into the duodenum and ends at the junction of the proximal 2/3rd and distal 1/3rd of the transverse colon. All the midgut is supplied by superior mesenteric artery as already described.

During the development around the 5th week the midgut is suspended from the dorsal abdominal wall by means of a short mesentry. The midgut at the same time also communicates with the yolk sac by means of vitelline duct or the yolk stalk at the apex. The midgut forms the primary intestine and its development is characterized by rapid elongation of the gut and its mesentries. The midgut is in open connection with the yolk sac by means of the vitelline duct at the apex. The part cephalic to this part develops into duodenum, jejunum and part of ileum, while the caudal part forms the lower ileum, caecum, appendix, ascending colon and part of the transverse colon (2/3rd proximal).

Herniation

As the intestines are developing they have the property of rapid elongation particularly of the cephalic limb. At the same time, the liver is also growing rapidly which accommodates the majority of the abdominal cavity, as a result of this the abdominal cavity becomes small and unable to accommodate all its contents. Hence temporarily all the intestinal loops enter the extra-embryonic cavity in the umbilical cord (approximately 6th week of development). This process is called physiological umbilical herniation.

Rotation of The Midgut

As the length of midgut increases, the primary intestinal loop rotates around an axis formed by superior mesenteric artery. This rotation when viewed from front is anticlockwise.

As rotation is going on, elongation of small intestinal loops continues, causing the jejunum and ileum to form a number of coiled loops. The large intestine on the other side though lengths considerably does not participate in the coiling process.

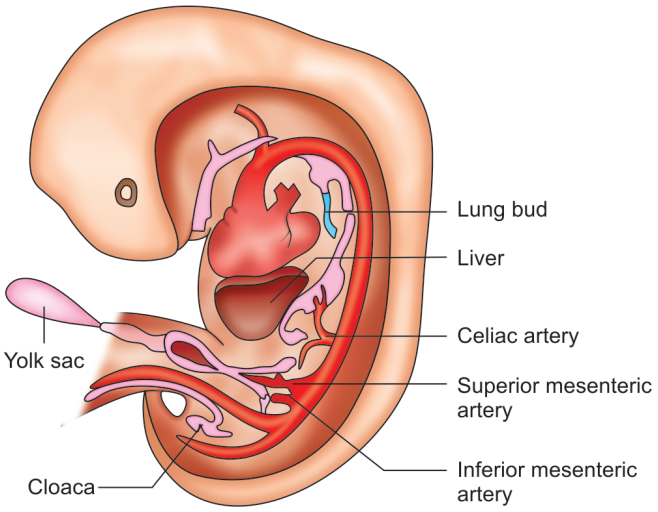

Fig. 6.15 Blood supply to the various developing GI system

Rotation occurs by around 90° during herniation and 180° during return of the intestinal loops back into the abdominal cavity causing a total of 270°.

Retraction of Herniation Loops

The loops of the intestine which have gone out slowly begin to come back to the abdominal cavity, probably due to reduction of the liver size, regression of mesonephric kidney and expansion of the abdominal cavity. The first part to re-enter the abdominal cavity is the proximal portion of the jejunum which occupies the left side. Subsequently the later loops settle more and more to the right side.

During this (6th week) a small conical dilatation of the primary intestinal loop appears which is the caecal bud. This is the last part of the gut to re-enter the abdominal cavity.

At the initial part the caecum lies just below the right lobe of the liver, but slowly then it descends down into the right iliac fossa. Thus the ascending colon and the hepatic flexure comes to lie on the right side of the abdominal cavity. During this time the narrow diverticulum grows at the end of caecal bud, which then is called the appendix. Thus the appendicular development is at the same time as the caecum descends. As a result of this the appendicular relations may change with colon or caecum (retrocaecal or retrocolic).

Mesenteries and The Loop of Intestine

With the rotation of the gut, the mesenteries having the blood supply also undergoes significant changes. With the right side shift of later loops of bowel, the mesentery also twists around the origin of the superior mesenteric artery. Later the ascending and descending colon gets plastered to the posterior abdominal wall due to the fusion of two layers of the peritoneum. The only parts which have free mesenteries are appendix, lower end of caecum and sigmoid colon. The transverse mesocolon fuses with the greater omentum and maintains its mobility. Later the mesentery of jejunoileal loops obtains a new line of attachment that extends from the region where duodenum comes intra peritoneal to the ileocecal junction.

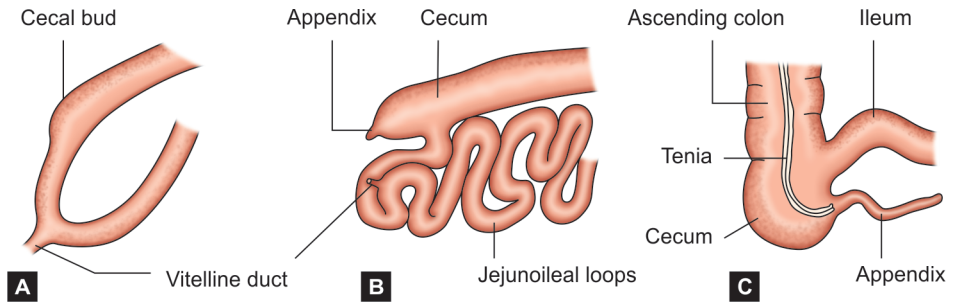

Fig. 6.16A to C Development of caecum and appendix **(A)** 7th week, **(B)** 8th week and **(C)** Newborn

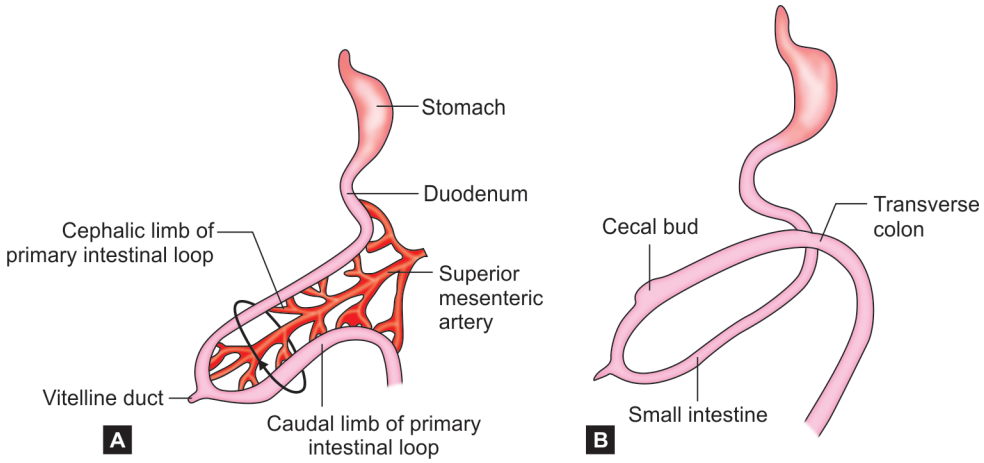

Fig. 6.17A and B Rotation of the intestinal loop along the superior mesenteric artery axis

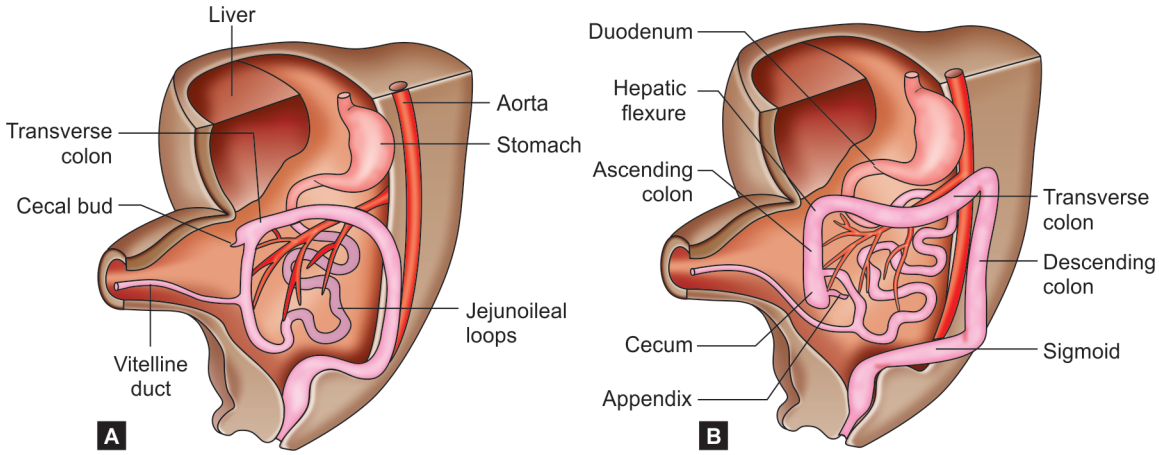

Fig. 6.18A and B Return back of intestinal loops and final position of the intestines in the abdominal cavity

Hindgut

The hindgut forms the later part of colon (distal 1/3rd of the transverse colon), descending colon and upper part of anal canal.

The hindgut in its terminal part slowly starts entering the posterior part of the cloaca that is the primitive ano-rectal canal. At the same time the allantois also enters the anterior part of the primitive uro-genital sinus. The cloaca and endodermal lined cavity is bound at its ventral part by ectoderm, this boundary is the junction of ecto and endoderm which forms the cloacal membrane. From this a mesodermal septum starts developing covering the yolk sac and the allantois, this separates the hindgut and the allantois. Slowly the urorectal septum comes to lie close to the cloacal membrane. The cloacal membrane ruptures at the seventh week creating an anal opening for hindgut and a ventral opening for urogenital sinus.

The upper 2/3rd of the anal canal is formed by hind gut (endoderm), lower 1/3rd by ectoderm, thus the anal opening is formed by the junction of ecto and endoderm (pectinate line). The blood supply of the hindgut is by superior rectal and the ectodermal part by the inferior rectal.

Physiology and Functions

The gastrointestinal system has a general histology with some changes depending on area and functional needs. There are 4 concentric layers—mucosa, submucosa, muscularis and the serosa.

The gastrointestinal tract does the function of inges-tion, digestion, selective absorption and excretion. All this start during early foetal life (8th week) and continues slowly till the 40th week. Swallowing starts in the second trimester and co-ordinated intestinal motility in the third trimester. The enzymes required to

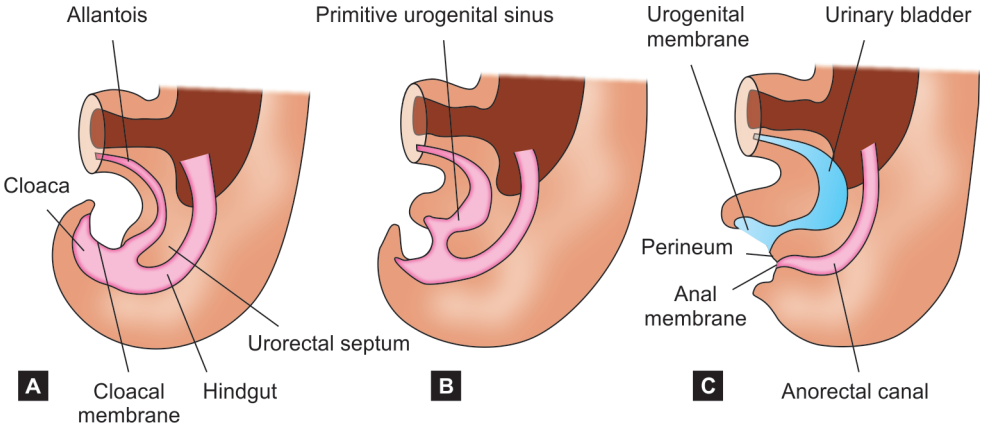

Fig. 6.19A to C Development of the anal canal and cloaca from the hindgut

digest sucrose and maltose are present early and those that digest lactose and proteins are present in the later life. The term infants GI system have a good ability to be managed only on enteral feeds, but this is compromised in cases of premature, IUGR, asphyxiated infants and babies of diabetic mothers, etc. Hence neonatal hypoglycemia is common in neonates especially in premature and hence glucose is added to all paediatric I.V. fluids. At birth the pH of stomach is acidic around 6 which then equalizes to adult levels by 3 months of age. Many normal infants exhibit discordination of swallowing and regurgitation, persistent gastro-oesophageal reflux beyond 6 weeks, this is pathological and may cause laryngospasm, paroxysmal cough, pneumonia, etc. All this is increased in prematurity.

GI Transit

The transit time through the GI tract for food and other ingested material depends on many factors.[4] About 50% of the meals in the stomach empty into intestine in an hour time and total empting takes about 2–3 hours. Subsequently 50% of the small intestine takes 1 to 2 hours to empty. Colon takes 12 to 50 hours for total transit. The gastric transit time is variable in neonates, infants and children. This is also changed by the contents (solids, liquids, etc). In unobstructed patients ½ life of clear isotonic fluids is 10–20 minutes. Pain, fear, anxiety, trauma, sepsis, narcotics all delay the empting.

Immune Function of the Gut

The GI system has very large area and with such a large area it is exposed to various pathogens which have to be prevented from entering the blood and the lymph, thus it provides a very efficient immune system.

To start with it has very low pH in the stomach which kills most of the fatal organisms. In addition the mucus has IgA antibodies which neutralize many toxins and micro-organisms. Still to help are also enzymes in saliva, bile, intestines, etc. The intestines contain bacteria which are health enhancing and these also prevent growth of potentially harmful bacteria. These bacteria breakdown the complex molecules which human body is not able to break. Gases and other wastes are made which are excreted, at the same time absorption of nutrient and water is also made. Also gut associated lymphatic tissue (GALT) provides additional protection.

Gut Anomalies

These are classified according to nature of problem:

Atresia: Interruption in lumen (oesophageal, duodenal, biliary, pyloric).

Stenosis: Narrowing of lumen (oesophagus, duodenal, pyloric).

Duplication: Multiplication due to incomplete recanalisation causing parallel lumen.

Malrotation: Rotation not completed or rotated in wrong direction due to some reason.

In neonates it presents as the bilious vomiting or the bloody stools.

In newborn there is failure to thrive due to infections, recurrent pain, diarrhoea, vomiting, later sepsis and peritonitis.

Ladd bands multiple in nature crossing the duodenum causing duodenal obstruction.

Volvulus

Twisting of the gut causing obstruction to the flow. This may also have compensation of the blood supply causing toxins to accumulate.

Foregut Malformation

Oesophageal atresia, stenosis and tracheoesophageal fistula:

They may be individual or associated with each other. All these results from either spontaneous posterior deviation of tracheoesophageal septum or may be due to the mechanical factors pushing dorsal wall of the foregut anteriorly causing unequal division of foregut into respiratory and digestive tract.

Its variants are:

1. Proximal part of esophagus forms a blind sac while the distal part is connected to the trachea by the narrow canal above the bifurcation.
2. Oesophagus has 2 blind ends with no traecheal connection (isolated atresia).
3. H-type, without oesophageal atresia.
4. Other variants where upper oesophagus is connected to trachea by narrow channel and lower end is blind.
5. Both oesophageal ends proximal are connected separately to trachea.

Oesophageal and tracheoesophageal abnormalities

These defects may be associated with other abnormalities. Tracheoesophageal fistula is a component of VACTERL association.[1]

V: Vertebral anomalies

A: Anal atresia

C: Cardiac defects

T: Tracheoesophageal fistula

E: Oesophageal atresia

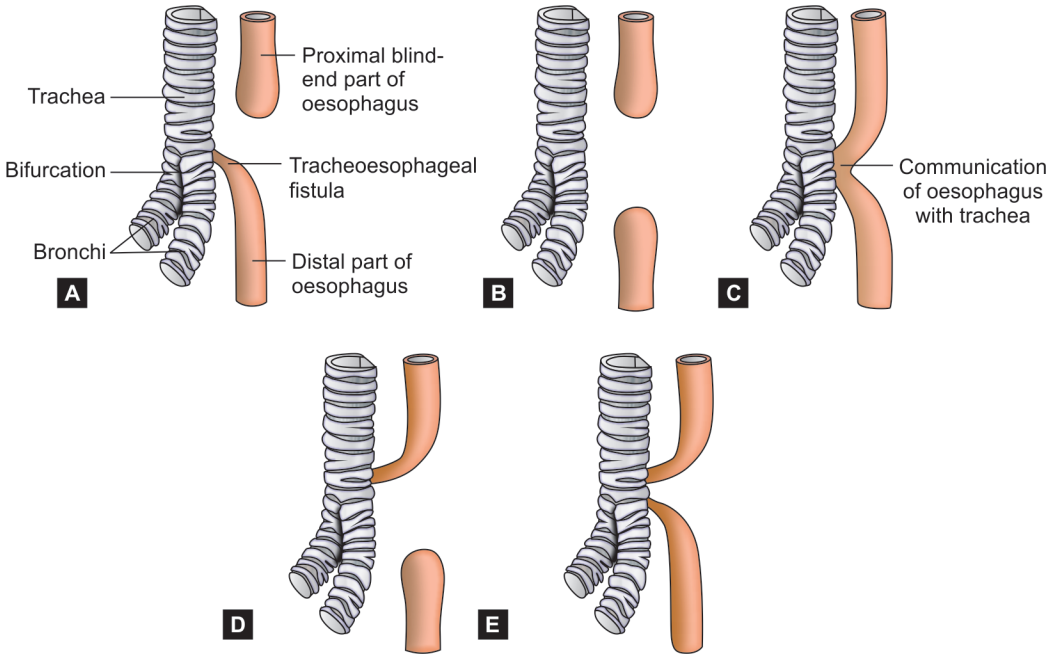

Fig. 6.20A to E Variations of oesophageal atresia and/or tracheoesophageal fistula in order of their frequency of appearance: **(A)** 90%, **(B)** 4%, **(C)** 4%, **(D)** 1% and **(E)** 1%

R: Renal anomalies

L: Limb defect

In case of atresia of oesophagus the normal passage of amniotic fluid into the intestinal tract is prevented resulting into poly hydramnious.

Sometimes lumen of the oesophagus may be narrowed, commonly in lower 1/3rd area resulting in oesophageal stenosis.

Occasionally hiatal hernia of congenital origin may be present due to insufficient lengthening of the oesophagus causing pulling up of the stomach through the diaphragmatic opening (congenital hiatal hernia).

Stomach

Pyloric stenosis is the most common of this (1:200 in males and 1:1000 in females) where the circular and longitudinal muscles of the stomach in the pyloric region hypertrophy causing delayed propulsion of the food forwards causing severe vomiting. In rare cases the pylorus may be totally atretic and rarest are stomach duplications and prepyloric septum.

Liver and Biliary System

Variations in liver lobulations are common but they are clinically not significant. Similarly variations (duplications and accessory ducts) of hepatic, common bile ducts and cystic ducts are also common. The more serious among all these (1:20000) are the malformations of the extra-hepatic biliary system in the form of atresia of the gall bladder or the bile duct. These may result due to persistence of the solid state of the duct and/or the gall bladder partly or fully. This may result in atretic gall bladder and ducts (in some cases mere cords). Sometimes atresia is limited to a part of the system (part of common bile duct), resulting in distension of the gallbladder and hepatic ducts. Clinically these manifest as increasing jaundice after birth. Duplications, partial subdivisions and diverticuli of the gall bladder are also not uncommon. Occasionally this problem occurs inside the liver causing intrahepatic biliary duct atresia and hypoplasia which is generally lethal.

Pancreas

The accessory pancreatic tissue (other than normal site) may be found anywhere from the distal oesophagus to the tip of the primary intestinal loop. Most frequent site is the wall of the stomach, duodenum, or in the Meckel's diverticulum.

Pancreatic bladder is the condition in which the ventral pancreatic bud grows out with the liver bud and forms the pancreatic nodule.

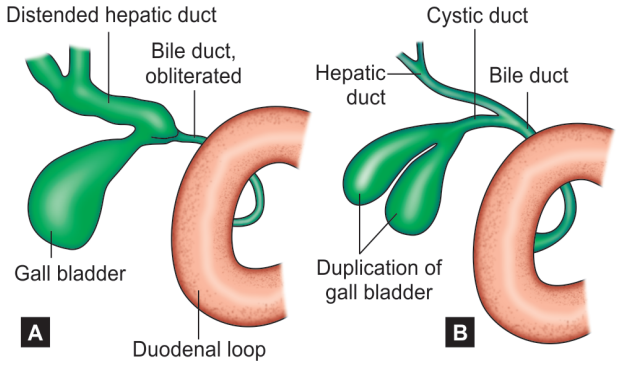

Fig. 6.21A and B Abnormalities of the gall bladder, bile, cystic and hepatic ducts

Annular pancreas is the rare malformation where the pancreatic tissue surrounds the 2nd part of the duodenum like a band. It is mostly asymptomatic but can occasionally cause obstruction due to constriction of duodenum. This is caused by growth of the bipid ventral pancreatic bud around the duodenum which fuses with the dorsal bud to form the ring.

Midgut Malformations

These malformations are common and generally caused by the abnormal digestive tube. development, abnormal and incomplete rotation and/or failure of the fixation and/or location or arrangements by itself or due to the neighbouring viscera during development. The malformations may be single or interconnected making the pathology more complex and less compatible with life.

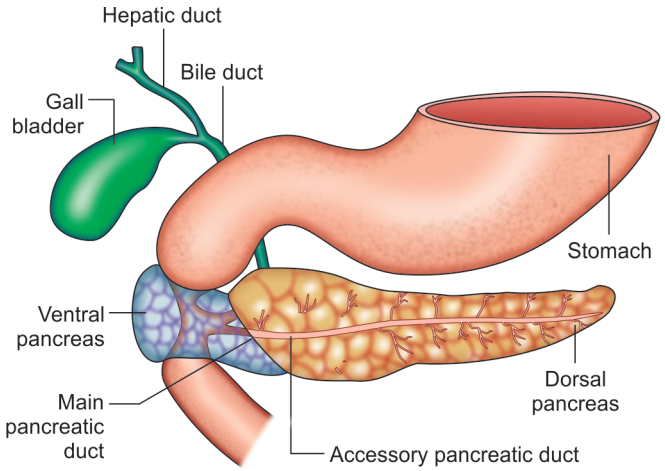

Fig. 6.22 Annular pancreas

Abnormalities of the Mesenteries

When the part of ascending mesocolon persists (mesentery connecting the abdominal wall and the colon), it gives rise to a condition called mobile caecum. In extreme conditions the entire mesentery of the ascending colon may persists due to failure of the fusion with the posterior abdominal wall leading to high chances of the volvulus of the caecum and colon due to abnormal movements. Similar reasons of the incomplete fusion of the mesentery may lead to the development of retrocolic pockets behind the ascending mesocolon causing the entrapment of the portions of the small intestine (retrocolic hernia).

Body Wall Defects

Omphalocoele (incidence 1 in 6500 births): In this there herniation of the abdominal viscera (stomach, spleen, liver, gallbladder, small and large intestine, etc.) through the enlarged umbilical ring and are covered by amnion.

This is caused by failure of the bowel to return to the body cavity from its physiological herniation during its 6th to 10th week, thus causing the abdominal visera to develop outside the embryo in the amniotic sac. Omphalocoele may be associated with severe and several cardiac and neural tube defects or may have association with chromosomal and genetic abnormalities. In rare cases there may be extrophy of the urinary bladder.

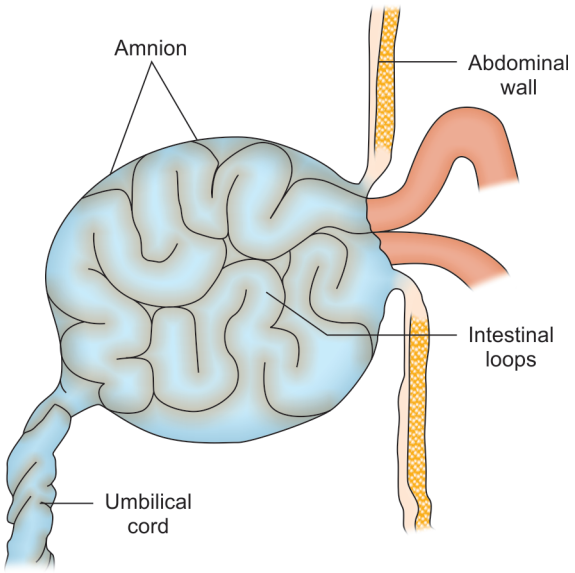

Fig. 6.23 Omphalocele

Gastrochises (Incidence 1:10000)

This is a condition where the abdominal contents protrude directly into the amniotic cavity through the defect caused by the abnormal closure of the body wall around the connecting stalk generally from the right side of the umbilicus. In this the viscera is not covered by amnion or by peritoneum, but there may be damage to the intestine as they are directly exposed to the amniotic fluid. No association is found with any chromosomal anomalies or any vital organ defects but volvulus is common due to compromised blood supply.

Vitelline Duct Abnormalities

In very minor percentage of people (2–4%) the entire or part of the vitelline duct remains patent or the band formed by the vitelline duct which connects ileum to the umbilicus (which should disappear) remains. This causes outpouching of the ileum causing a diverticuli called Meckel's diverticulum. This is generally present on the antimesentric border of the ileum 40–60 cm from the I–C junction in adults. It is generally asymptomatic but symptoms occur when the diverticuli contains gastric mucosa or the pancreatic tissue causing ulceration, bleeding or even perforation.

In some cases the vitelline duct gets converted to fibrous band or cord which connects the umbilicus to the ileum. In rare cases middle portion of this cord remains patent forming a cyst called enterocystoma or the vitelline cyst. Intestines may get strangulated, twisted or obstructed causing volvulus due to this band. In extreme cases the entire tract of the vitelline duct is patent forming a fistula called an umbilical fistula or a vitelline fistula which may discharge a faecal matter.

Gut Rotation Abnormalities

An abnormal rotation of the intestinal loop can cause twisting of the intestine which might compromise even the blood supply causing volvulus.

The normal rotation of the primary intestinal loop is 270° counterclockwise, sometimes the rotation is only by 90° resulting in colon and caecum to enter and lie on the left side of the abdominal cavity. The later returning loops settle on the right side, thus a left, sided colon is formed.

Reverse Rotation

In some cases the rotation occurs clockwise by 90°. Due to this the transverse colon passes behind the duodenum and lie behind the superior mesentery artery.

Duplication and Cyst (Overdevelopment)

The intestinal loops may duplicate anywhere along the length of the gut tube and sometimes cyst may also develop with the same (commonest site ileum). There may be associated findings like imperforate anus, gastrochises, omphalocoele, atresia, etc. Commonest cause is failure of normal recannalisation.

The cause of underdevelopment (atresia and stenosis) of the intestine may be due to lack of recannalisation and/or vascular accidents. In case of vascular accidents causing decreased blood supply either a part of the bowel is lost, remains as a fibrous band or bowel narrowing. Most common atresia occurs in duodenum, but even colon, jejunum or ileum is not excluded. Agenesis of the intestinal segment is also common but when extensive is incompatible with the life.

Mucoviscidosis is the adherence of the meconium to the intestinal wall secondary to deficiency of trysin secretion by the pancreas as a result the later being invaded by intestinal fibrosis of unknown origin.

Hindgut Malformations

This is generally caused due to problems of the urorectal septum.

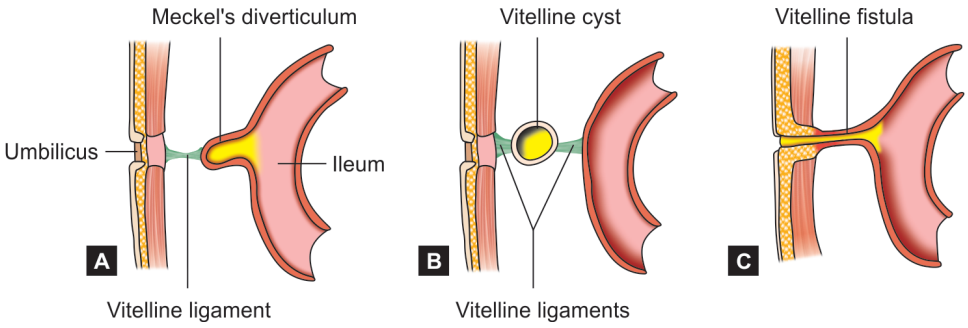

Fig. 6.24A to C Vitelline duct remnants

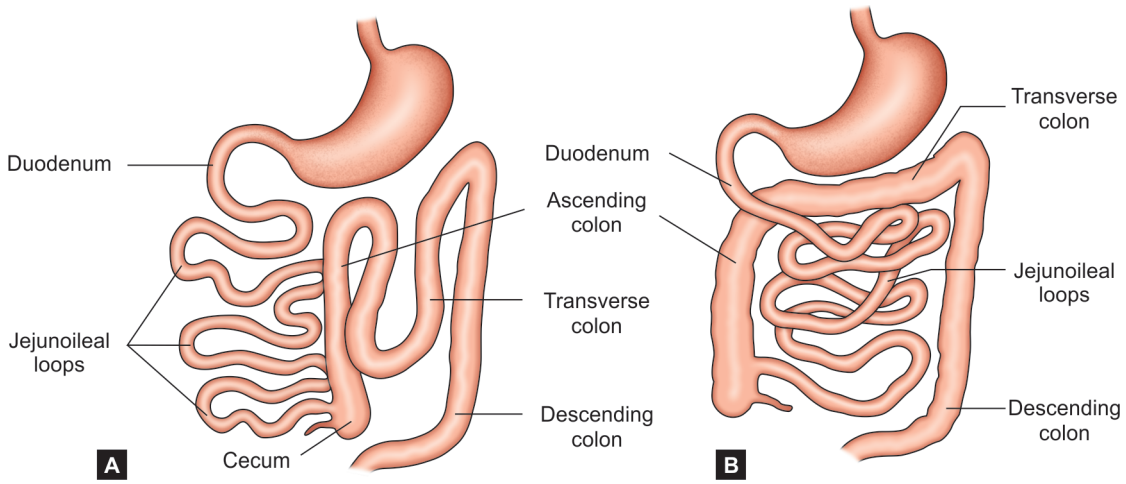

Fig. 6.25A and B Abnormal rotation of the primary intestinal loops. **(A)** Left sided colon and **(B)** Transverse colon behind the duodenum

Rectoanal atresia may be present or remain as a fibrous band. Imperforate anus may be present when the membrane fails to breakdown, this is a surgical emergency. Recto-uretral and recto-vaginal fistula are caused by abnormalities of the cloaca and urorectal septum when it is not able to extend till the end. Sometimes there may be absence of parasympathetic ganglia in the bowel wall causing a condition called **Congenital Megacolon (Hirschsprung's disease)**. It may involve rectum (common), sigmoid, transverse, right-sided colon and in rare cases the entire colon.

To concise the above in sequence:

Foetal part: Adult parts margins—organs formed—arterial supply—abnormalities.

1. **Foregut:** Oesophagus to 2nd part of duodenum — oesophagus, stomach, duodenum (1st and 2nd part), liver, gall bladder, pancreas—celiac trunk—oesophageal atresia and fistula, gastrochisis, duodenal atresia, pyloric stenosis.
2. **Midgut:** Lower duodenum to the proximal 2/3rd of the transverse colon—lower duodenum, jejunum, ileum, cecum, appendix, ascending colon and first 2/3rd of the transverse colon—superior mesenteric artery—intestinal atresia, malrotation, volvulus, Meckel's diverticulum.
3. **Hindgut:** Distal 3rd of the transverse colon to the upper part of the anal canal—last 3rd of the transverse colon, descending colon, rectum and upper part of the anal canal—inferior mesenteric artery—Hirschsprung's disease, anorectal malformations like fistula, imperforate anus.
4. **Other anomalies** of the abdominal wall and diaphragm causing abdominal wall defects, omphalocele and diaphragmatic hernia.

Key Point

Three development guts form the adult gut foregut, midgut and hindgut.

Must Remember Fact

Gastric empting is delayed in neonates in stress, pain trauma sepsis.

Take Home Message

Look out for other system abnormalities if one finds some GI system congenital abnormality.

SUMMARY

The endoderm forms the epithelial lining and the parenchymal derivatives of the digestive system. The gut extends from oropharynx to the cloacal membrane and is divided into pharyngeal gut, foregut (esophagus, tracheal bud, stomach duodenum till the bile duct origin, liver, pancreas), midgut (distal duodenum, jejunum, ilium, ascending colon, right 2/3rd of the transverse colon), hindgut (distal 1/3rd of the colon descending colon, sigmoid colon and upper anal canal). During development at 6th week, bowel grows rapidly and causes physiological herniation and then returns in the body by 270 degree rotation counterclockwise. Problems arise if these do not rotate completely or partially.

FAQ

Q. Does polyhydramnios in the antenatal period signify something?

ENDOCRINE SYSTEM

Consists of thyroid, parathyroid, pancreas, pituitary, adrenal, thymus.

Pituitary gland

It develops from two different parts:

1. An ectodermal outpocketing of the stomodium which is immediately in front of the oropharyngeal membrane called the Rathke's pouch.
2. A downward extension of the diencephlon, the infundibulum.

During the 3rd week of gestation the Rathke's pouch appear as an evagination from the oral cavity. Slowly it grows towards the infundibulam and then lose its contact with the oral cavity and come to lie anterior to the infunibulum.

Then later the cells of the Rathke's pouch in the anterior part divide rapidly to form anterior part of adenohypophysis. A small part of this pouch grows along the stalk of infundibulum to form pars tuburalis (stalk). The posterior part forms the pars intermedia. The infundibulum forms the stalk and the posterior lobe called the pars nervosa (neurological).

Congenital Defect

Sometimes Rathke's pouch persists in the roof of pharynx. These may give rise to cranio pharyngioma.

Congenital absence of pituitary gland is possible causing neonatal death.

Suprarenal Gland

The development of the suprarenal gland starts in the 5th week of gestation. The suprarenal gland is made of two parts.

- Cortex: Mesodermal origin
- Medulla: Ectodermal origin

During development the mesothelial cells which lie between the developing gonads and the roof of the mesentery start to divide and proliferate at the same time.[1] They also penetrate the underlying mesenchyme. These then differentiate in cells forming foetal cortex which is composed of large acidophilic organs. After that another set of cells which are smaller in size than the initial cells penetrate the mesenchyme from the mesothelial tissue. These cells surround the initial cells and later form the definitive cortex. After birth the foetal cortex regresses rapidly except for the outermost layer which forms the reticular zone. The adult type of cortex is only achieved at the puberty. During the cortex formation in the foetal life, cells of the sympathetic system origin invade in the medial part and gets arranged in cords and clusters which forms the medulla of the suprarenal gland.

Abnormalities

Adrenals may be absent or ectopic.

Thyroid

Thyroid gland develops as an epithelial proliferating growth from the floor of the pharynx between the tuberculum impar and the foramen ceacum. It then descends in front of the pharynx but at the same time remains connected to the tongue by the stalk called the **Thyroglossal Duct**. Over a period of time the gland losses its connection with the tongue as the duct disappears. The gland still goes downwards and passes the hyoid bone and laryngeal cartilages where it takes the final position (7th week) as a bilobed structure. The thyroid starts functioning in the third month when the follicular cells produce thyroxine and tri-iodothyronine. Parafollicular or C cells are derived from ultimo-branchial body which causes secretion of the calcitonin.

Abnormalities

Congenital hypothyroidism may be seen in thyroid dysgenesis. Thyroid dyshormonogenesis is also not uncommon (Pendral syndrome). Abnormal thyroid tissue may be present along the descent of the thyroid path, but commonest site is at the base of the tongue. The thyroglossal duct may remain in some (part, fully or partly) along the the path, sometimes even forming

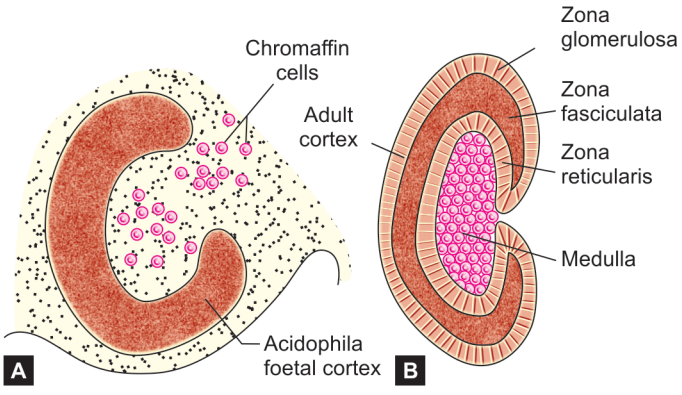

Fig. 6.26A and B Suprarenal gland formation

a cyst (thyroglossal cyst). Characteristics of this is that it is always in midline, and the most common sites is near the hyoid bone and at the base of the tongue. In occasional cases the cyst may communicate with outside causing thyroglossal fistula.

Parathyroid and Thymus Glands

These are paired bodies, one superior and one inferior, both on dorsal surface of the thyroid gland.

The 5th week witnesses the formation of the inferior parathyroid glands which arise from the dorsal region of the 3rd pouch (the ventral region forms the thymus). Both these start moving caudally and lose contact with pharyngeal wall. Actually the thymus pulls the parathyroid glands with it. Later the thymus enters the thoracic cavity and fuses with its part from opposite side completing the gland.[1] During this the parathyroid tissue of the 3rd pouch comes to rest on the dorsal surface of the thyroid gland, then labeled as inferior gland.

The dorsal surface of the 4th pouch forms the superior parathyroid gland. As the development proceeds the parathyroid tissue of the 4th pouch losses its contact with the pharynx and gets rested on the dorsal surface of the thyroid gland then labeled as superior parathyroid glands.

Abnormalities

Congenital absence of the parathyroid gland is not uncommon. There may be migration of the glands along the path of development. The inferior glands are more variable in position than the superior ones and are sometimes found at the bifurcation of the common carotid artery.

Endocrine disorders may be divided into three groups:

- Endocrine gland hyposecretion.
- Endocrine gland hypersecretion
- Tumors of endocrine glands (benign and malignant)

Congenital hypothyroidism (1 in 4000 newborn infants): It can occur due to the anatomic defect in the gland, iodine deficiency or inborn error of thyroid metabolism.

It is a condition of thyroid hormone deficiency since birth and is twice more common in females than in males.

Genetic causes like mutations in DUOX2, TSHR, TPO, TSHB, TG, PAX8, SLC5A5 in genes can cause congenital hypothyroidism.

Congenital hypothyroidism if not treated after birth can lead to growth retardation and intellectual disability of permanent nature. Decreased serum thyroid levels and increased thyroid stimulating hormone levels are the main stay for diagnosis of primary hypothyroidism. All of the developed countries screen the newborns for congenital hypothyroidism in the early weeks of life to prevent the permanent damage. The treatment consists of daily oral thyroxine.

Congenital Hyperthyroidism

It is very uncommon condition, hence details are not known properly but the course and treatment is the same as the adults.

Congenital Adrenal Hyperplasia

This results from the mutations of genes for enzymes mediating the biochemical steps for production of cortisol from cholesterol from adrenal glands (autosomal recessive). There is mutation of genes due to 21-OH deficiencies (found on 6p21.3 a part of HLA complex) which produces active and inactive genes. Mutants are formed due to gene conversion or recombination between the active and inactive genes. These cause hypo or hyper secretion of sex steroids causing alteration in the development of primary or secondary sex characters in infants and children.

Treatment consists of supplying the necessary glucocorticoids and mineralo corticoids according to the need.

Congenital Adrenal Hypoplasia

It is rare as compared to hyperplasia though some cases were found in Japan.

Congenital Diabetes

It is an extremely rare condition and very little is known about its pathogenesis.

Type 1 Diabetes Mellitus

It is a condition in which there is an organ-specific T-cell mediated autoimmune condition where there is cellular inflammation of the pancreatic islets and destruction of insulin producing beta cells.

Parathyroid Diseases

Hyper or Hypoparathyroidism

Congenital hypoparathyroidism is a condition where the babies are born without parathyroid tissue causing calcium deficiencies resulting in fragile bones and

developmental problems. Treatment consists of calcium supplementation.

Congenital hyperparathyroidism is secondary to maternal hypoparathyroidism.

Pituitary Gland

Congenital absence of pituitary gland may be present but will result in death in neonatal period.

SUMMARY

Pitutary develops from ectodermal outpouching (Rathke's pouch and extension of the diencephalon). Thyroid develops from epithelium from the floor of the pharynx. Parathyroid develops from 3rd and 4th pharyngeal pouch floor. Development problems occur if there is a remnant part at abnormal sites.

Pearl

Thyroid function in a newborn becomes important.

FAQ with Answer

Q. Why does thyroglossal cyst occur?

A. Thyroglossal cysts (TGCs) arise from a persistent epithelial tract, the thyroglossal duct, formed with the descent of the thyroid from the foramen caecum to its final position in the front of the neck.

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7

Essentials of Fluids, Electrolytes and Nutrition in Infants and Children

Mahesh Baldwa, Varsha Gupta and Sushila Baldwa

INTRODUCTION

Factors which determine the overall water weight of a human being include sex, age, bones, muscles and body fat percentage. Infants, have low bone mass and low body fat, are 73% water. Due to the high concentration of water, an infant's skin appears "dewy" and soft. Total body water (TBW) slowly becomes less after infancy, and by the time one becomes old age, total body water is only about 45%.[1] Adipose (fat) tissue is the least hydrated tissue in the body (20% hydrated), even bone contains more water compared to fat. By now skeletal muscle contains 75% water.

NORMAL PHYSIOLOGY AND ANATOMY OF THE BODY FLUIDS FOR PAEDIATRIC ANAESTHETIST (PA)

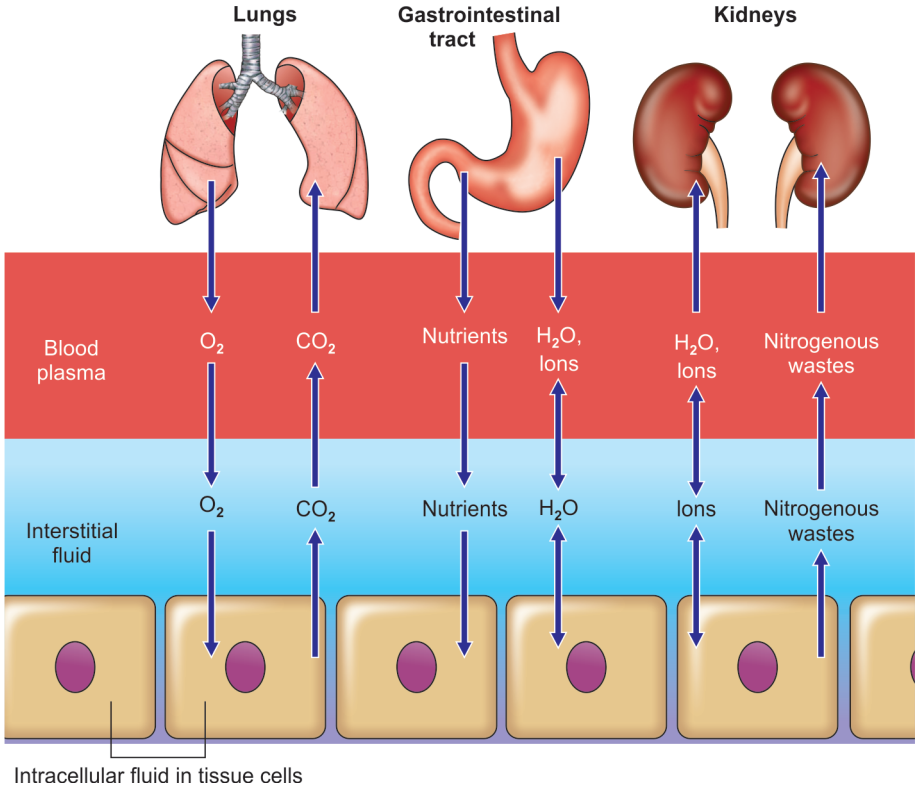
Why Compartments are known as Compartments?

Water constitutes and holds major percentage in each compartment as compared to colloids and crystalloid. Water acts as medium to carry colloids and crystalloid across the semi-permeable membrane. Each compartment operates independently, but interacts with neighboring compartments partitioned by semi-permeable membrane. Each compartment has unique colloid, electrolyte and water level and maintains the mean level by homeostatic mechanism. Only water moves depending on the concentration of crystalloids and collides across semi-permeable membrane of each compartment. Sometime false compartment are created by accumulation of fluids, blood within ventricles of brain, pleura of lungs or peritoneum and lumen of organs like intestine, etc. This fluid can be drained. This may be blood, pus, transudate or exudates. One has to keep in mind hidden nature of such compartments.

a. **Fluid compartments:** There are two main fluid compartments water occupies in the body. About two-thirds (2/3) is in the intracellular fluid (ICF) compartment. The intracellular fluid is the fluid within the cells of the body and is entirely enclosed by cell membranes. The remaining one-third of body water is outside cells, in the extracellular fluid compartment (ECF). The ECF is the body's internal environment and the cells external environment.[2] The ECF includes the interstitial fluid and the plasma. Exchange occurs between the ECF and ICF due to the permeability of cell membranes, but the two fluid compartments retain their distinctive characteristics. Although the ECF and ICF differ in terms of their ionic composition, osmolarities are same and no movement of water occurs between the two compartments. Alterations in the osmolarity of either compartment results in water/fluid shifts that eliminate the differences.[3]

b. **Three fluid compartments of the body:** There is exchange of gases, nutrients, water, and wastes between three above mentioned fluid compartments of the body. In the image below, the ECF compartment is divisible in two compartments: (1) Plasma, the fluid portion of blood which is 10% of TBW, and (2) interstitial fluid (IF) which is 3–4% of TBW, the fluid in the spaces between tissue cells.

Water losses are balanced by gains from eating, drinking, and metabolic generation of water.



FOUR BASIC PHYSIOLOGICAL PRINCIPLES AND SIMPLE PRINCIPLES IN THE REGULATION OF FLUIDS AND ELECTROLYTES APPLICABLE TO CHILDREN

1. **Homeostatic mechanisms fluids respond to changes in the ECF and not to ICF:** Receptors monitoring the composition of two basic components of the ECF—plasma and cerebrospinal fluid—detect significant changes in their composition or volume and trigger appropriate neural and endocrine releases. This makes functional sense, because a change in one ECF component will spread message rapidly throughout the extracellular compartment and affecting entire mass body's cells. In the striking contrast, the ICF is contained bound within individual cells that are physically and chemically isolated from one another by their cell membranes. Thus, changes in the ICF in one cell have no direct effect on the composition of the ICF in distant and far off cells and tissues, unless these changes create effect in ECF. So changes in ECF are key to homeostatic mechanisms.[4]
2. **No provision of receptors which can directly monitor fluid or electrolyte balance in body.** In other words, body receptors cannot detect how many litres of water or how many grams of sodium, chloride and potassium is contained in the body. Body has no mechanism to measure how many litres of water and how many grams of electrolytes body gains or losses during 24 hours. But body receptors *can* monitor *plasma volume* and *osmotic concentration*. This is because fluid continuously circulates between interstitial fluid and plasma in ECF. This is also true that there is continuous process of exchange between the ECF and the ICF, the plasma volume and osmotic concentration are good indicators of the state of fluid balance and electrolyte balance in body.[4]
3. **Principle of "water follows salt" and cells cannot move water molecules by active transport.** Normally movement of water across cell membranes and epithelia occurs passively. The principle is "*water follows salt*." Osmotic as well as oncotic gradients are generated by the active transport of specific ions, such as sodium and chloride etc. In body sodium and chloride ions (or other solutes) are actively transported across a membrane or epithelium, water follows the rule of osmosis. The principle is "*water follows salt*", accounts for water absorption by digestive system. The principle is

"*water follows salt*" also happens in kidney leading to conservation of water in the kidneys.[4]

4. **The body's content of water or electrolytes will rise if dietary gains exceed losses to the environment, and will fall if losses exceed gains.** This basic rule is important when one considers the mechanics of fluid balance and electrolyte balance. Homeostatic adjustments mainly affect the balance between urinary excretion and gut absorption. The physiological adjustments in renal function are regulated primarily by circulating hormones like aldosterone, antinatriuretic hormone, antidiuretic hormone. These hormones can also produce complementary changes in actual behavior of child. The combination of angiotensin II and aldosterone can give child a sensation of thirst, which stimulates child to drink fluids and develops a taste for salted foods.[4]

The Primary Regulatory Hormones

Major physiological adjustments affecting fluid balance and electrolyte balance are mediated by three hormones: (1) *antidiuretic hormone (ADH)*, (2) *aldosterone*, and (3) the *atrial natriuretic peptides (ANP)* and *brain natriuretic peptide (BNP)*.[4]

Antidiuretic hormone

The hypothalamus contains special cells known as **osmoreceptors**, which monitor the osmotic concentration of the ECF. These cells are sensitive to at least 2 percent change in osmotic concentration (approximately 6 mOsm/L). The rate of ADH release varies directly with osmotic concentration: The higher the osmotic concentration, more ADH is produced. Increased ADH has two important effects: (1) It stimulates water conservation from kidneys, reducing urinary water losses and concentrating the urine; and (2) It stimulates the thirst centre, promoting the intake of fluids.[4]

Aldosterone

The secretion of aldosterone by the adrenal cortex plays a major role in determining the rate of Na^+ absorption and K^+ loss along the distal convoluted tubule (DCT) and collecting system of the kidneys. The higher the plasma concentration of aldosterone, the more efficiently the kidneys conserve Na^+. Because "water follows salt," the conserved Na^+ stimulates water retention: As Na^+ is reabsorbed, and as sodium and chloride ions move out of the tubular fluid, water follows by osmosis. Aldosterone also increases the sensitivity of salt receptors on the tongue promoting consumption of salty foods. Aldosterone is secreted in response to rising K^+ or falling Na^+ levels in the blood reaching the adrenal cortex, or in response to the activation of the renin–angiotensin system. Renin release occurs in response to: (1) a drop in plasma volume or blood pressure at the juxtaglomerular apparatus of the nephron, (2) a decline in filtrate osmotic concentration at the DCT, or, as we will soon see, (3) falling Na^+ or rising K^+ concentrations in the renal circulation.[4]

Natriuretic peptides

The natriuretic peptides ANP and BNP are released by cardiac muscle cells in response to abnormal stretching of the heart walls, leads to elevated blood pressure or an increase in blood volume. This reduces thirst and block the release of ADH and aldosterone that might otherwise lead to the conservation of water and salt. The resulting diuresis (fluid loss at the kidneys) lowers both blood pressure and plasma volume, eliminating the source of the stimulation.

Fluid Shifts

A rapid water movement between the ECF and the ICF in response to an osmotic gradient is called a **fluid shift**. Fluid shifts rapidly happens in response to changes in the osmotic concentration of the ECF and reach equilibrium within minutes to hours.

1. **If the osmotic concentration of the ECF increases, fluid will become hypertonic as compared to the ICF.** Water will move from cells to the ECF until osmotic equilibrium restored. Osmotic concentration of the ECF will increase if one loses water but retain electrolytes.[5]
2. **If the osmotic concentration of the ECF decreases, that fluid will become hypotonic with respect to the ICF.** Water moves from the ECF to cells, hence ICF volume increases. Osmotic concentration of ECF will decrease if one gains water but does not gain electrolytes.[5]
3. **In sum, if the osmotic concentrations of the ECF changes, a fluid shift between the ICF and ECF will tend to oppose the change.** Because the volume of the ICF is much greater than that of the ECF, the ICF acts as water reserve. In effect, instead of a large change in the osmotic concentration of the ECF, smaller changes occur in both the ECF and ICF.[5]

Physiology of Major Electrolytes

Two cations, Na^+ and K^+, merit particular attention, because—(1) they are major contributors to the osmotic

concentrations of the ECF and the ICF, respectively, and (2) they directly affect the normal functioning of all cells. Sodium is the dominant cation in the ECF. More than 90 percent of the osmotic concentration of the ECF results from the presence of sodium salts, mainly sodium chloride (NaCl) and sodium bicarbonate ($NaHCO_3$), so changes in the osmotic concentration of body fluids generally reflect changes in Na^+ concentration. Normal Na^+ concentrations in the ECF average about 140 mEq/L, versus 10 mEq/L or less in the ICF. Potassium is the dominant cation in the ICF, where concentrations reach 160 mEq/L. Extracellular K^+ concentrations are generally very low, from 3.8 to 5.0 mEq/L.[6]

RENAL FUNCTIONS IN CHILDREN

Children have immature renal function at birth with reduced GFR by 25% of adult level. Hence concentrating capacity of newborn kidney for term infant is maximum 600–700 mOsm/kg as compared to adult kidney with maximum concentrating ability of 1200 mOsm/kg.[7] By four to five days of age in neonate there is a marked improvement in renal function, and the ability to conserve fluid and excrete an overload. After one month the kidney is approximately 60% mature even though GFR remains low. Fluid and sodium conservation is limited in newborns and infants, while excretion of water and electrolytes is possible even in premature infants. Tubular function is especially limited for special excretion and re-absorption mechanisms. Prematures have limited ability to reabsorb sodium, and will therefore become hyponatremic without adequate replacement. The thresholds for glucose and sodium bicarbonate are lower than in adults. Hyperglycemia may lead to osmolar diuresis with consequent deficits in water and sodium. By 18 months of age renal function is completely matured.

ECF and ICF in Children

The major difference between infants and adults is the fact that 40% of body water in newborns is extracellular fluid (ECF), while in adults, the ECF is 20%. This extracellular water is in the interstitial fluid volume, while plasma volume is proportionate at all ages. The high percentage of ECF causes a high turnover of water and electrolytes, especially sodium. A newborn child may lose 10% of its body weight if it drinks nothing for a day. Hence there has been a change in the recommended time for patients to be fasted. Fat and milk slow gastric emptying time, hence avoided preoperatively. For infants younger than one year, milk should be given up to 6 hours before surgery, and clear liquids up to 3 hours.

FLUID AND ELECTROLYTE HOMEOSTATIC MECHANISMS

1. Homeostatic mechanisms that monitor and adjust the composition of body fluids respond to changes in the ECF, not the ICF. Maintenance of normal fluid volume, composition, and pH in the ICF and ECF occurs due to three integrated processes:
   - fluid balance
   - electrolyte balance
   - acid-base balance.
2. There are receptors which are sensitive to changes in the composition of the plasma and thus give proper homeostatic signal.
3. The body content of water or electrolytes will rise if intake exceeds by dietary absorption and no corresponding physiological increase in outflow through urinary excretion.
4. Three hormones are involved in the regulation of fluid and electrolyte balance are
   - Antidiuretic hormone (ADH): ADH encourages water resorption at the kidneys and creates a desire to drink water.
   - Aldosterone: Aldosterone increases the rates of sodium resorption at the kidneys.
   - Antinatriuretic (ANF): ANF opposes these actions and promotes fluid and electrolyte losses in the urine.
5. Increase in water content without electrolytes will lower the osmolarities of the ECF and ICF.
6. Losing water without electrolytes will increase the osmolarities of both compartments. ADH secretion plays key role in both situations by regulating water intake and loss.

Electrolyte Balance

Sodium Ion Regulation

The rate of sodium absorption by intestine is directly proportional to sodium intake from diet. Sodium losses chiefly occur through urine and perspiration. Sodium filtered by GFR is reabsorbed by distal convoluted tubules and collecting segments of kidney with the help of circulating aldosterone. Sodium re-absorption is tied to absorption of a corresponding anion, which is usually chloride and/or bicarbonate, and the secretion of either

hydrogen in exchange of potassium ions. Changes in the rates of sodium uptake or excretion do not alter the sodium concentration of the ECF with help of osmotic movement of water. The volume excess changes in total fluid are regulated by the secretion of ADH and aldosterone and ANF. Identical homeostatic adjustments occur in response to volume depletion caused by blood or tissue fluid losses.

Potassium Ion Regulation

Potassium ion concentrations in the ECF are very low, and they are not as closely regulated by body. Potassium excretion increases as ECF concentrations rise, under aldosterone stimulation, and if pH rises. Potassium retention occurs when the pH falls.[3]

Calcium Ion Regulation

Total serum calcium levels in term infants decline from values of 10–11 mg/dL at birth to 7.5–8.5 mg/dL over the first 2–3 days of life. Approximately 50% of the total calcium biologically available is in the ionized form. Calcium concentrations can be reported either in milligram per deciliter (mg/dL) or in millimolar units (mmol/L). Conversion between the two methods is accomplished by dividing by 4 (e.g. 4 mg/dL of ionized calcium equal to 1 mmol/L). It is regulated by vitamin D, parathormone.

ACID–BASE BALANCE

A neutral solution contains hydrogen and hydroxyl ions in equal concentrations. The pH represents the negative log of the hydrogen ion concentration, and it ranges from 0 to 14. Acids dissociate in water and release hydrogen ions. Bases remove hydrogen ions or introduce hydroxyl ions. Salts dissociate with a little change on hydrogen or hydroxyl ion concentrations. Acids and bases may be categorized as strong or weak depending on their behavior building H ion concentration in solution. Normal body pH ranges from 7.35 to 7.45.Variations outside of this relatively narrow zone produce acidosis or alkalosis.[4]

The Maintenance of Normal pH

Disturbances to pH homeostasis are from ketoacidosis and lactic acid. The regulation of pH occurs through the bicarbonate buffer system operates in ECF. It removes hydrogen ions to stabilize pH. Pulmonary carbon dioxide is a volatile acid because it readily diffuses out of solution into the alveolar air of lungs. The loss of carbon dioxide at the lungs lowers the concentrations of hydrogen ions and bicarbonates in solution. Increase and decrease of the rate of respiration thus has a direct effect on pH. Renal mechanisms operate through kidneys vary their rates of hydrogen ion secretion and bicarbonate ion resorption depending on the pH of the extracellular fluids. In acidosis the rates of H^+ secretion and bicarbonate ion reabsorption and generation increase. Phosphate in ECF and protein buffer systems in both ECF and ICF are less important and less amenable to correction to paediatric anaesthetist. Any deviation from the normal range is extremely dangerous, because changes in H^+ concentrations disrupt the stability of cell membranes, altering structure of proteins, and activities of important enzymes.[4]

Disturbances in Acid–Base Balance

Respiratory acidosis results from the excessive accumulation of carbon dioxide in body fluids. The common cause is hypoventilation, which gets corrected by chemoreceptor reflexes. In the absence of usual homeostatic mechanisms, acute respiratory acidosis develops. Respiratory alkalosis is an uncommon condition associated with hyperventilation. Metabolic acidosis due to lactic acidosis or ketoacidosis results from any condition that depletes the normal reserves of bicarbonate ions. This can result from a loss of bicarbonate ions or their utilization in neutralizing of lactic acid and keto acids. The most frequent cause of metabolic acidosis is an inability to excrete hydrogen ions at the kidneys. It can also result from the bicarbonate loss by intestine in cases of chronic diarrhoea. Metabolic alkalosis occurs when bicarbonate ion concentrations become elevated. In rare cases it may occur following extended periods of vomiting where gastric HCL acid is lost.[4]

Fluid Balance and Fluid Administration

Total body water content is comparatively large in neonates and infants with respect to adult values after the age of 1 year. As age advances the amount of muscle mass increases, intracellular water content rises. Water turnover in the infant is more than double that of an adult. In infants approximately 40% of extracellular water is lost every day as urine, stool, sweat, and insensible losses via skin and airways and lungs. Dehydration can easily follow if reduction of intake (preoperative fasting for 6 hours) or increased loss of fluids occurs (which is most commonly due to vomiting and diarrhoea).

Table 7.1 Body water and blood volume with age

	Water (%) body weight	Extracellular volume (%) body weight	Blood volume (ml/kg)
Premature	90	60	100
Term neonate	80	40–45	90
1 year	60	25–30	80
Adult	55	18	70

1. Clinical assessment of fluid balance in children is aided by recognition of situations where deficits are likely:
   a. Gastrointestinal
   b. Pre- or postoperative ileus
   c. Pre- or postoperative sepsis
   d. Burns
   e. Trauma
   f. Pre- or postoperative bleeding.
2. Hypovolaemia and dehydration or salt and water depletion are diagnosed clinically
   a. Loss of turgor of skin
   b. Sunken eyes
   c. Sunken fontanelle
   d. Capillary refill time prolonged to >2 sec
   e. Tachycardia (rule out if caused by pain, fever, anxiety)
   f. Oliguria
   g. Cool peripheries, cold limbs
   h. Increased core-peripheral temperature gap
   i. Thready fast pulse
   j. Reduced level of consciousness/sensorium or irritable or toxic looking child 'the child that is confused might not be perfused'
   k. Hypotension is a late sign; often occurs only after >30% of blood volume is lost.
3. Shock is the clinical state when demand is higher than delivery of oxygen and nutrition to the cells of body.
4. Preoperative fluids and fluid resuscitation
5. Replace circulating volume with crystalloids (0.9% saline/RL) or colloids (plasma protein solution, or dextran/starch/hemaccele solution). Blood products are given for major or ongoing losses.
6. Extracellular fluid losses are replaced with isotonic crystalloid solution, e.g. 0.9% saline, RL solution.
7. Some situations are managed according to a local institutional protocol, e.g. burns, pyloric stenosis, diabetic ketoacidosis.
8. Blood volume is estimated at 90 mL/kg in neonates, 85 mL/kg in infants and 80 mL/kg in children.
9. In shock give fluid boluses of 20 mL/kg crystalloid or colloid, then re-assess.
10. Even after 40, 60, and 80 mL/kg without stabilization (depends on the dynamics of the clinical situation and expected ongoing losses) consider endo-tracheal intubation, inotropic support, and blood products.
    a. Consider blood after 15–20% of circulating volume is lost.
    b. Consider fresh frozen plasma after 50% of circulating volume is lost after giving blood.
    c. Consider platelets after 100% of circulating volume is lost after giving plasma.
    d. Rapid laboratory testing for specific factors and selective replacement may minimize blood product administration and the associated risks and costs.

INTRAOPERATIVE FLUID ADMINISTRATION

1. Child anaesthetist is required to replace a fluid deficit if any, provide maintenance requirements and replace ongoing intra-operative losses.
2. For elective cases fluid deficits is rarely a problem. Current recommendations about fasting times are relatively short in duration and IV fluids are given to children who are not able to drink fluids. Non-elective cases come to operation theatre with a fluid deficit need extra fluids. In most cases fluids are administered during preoperative resuscitation and preoperative preparation.
3. Maintenance fluids during surgery can be given as dextrose with saline or dextrose-free crystalloid, e.g. RL or 0.9% saline. Giving 0.9% saline is preferred over other fluids expect in newborns.
   a. Dextrose containing fluids are usually unnecessary except in premature babies, neonates, and babies receiving parenteral nutrition.
   b. Hypoglycaemia rarely occurs in healthy children during anaesthesia and surgery. Children show increase in dextrose levels during the perioperative period in response to fasting and stress of surgery.
   c. IV fluids containing 5% dextrose usually cause hyperglycaemia during surgery.
   d. Dextrose containing solutions are isotonic when administered but once the dextrose is metabolized, hence rest of fluid behaves free water leading to

hypotonicity in vascular compartment, hence there is a risk of hyponatraemia. ADH is secreted during the perioperative period (stress, pain, hypovolaemia, drugs) and further reduces plasma sodium concentration and osmolarity.

e. Children develop hyponatraemia readily compared to adults make them susceptible to its effects on the CNS. It is now considered to be a major risk in the perioperative care of children.

4. Fluid losses during surgery are by and large isotonic. Losses are replaced with crystalloid or colloids or blood products.

Maintenance Fluid Regimens

Maintenance fluid at birth to 7 days.

Term babies and babies with birth weight >1500 grams

Day 1: 10% Dextrose

Day 2 to 7: 10% Dextrose and sodium and potassium to be added after 48 hours

Preterm baby weighing 1000–1500 grams

Day 1: 10% Dextrose

Day 2 to 7: 10% Dextrose and sodium and potassium to be added after 48 hours

After day 7: Fluids to be given at 150–160 ml/kg/day and sodium supplementation at 3–5 mEq/kg should continue till 32–34 weeks corrected gestational age.

1. **Neonatal regimens**
   a. *Fluid requirement during the first 5 days in the neonate:*
      i. Day 1: 60 mL/kg/day
      ii. Day 2: 90 mL/kg/day
      iii. Day 3: 120 mL/kg/day
      iv. Day 4: 150 mL/kg/day
      v. Day 5: 150 mL/kg/day.
   b. *Electrolyte requirements:*
      i. Sodium: 2–4 mmol/kg/day (in contrast to fluid requirements, this is relatively stable)
      ii. Potassium: 2–3 mmol/kg/day.
   c. *Dextrose requirements:* Usually provided using a 10% solution for maintenance. A 20% solution is occasionally required in septic or fluid restricted neonates.
2. **Infants and children**
   a. There are several formulae used to calculate maintenance fluid requirements. These are derived from the relationship between body weight and metabolic rate (energy requirements). Infants require 100 kcal/kg/day and children 75 kcal/kg/day. 1 mL of water per kcal is required for metabolism.[8]
   b. A common formula is the 4-2-1 of Holiday segar:
      i. 4 mL/kg for first 10 kg
      ii. plus: 2 mL/kg for next 10 kg
      iii. plus: 1 mL/kg thereafter.
      iv. e.g. a child of 17 kg requires 40 + 14 = 54 mL/hour; a child of 24 kg requires 40 + 20 + 4 = 64 mL/hour.
   c. Electrolyte requirements in kilogram/day:
      i. Sodium 2–4 mmol/(mili Eq)/kg/day
      ii. Potassium 2–3 mmol/(mili Eq)/kg/day
   d. Maintenance electrolyte requirements per 100 calories/day
      i. Sodium 3 mEq (mmol) per 100 kcal/day
      ii. Potassium 2 mEq (mmol) per 100 kcal/day
      iii. Chloride 2 mEq (mmol) per 100 kcal/day
3. Additional losses: Depending on their nature, losses are replaced as appropriate, e.g.:
   a. Nasogastric losses: Volume for volume with Hartmann's solution or 0.9% saline with 10 mmol KCl per 500 mL.
   b. Stoma losses: 50–75% of losses as 0.9% saline with 10 mmol KCl per 500 mL.
4. Fluids should be administered through a volumetric pump with a pressure limit set.
5. Common solutions for maintenance are:
   a. 0.45% saline/5% dextrose
   b. 0.225% sodium/5% dextrose
   c. 10% dextrose is commonly used in premature children and neonates.
6. Monitoring of electrolyte concentrations is required if maintenance fluids are given for more than 24–48 hours. The formulae used are only a guide to estimate fluid requirements. In clinical circumstances, electrolyte derangements can occur. Hyponatraemia is a particular risk and may have devastating effect on brain.
7. Some anaesthetists restrict maintenance fluids to 50–75% of the calculated requirement during the postoperative period to reduce the risk of these problems.

Choice of Resuscitation Fluid upon Cause of the Deficit

Haemorrhage

Loss of RBCs diminishes O_2-carrying capacity, safety margin of about 9 times the resting O_2 requirement. Thus, non-O_2 carrying fluids (e.g. crystalloid or colloid solutions) may be used to restore intravascular volume

in mild to moderate blood loss. However, in severe shock, blood products are required.

Crystalloid solutions for intravascular volume replenishment are typically isotonic [e.g. 0.9% saline or Ringer's lactate (RL)]. H_2O freely travels outside the vasculature, so as little as 10% of isotonic fluid remains in the intravascular space. With hypotonic fluid (e.g. 0.45% saline), even less remains in the vasculature, hence this fluid is not used for resuscitation. Both 0.9% saline and RL are equally effective; RL may be preferred in hemorrhagic shock because it somewhat minimizes acidosis and will not cause hyperchloremia. Child patient's having acute brain injury, 0.9% saline is preferred. Hypertonic saline is not recommended for resuscitation because the evidence suggests there is no difference in outcome when compared to isotonic fluids.

Colloid solutions (e.g. hydroxyethyl starch, albumin, dextrans) are also effective for volume replacement during major haemorrhage. Colloid solutions have no advantage over crystalloid and albumin is associated with poorer outcomes in traumatic brain injury. Both dextrans and hydroxyethyl starch may adversely affect coagulation when more than 1.5 L is given.

Blood typically is given as packed RBCs, which should be cross-matched, but in an urgent situation, 1 to 2 units of type O Rh-negative blood are an acceptable alternative. When >1 to 2 units are transfused (e.g. in major trauma), blood is warmed to 37°C. Patients receiving >6 units may require replacement of clotting factors with infusion of fresh frozen plasma or cryoprecipitate and platelet transfusion.

Nonhaemorrhagic hypovolemia

Isotonic crystalloid solutions are typically given for intravascular repletion during shock and hypovolemia. Colloid solutions are generally not used. Patients with dehydration and adequate circulatory volume typically have a free water deficit, and hypotonic solutions (e.g. 5% D/W 0.45% saline) are used.

Common Terminology used for Fluid and Electrolyte Balance

Salt and water depletion

Dehydration or 'salt and water depletion' or 'blood loss' or 'plasma deficit' , the term 'dehydration' strictly means lack of water, which means to laymen lack of salt and water or even more loosely to describe intravascular volume depletion. The terms 'wet' and 'dry' also have imprecise meaning.

Using specific terminologies is better like using 'salt and water depletion' due to diarrhoea and vomiting or DKA or excessive use of diuretics is better instead using words like dehydration. Clinically visualized by dry tongue, loss of skin turgor, sinking of eye balls in children. Also 'blood loss deficit' specifies the cause due to bleeding/haemorrhage, which may be overt or hidden 'plasma protein deficit' specifies the cause which is commonly due to burns or malnutrition like Kwashiorkor or diseases of liver.[10]

Salt and water excess: This is common iatrogenic reason, resulting from excessive administration of saline, but is, of course, a feature of congestive heart failure and other oedema producing conditions. It takes 40–50% (2–3 litres in adults) of salt and water excess before the extracellular fluid is expanded sufficiently for oedema to become clinically apparent.

Solution: Fluid acts as solvent, e.g. dextrose or salt is dissolved.

Crystalloid: A term used commonly to describe all clear glucose and/or salt containing fluids for intravenous use (e.g. 0.9% saline, 5% dextrose, etc.).

Colloid: A fluid consisting of microscopic particles (e.g. starch or protein) suspended in a crystalloid and used for intravascular volume expansion (e.g. 6% hydroxyethyl starch, 4% succinylated gelatin, 20% albumin, etc.).[10]

Balanced crystalloid: A crystalloid containing electrolytes in a concentration as close to plasma as possible (e.g. Ringer's lactate, etc.).

Osmosis: This describes the process by which water moves across a semi-permeable membrane (permeable to water but not to the substances in solution) from a weaker to a stronger solution until the concentration of solutes are equal on the two compartments is termed osmotic pressure or, in the case of colloids, e.g. albumin, oncotic pressure which is proportional to number of atoms/ions/molecules in solution and is expressed as mOsm/litre (osmolarity) or mOsm/kg (osmolality) of solution. In clinical chemistry the term 'osmolality' is the one most often used.[10]

For example, out of approximately 280–290 mOsm/kg in extracellular fluid the largest single contributor is sodium chloride which dissociates in solution as Na^+ and Cl^- exert osmotic pressure independently, i.e. Na^+ (140 mmol/kg), contributes 140 mOsm/kg, and Cl^- (100 mmol/kg) contributes 100 mOsm/kg. Additional balancing negative charges come from bicarbonate (HCO_3^-) and other anions. In the intracellular space K^+ is the predominant cation. Because glucose does not

dissociate in solution, each molecule, although molecule is much larger in weight and size than NaCl salt molecule, dextrose behaves as a single entity in solution and at a concentration of 5 mmol/kg, contributes only 5 mOsm/kg to the total osmolality of plasma.[11]

Partially Permeable Membranes

The cell membrane and the capillary membrane are both partially permeable membranes although not strictly semi-permeable in the chemical sense. They act, however, as partial barriers dividing the extracellular (ECF) from the intracellular fluid (ICF) space and the intravascular from the interstitial space. Osmotic or oncotic shifts occur across these membranes, affected by physiological as well as pathological processes.[10]

Hyponatremia

Hyponatremia is defined as a serum sodium level of less than 130 mEq/L. It is not a cause for alarm until the serum sodium has dropped to less than 125 mEq/L.inadequate sodium intake can contribute to the development of hyponatremia, in the extremely premature babies with increased sodium loss.

Hypernatremia

Hypernatremia is defined as a serum sodium level greater than 150 mEq/L. It is not a cause for alarm until the serum sodium level has risen to greater than 155 mEq/L. Hypernatremia is very often seen in the first few days after birth in ELBW preterm infants and most often occurs when free-water intake is inadequate to compensate for very high insensible water loss (IWL).

Hypokalemia

Hypokalemia is defined as a serum potassium level of less than 3.5 mEq/L. Unless the patient is on digoxin therapy, hypokalemia is rarely a cause for alarm until the serum potassium level is less than 3.0 mEq/L.

Hyperkalemia

Hyperkalemia is defined as a serum potassium level of greater than 6 mEq/L measured in a nonhemolyzed sample. Hyperkalemia more alarming than hypokalemia, when serum potassium levels exceed 6.5 mEq/L or alternatively electrocardiographic changes have developed showing high potassium levels. ECG of hyperkalemia shows peaked T waves, as earliest sign, worsening to widened QRS, bradycardia, tachycardia, supraventricular tachycardia (SVT), ventricular tachycardia, and ventricular fibrillation.

Hypercalcemia

Hypercalcemia is rare in neonate. it is defined as a total serum calcium concentration of higher than 11 mg/dL or an ionized calcium concentration of higher than 5 mg/dL (1.25 mmol/L).

Hypocalcemia

Hypocalcemia is defined as calcium concentration of less than 7 mg/dL or an ionized calcium concentration of less than 4 mg/dL (1 mmol/L).[4] Early onset hypocalcemia may occur within the first 3 days of life in premature infants of mothers of poorly controlled diabetes and/or perinatal asphyxia.[4] Close observation of asymptomatic infant who has calcium level of more than 6.5 mg/dL or ionized calcium more than 0.8–0.9 mmol/L, requires calcium if calcium level drops. Late onset hypocalcemia develops after the first week of life is associated with conditions with high serum phosphate levels, which is also seen in hypoparathyroidism, maternal anticonvulsant use.[9] Hypocalcemia due to vitamin D deficiency resolves with D supplementation.

Anion Gap

The difference between plasma concentration of the major cation Na^+ (135–145 mmol/L) and the major anions Cl^- (95–105 mmol/L) and HCO_3^- (22–30 mmol/L), giving a normal anion gap of 5–11 mmol/L.

- Anion gap is enlarged in metabolic acidosis due to organic acids as seen in diabetic ketoacidosis, lactic acidosis, renal failure, and ingested drugs and toxins.
- Anion gap (mmol/L) = $(Na^+) - [(Cl^-) + (HCO_3^-)]$.[10]

Normal Anion Gap

The anion gap is normal in hyperchloraemic acidosis (e.g. after excess 0.9% saline administration). It is useful differential diagnosis of metabolic acidosis.

Strong Ion Difference (SID)

Stewart has described a mathematical approach to acid–base balance in which the strong ion difference $[(Na^+) + (K^+) - (Cl^-)]$ in the body is the major determinant of the H^+ ion concentration. A decrease in the strong ion difference is associated with a metabolic acidosis, and an increase with a metabolic alkalosis.[12] A change in the chloride concentration is the major anionic contributor to the change in H^+ homeostasis. Hyperchloraemia caused by a saline infusion, which will decrease the strong ion difference and result in a metabolic acidosis.

Strong ion difference (mmol/L) = (Na^+) + (K^+) – (Cl^-), e.g. if Na^+ is 140 mmol/L, K^+ is 4 mmol/L and Cl^- is 100 mmol/L, the SID is 44 mmol/L. The normal range is 38–46 mmol/L.

Base excess: Base excess is defined as the amount of strong acid that must be added to each litre of fully oxygenated blood to return the pH to 7.40 at a temperature of 37°C and a pCO_2 of 40 mmHg (5.3 kPa). A base deficit (i.e. a negative base excess) can be correspondingly defined in terms of the amount of strong base that must be added.

Acidaemia: An increase in the H^+ ion concentration or a decrease in the pH is called acidaemia

Acidosis: Processes that tend to raise the H^+ ion concentration or decrease in the pH is called acidosis

Alkalaemia: A decrease in the H ion concentration or an increase in the pH is called alkalaemia.

Alkalosis: Processes that tend to lower the H^+ ion concentration is called alkalosis. These may be metabolic or a combination of both.

Respiratory acidosis

CO_2 retention causing a rise in pCO_2 in respiratory failure leads to respiratory acidosis.

Respiratory alkalosis

Hyperventilation with a consequent lowering of pCO_2 leads to respiratory alkalosis.

Metabolic acidosis

Accumulation of organic acids such as lactate or hydroxybutyrate or of mineral acidic ions such as chloride cause a metabolic acidosis in which arterial pH falls below 7.4, bicarbonate is reduced and pCO_2 falls as the lungs attempt to compensate by blowing out more CO_2. This is known as compensated metabolic acidosis.

Metabolic alkalosis

Ingestion of bicarbonate or loss of gastric acid in vomiting can give rise in pH and a metabolic alkalosis.

Provision of maintenance of fluid and electrolyte requirements is to provide daily physiological fluid and electrolyte requirements.

Replacement: Provide for maintenance requirements and add like for replacement for ongoing fluid and electrolyte losses (e.g. slow blood loss, intestinal fluid loss).

Resuscitation: Administration of fluid and electrolytes to restore intravascular volume (haemorrhage, hidden internal bleeding, etc.).

Warning

Large volume fluid resuscitation is often associated with excessive electrolyte administration and may have physiological consequences (e.g. hyperchloraemic acidosis) or cause complications (e.g. pulmonary oedema, acute kidney injury).[15]

MONITORING OF PARAMETERS OF SIGNIFICANCE FOR ONGOING FLUID LOSSES/EXCESS

1. History sounding new alerts.
2. Fresh vomiting/diarrhoea/haemorrhage or excess (e.g. from intra-operative fluids).
3. Newly appearing autonomic pallor of face, sweating, combined with tachycardia, hypotension and oliguria are indicative of intravascular volume deficit.
4. New blood pressure fall is compatible with intravascular hypovolaemia, particularly when it correlates with other parameters such as pulse rate, urine output, etc. Systolic pressure does not usually fall until 30% of blood volume has been lost.
5. Decreasing skin turgor due to diminished in salt and water depletion.
6. Increase in sunken eyes due to ongoing salt and water depletion.
7. Fresh signs of pulmonary oedema means fluid load
8. Fresh signs of peripheral oedema (pedal scrotal sacral) occurs in volume overload, decreasing albumin.

Parameter significance for usual monitoring

1. Urine output < 30 mL/h (< 0.5 mL/kg/h)
2. Weighing: 24 h change in weight on same weighing scale (best measure of change in water balance which takes account of insensible loss. Simple to carry out by bedside)
3. Input and output charts
4. Haematocrit: Changes in fluid balance cause increase or decrease in the concentration of red cells
5. Serum sodium: Hyponatraemia most commonly caused by water excess.
6. Serum potassium: Hypokalaemia, nearly always indicates the need for potassium supplementation confirm with flat or lowered T waves in ECG.
7. Blood bicarbonate and pH levels for acidosis and alkalosis.

8. Chloride concentrations for iatrogenic hyperchloraemia.
9. The first indication of a falling intravascular volume is a decrease in central venous pressure (CVP).
10. Arterial lines and catheters to measure plumonary artery wedge pressure are useful to help direct fluid therapy in more complex patients.
11. Albumin: Dilution by infused crystalloids is one of the main causes of hypoglbuminaemia in surgical patients.
12. Urea: The rate of increase is of greater importance.

Must Avoid Things

Postoperatively, over hydration occurs in between 17 and 54% of patients and prolongs hospital stay, increases morbidity (e.g. pulmonary oedema)[15] where possible weigh the child before operation and postoperatively to get insight about over hydration.

Must Do Things in Time

Stop intravenous fluids as soon as oral (or nasogastric) intake is possible or when the patient is haemodynamically stable, to reduce associated complications (e.g. line sepsis).

Physiological oliguria

Oliguria occurring soon after uncomplicated surgery is usually part of the normal physiological response to injury, conserving salt and water in an attempt to maintain intravascular volume. Isolated oliguria in the first 48 hours after uncomplicated surgery does not necessarily therefore reflect hypovolaemia, although it if confirmatory features of intravascular hypovolaemia are present, e.g. tachycardia, hypotension, low central venous pressure decreased capillary refill, etc. then oliguria needs to be treated.[12]

Diuretics in fluid overload and pulmonary oedema

Loop diuretics may have a very short-term role in managing fluid overload and pulmonary oedema. In these patients start with very small dose of intravenous loop diuretics cautiously to try and establish a diuresis and treat the pulmonary oedema.

DIABETIC KETOACIDOSIS (DKA), HYPERGLYCAEMIC HYPEROSMOLAR NON-KETOTIC COMA (HONK)

Represent the two extremes of the spectrum of decompensated diabetes, although intermediate cases are not infrequent, depending on the precipitating cause and the percentage loss of insulin secretion. In both situations, hyperglycaemia causes an osmotic diuresis with excessive urinary losses of salt, water, and potassium, leading to ECF and intravascular volume depletion and the risk of prerenal acute kidney injury (AKI). With both types of decompensation, potassium is lost from cells and excreted in the urine causing a deficit, which only becomes apparent as hypokalaemia once insulin treatment is started. In severe cases the rate of K^+ loss from cells, combined with pre-renal AKI, can cause hyperkalaemia (> 5.5 mmol/L) with the risk of cardiac arrest.[77]

Summary of fluid and electrolyte therapy and outcome

Intravenous fluid therapy is an integral component of perioperative care, but its practice has often been based on dogma rather than evidence, and patients have frequently received either too much or too little fluid. There is a relatively narrow margin of safety for perioperative fluid therapy and either too much or too little fluid and electrolyte (particularly sodium chloride) can have a negative effect on physiological processes, and be detrimental to outcome. The goal of perioperative intravenous fluid therapy is, therefore, to maintain tissue perfusion and cellular oxygen delivery, while at the same time keeping the patient in a state of as near neutral fluid and electrolyte balance as possible.[10]

FAQ with Answer

Q. The paediatric anaesthetic is caring for a patient with hyperkalemia. Which investigation would be most important to monitor closely?

A. Continuous ECG monitoring for tall T waves.

TOTAL PARENTERAL NUTRITION (TPN)

If child is unable to get a healthy level of nutrition by taking in food through his or her intestines, then total parenteral nutrition (TPN) is the standard therapy. With total parenteral nutrition, a solution of essential nutrients (which are proteins, fluids, electrolytes, and fat-soluble vitamins) is given intravenously. Because TPN solutions are concentrated and thick, the solutions must be given by catheters that are placed in large veins in neck, chest, or groin. An infusion pump regulates the rate at which the TPN solution is given, so that concentrate does not overload other metabolizing organs.[13] The TPN constitute the following ingredients.

Summary

The main fluid in the body is water. Total body water is 60% of body weight. Distribution of water in three main compartments separated from each other by cell membranes. The intracellular compartment (ICF) is the area within the cell. The extracellular compartment (ECF) consists of the interstitial area (between and around cells) and the inside of the blood vessels (plasma).

Compartments of body and distribution of water by weight

Plasma	5%	**Solids**	40% (fat, protein, carbohydrates and minerals)
Interstitial	15%		
Intracellular	40%		
Total water	**60%**		

Cation Distribution				Anion Distribution			
Electrolyte	*Extracellular meq/liter*	*Intracellular meq/liter*	*Function*	*Electrolyte*	*Extracellular meq/liter*	*Intracellular meq/liter*	*Function*
Sodium	142	10	Fluid balance, osmotic pressure	Chloride	105	2	Fluid balance, osmotic pressure
Potassium	5	100	Neuromuscular excitability acid–base balance	Bicarbonate	24	8	Acid-base balance
				Proteins	16	55	Osmotic pressure
Calcium	5	—	Bones, blood clotting	Phosphate	2	149	Energy storage
Magnesium	2	123	Enzymes	Sulfate	1	—	Protein metabolism
Total +ve ions	**154**	**205**		**Total –ve** ions	**154**	**205**	

Carbohydrate

IV dextrose provides most of the energy in TPN. The caloric content of aqueous glucose is 14.28 kJ/g of glucose, which is equal to 142.8 kJ/100 mL of 10% glucose. As a result of the high osmolarity of concentrated glucose solutions, the maximum glucose concentration that can be delivered safely through a peripheral vein is 12.5%. With central venous access, a glucose concentration up to 15% is often used, and in special situations (e.g. when fluids need to be restricted), a concentration of as much as 25% may be used.

A glucose infusion rate expressed in milligrams of glucose/kg/min is the most appropriate way to express glucose administration because the rate accounts for the glucose concentration and the rate of infusion.

Very small premature infants who weigh less than 1500 g demonstrate impaired glucose tolerance. For this reason, in infants weighing less than 1 kg start at an infusion rate of 6 mg/kg/min. In infants who weigh 1 to 1.5 kg, start at 8 mg/kg/min. If the glucose infusion rate is in excess, hyperglycemia develops. If blood glucose levels are greater than 150–180 mg/dL, glucosuria can occur, which can lead to osmotic diuresis. This is controlled by either decreasing the glucose infusion rate or treating the baby with insulin. Persistence of hyperglycemia may need a continuous infusion of insulin.[16] Acute increase in the blood glucose concentration when the glucose infusion rate is unchanged are often the first sign of sepsis in the preterm infant.

Fat

At least 3% of the total energy should be supplied as essential fatty acids (EFA). This can be accomplished by providing a fat emulsion (e.g. intralipid, liposyn), 0.5 g/kg/day 3 times a week. Fat emulsions provide 37.8–42 kJ/g.

Parenteral fat emulsion is usually provided as a 20% lipid emulsion made from soybeans (e.g. intralipid). Intralipid is a concentrated source of energy with a caloric density of 8.4 kJ/mL (for 20% intralipid). Lipids play a primary role in supporting gluconeogenesis in parenterally fed preterm infants.[17] Start with 0.5–1.5 g/kg/day on first day and increase to 3–3.5 g/kg/day.

Limiting intralipid infusions in infants with sepsis and severe lung disease is often recommended, although no evidence supports this practice. The use of intralipid (as well as prolonged TPN and use of central venous lines) is a risk factor for candidemia in neonates.[18]

Neonates with hyperbilirubinemia who are on phototherapy often have intralipid intake restricted to

less than 2 g/kg/day (especially if bilirubin levels are rising while the infant is on phototherapy) because some evidence suggests that a high lipid emulsion intake may decrease bilirubin binding.[19] Monitor triglyceride levels and adjust infusion rates to maintain triglyceride levels of less than 150 mg/dL.

Infants with cholestasis (increase in conjugated bilirubin >2 mg/dL) due to parenteral nutrition [parenteral nutrition–associated liver disease (PNALD)] should preferably have their intralipid infusion reduced (e.g. to 1 g/kg/day, given over 12 h). Use of lipid infusions with omega-3 fatty acids (e.g. omegaven) may reduce cholestasis.

Protein

Term babies need 1.8–2.2 g/kg/day along with adequate nonprotein energy for growth. Preterm VLBW babies need 3–3.5 g/kg/day along with adequate nonprotein energy for growth. Providing more than 4 g/kg/day of protein is not advisable. Babies under stress or who have cholestasis are given limiting proteins to 2.5 g/kg/day because of severity of TPN-induced cholestasis which depends on the duration of TPN and the amount of amino acids infused.[20,21]

Protein administration should be started on the first day of life or as soon as fluid and electrolyte requirements have stabilized. It is better to maintain nonprotein-to-protein calorie ratio of at least 25–30:1. Role of supplements, such as additional inositol and carnitine, is under research. They have not yet been shown to be of benefit in large, randomized, controlled trials.[22,23] The addition of glutamine has not been shown to improve outcome.[24]

Minerals (Other than Sodium, Potassium, Chloride)

Once protein intake has been started, calcium and phosphorous should be supplemented to TPN. Calcium and phosphorous need to be concurrently administered for proper accretion. Ensure that solubility is not exceeded; if that happens, calcium and phosphorous spontaneously get precipitated. Also magnesium should be added to TPN once protein has been started.

Vitamins and Trace Elements

Vitamins A, D, E, and K are fat soluble. Vitamins B_1, B_2, B_6, B_{12}, C, biotin, niacin, pantothenate, and folic acid are water soluble. Vitamin supplementation should be started moment protein is added to TPN. The commercially available neonatal vitamin preparation provides appropriate quantities of all vitamins, except vitamin A. Vitamin A supplementation in ELBW infants has been shown to reduce death and bronchopulmonary dysplasia.[25] The usual dose of vitamin A is 5000 IU intramuscularly administered 3 times per week for next 4 weeks in ELBW infants who receive respiratory support at age 24 hours.

The trace elements zinc, copper, selenium, chromium, manganese, molybdenum, and iodine also should be added to TPN once protein is started. A commercially available solution containing trace elements can be used.

Complications of Total Parenteral Nutrition

TPN gives many children a chance to live long enough, productive lives. Still, patients receiving TPN are always at risk of complications from the procedure. Complications may include:

- Clotting (thrombosis) in central access veins
- Frequent infections in the central-vein access lines
- Inflammation of the gallbladder (cholecystitis)
- Bone disease (osteoporosis)
- TPN-induced liver damage or liver failure

TPN-induced liver failure occurs more often in children than adults. Some children who receive long-term TPN may develop social problems because TPN can severely limit their everyday activities.

Survival Prospects of Total Parenteral Nutrition

The long-term survival prospects of patients maintained through total parenteral nutrition vary, depending on the problems. Three-year survival of TPN-dependent patients ranges from 65 to 80 percent. 20 to 35 percent of patients fare poorly on TPN.[13]

What are the Risks of Total Parenteral Nutrition?

There are risks associated with TPN. Some of the most common are:

- **Infection.** It is important to be able to recognize the signs and symptoms of infection. Before child leaves the hospital on TPN, parents are counselled about signs and symptoms of infection. The parents must inform doctor immediately if child develops fever or experiences any of the following at their catheter site:
  a. Tenderness
  b. Warmth
  c. Irritation
  d. Draining
  e. Swelling
  f. Redness
  g. Pain
- **TPN liver disease or damage.** TPN increases the risk of having liver disease as well as damage. Infants on

TPN are more at risk for liver disease than older children and adults. The organs of infants are still developing. They are not as capable of handling the burden and metabolic strain of TPN. Children who are on TPN for longer duration are more at risk than those who are on TPN temporarily or for a short time. Ttransplant patients may also receive a liver transplant at the same time due to liver disease associated with TPN.[13]

- **Growth and developmental delays.** Although TPN will help your child grow and develop, TPN cannot be given life long since it is not complete nutrition like eating a regular diet. Children on TPN may still be smaller and less developed than other children of their age eating normal food orally.

REFEEDING SYNDROME

Definition

Refeeding syndrome is defined as severe, (and potentially fatal) electrolyte and fluid shifts associated with metabolic abnormalities in malnourished children undergoing refeeding, whether orally, enterally, or parenterally. The cardinal feature is hypophosphataemia, other biochemical derangements are usual including disorder of sodium and fluid balance, changes in glucose, protein and fat metabolism, thiamine deficiency, hypokalaemia and hypomagnesaemia. It is often forgotten.[14]

Pathophysiology

Prolonged Fasting

In early starvation, blood glucose levels decline, resulting in declining insulin and increasing glucagon levels. This stimulates glycogenolysis in the liver and lipolysis of triacetylglycerol in fat reserves producing fatty acids and glycerol which are used by tissues for energy and converted to ketone bodies in the liver. As glycogen reserves get depleted, gluconeogenesis is stimulated in the liver, utilising amino acids (derived from the breakdown of muscle mass), lactate and glycerol leading to synthesis of glucose for use by the brain cells and red blood cells. The main consequence of these changes is that body switches main energy source from carbohydrate to protein and fat. The basal metabolic rate decreases by as much as 20–25%.[13]

As fasting continues, the body aims to conserve muscle mass and protein. The tissues in turn decrease their use of ketone bodies, and use more and more fatty acids as their main energy source. This results in an increase in blood levels of ketone bodies, promoting the brain to switch from dextrose to ketone bodies as its main energy source. The liver decreases its rate of gluconeogenesis due to the reduced need for glucose by the brain thus preserving muscle protein which is its source of amino acids. As a result, several intracellular minerals become completely depleted. The concentrations of minerals like phosphate may remain normal.[13]

Refeeding

The underlying cause of refeeding syndrome is the metabolic and hormonal changes caused by quick and rapid refeeding, be it enteral or parenteral. On refeeding, absorbed glucose leads to increased blood glucose levels, increasing insulin and decreasing glucagon secretion. The net result of all these changes is the synthesis of glycogen, fat and protein. This new anabolic state in child requires minerals such as phosphate and magnesium and cofactors such as thiamine. Insulin stimulates the absorption of potassium into the cells (via the Na-K ATPase symporter), with both magnesium and phosphate also taken up by cells. Water is drawn into the intracellular compartment (ICF) by osmosis. This decline in serum levels of phosphate, potassium and magnesium further, which are responsible for clinical features of refeeding syndrome.[14]

KEY ELEMENTS AND MINERALS

Phosphorus

Phosphorus is a predominantly intracellular anion. It is essential key for almost all intracellular processes and structural integrity of the cell membrane. It is important for energy storage—adenosine triphosphate (ATP), for enzyme/and second messenger activation by phosphate binding, for control of the affinity of the oxygen binding to haemoglobin (via 2,3-diphosphoglycerate (DPG), ATP). It is very important in the regulation of pH by acid–base buffering.

In refeeding syndrome, long-term depletion of phosphorus in the body of child occurs along with a greatly increased use of phosphate in the cells resulting in insulin surge. This leads to all round deficit in intracellular and extracellular levels of phosphorus. In this environment, even small drops in serum levels of phosphorus may lead to widespread dysfunction of the cellular processes.

Potassium

Potassium is the main intracellular cation. This is depleted in undernutrition, whilst its serum concentration usually remains within the normal range. On refeeding, insulin causes potassium to go into the cells. This causes symptomatic as well as real hypokalaemia and as a result, derangements in the electrochemical membrane potential, potentially leading to abnormalities in cardiac rhythm and even cardiac arrest may occur.

Magnesium

Magnesium is an important intracellular cation. It is an essential cofactor in most cellular enzymatic systems including oxidative phosphorylation and ATP production. It is also important for the structural integrity of DNA, RNA and ribosomes. In addition it regulates membrane potential, and deficiency can lead to mainly cardiac dysfunction and neuromuscular dysfunctions. Magnesium and potassium levels are linked, hence severe hypomagnesaemia will lead to hypokalaemia. Therefore, only replacing potassium will not correct potassium deficit, as magnesium replacement has to take place concurrently.

Glucose

After starvation, glucose intake suppresses gluconeogenesis by leading to the release of insulin and the suppression of glycogen. If it is taken in large quantities, glucose intake may therefore result into hyperglycaemia, leading to osmotic diuresis, dehydration, metabolic acidosis and ketoacidosis. Excess glucose also leads to lipogenesis (again result of insulin stimulation). This can lead to fatty liver, increased CO_2 production, hypercapnoea and respiratory failure.

Vitamin Deficiency

Starvation commonly leads to several vitamin deficiencies. The most essential of these with respect to refeeding is thiamine, as it is an essential coenzyme in carbohydrate metabolism. Deficiency in thiamine can result into Korsakoff's syndrome (retrograde and anterograde amnesia, confabulation) and Wernicke's encephalopathy (ocular abnormalities, ataxia, confusional state, hypothermia, coma).

Sodium, Carbohydrate and Fluid

Consumption of carbohydrate result into rapid decrease in renal excretion of sodium and water. If fluids are then given to maintain a normal urine output, patients may quickly become fluid overloaded. Matter becomes worse by the loss of cardiac muscle mass during starvation. This can result into cardiac myopathy and reduced cardiac contractility further leading to resulting in acute congestive cardiac failure.

Management

Treatment of Refeeding Syndrome

The re-introduction of feeding needs to be done with caution. Earlier guidelines have stressed importance of proper replacement of electrolytes, vitamins and minerals before starting of feeding, be that enterally or parenterally. This has potentially risks prolonging the period of malnutrition National Institute for Health and Clinical Excellence (NICE) guidelines says replacement be parallel with feeding.

Vitamin replacement should be started straightaway, with thiamine and other vitamin B to reduce the incidence of Wernicke's encephalopathy or Korsakoff's syndrome, with 200–300 mg oral thiamine daily, and 1–2 tablets vitamin B of high potency 3 times daily, and multivitamin or trace element supplement once daily. This replacement once began should be continued for at least 10 days in a row.[9]

If levels of key electrolytes are measured to be low, they can be supplemented via oral, enteral or intravenous routes depending on how low the levels are and what methods of refeeding are possible a given child patient. There is a little good quality evidence on the best replacement regimes, (where future research needs to be focused) but NICE have made working recommendations, including potassium (2–4 mmol/kg/day), phosphate (0.3–0.6 mmol/kg/day), and magnesium (0.2 mmol/kg/day intravenously or 0.4 mmol/kg/day orally).

The rate of refeeding from these same guidelines depends on the severity of the malnutrition prior to refeeding. In moderate risk child patients (patient who has eaten a little or nothing for more than 5 days), the recommendation is to feed at a rate of no more than 50% of the energy requirements. If after careful monitoring of clinical and biochemical status, all is well this rate can start to be increased carefully but slowly. If the patient falls into one of the high risk categories, replacement of energy should be started slowly with a maximum rate of 10 kcal/kg every 24 hours. It can then be subsequently increased to meet or exceed full needs over the next 4 to 7 days, and as before, particular

caution needs to be observed to biochemical indices and fluid balance. In patients who are very malnourished (body mass index ≤ 14 or a negligible intake for two weeks or more), the NICE guidelines recommend that refeeding should start at a maximum of 5 kcal/kg/24 hours, with active continuous ECG cardiac monitoring owing to the risk of cardiac arrhythmias. Circulatory volume should also be replaced but care should be taken not to overload child patients.

Why use the NICE guidelines on refeeding syndrome?

1. The guidelines are the most recent comprehensive review of the literature on refeeding syndrome.
2. The guideline developing group was strongly multi-disciplinary who had wide ranging consultation with both professional and patient party as stakeholders.
3. The guidelines clearly identified points of good medical practice and suggested areas for further research.
4. The new guidelines give explicit clinical criteria for patients "at risk" and "highly at risk" of developing refeeding syndrome, enabling better identification and prevention of morbidity and mortality.
5. For patients with electrolyte deficits the new guidelines recommend immediate start of nutritional support at a lower rate, rather than waiting till the electrolyte imbalance has been corrected (as was recommended by earlier existing guidelines), thus potentially avoiding further nutritional deterioration in patients. For NICE guidelines visit www.nice.org.uk.

CONCLUSIONS

Refeeding syndrome is an important condition which is often diagnosed late in patients at risk. The key to better patient care in this area is prevention by increased clinician awareness and involvement of specialist dietetic support. If patients are diagnosed or suspected, then there are proper and new guidelines in place to help with management. It must be stressed that many of the recommendations are not based on high quality evidence and this shall help in highlighting areas that need future research.

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8

Thermoregulation in Neonates

Rachana Chhabaria

ABSTRACT

Newborns are prone to hypothermia due to immature thermoregulatory system. Heat loss is further exaggerated under anaesthesia for surgery. This chapter highlights the physiology of temperature regulation, various sites used for monitoring temperature, mechanisms by which heat loss occurs and ways to prevent heat loss in newborns. There are mechanisms for heat generation to compensate for heat loss, which are explained, along with effect of anaesthesia on temperature regulation.

Humans are considered as homeothermic organisms as they maintain a constant body core temperature independent of changes in ambient temperature (within a limited range). Body temperature is one of the physiological parameters effectively controlled by the body. Normal body temperature is essential to provide necessary thermal environment for appropriate function of enzymatic systems. Thermodynamically, the human body is considered a three compartment model consisting of a central (core), a peripheral, and a shell compartment. The central compartment consists of the vessel-rich group of organs (brain, heart, lungs, liver, kidneys, and endocrine glands). The core temperature refers to the temperature of the central compartment and under normal conditions it is maintained within ± 0.2°C of its set point of 37.0°C. This is called the interthreshold range, and within this narrow range no thermoregulatory effector responses are triggered to control the body temperature, and the human organism behaves in a poikilothermic manner. The peripheral compartment consists of the musculoskeletal system, which acts as a dynamic buffer between the central and the shell compartment. The shell compartment consists of the skin, which acts as a barrier between the body and the environment.

Thermoregulation refers to the ability to balance between heat production and heat loss in order to maintain body temperature within a certain "normal" range. Temperature control is subjected to a circadian rhythm and the control within these rhythms is very tightly maintained by an effective thermoregulatory system. Extremes of environmental temperature, anaesthesia and surgery can significantly attenuate the normal thermoregulatory system, resulting in cellular and tissue dysfunction. This explains the need for strict temperature control and regulation by monitoring and appropriate measures.

Due to immaturity of thermoregulatory system and sudden change of environment from intrauterine to extra uterine life, neonates, terms and preterms are susceptible to heat loss and experience difficulty in maintaining their temperature than adults.

The definition of hypothermia is variable, although most acceptable is core temperature of less than 36.1°C (97°F) as being hypothermic.

Hypothermia may be graded into three categories according to severity: mild [33.9–36.0°C (93.0–96.8°F)], moderate [32.2–33.8°C (89.9–92.8°F)], or severe [below 32.2°C (89.9°F)].

THERMAL ENVIRONMENT AND BODY TEMPERATURE

Two interrelated concepts regarding thermal care:

1. "Set point" defines the controlled temperature in the thermoregulatory system and is set at 37 ± 0.2°C.
2. "Neutral thermal zone" (or environment) is defined as the ambient temperature at which the oxygen

demand reflected by the metabolic rate is minimal and thermoregulation is achieved through non-evaporative physical processes alone means (that is, by vasomotor control). For unclothed adults, the neutral temperature is about 28°C; for neonates—32°C; and for preterm infants—34°C. Within this range, the infant is in thermal equilibrium (thermoneutrality) with the environment, the cutaneous arteriovenous shunts are open and skin blood flow is maximal. The lower temperature limit of thermal regulation in adults is 0°C, whereas that in newborns is 22°C. In general, maintaining the core temperature in a cool environment leads to increased oxygen consumption and metabolic acidosis may develop. However, oxygen consumption in a full-term neonate does not correlate with a decreased rectal temperature but rather correlates directly with the skin-to-environment temperature gradient. Oxygen consumption is minimal with skin-to-environment temperature gradients of 2°C to 4°C. Therefore, at environmental temperatures between 32°C and 34°C and an abdominal skin surface temperature of 36°C, the resting neonate is in a state of minimal oxygen consumption (i.e. the thermoneutral state). Given the significance of the skin-to-environment temperature gradient associated with a state of minimal oxygen consumption, normal rectal temperature does not imply a state of minimal oxygen consumption.

In view of immature thermoregulation in neonate, the head is of special importance because it comprises up to 20% of the total body surface area and forms the source for highest regional heat flux. Furthermore, a large caloric heat loss occurs from the head due to the thin skull bones, often sparse scalp hair, and the close proximity of the highly perfused brain (with core temperature) to the skin surface. Facial cooling may increase oxygen requirements by up to 23% in the full term and 36% in the preterm infant, which indicates the importance of the practice of covering the infant's head to minimize heat loss.

Thermoregulatory vasomotor response causing vasoconstriction and vasodilatation are most likely established during the first day of life in both the preterm (>1 kg) and the full-term neonate. Vasoconstriction leads to decreased cutaneous blood flow and an increased effect of tissue insulation; these results in an overall reduction in conductive and convective heat loss. However, vasoconstriction abilities are outmatched by propensity for heat loss due to limited layer of subcutaneous fat; limited development of muscle and other tissues that provide insulation.

Sweat production is observed in infants of 29 weeks gestational age; maturation of this pseudomotor response is enhanced by extrauterine development. However, the response is slower, less efficient than in older child or adult, and occurs at a higher environmental temperature.

Heat dissipation in the premature or small-for-gestational-age infant represents the extreme of thermal regulation in the neonate, thereby challenging their thermoregulating capacity. In small-for-gestational-age infants, a slightly lower skin surface area-to-volume ratio and an increased motor tone offer some protection when compared with the premature infant for heat loss or transfer. The extended or "spread eagle" posture, for instance, increases heat loss by as much as 35 percent when compared to a flexed (foetal) position. In addition to the physical limitations of heat conservation in infants and children, surgery can further increase heat loss and fluid requirements by exposing the visceral surfaces of the abdomen and thorax, thereby exacerbating evaporative and convective heat and water losses.

Physiology of Thermal Regulation

The human body tolerates cold temperatures with a three-fold greater margin than hot temperatures. Like other control systems in the body, the thermoregulatory system depends on a negative feedback loop to maintain the body temperature within narrow limits.

The body's principle temperature regulation centre is the hypothalamus, which integrates afferent signals from temperature-sensitive cells found in most tissues, including other parts of the brain, spinal cord, central core tissues (i.e. brain, heart, lungs, liver, kidneys, and endocrine glands), respiratory tract, gastrointestinal tract, and the skin surface. The processing of thermoregulatory information occurs in three stages:

1. Afferent thermal sensing
2. Central regulation
3. Efferent response

Afferent Thermal Input

Distinct central and peripheral thermoreceptors sense ambient temperature of the body. Central thermosensitive receptors are located in the brain and the spinal cord and in close proximity to the great vessels, the viscera, and the abdominal wall. Warm and cold receptors in the skin form the peripheral thermoreceptors.

Warm receptors outnumber cold receptors by 10-fold, acknowledging the importance of detecting and correcting an increase in body temperature than a decrease in body temperature. Each receptor type transmits the information through an afferent nerve conduction pathway and the velocity is related to the intensity of the stimulus and the rate of temperature change than to the type of nerve fibre.

Impulses from the cold-sensitive receptors, which have their maximal discharge rate at a temperature of 25°C to 30°C, is transmitted by A delta fibres to the preoptic area of the hypothalamus.

Impulses from the peripheral warm receptors, which have their maximal discharge rate at 45°C to 50°C, is transmitted by unmyelinated C fibres. These C fibres also detect and convey nociceptive impulses, explaining why intense heat cannot be distinguished from severe pain. Most afferent thermal impulses are transmitted along the spinothalamic tracts in the anterior spinal cord.

Central Regulation

Afferent thermal information is integrated in the preoptic area of the anterior hypothalamus, which contains cold- and heat-sensitive neurons. The cold-sensitive neurons predominate the heat-sensitive neurons in the ratio of 4:1. This area also receives and processes non-thermic afferent information, which controls the adaptive mechanisms and the behaviour of the organism. The hypothalamus compares the afferent information with the threshold temperatures for heat and cold and then carefully regulates mechanisms for heat generation and dissipation to maintain body temperature within the narrow limits of its set point (interthreshold range). The posterior hypothalamus controls the descending pathways to the effectors.

Under normal conditions, the contribution of the central thermoreceptors to thermal regulation is limited by the marked predominance of the input of peripheral receptors. Central receptors take over thermoregulation if the sensory input from peripheral sensors is disrupted (e.g. central neuraxial anaesthesia or spinal cord transection), but they are less efficient compared with peripheral thermoreceptors.

The threshold represents the central temperature which initiates a particular regulatory effector response. When the integrated input from all sources exceeds the upper or falls below the lower threshold, efferent responses are initiated from the posterior hypothalamus to maintain normal body temperature. The slope of the response intensity plotted against the difference between the thermal input temperature and the threshold temperature is called the *gain* of that response (i.e. the intensity of the response).

The difference between the lowest temperature at which warm responses are triggered and the highest temperature at which cold responses are triggered is the thermal sensitivity of the system. The interthreshold range, i.e. temperature range over which no regulatory responses occur, changes from approximately 0.4°C in the awake state to approximately 3.5°C during anaesthesia. The interthreshold range is wider in the hypothermic state than in the hyperthermic state as compared with normal human body temperature (37.0 ± 0.2°C). This physiologic system acts as an "all-or-none" phenomenon. Central regulation is fully functional in infancy but may be impaired in the premature.

Efferent Response

Mean body temperature (MBT) is a physiologically weighted average temperature reflecting the thermoregulatory importance of various tissues especially of the central compartment.

In unanaesthetized subjects, the mean body temperature can be calculated as:

$$MBT = 0.85 \text{ (central T)} + 0.15 \text{ (skin T)}$$

where T denotes the temperature measured in °C.

Temperature regulation is a system of thresholds and gains for each particular thermoregulatory response and these responses are actively regulated by the hypothalamus when temperatures exceed the interthreshold range. Efferent responses are behavioural changes or autonomic changes, initiated to either increase or decrease heat loss depending on the central interpretation of the afferent input. Skin temperature is the most vital parameter triggering behavioural changes, but the thermal input from the skin contributes only about 20% for the thermoregulatory autonomic response. The majority of the autonomic response depends on the afferent information from the central core compartment, which includes the brain (parts other than the hypothalamus), the spinal cord, and deep abdominal and thoracic tissues, with each of them contributing about 20% to the central thermoregulatory control.

Efferent Responses to Hypothermia

1. **Behaviour responses:** Quantitatively the most important thermoregulatory effectors in humans (e.g. heating the home, looking for shelter, putting on a jacket, etc.), mainly contribute in decreasing heat loss. These are much more efficient than all of the autonomic responses combined and the newborns are unable themselves and dependent on caretakers to do these.
2. **Autonomic responses:** Cutaneous vasoconstriction, the first and the most consistent one. Total digital skin blood flow can be categorized into a nutritional (capillaries) and a thermoregulatory (arteriovenous shunts) component. Competent abilities to regulate skin blood flow are documented in infants weighing >1 kg. Cutaneous blood flow is drastically reduced in arteriovenous shunts of the hands, feet, ears, lips, and nose (1% of the normal blood flow in an environment with neutral temperature). These shunts are typically 100 µm in diameter, can divert 10,000 times as much blood as a capillary with a 10 µm diameter. Shunt flow is primarily regulated by norepinephrine, by binding to peripheral α_2-receptors which are sensitized by local cooling and inhibited by temperatures equal to or higher than 35°C. In spite of the thermoregulatory vasoconstriction, the resulting reduction of heat loss from the hands and feet decrease by 50%, but only by 17% from the trunk, resulting in an overall heat loss reduction of only 25%. Other responses include non-shivering thermogenesis and shivering which increase metabolic heat production.

The ability to increase metabolic rate in response to cold stress begins around 28–30 weeks post-conceptional age. Post-conceptionally older infants can increase heat production, but the response is weaker than in the adult. Shivering response is not well developed in newborns and they cannot initiate increased tone and shivering to increase heat production. Lower post-conceptional aged and ill infants are prone to decreased motor tone and less activity, resulting in decreased heat production. Infants with poor tone cannot use flexion posture effectively to reduce surface area and hence decrease heat loss. Heat production needs are met primarily through non-shivering thermogenesis. This depends on the amount of brown fat stores which are inversely related to gestational age. Heat production increases oxygen consumption, challenging the immature cardiovascular and pulmonary systems.

Efferent Responses to Hyperthermia

1. **Behaviour responses:** Wearing light clothing, cold sponging.
2. **Autonomic responses:** Sweating, this triggers massive pre-capillary vasodilatation with marked increase in skin blood flow, allowing for huge amounts of heat to be transported to the skin, which then dissipates to the environment, mainly by evaporation due to preconditioning by sweat. Sweat production is observed in infants of 29 weeks gestational age; maturation of response is enhanced by extrauterine development. This response is slower, less efficient than in older child or adult, and occurs at a higher environmental temperature.

Temperature Monitoring

Temperature is most commonly measured in degrees Celsius (or centigrade), or may be measured in degrees Fahrenheit. In the System International the temperature unit used is Kelvin (K), where 0 K = –273.15° C and it includes absolute zero temperature. The following formulas can be used to convert from one unit to the other:

$$^{o}\text{Celsius} = 0.56 \times (^{o}\text{Fahrenheit} - 32)$$

$$^{o}\text{Fahrenheit} = (1.8 \times {}^{o}\text{Celsius}) + 32 \text{ Kelvin} = (273 + {}^{o}\text{Celsius})$$

The American Society of Anaesthesiologists guidelines state that "every patient receiving anaesthesia shall have temperature monitored when clinically significant changes in body temperature are intended, anticipated or suspected". An appropriate measurement of temperature, at an appropriate site with an accurate sensor to detect perioperative changes is mandatory.

Today, the thermometers used in clinical practice are thermistors and thermocouples. The thermistor type thermometer is based on an exponential, temperature dependent change in the electrical resistance of a semiconductor resistor, which consists of a tiny drop of metal (e.g. copper, nickel, manganese, or cobalt). This change in resistance is used to measure temperature. The thermocouple thermometers consist of two different metals, often copper and constantan (a copper-nickel-manganese-iron alloy), to sense the temperature. The principle behind thermocouples is the Seebeck effect, which states that a small electrical current is generated at the junction between two different metals (of the thermoelectric series) that are exposed to a temperature gradient. The magnitude of this voltage is temperature

dependent and is used as a measurement of the temperature. Both, thermocouple and thermistor probes are inexpensive and sufficiently accurate for clinical purposes, explaining their wide usage in daily practice.

Depending on the site of measurement, body temperature varies widely. The central tissues maintain a constant temperature (core temperature) because of their high perfusion. The peripheral tissues usually maintain a significantly reduced homogeneous temperature. Therefore, the temperature in the central and peripheral compartments may differ by several degrees within small measurable distances of each other.

Core temperature is of the greatest clinical interest because it is the most vital thermoregulatory controller in the body. Core temperature may be measured at a number of sites within the body, including tympanic membrane, naso-pharynx, distal oesophagus, the pulmonary artery, and, with some limitations, bladder and rectum. These sites usually provide similar readings in awake as well as anaesthetized humans undergoing non-cardiac surgery, but may actually represent different temperatures under certain conditions whose physiologic and clinical implications may vary.

Body temperature can be monitored at various anatomic sites. The precision and accuracy of measurements at these sites vary and each site has its advantages and disadvantages. The ideal site of temperature monitoring should reflect core temperature, be non-invasive and be associated with none or only minimal morbidity. Various sites include:

1. **Tympanic membrane:** Considered the most ideal site to monitor core temperature. It is not necessary for the temperature probe to directly contact the tympanic membrane to obtain an accurate reading. It can simply be done by sealing the external auditory canal by the probe and allowing the air column trapped between the probe and the tympanic membrane to reach a steady state. The tympanic membrane temperature may not be accurate in some situations. In the initial post-cardiac reconstructive surgery period in infants and children, tympanic membrane temperature does not correlate well with brain temperature and thereby fails to provide an accurate estimate of central body temperature. With difficulties obtaining appropriate-sized thermistors and clinical reports of tympanic membrane perforation, its clinical use is no longer encouraged.
2. **Naso-pharynx:** Nasopharyngeal temperature probes are considered to provide a good estimate of the hypothalamic temperature, thereby accurately reflecting the core temperature, provided the probe is adequately placed (i.e. placing the tip of the temperature probe in the posterior nasopharynx close to the soft palate). However, when used in combination with un-cuffed tubes with a moderate to large air leak, the resulting airflow may lead to inaccurate reading. Slight and self-limiting bleeding from the nose is commonly noticed (especially in children with large adenoids), and its preclusion in mask anaesthesia has limited its routine use.
3. **Oro-pharynx:** Oral temperature is considered less accurate and hence not recommended as an accurate intraoperative temperature-monitoring site.
4. **Oesophagus:** Oesophageal temperature probes when combined with an oesophageal stethoscope decently reflect the core temperature, making this site particularly attractive in the paediatric population. In infants and children, and in cachectic patients, the thermal insulation between the tracheobronchial tree and the oesophagus is minimal due to thin tissue planes. This may result in erroneous temperature readings, especially when the respiratory gas flow is high and there is a significant temperature gradient between the respiratory gases and the body temperature. In order to measure the central temperature the tip of the probe should be properly placed in the distal third of the oesophagus at the point where the heart sounds are the loudest. In children with endotracheal intubation, oesophageal temperature is more reliable than rectal temperature and more practical than tympanic membrane temperature.
5. **Axilla:** It is considered the most convenient site for monitoring temperature in children so most widely used. They are frequently malpositioned and can be unreliable if not adequately placed. The accuracy of the axillary probe depends on careful position of the tip of the probe close to the axillary artery with the arm tightly adducted. Axillary temperature can be as accurate as tympanic membrane, esophageal and rectal temperature sites in measuring core temperature. Maintaining low room temperature or infusing cold solutions at high flow rates in small children in the same extremity as the axillary temperature is monitored may result in falsely low temperature readings. Falsely high readings may be recorded when the tip of the probe senses the hot air from a forced warming air device.
6. **Rectum:** The rectal temperature can provide accurate core temperature measurements, is easy to access

and associated with minimal morbidity. But may impose problems if the probe becomes embedded in faeces, exposure of the probe to cooler blood returning from the legs, the influence of an open abdominal cavity during laparotomy, or bladder irrigations with either cold or warm solutions on the probe proximity. Absolute contraindication to the use of a rectal probe includes imperforate anus, and relative contraindications include inflammatory bowel disease, rectal tumours, neutropenia or thrombocytopenia, coagulopathy, and circumstances in which the bowel or bladder is to be irrigated.

7. **Bladder:** It is considered to be one of the most accurate sites for measuring core temperature; identical to pulmonary artery temperature provided urinary output is high. When urinary output is normal or less than normal, this site fails to reflect the core temperature.
8. **Pulmonary artery:** A pulmonary artery catheter with a distal-tip thermistor can accurately reflect pulmonary blood temperature, but its use is limited, in critically ill children due to its invasive nature.
9. **Skin:** Skin surface is considered the least invasive site and highly unreliable measure of the core temperature. It varies dramatically depending on the part of the body where the skin temperature is measured.

The site or sites of temperature monitoring depends on the operative procedure. For children undergoing cardiac surgery temperature is usually measured at multiple sites (e.g. rectum, bladder, oesophagus, naso-pharynx, tympanic membrane).

Heat Loss Mechanisms

Humans are homeothermic, with the ability to dissipate and produce heat in a controlled manner. Heat loss is governed by the physical laws of conduction, radiation, convection, and evaporation and is a two-stage process. The first stage is internal redistribution of heat, in which heat is dissipated from the central core compartment to the periphery and the skin surface. The second stage in the process is the transfer of heat from the skin surface to the environment.

Heat transfer occurs from a warmer to a cooler object, never from a cooler to a warmer object. This means that the warmer object, in the operating room setting, which is exclusively the patient losses heat to the surrounding environment (operating room walls, tables, etc.).

In a thermoneutral environment, total heat loss by the neonate occurs via four mechanisms (Table 8.1).

Table 8.1 Mechanisms (by percent) of heat loss in neutral thermal environments

Radiation	39%
Convection	34%
Evaporation	24%
Conduction	3%

Physiological manipulations in regional blood flow and changes in the thermal conductance properties of the insulating tissue can influence gradients in both stages.

Changes in the operating room environment, e.g. the air and/or room temperature can affect the overall magnitude of the heat loss as well as the relative contributions of each of these mechanisms.

Radiation

It is the mechanism in which there is transfer of heat between two objects of different temperature not in direct contact with each other (e.g. radiation is the mechanism by which the sun warms the earth). The emitted radiation carries energy in the infrared light spectrum from the warmer to the cooler object. This leads to cooling of the warmer object and warming the cooler object.

The following factors affect radiant heat flux:

1. **The emissivity of the radiating surfaces:** It is the power to emit or give off heat by radiation. The emissivity of a neonate's skin is relatively constant. Clothing and blankets reduce emissivity as well as provide insulation. As radiation involves heat exchange between solid surfaces, the surface temperature and emissivity of solid objects surrounding the infant should be considered.
2. **The temperature gradient between the solid surfaces:** Radiant heat transfer is driven by the temperature gradient between the solid surfaces. The infant's skin temperature is typically warmer than other surrounding surfaces, so this leads to heat loss from the infant's surface to surrounding solid surfaces. The infant gains heat via radiation when placed below a radiant heating source, which is warmer than the infant's skin temperature.
3. **The surface area of the solid surfaces:** The infant's large body surface area to body mass potentiates radiant heat loss. Solid surfaces surrounding the infant are enormous in comparison to the infant's surface area, causing more radiant heat loss. For the supine infant, the largest surface areas to which

radiant heat is lost are directly above (30%) and to the sides (17%) of the infant. Thus, the mattress surface adjacent to the infant, even though not in direct contact can be an important avenue for radiant exchange.

4. **The distance between the solid surfaces:** The closer the two solid surfaces, the greater the radiant heat flux. In both, the awake and the anaesthetized state, radiation is the most important mechanism of heat loss in the neonate. Heat exchange by radiation is based on the Stefan-Boltzmann law of radiation:

$$H = esA (T_1^4 - T_0^4)$$

Where, H is the energy transferred in Joules per second;
e is the emissivity (0–1, human body is approximately 0.7);
s is the Stefan-Boltzmann constant, 5.67×10^{-8} (Joules/$s \cdot m^2 \cdot k^4$);
A is the surface area (m^2); and
T is the temperature of the two bodies (K).

Using this equation with a body surface area for a neonate of 0.25 m^2, increasing the room (wall) temperature from 21° C to 30° C decreases the radiation heat loss by 63%. Thus, the radiant heat loss can be substantively reduced by increasing the ambient room temperature of the operating room, thereby reducing the temperature gradient between the neonates and surrounding. A thin single-layer covering can dramatically reduce the losses by radiation and provide thermal comfort.

Conduction

It is the mechanism in which there is transfer of heat between two surfaces in direct contact. It is the heat flux between the infant's body surface and other solid surfaces.

The following factors influence conduction:

1. The solid surface conductivity coefficient: The greater the conductivity, the greater the heat flux between the infant and the solid surface in contact.
2. The size of the surface area of contact between the infant and the solid surface:
   Larger the surface area in contact with the object, the greater is the heat flux. In the supine position, an infant has approximately 10 percent of his surface area in contact with the mattress. In a prewarmed incubator or under a radiant warmer, in preheated the operating room table/sheets, conductive loss is not significant.
3. **The temperature gradient between surfaces:** Warming pads and similar devices typically reduce heat loss by decreasing gradient between the infant and the solid surface.

The physiologic factors controlling conductive heat loss in newborns are cutaneous blood flow and the thickness of the subcutaneous tissue which provides insulation. This is further poorly developed in preterms.

Measures to prevent conductive heat loss include

- Warming solid surfaces before they come in contact with an infant, ensuring that the infant's skin is not in direct contact with metallic surfaces.
- Warming cool irrigation solutions and intravenous fluids.
- Providing insulation between the infant and the solid surface by covering infants with disposable drapes, this decreases the cutaneous heat loss by 29%.
- Wrapping X-ray plates with warmed blankets, weighing infants with a warmed blanket.

Convection

It is the mechanism in which there is transfer of heat between a solid surface (the infant) and moving molecules such as air or liquid. The thin air layer adjacent to the skin is heated by conduction from the body but the ambient air currents carry heat away from the body. Changes in body posture and minute ventilation may affect convective heat loss. Factors determining convective loss that are relevant to nursing care include the following:

1. **Skin surface area:** The infant's large surface area to body mass results in increased loss by convection. The exposed surface area should be reduced to minimise convective heat loss.
2. **Airflow velocity and turbulence:** These affect the convective heat loss in direct proportion.
3. **Temperature gradient between infant skin and air or liquid:** The larger the gradient between the infant's skin temperature and the surrounding ambient temperature, the greater is the heat loss or gain. Interventions increasing the ambient air temperature reduce the gradient and convective heat loss, e.g. use of incubator decreases the gradient between air and skin temperature. Airflow velocity in a closed incubator is fully consistent, but opening portholes or side panels can alter airflow creating turbulence. Therefore clothing and blankets should be used in incubators to reduce the infant's exposed surface area as well as provide external insulation.

Evaporation

It is the mechanism in which heat is loss through vaporization of water from the body or a mucosal surface. This uses the latent heat of vaporization of water as its source and is an energy-dependent process. This energy for sweat has a value of 2.5×10^6 J/kg, causing its transition from the liquid to the gaseous state. This signifies the power of the human sweating mechanism for dissipating heat. A healthy adult in good physical condition can produce up to 2 L of sweat per hour, dissipating approximately 5×10^6 J/hr or 1.4 kW by sweating mechanism. Under conditions of thermal neutrality, evaporation accounts for 10% to 20% of heat loss.

Evaporative loss occurs by:

1. Sensible water loss by sweating
2. Insensible water loss from the skin, respiratory tract, and open surgical wounds
3. Evaporation of liquids applied to the skin such as antibacterial solutions.

Sensible water loss by sweating depends on the infant's ability to sweat and development of sweat glands. Full-term neonates have mature sweat glands and sweat when rectal temperature is between 37.5°C and 37.9°C and ambient temperature exceeds 35°C. Maximum rate of sweat production is comparable in infants small for gestational age in spite of slower onset of sweat production. Premature neonates with a gestational age of less than 30 weeks do not produce sweat as their sweat glands are not yet fully developed.

Insensible water loss from the skin (transepidermal loss) depends on gestational age and the degree of keratinisation of the epidermal stratum corneum. Mature keratin, which consists of tough fibrous protein is relatively water impermeable and protects the underlying epithelium. Keratin formation is directly related to gestational age, thus premature neonates loose heat through evaporation via the immature permeable skin. In the very low birth weight (VLBW) infant, evaporative loss alone is greater than the heat-producing capabilities. Keratinisation under influence of extrauterine environment increases over the first three to four weeks of postnatal life, decreasing evaporative heat loss. Adhesive dressings which strip the keratin layer increase evaporative loss.

A small amount of heat is lost via evaporation of water from the trachea-bronchial epithelium, which humidifies the dry respiratory gases inspired. Humidification of dry inspired respiratory gases by evaporating water from the trachea-bronchial epithelium results in only a small heat loss. In adults, respiratory losses lead to 5% to 10% of the total heat loss during anaesthesia and surgery and total insensible losses lead to approximately 25% of the total heat dissipated. Children have higher respiratory rate and higher minute ventilation per kilogram, this leads to higher heat loss, approximately up to 33% of the total heat loss. This loss is exaggerated with use of cool, dry gases as compared to warm, moisturized gases. Heat loss by evaporation is maximum from a large surgical incision and may equal all other sources of intraoperative heat loss when combined. Evaporative loss may be increased further when the child is covered with wet drapes or skin is kept wet. Evaporative heat loss may be decreased when neonate is draped with warm gamgees.

Factors affecting evaporative losses include the following:

1. The infant's surface area: Greater the surface area available, greater is the heat loss by evaporation.
2. Vapour pressure, which is governed by air pressure, temperature and humidity.
3. Air velocity: Evaporative heat loss is *potentiated* by the increased speed and turbulence of airflow.

Heat Generation

In order to maintain a constant body temperature, thermal regulation in the homeothermic provides the ability to generate heat in a cool environment along with the ability to dissipate heat in a warm environment.

Heat is generated by increasing the metabolic rate and oxygen consumption.

The three of the four physical mechanisms that account for heat loss (i.e. conduction, radiation and convection) can theoretically also be used to passively warm a child. This passive re-warming helps in increasing the temperature of a neonate postoperatively in a short period due to the same factors which lead to rapid heat loss.

The human body has the ability to actively produce heat and heat generation is achieved by four mechanisms:

1. Voluntary muscle activity
2. Non-shivering thermogenesis
3. Involuntary muscle activity (shivering)
4. Dietary thermogenesis

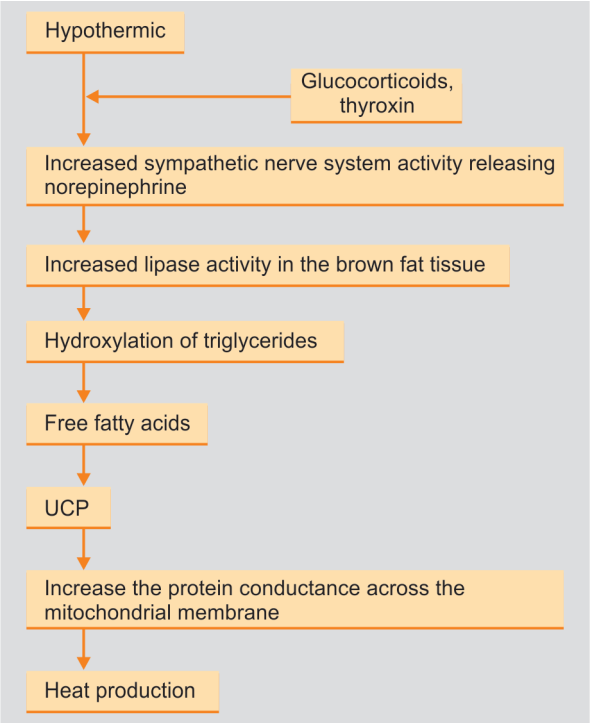
The behavioural aspect of heat production by voluntary muscle activity has limited importance in infants with low muscle mass and is absent in the perioperative period. Of the remaining, non-shivering thermogenesis is the main mechanism for heat production in the

neonate and shivering thermogenesis is the main mechanism for heat production in the adult. The contribution of non-shivering thermogenesis in adults is still debatable. The contribution of non-shivering thermogenesis to maintain the body temperature rapidly decreases after the first year of life along with rapidly increasing the contribution of shivering thermogenesis. The appropriate time and developmental factors which control the switch from non-shivering to shivering thermogenesis in an infant still remain to be elucidated.

Non-shivering Thermogenesis

Non-shivering thermogenesis is defined as an increase in metabolic heat production (above the basal metabolism) which is not associated with muscle activity. It primarily occurs through metabolism of brown fat, but to a lesser extent also occurs in skeletal muscle, liver, brain, and white fat. Brown fat differentiation in the human foetus begins at around 26 to 30 weeks of gestational age, comprising 2% to 6% of the newborn's total body weight. It is located in six main areas: between the scapulae, in small masses around blood vessels in the neck, in large deposits in the axilla, in medium-size masses in the mediastinum, around the internal mammary vessels in the mediastinum, and around the adrenal glands or kidneys.

Brown fat is highly vascularized and richly innervated with primarily β-sympathetic nerve fibres that are responsible for the uncoupling of oxidative phosphorylation. The brown colour is by the abundance of mitochondria in the cytoplasm of its multinucleated cells. These mitochondria are tightly packed with cristae and have a high content of respiratory chain components. They are unique in their ability to uncouple oxidative phosphorylation, resulting in heat production instead of generating adenosine triphosphate. The activation of brown fat metabolism results in an increased proportion of the cardiac output (up to 25%) being diverted through the brown fat, thereby facilitating the direct warming of the blood. Inhalational anaesthetics attenuate non-shivering thermogenesis as soon as 5 minutes after starting halothane, isoflurane, or enflurane or 50% nitrous oxide, but this effect wanes within approximately 15 minutes of discontinuing the anaesthetic agent. During general anaesthesia in children, neither mild core hypothermia nor cold exposure may trigger non-shivering thermogenesis. Non-shivering thermogenesis is also reduced in infants anaesthetized with fentanyl and propofol.



Prematures, full-term neonates, and infants can double their metabolic heat production during cold exposure with non-shivering thermogenesis. This is possible within hours after birth and may persist up to the age of 2 years, but overall has limited ability to compensate for hypothermia.

Shivering Thermogenesis

As the infant and child keep growing, shivering thermogenesis gradually presumes a significant role in thermoregulation. The precise mechanisms and/or factors that lead to this development are still unclear. The role of shivering in thermogenesis gets activated only when all the other mechanisms like the behavioural responses, non-shivering thermogenesis (both ineffective under anaesthesia), and maximal vasoconstriction are unable to maintain body temperature within the interthreshold range. Shivering has limited role in maintaining body temperature in neonates and infants because:

1. The musculoskeletal system is immature
2. Muscle mass is limited

Shivering is characterized by involuntary, irregular muscular activity beginning in the muscles of the upper body, most commonly the masseter. The intensity is greater in central muscles than in peripheral muscles. This leads to metabolic heat production by up to sixfold, which is sustainable by only a twofold.

Shivering occurs in two types of electromyographic patterns:

1. Basal, continuous shivering with a low intensity at a rate of 4 to 8 Hz, associated with type 1 muscle fibres.
2. Superimposed bursts with a high intensity at a rate of 0.1 to 0.2 Hz, associated with type 2 fibres, creating typical "waxing and waning" pattern.

Cold receptors transmit impulses from the skin and the spinal cord to motor centre for shivering, located in the dorsomedial part of the posterior hypothalamus adjacent to the wall of the third ventricle. This then stimulates anterior motor neurons of the spinal cord resulting in increased skeletal muscle tone throughout the body, which when exceeded causes shivering. Under warm conditions, the shivering centre is inhibited by impulses from the heat-sensitive area in the preoptic region of the anterior hypothalamus.

Effects of Shivering

1. In healthy children: Increased muscle activity → oxygen consumption and carbon dioxide production increase → increase in cardiac output (up to 400% to 600% for a brief period)
2. In children with limited haemodynamic or coronary or pulmonary reserves:

   Increase in oxygen consumption → decrease mixed venous oxygen content → decrease arterial oxygen content (due to V/Q mismatch) → decrease tissue oxygen delivery → tissue hypoxia

An inverse ratio exists between intraoperative temperature and postoperative oxygen consumption, as well as between different anaesthetic agents and postoperative oxygen consumption. Shivering is an unpleasant experience for the child as well as the parents in the postoperative period. This can cause increased intraocular and intracranial pressure, wound dehiscence and dental damage. Postoperative shivering has an inverse relation to the core body temperature. But shivering has also been observed in children maintained strictly normothermic during isoflurane or desflurane anaesthesia. This suggests nonthermoregulatory mechanisms also control shivering with pain contributing as a significant factor. Meperidine, clonidine and doxapram have been proven to be effective in attenuating shivering after anaesthesia.

Dietary Thermogenesis

Stimulation of energy expenditure and thermogenesis by certain nutrients (i.e. proteins and amino acids) is a known phenomenon. In spite of muscle paralysis and decreased metabolic rate during general anaesthesia, small amount of infusion of amino acids, fructose may increase heat generation under anaesthesia. The exact mechanisms causing thermogenesis is still not fully understood. Dietary thermogenesis can result in hyperthermia in awake state as well as during anaesthesia with attenuated thermoregulation.

Anaesthesia and Hypothermia

General anaesthesia decreases the temperature threshold at which a thermoregulatory response to cold stress is initiated. Mild intraoperative hypothermia [33.9–36°C (93.0–96.8°F)] which occurs commonly, results from a combination of events:

1. A 30% reduction in the metabolic heat generation during anaesthesia
2. Increased exposure to the environment
3. Anaesthesia-induced central inhibition of thermoregulation
4. Internal redistribution of heat within the body

Hypothermia has a typical profile during general anaesthesia and usually develops in three phases:

1. Internal redistribution of heat,
2. Thermal imbalance, and
3. Thermal steady-state (plateau or re-warming phase).

Internal Redistribution

The concept of internal redistribution of heat refers transfer of heat within the compartments within the body, and not heat loss to the environment. The human body divided into three compartments—the central (or core), peripheral, and skin (or "shell") compartments.

At rest, the central compartment, i.e. vessel-rich group of organs receive approximately 75% of the cardiac output, representing approximately 10% of the body weight in adults and about 22% in neonates. In awake state, the central compartment accounts for approximately 66% of the body mass in an adult, which expands to about 71% during general anaesthesia.

The peripheral compartment consists of the remaining body mass, acting as a dynamic buffer to accommodate any changes in core temperature caused by vasodilatation or vasoconstriction.

Last, the skin compartment acts as a barrier between the first two compartments and the environment.

After induction of anaesthesia, peripheral vasodilatation increases the size of the central compartment, leading to redistribution of its heat over a larger volume.

The core temperature decreases rapidly, by 0.5°C to 1.5°C within the first hour of anaesthesia Furthermore, the decrease in metabolic heat production caused by anaesthesia reduces the amount of energy available to compensate for the enlargement of this compartment. The internal redistribution compresses the peripheral compartment while expanding the central compartment. This explains the decrease in core temperature (the same amount of heat getting distributed to a larger volume), with a corresponding increase in the temperature of the peripheral and skin compartments.

Thermal Imbalance

During this second phase of the hypothermic response, reduced heat production and increased heat loss to the environment leads to thermal imbalance. This lasts for 2 to 3 hours, resulting in a linear decrease in mean body temperature (typically 0.5–1.0°C/hr). Anaesthesia leads to decreased heat production by limiting muscular activity, reducing the metabolic rate, and eliminating the work of breathing. Heat loss occurs by radiation, convection, evaporation, and conduction from the patient to the environment, as a function of the temperature gradient between the skin and ambient structures (i.e. air, walls, and ceiling).

Thermal Steady State (Plateau or Re-warming)

1. **Adults:** The third phase consists of a thermal steady-state plateau, which occurs when metabolic heat dissipation to the environment equals heat production and the core temperature remains constant. This plateau occurs between 34.5°C (94.1°F) and 35.5°C (95.5°F). To maintain the core temperature, heat production must increase and/or heat loss must be decreased to prevent further fall in temperature.
2. **Infants:** The third phase in infants and small children consists of a re-warming phase rather than a plateau phase. Heat production under anaesthesia is decreased by inhibiting muscular activity and non-shivering thermogenesis and reducing metabolic heat generation. This re-warming phase occurs as a result of intense vasoconstriction within the peripheral and central compartments. This compresses the central compartment, and the metabolic heat produced is distributed within this compartment, thus increasing the core temperature. In comparison to adults, the intraoperative thermoregulatory response in infants is not effective enough to increase the core temperature in low ambient temperatures. With either active or passive re-warming, significant physiologic stress response occurs in the infant. Passive surface re-warming (by warm blankets, bundling, or other measures) turns off the skin cold receptors. If the normal core temperature is not reached or maintained by passive surface re-warming, hypothermia may result in hypoventilation or even apnoea, relative anaesthetic overdose (reduced minimal alveolar concentration at lower temperatures), and finally, metabolic acidosis.

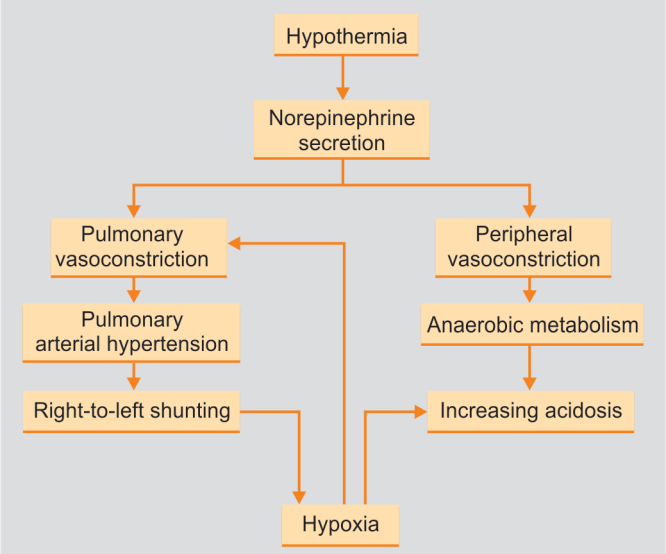


Fig. 8.1 Vicious circle due to prolonged hypothermia[2]

Hypothermia further delays factors of coagulation cascade causing exaggerated blood loss during surgery. Wound healing is also delayed as explained in Fig. 8.2.

SUMMARY

Newborns are susceptible to hypothermia physiological with small size and increased body surface area, immature thermoregulatory system, musculoskeletal system and inadequately developed skin. Hypothermic loss is further exaggerated in preterms and small for gestation. Temperature should be monitored mandatorily in newborns in the intensive care and during surgery under anaesthesia. All measures to prevent heat loss under anaesthesia as well as during transportation should be taken. Measures for passive re-warming should be taken whenever babies become hypothermic. A thorough knowledge of physiology of temperature regulation, its effects under anaesthesia and measures to prevent hypothermia, is essential to provide safe anaesthesia.

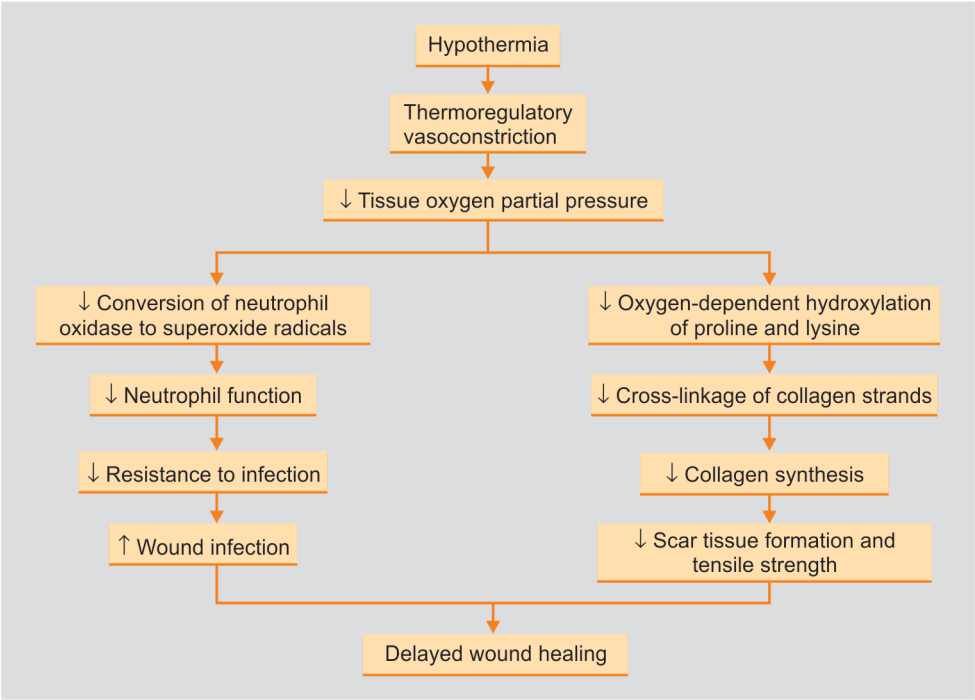


Fig. 8.2 Hypothermia and its effects on wound healing[2]

Key Points

1. Thermoregulation refers to the ability to balance between heat production and heat loss in order to maintain body temperature within a certain "normal" range. In normal conditions it is maintained within ± 0.2° C of its set point of 37.0° C, called the interthreshold range.
2. Thermoregulatory system is immature in neonates. Heat loss occurs with small size and high body surface area, and the head is of special importance because it comprises up to 20% of the total body surface area and forms the source for highest regional heat flux.
3. The thermoregulatory system depends on a negative feedback loop to maintain the body temperature within narrow limits. It includes afferent sensing receptors, the central regulatory hypothamalus and the efferent responses.
4. Temperature monitoring is mandatory as per ASA guidelines and various sites can be used to monitor temperature intraoperatively.
5. The various mechanisms by which heat transfer occur are radiation, evaporation, conduction and convection. These leads to heat loss from neonate to environment and the same can be used to re-warming.
6. The human body has the ability to actively generate heat; non-shivering thermogenesis forms the most important mechanism in neonates.
7. Hypothermia during general anaesthesia develops in three phases in neonates: internal redistribution of heat, thermal imbalance, and thermal steady-state (re-warming phase).
8. Hypothermia in neonates can lead to stress response causing impaired coagulation, apnoea, acidosis, and hypoxia. It can cause delayed wound healing.

FAQs with Answers

Q. What is interthreshold range?

A. The interthreshold range under normal conditions refers to the temperature of the central compartment maintained at set point of 37.0°C ± 0.2°C, and within this narrow range no thermoregulatory effector responses are triggered to control the body temperature, and the human organism behaves in a poikilothermic manner.

Q. When does thermoregulatory vasomotor and pseudomotor response develop in newborns?

A. Thermoregulatory vasomotor response causing vasoconstriction and vasodilatation are most likely established during the first day of life in

both the preterm (>1 kg) and the full-term neonate. Sweat production is observed in infants of 29 weeks gestational age; maturation of this pseudomotor response is enhanced by extra-uterine development.

Q. What are mechanisms of heat loss under anaesthesia?

A. Radiation, evaporation, conduction and convection.

Q. What are the various ways to prevent heat loss in the operating theatre?

A.
- Transportation of neonate in incubators
- Raising the ambient temperature of OT
- Placing the neonate under radiant warmer during procedure
- Placing the neonate on pre-warmed heating mattress
- Covering the neonate with plastic sheet, warm gamgees
- Using warm solutions to clean surgical parts
- Using warm IV fluids intraoperatively
- Using warmed humidified gases

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9

Essentials of Haematology

Anjana Sahu

ABSTRACT

Paediatric age group is the most vulnerable group for haematological disorders. Haemolytic patients may have multiorgan dysfunction. Therefore, for paediatric anaesthesiologist, it should be of great concern to know the status of the major organs and should be optimising preoperatively. The children with hematological derangement may have repeated infection, severe abdominal and/or bone pain, failure to thrive, poor mental growth, require multiple transfusion and may develop typical haemolytic facies. An anaesthesiologist may encounter the surgical procedure which may be the part of treatment of haemolytic anaemia disease itself such as palliative splenectomy. These children may require some other surgical procedures having origins in haemolytic anaemia to cholelithiasis, dental carries, etc.

INTRODUCTION

Paediatric hematological system is an intricate and complex system of the body. The study of blood and its components is known as haematology. Blood has all the essential cells which help to maintain tissue oxygenation as well as to fight against the infections. The components are red blood cell (RBC) or erythrocytes, white blood cells or leukocytes, platelets and plasma which is rich in coagulation factors. Genetic mutations are common cause of functional derangement of hematological system. Haemolytic anaemia occurs due to ineffective erythropoiesis and lysis RBCs. Neonate and infants have different physiological aspects of haematology as compared to adult, therefore, for better understanding we discuss a little about it before proceeding for anaesthesia consideration in these patients. Earlier morphology and quantitative analysis of blood cells were the available methods of diagnosing bleeding disorder but now in the modern era it has been shifted to higher level with the invention of biochemical and genetic engineering. These methods allow to detect the root cause and to treat more precisely.

PHYSIOLOGY OF ERYTHROCYTE

During foetal life hematopoiesis occurs in three phases: Mesoblastic, hepatic and myeloid. Mesoblastic phase starts in the yolksac from 10 to 14 days of gestation and regresses by 10 weeks. Hepatic phase starts from 5^{th} week and occurs in the placenta till 10–12 weeks and in the liver till the second trimester. Myeloid phase starts from 20 to 24 weeks and remains throughout the life. In the body there is balance in the production and destruction of RBCs. Bone marrow is the main site of synthesis of RBCs and old and defective RBCs are sequestrated through the spleen. Excess but ineffective production leads to enlargement of bone marrow as well as spleen (splenomegaly) owing to defective erythrocyte. Normal survival of a RBC is 90–120 days. In neonate lifespan of RBC is about 80–100 days while 60–80 days in preterm infants.

Haemoglobin

An erythrocyte contains 95% of haemoglobin as major protein. Haemoglobin has two components, the heme particle and four globin chains. The heme has iron content and carries oxygen in the blood and there are two pairs of globin chain, alpha (α) and beta (β). In intrauterine life, the arrangement of globin chains differs with the stages of gestation. There are epsilon ε, gamma γ, theta ζ and delta δ chains apart from α and β chains.

Embryonic stage has the haemoglobins Gower 1 (ε_4 or $\zeta_2\varepsilon_2$), Gower 2 ($\alpha_2\varepsilon_2$), Portland ($\zeta_2\gamma_2$), Foetal ($\zeta_2\gamma_2$), foetal stage has haemoglobins Foetal ($\zeta_2\gamma_2$), haemoglobin A ($\alpha_2\beta_2$) and adult stage has haemoglobin A ($\alpha_2\beta_2$), haemoglobin A_2 ($\alpha_2\delta_2$) and foetal haemoglobin ($\alpha_2\gamma_2$). During intrauterine life the major number of Haemoglobin is foetal haemoglobin (HbF). Normal haemoglobin distribution in extrauterine life is >95% HbA, <3.5% HbA_2 and <2.5% HbF. Their arrangement is controlled by various genes present on different chromosomes. Mutations of genes lead to disorder of particular cell and affect its function.

Erythrocytes cell membrane is made up of various proteins which help to maintain the integrity of the cell. Neonatal RBC membrane is more resistant to osmotic lysis as compared to adult. Deficiency of membrane protein can lead to membrane hereditary spherocytosis. Normally mean corpuscular volume decreases after birth from 100–130 fl to 70–85 fl by the age of one year. Its persistent increased level indicates α thalassemia in newborn. Usually in newborn the appearance of nucleated RBCs and reticulocytosis is normal phenomenon but persistence is suggestive of haemolytic anaemia. The various hematological components level is shown in Table 9.1

ERYTHROCYTE METABOLISM

There are series of enzymes involve in the oxidative energy generating pathways in the metabolism of erythrocyte. Deficiency of any of these enzyme lead to defective formation of erythrocyte such as pyruvate kinase, glucose 6 phosphate dehydrogenase. Foetal and neonatal RBCs utilize more glucose and galactose as compared to adults. ATP generation is also more in preterm and term infants RBC than in adult RBC.

Oxyhaemoglobin dissociation curve

The haemoglobin oxygen saturation is plotted against the different partial pressure of oxygen. P_{50} is the value that the haemoglobin is 50% saturated with oxygen at particular partial pressure (PaO_2). In adult haemoglobin P_{50} is achieved at 26.3 PaO_2 while in foetal haemoglobin it is at 19.4 PaO_2 (Fig. 9.1). This shows the affinity of foetal haemoglobin is higher for oxygen and curve shifts to the left. This is helpful in intrauterine life to extract oxygen from maternal haemoglobin but in extrauterine life it has deleterious effect. Actually this property of foetal haemoglobin helps in diffusing oxygen from maternal haemoglobin at placental level. The 2,3 diphosphate glycerate (2,3-DPG) is produced during glycolysis in RBCs and it is present in higher amount at placenta. The 2,3-DPG interacts with β chain and increases dissociation of oxygen from HbA and shifts the curve to right. The HbF has α and γ subunits instead

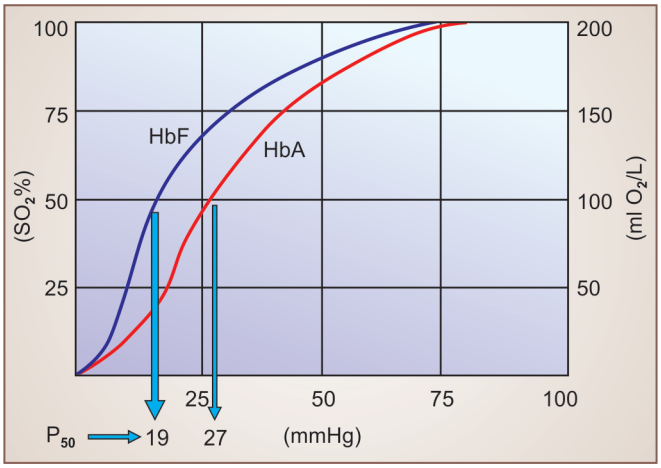

Fig. 9.1 Oxyhaemoglobin dissociation curve for foetal haemoglobin and adult haemoglobin

Table 9.1 Levels of various haematological components

Age	Hb (gm/dL)	HCT (%)	RC(%) (%)	WBC count (/mm³)	PC (/mm³)	PT (sec)	INR	APTT (sec)	Fibrinogen (mg/dL)	BT (min)
Preterm	13.6	43.6	—	7,710	260,000	13	1	53.6	243	3.5
At birth	17	55	5	18,000	300,000	13	1	42.9	283	3.5
1 year	12	36	1	10,000	300,000	11	1	30	276	6
Child	13	38	1	8,000	300,000	11	1	31	279	7
Adult	15	45	1.6	7,500	300,000	12	1	28	278	5

Haemoglobin (Hb), Haematocrit (HCT), Reticulocyte count (RC), Platelet count (PC), Activated partial thromboplastin time (APTT), Bleeding time (BT). The values are expressed as mean.[1]

Source: Modified and adapted from Essential of Haematology, Ch-9 Charles J. Cote. A practice of anaesthesia for infants and children.

of β, therefore it has a poor response to 2, 3-DPG and shows greater affinity for oxygen. The preterm infants contain high concentration of HbF and less of 2, 3-DPG therefore they need more amount of oxygen to prevent hypoxic event. The level of erythropoietin is high in preterm child as a result of decreased oxygen delivery at the tissue level which stimulates the hormone production. Owing to increased affinity for oxygen of HbF, there is difficulty in delivering oxygen at tissue level. To overcome this there is increased production of RBCs per blood volume and also exaggerated Bohr reaction in foetus. Acidic pH shifts the oxy-haemoglobin curve to right and helps in dissociation of oxygen at tissue level. Gradually in the third trimester the level of HbF starts decreasing and HbA increasing. Infant has high haemoglobin concentration at birth which gradually decreases to acquire the adult haemoglobin with increase in age. Concomitantly there is increase in concentration of 2, 3 –DPG. Both 2, 3-DPG and HbA enhance the extraction of oxygen from haemoglobin molecule at cellular level. In well oxygenated preterm child the oxygen releasing capacity is higher at 8 to 9 weeks than birth despite low oxygen content and haemoglobin concentration.

This transition of HbF leads to Pentose phosphate pathway is more vulnerable to oxidant induced injury as there is less number of membrane sulfhydrol groups in RBCs and decrease antioxidant capacity of newborn plasma. Also there is decrease number of Glutathione peroxidase in newborn RBCs as compare to adult RBCs. Therefore, newborn RBCs eventually develop glutathione instability and Heinz body formation on oxidant exposure.

Anaemia

Anaemia is defined as a reduction of haemoglobin concentration or RBC volume below the normal range. There are various causes of anaemia like nutritional, metabolic, environmental, infection, drugs, hereditary, etc. Iron deficiency anaemia is the most common cause of anaemia in children. Symptoms become apparent when haemoglobin level falls below 7–8 gm/dL. Sign and symptoms include sleepiness, pallor, irritability, decrease exercise tolerance, weakness. Gradually symptoms become severe in case of long standing anaemia such as tachypnea, shorteness of breath due to pulmonary hypertension, tachycardia, cardiac dilatation and high output cardiac failure.

Neonatal anaemia may occur due to placenta previa, abruption placenta, placental laceration, fetomateranal blood loss and twin-twin transfusion. The haemoglobin concentration per blood volume is higher therefore small amount of blood loss develops significant anaemia. These neonates present with pallor, hypovolemia, and hypotension. These patients do not show hyperbilirubinaemia as found in haemolytic disorder. The treatment lies with the infusion of crystalloid and blood transfusion in severe cases. At birth the haemoglobin level is 14–20 gm/dL which decreases to approximately 11 gm/dL by the age of 4–5 months. This is known as physiological anaemia of infancy. It is a normal response and adaptation to extra-uterine life.

Transfusion therapy is required to achieve normal level of blood indices and it improves the quality as well as the quantity by infusing the number of blood components. It improves the oxygen carrying capacity, immunological function and hemostatic functions. In children the recommendations for transfusion practice varies and it should be preferred to consult paediatrician before if excessive blood loss and fluid shifts suspected. The blood volume (BV) varies with the age in paediatric group. The preterm has blood volume 90–100 mL/kg which constitutes a greater proportion of body weight in comparison to full term neonate with blood volume 80–90 mL/kg. The infant between 3 months and 1 year has BV of 70–80 mL/kg and old child has 70 mL/kg. Anaemic preterm infants require blood transfusion to prevent apnoeic spell, respiratory and cardiac failure and neurological dysfunction. Fall of the haemotocrit level during intraoperative period define the requirement of blood transfusion. The normal healthy infant does not require blood transfusion until the fall of haemotocrit level 20–25%. The maximum allowable blood loss (MABL) is estimated by the formula of simple proportion:

$$\text{MABL} = \frac{\text{EBV} \times \left(\text{Child's haematocrit} - \text{minimum accepted haematocrit}\right)}{\text{Child's haematocrit}}$$

EBV is effective blood volume for the age. The calculation obtained through this formula is only a rough estimation of blood loss because the haemotocrit varies with rapid blood loss and the crystalloid infusion.

For infants and children that require massive transfusions, hyperkalemia will likely be a result. Be prepared to deal with it.

HAEMOLYTIC ANAEMIA

Haemolytic anaemia is caused by lysis of erythrocytes and ineffective erythrocytosis. Any anatomical,

Table 9.2 Causes of haemolytic anaemia in newborn

Congenital red blood cell disorder	Acquired red blood cell disorder
Red blood cell membrane disorder	Drug induced:
Hereditary spherocytosis	Toxins
Hereditary elliptocytosis	DIC
Red blood cell enzyme defect	Infections:
Glucose 6 phosphodehydrogenase	Thrombocytic thrombocytopenic purpura
Pyruvate kinase	Congenital heart disease
Haemoglobinopathies	Extra corporeal membrane oxygenation:
Sickle cell disease	Hemangioma
Thalassemia	

physiological and biochemical error in the RBC can lead to haemolytic anaemia.

It is classified as disorder of membrane proteins, disorder of enzymes and disorder of haemoglobin. Table 9.2 shows haemolytic anaemia in newborn due to red cell disorder.

How to Detect Bilirubin

Hyperbilirubinaemia with normal hepatic function is the marker of excessive red cell destruction. The occurrence of hyperbilirubinaemia in the first week after birth is known as physiological jaundice and it is a normal phenomenon. In term neonate and preterm neonate it is approximately 12 mg/dL (peak at 4th day) and 15 mg/dL (peak at 7th day) respectively. Normally the hyperbilirubinaemia in neonate occurs due to increase level of circulating red cell mass at birth, decrease life span of RBCs and increase enterohepatic circulation of bilirubin. In case of accelerated hemolysis the hyperbilirubinaemia is found more than this normal physiological value. Mild anaemia and reticulocytosis is normal findings in neonate but excessive hyperbilirubinaemia is the only factor which indicates haemolytic disease of newborn.

Carboxyhaemoglobin

Carbon monoxide has been produced from breakdown of heme group and carried in blood as carboxyhaemoglobin. It is also the marker of exccesive destruction of RBCs. The exhaled carboxyhaemoglobin is measured from lungs.

Hyperbilirubinaemia and carboxyhaemoglobin are the indicator of ongoing hemolysis, therefore, these neonates should be closely monitored and evaluated for cause of hemolysis.

Increased lactic dehydrogenase (LDH) is also a maker of destruction of RBCs which is released from LDH 2 isozyme from RBC.

The haptoglobin interacts with free haemoglobin and forms haptoglobin-haemoglobin complex. The decreased level of haptoglobin is an indicator of intravascular hemolysis.

DISORDER OF ERYTHROCYTE MEMBRANE PROTEIN

Hereditary Spherocytosis

Hereditary spherocytosis (HS) is the most common inherited haemolytic anaemic disorder. The incidence is approximately one in 5000.[2] Most of the HS has autosomal dominant inheritance (> 60%), however, some has sporadic mutation (20%) and remaining has autosomal recessive inheritance. There is defect in RBC membrane protein especially spectrin, ankyrin and band 3. These membrane proteins maintain the integrity of RBC membrane by maintaining surface tension. Defect in these proteins lead to osmotic fragility and hemolysis.

Clinical Manifestation

These patients are usually asymptomatic but may become symptomatic on exposure to bacterial or viral infections.[3] Neonate presents with anaemia and hyperbilirubinemia. Infant and young children present signs of anaemia (pallor, easy fatigability, weakness, exercise intolerance, irritability, palpitation,) and splenomegaly. In severe case jaundice has become the major feature in addition to severe anaemia. Pigmented gall stones are seen in 5% of children less than 10 years of age.[4]

Aplastic crisis is a severe form of HS is seen when these patients suffer from Parvo B19 virus infection.[5] There is fever with chills, lethargy, vomiting, diarrhoea, maculopapular rashes over the face, trunk and extrimities. They may require emergency splenectomy. All patients should be vaccinated against capsular organism before splenectomy.

Splenectomy is considered in case of severe anaemia (Hb < 10 gm%) and reticulocytosis (> 10%), hypoplastic

or aplastic crisis, poor growth and cardiomegaly. Splenectomy should be preferred after 4–5 years of age as immunological function is poorly develop in younger children.

Laboratory Investigation

Peripheral blood smear: Increase reticulocytes, polychromatophilic reticulocytes and spherocytes. Spherocytes are dense, round, hyperchromatic cells with lack of central pallor and have decrease mean cell diameter. In severe cases these spherocytes become dense, irregular, contracted or budding spherocytes.

Red blood cell indices: Normal or decrease haemoglobin 4–12 gm/dL, increase mean corpuscular haemoglobin concentration MCHC 36–38 gm% RBCs, Mean corpuscular volume is low shows dehydrated state of red cell.

Osmotic fragility test shows positive result as there is decrease in surface area in relation to cell volume. In this test the RBCs are suspended in the hypotonic buffered sodium chloride solution and membrane protein analysis has been carried out.

Indirect hyperbilirubineamia, increase fecal urobilinogen and erythroid hyperplasia of bone marrow are other markers of HS.

Treatment

Once the diagnosis confirmed, child should be called for regular follow-ups and screening should be done to know the spleen size, growth, iron stores, infection with Parvo virus B19 and presence of gall stones. Usually children are put on folate therapy 25 mg/day till 5 years of age and 5 mg/day thereafter in case of moderate to severe HS. In case of severe HS with splenomegaly, splenectomy should be considered as it checks the ongoing hemolysis, helps in returning of normal haemoglobin level. Splenectomy will be of benefit in all cases with severe HS and some with moderate HS, but is usually not needed in mild cases.[6]

Cholecystectomy can either be done alone in case of cholelithiasis or in combination with splenectomy.[7] After splenectomy patient's condition improves and there is no reported incidence of cholelithiasis.[8]

Anaesthetic Consideration

Preoperative presence of anaemia, thrombocytopenia, jaundice and splenomegaly is of great concern in a child posted for either splenectomy or cholecystectomy. After splenectomy patient improves dramatically, however, in initial period potential thrombocytosis happens but it will be transient.[1] However, Das et al. reported in their study that the risk factor for thromboembolism was increased with c-reactive protein, persistant thrombocytosis and elevated D-dimer following splenectomy in children.[9] Postoperatively there is increased risk of overwhelming infection with encapsulated organisms such as by *Streptococcus pneumoniae, Neisseria meningitidis* and *Haemophilus influenzae* type B. Especially younger children below 5 years of age are vulnerable to these infections, therefore, prophylactic vaccination against capsular organisms should be done before splenectomy. During intraoperative period avoid intramuscular injections and drugs associated with increase bleeding risk. Drugs such as aspirin, other NSAIDs and antiplatelets should be avoided. Splenectomy can be done either through conventional laparotomy or laparoscopic. Nowadays laparoscopic splenectomy is gaining popularity over conventional open splenectomy. Laparoscopic splenectomy decreases morbidity and hospital stay.[10] It is minimally invasive procedure, safe, effective and associated with less pain.[11] Partial splenectomy is done in case of young child below 5 year age. The immune functions not fully developed, therefore, they are more prone to develop postsplenectomy sepsis.

DISORDER OF ENZYMES

Glucose 6 Phosphate Dehydrogenase

Glucose 6 phosphate dehydrogenase deficiency G6PD is the most common hereditary RBC enzymatic disorder. It has been estimated that approximately 400 million peoples are affected with this disease.[12] It is an X-linked disorder affecting male population. G6PD enzyme is one of important enzymes of phosphogluconate pathway in the erythrocyte. G6PD catalyzes the process through which glucose 6 phosphate is converted into phosphogluconate.[13] The nicotinamide adinine dinucleotide phosphate (NADPH) is produced during this process which keeps the glutathione in the reduced state (functional) (Fig. 9.2). This pathway interacts with environmental oxidants and prevents globin denaturation. G6PD deficiency leads to denaturation of Haemoglobin and it gets precipitated inside the RBC known as Heinz bodies. This leads to damage of RBC membrane and the onset of haemolytic anaemia. Whenever patient exposes to certain metabolic disorder, infection, ingestion of certain drugs and fava beans widespread hemolysis occurs (Table 9.4).[14]

Table 9.3 Anaesthesia consideration in hereditary spherocytosis

Preoperative
Haemoglobin, reticulocyte count, platelet count
History of transfusions and special blood requirement such as extended phenotype, matching or leukocyte reduction
History of infections, aplastic crises
Check pre-splenectomy vaccination
Intraoperative
Antibiotic coverage
Blood and blood products if bleed
Avoid intramuscular injections
Avoid platelet inhibitory drugs: NSAIDs
Regional anaesthesia should be used cautiously in case of thrombocytopenia
Nasal intubation, nasogastric tube insertion also be done with care
Postoperative
Potential thrombocytosis but transient
Regular haemoglobin and platelet level
Maintain sterility and hygiene

Source: Modified and adapted from Essential of Haematology, Ch-9 Charles J. Cote. A practice of anaesthesia for infants and children.

It has provided some protection against the malaria especially against the deadliest form plasmodium falciparum.[13]

Clinical Manifestation

Acute neonatal anaemia, jaundice and abdominal or lumbar pain are common manifestations. Two types of clinical syndrome is encountered; chronic nonspherocytic hemolitic anaemia and episodic haemolytic anaemia.

Table 9.4 Drugs triggering hemolysis in glucose-6-phosphate dehydrogenase

Ibuprofen, Aspirin
Chloroquine, Primaquine, Pamaquine, Quinine
Chloramphinicol, Ciprofloxacin, Sulphonamide
Thiazide, Furesamide
Ranitidine, Antiemetics
Nitrates, Dopamine, Beta-Blocker
Barbiturate, Phenytoin, Benzodiazepine, Insulin
Methylene Blue, Local Anaesthetic

Table 9.5 Anaesthesia consideration in G6PD deficiency

Preoperative
History of haemolysis and offending factors
Haemoglobin, reticulocyte count
Intraoperative
Avoid triggering agents
Maintain good hydration, ABG
Cautiously use of triggering agent in infants
Monitor haemoglobin and urine output in high risk cases (on Cardiopulmonary bypass)
Postoperative
Haemoglobin, reticulocyte count, urine output in case of hemolysis

Source: Modified and adapted from Essential of Haematology, Ch-9 Charles J. Cote. A practice of anaesthesia for infants and children.

Laboratory Investigation

It includes complete blood picture, if there is recent history of hemolysis there would be anaemia, reticulocytosis, decrease serum heptoglobin and an

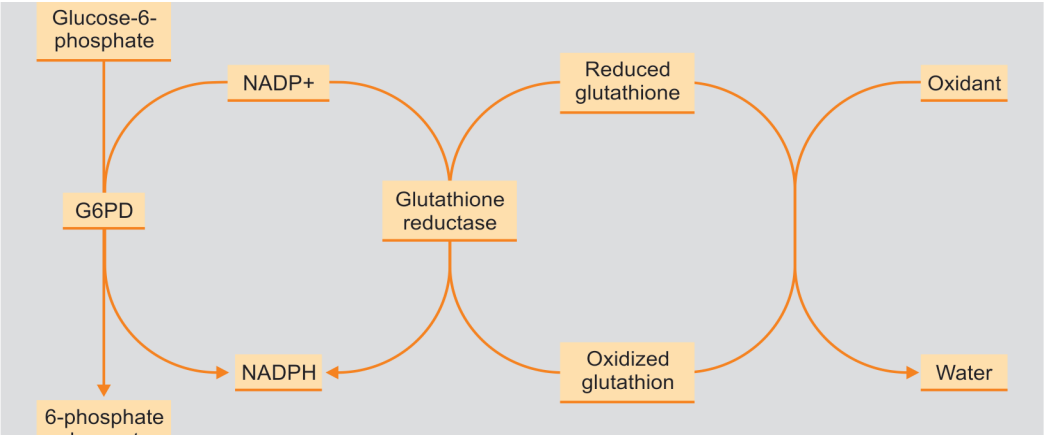

Fig. 9.2 Glucose-6-phosphate

elevated indirect bilirubin. Heinz bodies are seen on peripheral smear. Fluorescent spot test is the specific test to diagnose G6PD.

Anaesthetic Consideration

History of previous episodes of haemolysis, frequency of blood transfusion and exposure to precipitating factors are suggestive of type and severity of disease. Drugs used during anaesthesia should be given with precaution such as thiopentone sodium, non-steroidal antiinflammatory agents, ranitidine, anticonvulsant, certain antibiotics, diuretics, insulin.[15,16] Table 9.4 shows the list of drugs triggering hemolysis in G6PD deficiency. Surgical stress could be a precipitating factor, therefore, proper anxiolysis and good coverage of analgesia is required during perioperative period. Drugs such as benzodiazepins, propofol, ketamine, codein or codein derivative, fentanyl are safe and do not cause any haemolytic crisis in G6PD deficiency.[17] Benzocaine, lidocaine, articaine, prilocaine, silver nitrates should be avoided as they may induce methaemoglobinaemia and methlyne blue is ineffective in these patients.[18,19] Avoid acidosis and hyperglycaemia which are known to cause hemolysis. Postoperatve hypotension may not be a good guide of ongoing haemolysis but hematuria could be a reliable sign. Therefore, these cases require adequate monitoring of urine output. Actual hemolysis starts after 24–48 hours of exposure to triggering agent. Remove the trigger agent, maintain hemodynamics with vaso-pressors and maintain good urine output by infusing crystalloids. Consider blood transfusion in case of low haemoglobin. If patient gets discharge early, family should be informed about the sign and symptoms of acute hemolysis such as pallor, cyanosis, headache, breathlessness, jaundice, yellowish discoloration of sclera, lethargy, weakness, lumbar or substernal pain, dark-coloured urine. So that they should report to the clinician immediately for early intervention.

DISORDER OF HAEMOGLOBIN (HAEMOGLOBINOPATHIES)

Thalassemia

Thalassemia is due to reduced or deficient production of one of the globin chain of haemoglobin. The disease is prevelant in mediterranean, African and southeast Asian ancestors. It is an autosomal recessive disorder. Homozygous or heterozygous for either globin chain is known as a major or minor (trait) disease. Each year approximately 400,000 babies born with serious haemoglobinopathies and carrier frequency is about 270 million.[20] Approximately 32,400 infants in India born with serious haemoglobinopathies per year.[21]

Alpha (α) thalassemia occurs due to decrease production or absence of α chain and excess of β chain. In α-thalassemia mutation occurs at two closely located gene loci on chromosome 16. It means that four globin gene control the globin synthesis. It mainly affects HbA (α_2, β_2) and HbA_2 (α_2, δ_2). There is excess production of beta chain. In case of neonate there is excess production of uncontrolled γ chain as foetal haemoglobin contains γ. Number of mutant gene controlling the formation of globin chain will decide the clinical presentation. Four gene deletions is most serious presentation. These patients die in intrauterine life (hydrops foetalis) or may be stillborn or may die shortly after birth. Three gene deletions or haemoglobin H (HbH) show picture of chronic haemolytic anaemia and have history of multiple transfusion. This hemolysis is triggered by exposure to stress and oxidants. Two gene deletions have mild type of presentation and insignificant microcytic anaemia. Single gene deletion patients are silent carrier with no anaemia.

Beta (β) thalassemia is due to decrease production of beta chain and excess of alpha chain. In β thalassemia there is two globin gene defects on chromosome 11. Approximately 200 mutations found in α gene including substitution, inclusion and deletion. It is rare but carries poor prognosis. Clinical manifestation is of microcytic hypochromic anaemia. β thalassemia is again classified into three classes:

β thalassemia major

β thalassemia major is also known as cooley's anaemia or mediterranean anaemia. It is homozygous for β globin chain. Clinical presentations are of prehepatic jaundice, hepatosplenomegaly, thrombocytopenia, and severe microcytic anaemia. Along with these patients may have bony deformity of skull, vertebrae, facial, long bones and pelvis. Patient may develop high output congestive cardiac failure due to chronic anaemia and hemochromatosis. Patient also has liver and endocrine dysfunction. It is a severe life threatening condition and patient may die if left untreated. Patient requires frequent blood transfusions in first few years of life to combat anaemia. Patient may have recurrent fever and exposed to risk of getting multiple blood transfusion related infection such as HIV, hepatitis B or C. Children have delayed milestones and poor growth and may die in 5–6 years of age.

β thalassemia intermedia

β thalassemia intermedia is not that severe condition as major. Symptoms lie between major and minor state. Patient may have mild microcytic anaemia and may or may not need blood transfusion. Patient has symptoms of pathological fracture especially long bone fracture. Owing to ineffective erythropoiesis patient develops gall stones and splenomegaly. There is increase risk of venous thrombosis, pulmonary embolism, stroke and cardiomyopathy.

β thalassemia minor

β thalassemia minor is also known as thalassemia trait or carrier. It is an asymptomatic condition. Patient of this category has mild microcytic anaemia and does not need blood transfusion.

Sometimes β thalassemia is associated with other haemoglobinopathies like HbE, HbC or HbS.

Pathophysiology

Abnormal globin polymers aggregate and precipitate inside the RBCs known as inclusion bodies and destroy its membrane resulting into formation of abnormal RBCs. These abnormal RBCs are phagocytised inside the bone marrow and some comes out into the circulation leading to haemolytic anaemia. Decreased oxygen carrying capacity of blood owing to low haemoglobin content triggers release of erythropoietin and there are proliferation of premature erythroblasts to form erythrocytes. They are defective with globin precipitate and this results into ineffective erythropoiesis. This also initiates extramedullary erythropoiesis in liver and spleen.

Anaemia is due to ineffective erythropoiesis, increase peripheral hemolysis and overall low haemoglobin synthesis. Haemolytic anaemia leads to increase hemocromatosis. This increases iron load and damages the heart, bones and endocrine organs. Bony cortex becomes brittle and fragile and also gets easily fractured. There is enlargement of bone marrow and widening of bone especially face and skull bone. In severe cases splenomegaly, congestive cardiac failure and arrhythmias occur.

Laboratory Investigation

Peripheral blood smear, haemoglobin electrophoresis, bone marrow aspiration, iron studies, imaging studies such as computed tomography, magnatic resonance imaging, ultrasonography, echocardiography depending on the severity.

Treatment

Patient requires frequent blood transfusion and may undergo palliative splenectomy. Due to increase iron deposits patient requires iron chelation therapy. Currently phenotypic matching and leukocyte depleted blood transfusion; hormone and vitamin D therapy are being used. The bone marrow transplant and peripheral blood stem transplant are advanced therapies to cure haemoglobinopathies. Studies are still going on to find the cure. Gene modulation, erythropoietin, foetal haemoglobin modifier anti-oxidants are under investigation.

Anaesthetic Consideration

Careful evaluation of family history and history of multiple transfusions suggestive of thalassemia should be carried out. Planning of anaesthesia depends on the severity of disease and multiorgan dysfunction. Apart from routine investigations, special investigation should be done depending upon the organ dysfunction. Difficult airway suspected in case of maxillofacial bony deformity. Therefore keep difficult airway cart ready. Assess airway, size of the liver and spleen

Table 9.6 Anaesthesia consideration in thalassemia

Preoperative
Haemoglobin,
Appropriate available crossmatch (antibody-matched, leukocyte depleted)
Endocrine work up for diabetes mellitus, hypopituitarism, etc.
Cardiac evaluation
Liver functions
Airway assessment
Pre-splenectomy immunisation
Intraoperative
Difficult airway preparation
Gentle handling of demineralised extremities and proper padding to pressure points
Monitor cardiovascular function and post-splenectomy hypertension
Physiologic effects of laparoscopy on respiratory and circulatory function
Thromboembolism prophylaxis
Postoperative
Monitoring includes cardiovascular function
Thromboembolism prophylaxis

Source: Modified and adapted from Essential of Haematology, Ch-9 Charles J. Cote. A practice of anaesthesia for infants and children.

preoperatively. Chest X-ray to know the status of lungs as lung congestion might be there due to anaemia and repeated blood transfusion. Preoperative vaccination should be checked. Adequate blood, type specific antibody matched and leukocyte depleted plasma should be arranged before surgical procedure. Regional anaesthesia is safe to avoid systemic complications but may have difficulty in positioning and performing procedure. In severe cases general anaesthesia is safe, however, difficulties can occur in securing of airway due to bony deformity of skull and vertebrae. Apart from splenectomy and cholecystectomy children may come for vascular access placement for frequent blood transfusion. Also, demineralised bones are prone to fracture and older children may come for osteotomies for bony deformities. The sodium nitroprusside should be administered with caution during open heart surgeries or in other cases.

SICKLE CELL ANAEMIA

Sickle cell disease (SCD) is a congenital haemoglobinopathic disorder. Sydenstricker and associates described the first occurrence in children, recognised the association with haemolytic anaemia and introduce the term crisis to describe periodic acute episodes of pain.[22] Haemoglobin comprises active heme group and two globin chain. Mutation occurs at sixth codon of β globin chain and encodes valine instead of glutamate. Sickle cell anaemia is severe and homozygous form of HbS. It has >90% of circulating HbS. Sickle cell trait is mild form with single allele HbS (<50%) and HbA. Compound heterozygous is with HbS and HbC. SCD may be associated with α thalassemia known as sickle β thalessemia (S/β^o or S/β^+). Intrauterine life, the major concentration of Hb is Foetal Haemoglobin HbF, while HbA and HbA_2 are in minor. Normal haemoglobin distribution in extrauterine life is >95% HbA, <3.5% HbA_2 and, <2.5% HbF. In India haplotype is found in Odisha and Pune region. These patients have mild disease and there is increase level of foetal haemoglobin. HbF inhibits HbS polymerisation in sickle cell anaemia and it is considered as powerful modulator of the clinical and hematological features of sickle cell anaemia.[23] Studies found that higher concentration of HbF were associated with reduced rate of acute painful episodes, fewer leg ulcers, less osteonecrosis, less frequent acute chest syndromes and reduced disease severity.[23] Therefore, nowadays increasing the level of HbF is geared up as one of the treatment modality.[24]

With increase in haemolytic episodes 30–50% of children may develop cholelithiasis.[25] Most of the gall stones are pigmented and made up of calcium bilirubinate. Severe right hypochondriac pain and fever of cholelithiasis require cholecystectomy at an early age. Patient develops characteristic haemolytic facies with frontal bossing, wide intercanthal distance, flat nose or depressed nose bridge, malar prominence and muddy sclera along with pallor and icterus. Sickle with thalassemia β^o present with haemoglobin 6–10 gm/dL, vaso-occlusive crises and aseptic necrosis of bone. Sickle with thalassemia α^+ present with haemoglobin 10–14 gm/dL and rarely vaso-occlusive crises and avascular necrosis.

Sickle cell disease or anaemia is also known as vaso occlusive disease. Oxygen is extracted from HbS results in deformation of erythrocyte into sickle shaped. Sickling occurs in case of oxidative stress (PaO_2 <40 mmHg) and it occludes the microvascular circulation leading to tissue ischaemia and infarction. Gradually it involves all the systems leading to multiorgan failure. Deformed red blood cells obstruct the flow leading to severe bone and joint pain, renal insufficiency to concentrate, stroke, acute chest syndrome (ARDS) and heart failure.

Clinical Manifestation

Frequent bacterial infections are common due to abnormal immune function. Recurrent episodes of fever and bone or joint pain (Dactylitis) are common manifestations. The precipitating factors are physical stress, infection, acidosis, dehydration, hypoxia, and exposure to cold or sometime swimming. Newborn with sickle cell anaemia is usually not anaemic and asymptomatic due to presence of HbF.

The most fatal is splenic sequestration or splenic crisis in infant and young children. Patients experience severe form of abdominal pain, anaemia and hypovolumic shock. These patients require aggressive supportive treatment and emergency splenectomy. Sometime patients undergo autosplenectomy due to splenic infarction. Acute splenic sequestration is a life threatening complication in infants. In case of severe anaemia 5 mL/kg packed red blood cell transfusion should be considered and after the acute attack prophylactic splenectomy should be done.

Acute chest syndrome present with fever, dysponea, tachyponea, cough, wheezing, pulmonary hypertension and respiratory failure. Decreased oxygen saturation, acidosis, hypoxia and diffuse lung infiltrations are other

characteristic features. Good hydration, antibiotic coverage, oxygenation can improve the lungs but severe cases might require mechanical ventilation.

Treatment

All children should receive oral prophylactic dose of penicillin VK (125 mg twice a day up to 3 years, then 250 mg twice a day) till the age of 5 years. After 5 years of age, the prophylactic dose recommended only for those children who has history of pneumonia. In case of penicillin allergy erythromycin ethyle succinate 10 mg/kg twice a day is recommended. British Journal of Haematology (BJH)[26] has given the guideline for blood transfusion in sickle cell disease is shown in Table 9.7.

Anaesthetic Consideration

History of previous attacks and repeated hospitalization is important part of preanaesthetic checkup. It provides the valuable information about the extent, pattern and severity of the disease. Degree of organ dysfunction should be judged by all essential investigations. Pulse oximetry, chest X-ray, BUN and creatinine, ECG, haemotocrit are routinely advised investigation to know the organ dysfunction. Rarely echocardiography and arterial blood gas is advised. Patients may present with sepsis, renal insufficiency, splenomegaly, pulmonary hypertension, stroke, seizures and cardiac failure. Previous history of blood transfusion will guide us the patient response to the treatment. All patients who are posted for splenectomy should receive vaccination against the capsular organism such as pneumococcus, Streptococcus, *Haemophilus influenzae*. In younger patient sometime partial splenectomy is done to provide immune action against these infections but later life they might require total splenectomy. Goal for prophylactic blood transfusion is to achieve haemoglobin 10 gm/dL as above this limit hyperviscosity syndrome may occur. Exchange transfusion is no longer advised as there is increase risk of red blood cell alloimmunisation. It is indicated in case of severe anaemia and if when phototherapy and other measures fail to control bilirubin load. In this technique antibody coated RBCs are replaced with RBCs negative for antigen to which mother is alloimmunized. In sick or preterm neonate additional platelet therapy should be considered during exchange transfusion. Prophylactic transfusion has controversies like some studies are *pro and say* it is always beneficial to transfuse preoperatively as it is helpful to prevent sickling by maintaining good amount of haemoglobin. Perioperative consultation with haematologists and paediatric intensivists is helpful in treating these patients. Surgical procedures are classified according to the need of blood transfusion. Low risk surgeries are inguinal herniotomy and extrimities, intermediate risk surgeries include intra-abdominal and high risk surgeries are intracranial and intrathoracic. Minor low risk surgeries rarely require transfusion. In sickle cell disease the history of episodes of vaso-occlusive phenomenon tells the severity and pattern of the disease, therefore, as an anaesthesiologist we should check the extent of organs dysfunction preoperatively. All the triggering factors leading to oxidative stress during intraoperative period should be avoided. Factors such as hypothermia, hypoxia, hypercarbia, acidosis and dehydration should be avoided.[27] Keep the operating theatre little warm maintain the temperature around 80–85° F and keep the patient also warm with the help of warming blankets and infusing warm fluids. Maintain good and peaceful environment inside the operation theatre. Give adequate dose of anxiolytic and analgesia with 100% oxygenation. To avoid hypoxic crises administered 100% oxygen a few minute before and after the intubation or extubation. Acute chest syndrome and pain are two most frequently encountered postoperative complications. Along with these fever or infection, vaso-occlusive crisis and transfusion related complications may occur in the perioperative period (Table 9.8).

Anaesthesiologist is often called for pain management in case of acute sickle crisis. Lower extremity pain due to vaso-occlusive crisis can be managed with continuous neuraxial blocks. Analgesia is managed with opiates and NSAIDs should be used with caution in case of renal involvement.

When rapid reduction of level of HbS is necessary, as in CNS crisis exchange transfusion, ET has been preferred. 60–80% decrease in number of circulating sickle cells in 6–12 hrs by exchanging two times the red cell mass (2 × Blood volume × Haematocrit). In determination of the total blood volume or number of units of blood needed for the exchange, one must take into consideration the pack red cell mass in a unit of blood.

Table 9.7 BJH guideline for blood transfusion in SCD

Top-up (Standard) transfusion	Splenic and hepatic sequestration Aplastic crises
Exchange transfusion	Chest syndrome, stroke, priyaprism
Hypertransfusion	Stroke, renal failure (in case of recurrence)

Table 9.8 Anaesthesia consideration in SCD

Preoperative
Screening of at risk children
Consultation with haematologist
History of acute chest syndrome, vaso-occlusive pain crises, hospitalization, transfusions, transfusion reactions
Neurological assessment (stroke, cognitive limitation)
History of analgesic and other medications
Haemoglobin, haematocrit
Oxygen saturation (room air), chest X-ray
Pulmonary function tests (if the history suggestive)
Echocardiography (if the history suggestive)
Neurological imaging (if the history suggestive)
Renal function tests
Transfusion crossmatch (antibody matched, leukocyte depleted, sickle negative)
Transfusion parenteral hydration if nil per oral
Pain management
Bronchodilator
Appropriate antibiotic coverage
Pre-splenectomy immunisation
Intraoperative
Maintenance of oxygenation, perfusion, normal acid–base status, temperature, hydration
Type specific blood for transfusion
Appropriate anaesthesia procedure and postoperative analgesia
Laparoscopic consideration
Appropriate antibiotic therapy
Judicious use of tourniquets, cell saver and cardiopulmonary bypass
Postoperative
Haematologist consultation
Monitoring of complication especially acute chest syndrome and vaso-occlusive crises
Maintenance of oxygen saturation monitoring and supplementation as required including supplemental oxygen in the first 24 hours regardless of oxygen saturation
Good hydration
Antibiotic coverage
Pain management
Early mobilization
Incentive spirometry and bronchodilator therapy

Source: Modified and adapted from Essential of Haematology, Ch-9 Charles J. Cote. A practice of anaesthesia for infants and children

Initially by PCV once HCT reaches 35, PCV diluted with appropriate electrolyte solution or plasma. BJH recommends the haemoglobin level at 8–10 gm/dL in preoperative period which is as effective as ET and safe practice. Minor and straightforward cases such as tonsillectomy and cholecystectomy can be done without transfusion. The major cases such as hip or knee replacement, organ transplantation, eye surgery and major intraabdominal surgeries may require preoperative transfusion. Maintain HbS below 20% by transfusion of RBCs.

Researcher from cooperative study of sickle cell disease found comparable complication rates in both HbSS and HbSC groups and suggested that regional anaesthesia were at higher risk of complications than those undergoing general anaesthesia.[28]

Simple transfusion to raise the Hb levels to 10 gm% in all SS group. The choice should be antigen-matched, leukocyte-depleted packed red cells. All patients, especially those with prior occurrence of pulmonary dysfunction or a history of multiple hospital admission, should receive a minimal 12 hrs of oxygen treatment and maintenance of intravenous fluid to avoid dehydration. High-risk patients should be monitored for oxygenation and regular measurement of input, output and weight.

COAGULATION SYSTEM

Any injury to vessel wall initiates coagulation (clotting) cascade. There are two main pathways and a common pathway involve in clotting mechanism. Intrinsic pathway occurs at sub endothelial wall whenever there is breech in the integrity of vascular wall. Extrinsic pathway occurs at tissue level and it potentiates the intrinsic pathway and common pathway. Three mechanisms occur to reduce the blood loss or to stop further loss.

1. **Vascular spasm:** As soon as there is breech in vessel wall, the vascular smooth muscle contraction occurs immediately to reduce the further blood loss.
2. **Platelet plug:** There is formation of platelet plug as a result of platelet adhesion, platelet release reaction and platelet aggregation, this is known as primary hemostasis. When there is injury to vessel wall, the breeched endothelium is exposed to circulating platelets. Platelets adhere to collagen with the help of collagen glycoprotein surface receptor Ia/IIa. The chemical messangers like adinosine diphosphate (ADP), serotonin, thromboxane A_2 released by these adhere platelets and attract more platelet to stick with them resulting into formation of platelet plug. This process is also strengthen by activation of

von Willebrand factor vWF which is released by endothelium and platelets. It also carries factor VIII.

3. **Blood coagulation mechanism:** Haemostasis is the complex physiological process that ceases the blood loss from the bleeding vessels. The coagulation factors are activated by intrinsic, extrinsic and common pathways to form fibrin clot is known as secondary haemostasis. This occurs simultaneously with primay haemostasis to prevent further blood loss. The fibrin clot is formed over the platelet plugs and seals the broken blood vessel. Intrinsic pathway is initiated when sub-endothelial surface is breeched, also known as contact activation pathway. This involves a series of activation of XII or Hageman factor, XI, prekallikrein and high molecular weight kininogen (HMWK) clotting factors. The factor XII is activated by kallikrein and interacts with HMWK to activate factor XI. Activated XII also activate prekallikrein to convert into kallikrein, which in turn, can convert HMWK into bradykinin. Bradykinin is a potent vasodilator and increases vascular permeability. Activated factor XI further activates factor IX. Now on the platelet surface in presence of factor IXa, factor VIIIa, phospholipid and calcium factor X is activated. Extrinsic pathway is initiated when tissue factor is exposed to factor VII and factor VIIa is formed. Extrinsic pathway plays a major role in the coagulation cascade and it is the primary pathway. Factor VIIa potentiates Xa. From this step the common pathway starts. Xa and Va then catalyze the reaction of conversion of prothrombin (Factor II) into thrombin. This thrombin converts soluble fibrinogen (factor I) into insoluble strands of fibrin. And multiple fibrin fibres join together and form fibrin clot. This thrombin also activates factor IX, factor VIII, factor V and factor XIII. Factor XIII provides stability to the fibrin clot.

In Case of Deficiency of Coagulation Factors the Blood Indices are Affected

Prothrombin time (PT): PT is the time that measures the clotting tendency of blood. It measures the efficacy of extrinsic pathway of coagulation. PT is used to measure the factors I, II, V, VII and X. PT and its derived measures such as prothrombin index and international normalized ratio are also used to measure the extrinsic pathway. Calcium containing thromboplastin reagent is added to citrated plasma sample and time taken to clot formation is noted by using an automated instrument. The reference range varies with the laboratories as type of instruments and amount of thromboplastin reagent differ. However, the normal prothrombin time is 10–11 seconds. It is usually prolong in neonate owing to poor availability of vitamin K. It is increased in case of clotting factor deficiency (level < 30%), liver damage, vitamine K deficiency, anticoagulant therapy warfarin.

Activated partial thromboplastin time (APTT): It measures the intrinsic pathway of coagulation and it has been measured with PT to know the deficiency of other factors. Proteins of intrinsic pathway are present in liquid form. When blood comes in contact with foreign object or damaged endothelial cell initiates clotting cascade. This process is monitored by standard clinical clotting assay known as activated partial thromboplastin time. In this test the partial thromboplastin reagent deficient tissue factor is mixed with citrated plasma sample and in this mixture surface contact agent (celite, kaolin, silica, etc.) is added. This is incubated for 3–5 minutes and calcium chloride is added. Factor XII, prekallikrein or HMWK deficiency results into markedly prolonged APTT without significant clinical bleeding. Isolated prolongation of APTT occurs in case of deficiency of factors VIII, IX or XI with clinical bleeding. Usually the reference level for children and adult is 26–35 seconds, while a little longer 30–54 seconds in term infants and even longer in preterm infants. The sensitivity depends on the specific reagent used. Most of the APTT reagents cause prolongation of APTT in case of deficiency of factor VIII less than 35 percent. It is also a useful method to monitor standard heparin therapy. Sometime contamination of patient sample with heparin may cause prolongation of APTT. Polycythemic infants also show prolonged APTT as citrate to plasma ratio has not been corrected for high haematocrit level.[29]

Thrombin Time (TT)

It measures reduced level and function of fibrinogen. The test is performed by adding bovine thrombin to the citrated plasma sample and time to clot formation is recorded. Time is 16–18 seconds.

Bleeding Time (BT)

Bleeding time originally described by Harker and Slichter. It gives us idea of platelet number and function. The normal bleeding time ranges from 3 to 9 minutes. It is pronged when the platelet count below the 100,000/µL and also in case of deranged platelet function (congenital or acquired), vasculitis, connective tissue disorder, and vWD. In this test a spring loaded blade is

used, which makes a linear cut of 1–2 mm depth and bleeding blotted away by using filter paper and time is recorded with stopwatch.

Specific Clotting Factor Assay

This can be carried out by mixing the diluted test plasma with specific factor deficient substrate plasma. Clotting time is measured.

Disorder of Coagulation Factor

Haemophilia

Haemophilia is a hereditary disorder of coagulation factors. Haemophilia A and haemophilia B occur due to deficiency of clotting factor VIII and IX respectively. The incidence of haemophilia is 1 in 5000 males.[30] It is an X-linked recessive disorder, therefore, males are the affecting gender and females act as a carrier. Usually patient presents with bleeding disorder. The extrinsic pathway (tissue factor) requires factor VIII and factor IX for normal thrombin formation and therefore deficiency of either factor leads to impairment in production of thrombin and fibrin. This disruption in hemostasis leads to delay in clot formation and bleeding diathesis occur.

Haemophilia A accounts for 85–90% of total haemophilic disorder and is due to deficiency of factor VIII (antihemophilic factor). Haemophilia B or Christmas disease is due to factor IX (plasma thromboplastin component). Depending upon the factors concentration, patients are classified into three groups: Mild, moderate and severe. Mild group has 5–50% of normal level of clotting factor VIII or IX, moderate group has 1–5% of normal level of clotting factor while in severe group <1% (1 unit/dL) of normal level of clotting factor. Minimal haemostatic level of factor VIII is 0.3–0.5 U/mL and factor IX is 0.2–0.5 U/mL.

The genes for factor VIII and factor IX are present on long arm of X chromosome. Numerous genetic mutations are found in haemophilia but most common genetic mutation is gene inversion in haemophilia A and missense point mutation in haemophilia B.

Clinical Features

The patient of mild group may remain asymptomatic till adulthood or throughout life. Patient of haemophilia presents with unexplained bleeding, easy bruising, painful bleeding joints (hemarthrosis), nose bleed, gum bleed, blood in urine or stool and intramuscular bleed. The hallmark of haemophilia is musculoskeletal haemorrhage. Study shows 40–60% of children with severe haemophilia A are clinically symptomatic as newborn, approximately 40% may become clinically symptomatic by age of one year and approximately 50% show major bleed by the of age one and half year.[31] About 30% of child experience bleeding at the time of circumcision.[32] Along with it 1–2% of neonate may have an intracranial haemorrhage ICH.[33] In children the risk of ICH varies from 2 to 8%. Bleeding joints are common in older infants and children while rare in neonate. Severe factor VIII deficiency is most common hereditary disorder of neonatal age group. Diagnosis can be made when child begins to crawl and walk. Ankle joint haemorrhage is most common presentation when toddler tries to maintain upright posture. Other joints involved are knees and elbows.

Laboratory Investigation

If clinical manifestations and family history are suggestive of disease, then PT, APTT, BT, fibrinogen or TT, platelet count should be carried out. PT is found normal in haemophilia but APTT is prolonged in factor VIII or IX. Identify vWF also.

Anaesthetic consideration

Most of the haemorrhagic disorders have familial inheritance, therefore, family history may give valuable information related to the disease. Children of mild group may have not been experienced of spontaneous bleeding episodes but during surgery they are at risk. Screening of the patient should be carried out for the factor deficiency and clotting factor level should be normalised before taking the patient for surgery. According to The Royal Children's Hospital (RCH)[34] recommendation, the peripheral venous cannulation should be performed very carefully. Distraction, relaxation and sometime mild inhalational sedation technique is required. Invasive procedures such as arterial cannulation and lumbar puncture should only be attempted after appropriate clotting factor replacement.[34] Do not give intramuscular injections. NSAIDs (e.g. Ibuprofen, diclofenac, ketorolac) should be avoided, paracetamol, codein/codein derivative, morphin and tramadol can be given for analgesia.

In case of oral bleeding, torn frenulum or for tooth extraction, the aim of achieving the factor levels is 30–40 units/dL with replacement therapy. The tranexamic acid or e-aminocaproic acid can be used as supplement therapy with replacement therapy to stabilize the clot until healing. In case of oral surgery nasal intubation should be avoided as far as possible as it may cause injury to adenoids and uncontrollable

bleeding provoked. Make the endotracheal tube soft with warm water and do careful oral intubation. After oral intubation, fix the tube with adhesive by keeping the mouth probe in place which widens the intraoral space.

In case of severe haemophilia minimum hemostatic level should be achieved 100%, then 50% until wound healing begins, then 30% until wound healing is complete. Start the therapy with 30–50 U/kg, 12 hourly or by continuous infusion.

Desmopressin DDAVP is a synthetic vasopressin analog which significantly increases the level of factor VIII and vWf. It is the treatment of choice in cases of mild and moderate haemophilia A if patient had responded well to the drug during therapeutic trial. It is not effective in case of severe haemophilia A, severe vWd and in any form of haemophilia B.[35] The side effect of desmopressin are headache, flushing, tachycardia, hypotension and rarely hyponatremia. Fluid intake should be limited to the maintenance levels for at least 24 hours. In case of repeated dosing serum sodium level should be checked. Usually DDAVP is not recommended in children less than 3 years as documented studies show hyponatremia and seizures. It is relatively contraindicated in known case of epileptic disorder. RCH recommended dose of intravenous desmopressin is 0.3 µg/kg and should be administered in 25 to 50 mL of normal saline over 20 to 30 minutes. It should be given one hour before the surgery as the maximum response seen at 30 to 60 minutes after the administration.

Choice of replacement therapy (concentrates) depends on the purity and viral inactivation. Fresh frozen plasma contains all the clotting factors and can be used as a replacement therapy in all bleeding disorders. FFP and cryo poor plasma contain factors IX, XI, X, VII and widely used for treating haemophilia B. Cryoprecipitate which is obtained by slow thrawing of FFP at 4°C for 12–24 hrs is used to treat of haemophilia A as it contains factor VIII, vWF, XII and fibrinogen. World Federation of Haemophilia (WFH) has given the guideline over treatment preference for bleeding disorder. They have advised to use factor concentrates instead of giving FFP. Commercially available lyophilized FVIII is preferred in case of haemophilia A. it is given by calculating the exact unit required to achieve the desired level. The formula to obtain the amount requires is patient body weight in kilogram multiplied by desired level multiplied to 0.5. In case of children it should be transfused at the rate of 100 unit per minute. The half life of factor VIII is approximately 10 to 12 hours. Therefore, factor VIII should be given in continuous infusion to maintain steady plasma level. Factor IX is also given by calculating the dose through the formula where desired factor level is multiplied by the body weight (kg). The half life of factor IX is approximately 18 to 24 hours, therefore, it does not need to be given as often.

Replacement materials should be infused to achieve a level of 80 units/dL of factor IX and 100 units/dL of factor VIII; the levels should be maintained at greater than 50 to 60 units/dL for 7–10 days postoperatively. Lower doses to maintain levels at greater than 20–30 units/dL for an additional 1–2 weeks may then be used and continued till complete healing has occurred.

Prothrombin complex concentrate (PCC) can be an effective and alternative therapy in haemophilia. PCC is thrombogenic and risk of thrombosis increased in patient using high or repetitive doses, in patient with impaired fibrinolysis (liver disease or after the treatment with antifibrinolytic agents), and in patient with impaired ability to clear activated clotting factors (liver disease).[35] International Society of Thrombosis and Hemostasis has recommended adding of 100 units of heparin to each of 500 units of factor IX concentrate.

Sometimes acquired factor VIII or IX inhibitors coagulopathy are seen in patients with repeated transfusions. These patients have produced antibodies against these factors and become prone to increase blood loss during surgery in spite of factor transfusion. In these patients bypass agents recombinant factor VIIa or activated prothrombin complex concentrates transfusion is beneficial. About 10–15% of haemophilia A and 1–3% of haemophilia B patients may develop inhibitors against the factors and fail to respond routine replacement therapy. Most of the inhibitor develops as early as after 10–20 days of exposure in case of severe genetic disorder. Therefore, all known bleeding disorder should be screened for both factors as well as for inhibitors. The Bethesda assay has been used to know the inhibitor levels. On the basis of Bethesda titre, the patients are divided into two categories. High responder has Bethesda titre more than 10 and having high titre antibody which may become hundreds or thousands on repeated exposure. Low responder has Bethesda titre less than 10 and maintain at this even on repeated exposure. Very low titre cannot be detected and show low clinical recovery and short half life of clotting factor. Children should be screened every 3–12 months or 10–20 exposure days. Low responder can be treated with factor VIII concentrate infusion but high

Table 9.9 Anaesthesia consideration in hemophilia

Preoperative
Hematologist consultation
Identify and treatment plan
Multiple surgery in one time
Preoperative DDAVP as it increases the factor VIII significantly
Discontinuation of anti-platelet drugs
Inhibitor level
Intraoperative
Judicious use of regional anaesthesia, intramuscular injections, nasogastric tube insertion, nasal intubation
Judicious use of potential bleeding medication
Coagulation profile for factors VIII and IX
Consider transfusion of factor concentrates if not responding check for inhibitor levels
Recombinant activated factor VII in severe bleeding
Postoperative
Maintain factor level for specified time period as advised by hematologist
Available blood products
Anticipate and treat bleeding episode

Source: Modified and adapted from Essential of Haematology, Ch-9 Charles J. Cote. A practice of anaesthesia for infants and children

responder needs aggressive treatment with porcine factor VIII concentrate, recombinant factor VIIa, or with PCC. Recombinant factor VIIa is administered as a bolus injection and a treatment consists of 90 µg/kg every two hours for three doses. The concurrent administration of tranexamic acid increases clot stability. An alternative therapy is an activated prothrombin complex concentrate. This is a plasma-derived product, and is given at a dose of 50–100 units/kg, maximum daily dose of 200 units/kg. The use of tranexamic acid should be avoided with PCC as it may increase the risk of thromboembolism.

Antifibrinolytic drugs such as tranexamic acid, epsilon amino caproic acid in case of mucosal bleed as an adjunct. These durgs should not be given with PCC as there is potential thrombotic complication may occur. Avoid antifibrinolytics in case of renal bleeding as unlysed clot behave like stones causes ureteric colic and obstructive nephropathy.

Avoid platelet inhibitory drugs such as acetylsalicylic acid and non-steroidal anti-inflammatory drugs such as acetoaminophan paracetamol can be given safely.

Apart from these measures researchers are going on to treat haemophilia with genetic modifications. Gene therapy, cell therapy and tissue engineering have been recently developed modalities helpful in treating haemophilia. Induced pluripotent stem cells technology is also one of the recently developed techniques in treating haemophilia.

von Willebrand Disease

von Willebrand disease (vWD) is a most common hereditary bleeding disorder where von Willebrand factor (vWF) is defective or deficient. The vWF is essential plasma protein for the initial adherence of platelet to the injured endothelium and it also acts as carrier protein for the clotting factor VIII. The prevalence is 1 in 1000 to 3 in 100,000 of population.

vWF is produced from megakaryocytes and endothelial cells and stored in cellular granules known as Weible-Palade body in the endothelial cells and alpha granules in platelets.

vWD is broadly divided into three type. Type 1 and type 2 are autosomal dominant while 3 is ressecive type

Type 1: This is most common (75%) variant of vWD. It is characterized by decrease quantity of normal vWF. Patients show mild to moderate bleeding.

Type 2: This has qualitative defect in vWF and subdivided into 2A, 2B, 2M, 2N. Each subgroup has different genetic determinants but shows no clinical difference. They usually manifest moderate bleeding.

Type 3: Double heterozygous for vWF antigen is most severe but rare variant. This is characterized by absence of vWF as well as decrease vWD activity and factor VIII.

Clinical picture: Most common manifestation of this disease is mucocutaneous bleeding such as gum bleeding, epistaxis, skin bruise, menorrhagia and gastrointestinal bleeding. They experience excessive bleeding during trauma and surgery. Rare cases require blood transfusion.

Laboratory findings: Apart from routine investigations and cogulation profile, specific tests include vWF antigen assay, factor VIII asssay and ristocetin cofactor assay (it is a functional assay of platelet aggregation in presence of ristocetin). Bleeding time is prolonged. In mild case APTT is normal but in severe cases it is prolonged.

Anaesthetic Consideration

Both the disorders of clotting pathway can be presented with same complaints of repeated brusing and epistaxis but the large haematomas and haemathroses are

associated mainly with haemophilia. History of recurrent epistaxis, bruising and postoperative bleeding after surgery especially tonsillectomy in either parents is also helpful in making diagnosis. A careful family history may identify the same symptoms in the parents or a sibling is suggestive of familial disorder. Patient should be optimised before surgery once diagnosis confirmed or in case of emergency surgery keep adequate blood and blood products ready. Patients who are more than 2 years of age, who have vWD and had not received vaccination, should be immunized against hepatitis A and B. Anaesthetic goal is cessation of bleeding or prophylaxis for surgical procedures. Avoid NSAIDs especially aspirin and other platelet inhibitory drugs. Avoid using blood components to control bleeding in the most of the cases of vWD. The DDAVP should be administered 90 minutes before the operation at a dose of 0.3 µg/kg which will increase the vWF and factor VIII to normal (>100 IU/mL). One thing is very important in using DDAVP that fluid restriction should be needed as younger children are prone to develop hyponatremia and seizures. In case of qualitative deficiency of vWF, vWF concentrates and factor VIII concentrates transfusions are required. In the post operative period the minor bleeding can be controlled with antifibrinolytic agent tranexamic acid.

Table 9.10 Anaesthesia consideration in vWD

Preoperative
Haematologist consultation
Determination of actual and desired factor
Discontinue platelet inhibitory drugs
Intraoperative
Judicious use of regional anaesthesia, intramuscular injections, nasogastric tube insertion, nasal intubation. Judicious use of potential bleeding medication
Coagulation profile
Consider transfusion of blood and factor concentrates
Consider use of antifibrinolytic drugs (e-aminocaproic acid, tranexamic acid)
Recombinant activated factor VII in severe bleeding
Postoperative
Factors levels VIII and vWF
Blood and blood products
Appropriate management of bleeding episodes
Watch for thromboembolic phenomenon

Source: Modified and adapted from Essential of Haematology, Ch-9 Charles J. Cote. A practice of anaesthesia for infants and children

DISORDER OF PLATELETS

Platelets are small cells of 1 to 4 mm diameter. The normal platelet count is 150,000–450,000/µL. The lifespan of a platelet is normally 7–10 days. Two-thirds of total platelets are present in the blood and approximately one-third are sequestrated in the spleen at any one time. Therefore, approximately 15,000 to 45,000/µL must be produced every day to maintain steady state. Platelets are important and essential component of hemostasis. Primary hemostasis is achieved by forming the platelet plug. Excessive bleeding may occur, if platelet count is low or platelet function is defective. The clinical manifestations of platelet type bleeding are of skin or mucous membrane bleed. Patechiae, eccymosis, epistaxis, menorrhagia, and gastrointestinal bleeding are common manifestation. Rarely hemarthrosis and deep muscle bleed. Platelet count is low may be because of reduced production or increase consumption.

Platelet membrane provides receptors for the formation of coagulation-complex. These receptors are integrin α/β heteroduplexes, the leucine rich receptor glycoprotein GPIb-IX complex, the G-protein-coupled-receptors (GPCRs) and immunoglobulin. Inherited platelet disorder occurs due to defect in these receptors. Children show early onset of skin and mucous membrane bleeding.

Glanzmann Thrombasthenia

Glanzmann thrombasthenia is the disorder of defective platelet integrin αIIb-β receptor. It is an autosomal recessive disorder characterized by failure of platelets to bind fibrinogen and aggregation. Clinical manifestations are repeated mucocutaneaous bleeding, gastrointestinal bleeding, joint bleeding and intracranial bleeding. Menorrhagia is a severe condition in teenage girls. Surgical procedure may bleed excessively. These patients require platelet transfusion therapy and in severe condition recombinant activated factor VII therapy as supplement to platelet transfusion.[35]

Bernard-Soulier Syndrome

Bernard-Soulier syndrome is also an inherited bleeding disorder of defective GPIb-IX complex platelet receptor. Syndrome is characterized by low platelet count along with deranged qualitative function of platelet and presence of macrothrombocytes. Clinical manifestations are same of skin and mucous membrane bleeding. Platelet transfusion, DDAVP and recombinant activated factor VII have been using as treatment modalities to optimise the patient.

Thrombocytopenia absent radii

Thrombocytopenia absent radii (TAR) is the congenital condition with decrease platelet count. Child is born with hypomegakaryocytic thrombocytopenia and bilateral absence of the radii. The platelet count is as low as 10^4/mL but soon improves with age and become normal after the age of one year. The child may have severe thrombocytopenia if expose to environmental stresses such as a viral infection. Child often has other skeletal abnormalities apart from obvious bilateral absence of and along with these approximately 30% may have associated cardiac anomalies such as tetralogy of fallots and atrial septal defect. Severe anaemia occurs owing to blood loss.

Fanconi Anaemia

It is primarily an autosomal genetic disorder and is characterized by pancytopenia resulting from complete bone marrow failure. There is macrocytosis/megaloblastic anaemia with unusual large red blood cells, neutropenia and thrombocytopenia, subsequently patient may develop acute myelogenous leukemia. The clinical manifestation arises by the age of 7 years with Fanconi anaemia, however, thrombocytopenia has been reported in neonates. Patient is short stature, abnormalities of skin, arm, head, kidney, ear and developmental disabilities. Bone marrow transplant is curative treatment in severe bone marrow failure.

May-Hegglin Anomaly

There is circulating giant platelets and Döhle bodies in white blood cells. Patient has thrombocytopenia with increase risk of bleeding.

Wiskott-Aldrich Syndrome

It is an X-linked disorder characterized by eczema, immunodeficiency and thrombocytopenia. Circulating platelets are small in size. Defect in B and T lymphocytes leads to immune dysregulation. Patient may die in early age from overwhelming infection owing to immune thrombocytopenia or haemolytic anaemia. Patient may die in second decade from lymphoma like illness.

Treatment includes steroid, intravenous immunoglobin or vincristine or plasmapheresis. Splenectomy helpful in thrombocytopenia and bleeding but it increases the risk of opportunistic infection. Bone marrow transplant is effective treatment.

Idiopathic thrombocytopenic purpura (ITP)

This condition is also known as autoimmune thrombocytopenia as it usually occurs after the viral infection or immunisation. It is unrelated to drug ingestion. The diagnosis is made by excluding of other causes of thrombocytopenia. The incidence in children is about 50 cases in 1,000,000. Peak prevalence occurs in children of 2–4 years and approximately 40% patients are below the age of ten years. This is the most common condition present in operative setting owing to acute onset of thrombocytopenia. It is generally self limiting and benign condition. Acute ITP resolves spontaneously within 6–8 weeks, while chronic purpura lasts more than 6 months without specific cause. The neonate born from affected mother need to be observed for a few days as they may be affected by the disease and the platelet count would be dropped as soon as splenic circulation established.

Clinical Manifestation

There are petechiae or purpura over the bony prominences. Bleeding from gum, nostril and menorrhagia are common manifestations. Severely low platelet patients may have intracranial, gastrointestinal and other major organ bleeding. However, the rate of platelet production is high in the bone marrow to balance the rate of destruction. Microangipathic haemolytic anaemia occurs as red blood cell enters microvascular circulation they become distorted due to thrombosis.

Investigation

Low platelet count on complete blood count and may be as low as $<2000/\mu L$. Presence of autoantibodies against the platelets is found on antibody titre. Bone marrow examination is needed in case of difficult diagnosis.

Treatment

Corticosteroid, intravenous immunoglobulin (IVIG), intravenous anti-D rhesus immunoglobulin (IVRhIG) and platelet transfusion are the available treatment modalities. Corticosteroid may be helpful in increasing platelet count. But the long term therapy associated with toxicity which limits its use. The American Society of Haematology (ASH) guideline for treating children is based on platelet count while British Society of Haematology (BSH) is more towards conservative 'wait and watch'.[36] Children who have developed chronic ITP or refractory ITP may put on immunosupresssent or chemotherapeutic agents. Splenectomy must be considered in case of old children and chronic ITP with very low platelet count.

Anaesthetic consideration

Severe ITP with bleeding manifestations should be treated with high dose of parenteral corticosteroids, intravenous immunoglobulin and platelet transfusion. If children develop chronic ITP with very low platelet count (10,000 to 20,000 µ/L), splenectomy provides some protection. Approximately 50% of patients show permanent remission after splenectomy. These children should be vaccinated against capsular organism prior splenectomy and should be given antibiotic coverage postoperatively. In case of emergency surgery or intracranial bleed IVIG and platelet transfusion should be given first. Consider platelet transfusion if counts are below 50,000 µ/L with bleeding manifestations. Transfused platelet may improve ongoing process of hemostasis by participating in the process or there may be some posttransfusion increment and reasonable survival in the platelet. Child born with known ITP mother may have low platelet count but the known incidence is low. The platelet count may continue to fall 7 or more days following delivery, therefore, it is must checking the platelet count every 2 or 3 days until it shows rising trend. The platelet count may be improved in preparation for surgery using a course of intravenous immunoglobulins at a dose of 0.4 mg/kg daily for 5 days, a target platelet count of 80–100×10^9/L being considered adequate to secure hemostasis at operation.[37] ASH guideline for managing platelet deficiency is given in Table 9.11 and for consideration of splenectomy is shown in Table 9.12.

Table 9.11 ASH guideline for managing platelet deficiency

ASH guideline	
Platelet count > 30,000 asymptomatic or minor purpura	No hospitalisation
Platelet count < 20,000 with significant bleeding	IVIG, anti-D IG or corticosteroid
Platelet count < 10,000 with minor purpura	Corticosteroid, IVIG
Platelet count < 10,000 with severe threatening bleeding	Parental high dose life corticosteroid, IVIG and platelet transfusion

Table 9.12 ASH guideline for considering platelet transfusion for elective splenectomy

Appropriate preoperative therapy	Inappropriate preoperative therapy
• Platelet count < 30,000 need to be given prophylactic IVIG • Platelet count < 10,000 need to be given prophylactic IVIG, parental glucocorticoids, anti-Rh (D)	• Platelet count > 50,000 IVIG, oral glucocorticoid, anti-Rh (D) • Platelet count > 30,000 parental glucocorticoid • Platelet count > 20,000 platelet transfusion

Splenectomy

For elective splenectomy patients ASH has given the guideline as appropriate and inappropriate preoperative therapy.

Disseminated intravascular coagulation (DIC)

Excessive consumption of clotting factor and platelets leads to DIC. It may occur due to gram negative sepsis, abruption placenta or amniotic fluid embolism (Table 9.14). The International Society on Thrombosis and Hemostasis (ISTH) has developed a consensus definition of DIC which is "…an acquired syndrome characterized by the intravascular activation of coagulation with loss of localisation arising from different cause. It can originate from and cause damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction."

DIC is resulted due to hypofibrinogenemia as a process of exaggerated fibrinolysis. Owing to this there

Table 9.13 Anaesthesia consideration in ITP

Preoperative
Haemoglobin, platelet count
History of platelet transfusion
History of corticosteroid medication
History of infection
Presplenectomy antibiotic prophylaxis and immunisation
Haematologist consultation
Discontinuation of platelet inhibitory medications
Intraoperative
Antibiotic coverage
Stress corticosteroid coverage
Pharmacological therapy or platelet transfusion
Physiologic effects of laparoscopy on respiratory and circulatory function
Judicious use of regional anaesthesia, intramuscular injections, nasogastric tube insertion, nasal intubation
Judicious use of potential bleeding medication
Postoperative
Haemoglobin and platelet count
Infection
Steroid coverage
Postoperative analgesia

Source: Modified and adapted from Essential of Haematology, Ch-9 Charles J. Cote. A practice of anaesthesia for infants and children

Table 9.14 Causes of DIC

Infection	Septicaemia, e.g. meningococcal Protozoa: malaria
Obstetric causes	Abruption placenta, placenta previa, pre-eclampsia, amniotic fluid embolism, placental laceration
Malignancy	Haematological malignancies
Shock	Trauma, burn
Extracorporeal circulation	Cardiopulmonary bypass
Intravascular haemolysis	ABO incompatible blood transfusion

are fibrin (ogen) degradation products and D-dimer increased in the blood. There is fibrin deposition in the microvasculature, consumption of clotting factors, and endogenous production of thrombin and plasmin. This damage to microvascular circulation leads to vasodilation, loosening of endothelial gap and capillary leak leading to shock. Furthermore, activation of coagulation cascade excessive thrombin formation occurs resulting into widespread microthrombus formation and ischeamic damage to multiple organs. This consumption of clotting factors and platelets has been led to disseminated bleeding.

Table 9.15 Anaesthesia consideration in DIC

Preoperative
Find out the primary cause and treat accordingly
CBC with platelets, coagulation profile including APTT and D-dimer
Preoperative transfusion of factors to achieve the required level
Platelets, FFPs, cryoprecipitate transfusion
Keep adequate blood and blood products ready
Intraoperative
Peripheral wide bore intravenous lines
Planned general anaesthesia with all resuscitative measures
Maintain good haemodynamics by infusing blood and blood products
Maintain adequate urine output, temperature
Inotropic supports if required. If septicaemia is the primary cause, then appropriate antibiotic coverage
Continue mechanical ventilation
Postoperative
Postoperative mechanical ventilation
CBC, platelet count and coagulation profile
Chest X-ray
Appropriate antibiotic

Clinical Manifestation

Child presents with shock, widespread purpura and petechiae.

Laboratory Investigation

Diagnosis is made with clinical picture of the sick child. Biochemical markers such as low platelet count on quantitative analysis of blood for platelets, there would be low level of clotting factors II, V and VIII. D-dimer is also increased (>2 µg/mL). PT and APTT are also prolonged. But no single investigation is reliably diagnoses DIC.

Treatment and Anaesthesia Consideration

As DIC is a secondary disease the primary underlying cause should be treated first. Child may not require replacement therapy. Appropriate and higher antibiotic coverage with transfusion of platelets and other clotting factors are considered for the treatment of DIC. FFP 10–15 mL/kg, cryoprecipitate 5 mL/kg (rich in fibrinogen), factors concentrate and platelets concentrate have been used to treat the ongoing bleeding. Cryoprecipitate 1 U/5 kg will raise the plasma fibrinogen level 50–100 mg/dL and it lasts for four to five days. Antithrombin III is useful to treat DIC in septicaemia. Also protein C concentrate is helpful in DIC in paediatric group but therapeutic support still needed. Prostacyclin may be used in case of known defective platelet activation pathology. Aprotinin may be advocated in case of fibrinolysis. But use of heparin is controversial, however, it has been proved its benefit in amniotic fluid embolism. Use of antifibrinolytics depends on coagulation profile though its use is complicated as it forms permanent fibrin clot, which is certainly not helpful in small renal vessels.

Paediatric Anaesthesia Pearl

More common form of bleeding is due to non-haematological cause and which is surgical bleeding which leads to cardiac arrest and must be anticipated and managed aggressively.

One Fact to Remember

One thing is very important in using DDAVP that fluid restriction should be needed as younger children are prone to develop hyponatremia and seizures.

Take Home Message

Avoid use of Platelet inhibitory drugs such as acetylsalicyclic acid and non-steroidal anti-inflammatory drugs for pain relief. Prefer paracetamol.

KEY POINTS

- Paediatric haematology differs in many aspects from adult haematology. Soon after birth transition of haematological components occurs from foetal to neonate and to infant.
- Foetal haemoglobin is present in highest concentration in the intrauterine life, however, level starts falling from third trimester.
- Soon after birth the rapid transition takes place and the concentration of foetal haemoglobin decreases while adult haemoglobin increases.

Table 9.16 Clinical pearls for all hematological disorders

Preoperative evaluation
History of familial bleeding disorder
History of transfusion
History of medication
History of recurrent infection
History of repeated bruising and epistaxis
Type and pattern of the disease
Clinical manifestation
Anaemia: Pallor, lethargy, weakness
Jaundice: Icterus, discoloration of urine
Splenomegaly: Abdominal pain and lump
Thrombocytopenia: Repeated bruising and epistaxis
Investigations
Routine
CBC, haemoglobin, reticulocyte count, platelet count
Liver function test, coagulation profile
Renal function test
Ultrasonography specific
Clotting factor assay
Echocardiography
Anaesthesia consideration
Preoperative optimisation with prophylactic pharmacological methods and transfusion
Available resources
Pre-splenectomy vaccination and antibiotic prophylaxis
Avoid triggering agents
Avoid hypoxia, hypercarbia, acidosis and shivering
Avoid intramuscular injections: In case of deranged coagulation profile avoid nasal intubation, nasogastric tube insertion, arterial cannulation
Avoid platelet inhibitory drugs: Aspirin, other NSAIDs
Monitoring includes haemodynamics, urine output, central venous pressure, temperature
Estimation of blood loss and appropriate transfusion
Postoperative haemoglobin level and coagulation profile

- After birth the larger part of total haemoglobin concentration is composed of HbA >95%, and lesser is of HbA2 <3.5% and HbF <2.5%
- Foetal haemoglobin has higher affinity towards oxygen, therefore, oxyhaemoglobin curve shifts to left. This property helps to extract oxygen from maternal haemoglobin.
- The haematological disorder manifests commonly early in life and requires early intervention.
- Red blood cell disorders lead to haemolytic anaemia, hyperbilirubinaemia, splenomegaly and cholelithiasis.
- Optimise the hematological indices preoperatively to reduce the risk of increase blood loss and also avoid triggering agents during intraoperative period leading to onset of hemolysis. Maintain near normal hemodynamics, temperature and adequate urine output.
- Red blood cell membrane disorders such as hereditary spherocytosis due to membrane protein deficiency.
- Enzymatic defect such as glucose-6-phosphate dehydrogenase deficiency makes the red blood cells vulnerable to oxidant injury.
- Haemoglobinopathies includes thalassemia and sickle cell anaemia.
- Coagulation cascade involves intrinsic or contact pathway, extrinsic or tissue pathway and common pathway. There are series of activation of clotting factors which coordinate process of haemostasis.
- Haemophilia occurs due to factor VIII or factor IX deficiency and requires factor transfusion to achieve normal level before surgery.
- von Willebrand disease occurs due to deficiency of von Willebrand factor which releases from endothelial cells and platelets.
- Platelet disorder leads to repeated bruising, petechiae, purpura and menorrhagia requires platelet transfusion.
- Disseminated intravascular coagulation is the secondary manifestation of primary aetiology and requires treatment of primary disease. It may require blood and blood components to improve outcome.

SUMMARY

Children with hematological disorders may present with anaemia, jaundice, thrombocytopenia and abdominal pain due to splenomegaly or cholelithiasis. They are vulnerable to bacterial and viral infection as

their immunity has been compromised. They had history of repeated infections, multiple transfusions of blood and its components and also history suggestive of familial inheritance. Special care to be given to these patients and pre-anaesthetic check up requires proper evaluation to know the extent of various organs dysfunction due to haematological disorder. Pre-operative optimisation of blood components should be done before the procedure. Intraoperative period includes proper planned anaesthetic management depending on the general condition of the patient. Postoperative care includes special attention towards the maintenance of asepsis and the optimisation of factors level required for wound healing.

FAQs with Answers

Q. What are the transfusion criteria for platelet transfusion in case of platelet disorder?

A. BCSH Guideline for platelet transfusion 2003.

The target platelet levels for different procedure and disease are given in Table 9.17.

Q. What is the sequence of preference for transfusion of blood products of different blood group in ABO blood group?

A. BCSH Guideline for ABO Transfusion is given in Table 9.18.

Group O FFP should only be given to patients of group O while group AB FFP can be given to patients of any ABO group.

Q. What do you mean by leucocyte depletion?

A. All components other than granulocytes should be leucocyte depleted that is not more than 5×10^6 leucocytes per unit at the time of preparation.

Q. How much volume can safely be transfused in children and neonates?

A. Consider Table 9.19.

Table 9.18 ABO blood group transfusion guideline

Blood group		RBC	Platelets	FFP
A	First choice	A	A	A/AB
	Second choice	O	O	—
B	First choice	B	B*	B/AB
	Second choice	O	A/O	—
O	First choice	O	O	O
	Second choice	—	A	A/B/AB
AB	First choice	AB	AB*	AB
	Second choice	A/B	A	A
	Third choice	O	—	—

*means group B and AB platelet concentrates may not be available.

Table 9.19 Safe volume transfusion in children and neonate

RBC	
1. Exchange transfusion:	
Term infant	80–100 mL/kg
Preterm infant	100–200 mL/kg
2. Top-up transfusion	10–20 mL/kg
Platelet concentrates	
Child <15 kg	10–20 mL/kg
Child >15 kg	Single apharesis unit/ standard pool
Crayoprecipitate	5–10 mL/kg
Children (15–30 kg)	5 units
Children (>30 kg)	10 units
FFP	10–20 mL/kg

Q. Should one do routinely haemoglobin level for children undergoing planned surgery and what is the haemoglobin level required?

A. One purpose of the routine preoperative measurement of Hb is to detect anaemia which is not clinically apparent. The conventional threshold

Table 9.17 Target platelets level in different procedure and disorder

Lumber puncture, epidural anaesthesia, gastroscopy and biopsy, laparotomy, transbronchial biopsy, liver biopsy	More than 50×10^9/L
Indwelling central venous cannulation, arterial line	More than 50×10^9/L
Brain and eye surgery	More than 100×10^9/L
Bone marrow aspiration and biopsy in severe thrombocytopenia	Can be done without platelet transfusion with adequate surface pressure
Trauma	Aim should be more than 50×10^9/L
DIC	Correct underline pathology and aim to maintain platelet level more than 50×10^9/L

for anaemia below which postponement of surgery or preoperative transfusion might be considered is an Hb level of 10 g/dL. Now, there is evidence to suggest that the risks of surgery do not rise significantly until the Hb level falls below 7 g/dL.

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10

Essentials of Pharmacology in Infants and Children

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ABSTRACT

Maturation of anatomical and physiological system distinguishes Paediatric group as a specific population with major pharmacological differences from their older counterparts.

Larger body water content, immaturity of hepatic biotransformation pathway, increase organ blood flow, decrease protein binding and high metabolic rate are the essential findings in paediatric population. The following chapters discuss the ways in which this difference affects response to drug.

INTRODUCTION

When administering anaesthesia to paediatric population it is vital to understand developmental pharmacology in them. There are numerous reasons for altered pharmacokinetics and pharmacodynamics in neonates, infants and children.

Let us understand following terms:

Pharmacokinetics: Describes the absorption, distribution, metabolism and elimination of drugs. Another way of describing it is "the effects of the body on Drugs".[1]

- **Pharmacodynamics:** Describes the effects of drugs on the body.[1]
- **Phase I metabolism:** Biotransformation to render the drugs more polar (to prepare for elimination) by means of oxidation, reduction or hydrolysis.[1]
- **Phase II metabolism:** Biotransformation to render the drug more polar (to prepare for elimination) through conjugation reactions such as glucuronidation, sulfation and Acetylation.[1]
- **Volume of distribution** (V_d): Volume of distribution denotes the volume of fluid and tissue into which drug appears to distribute with concentration equal to those in plasma.[2] Drugs with a less volume of distribution are mainly present in plasma or they are extensively bound by plasma proteins (e.g. heparin, warfarin). Drugs with a slightly higher volume of distribution are mainly present in extracellularfluid (e.g. muscle relaxants). Drugs with higher volume of distribution have extensive tissue distribution of drug.[1]
- **Half-life**: Half-life of drug is the time taken for half of the drug dose to get eliminated. Shorter the half-life, quicker it is eliminated. When drug concentration is around 5%, it is said to be negligible. Therefore, around 4 or 5 half-life must elapse until drug is eliminated, e.g. if half-life of drug is say 4 hrs and drug strength is 1000 mg, after 4 hrs, 500 mg is left, after 8 hrs 250 mg is left and after 12 hrs 125 mg is left and so on. A prolonged terminal half-life may reflect an increase volume of distribution or reduced clearance or both. Similarly shorter terminal half-life may represent decrease volume of distribution or increased clearance or both.[1]
- **Bioavailability:** Describes the extent and rate of uptake of an active drug into the body. It is expressed as a percentage when compared to intravenous administration of same drug.
- **Clearance**: It is the ability of body to eliminate drug.
  1. ***Hepatic clearance:*** It quantifies the loss of drug during its passage through liver which results due to hepatic metabolism and biliary excretion.

It is determined by following parameters:

a. *Hepatic blood flow:* Which reflects drug delivery to liver. It is decreased in congestive cardiac failure, volume depletion, hypocapnia, circulatory shock, patients on beta blocker, increased abdominal pressure.[3,4]
b. *Plasma protein binding:* Decrease protein binding results in increase free drug concentration which interacts with liver enzymes, thus augments hepatic clearance of drug, e.g. hypoalbunemia, drug displacement by other substance present in blood like bilirubin, free fatty acids, etc. increase protein binding of drug results in decrease hepatic clearance of it.[1]
c. *Intrinsic clearance:* It is the ability of hepatic enzyme to metabolise drug. Variation in liver enzyme activity affects clearance, e.g. liver failure.[1]

Liver is an important organ for drug elimination hence it is vital to know whether drug has high or low hepatic extraction ratio.

Drugs with high extraction ratio (lignocaine, propranolol, ketamine, fentanyl, sufentanyl, morphine, nitroglycerine, verapamil) and intermediate extraction ratio (methohexital, midazolam, alfentanyl) are almost completely removed from liver and their metabolism is limited by hepatic blood flow. A drug with low hepatic extraction ratio (bupivacaine, ropivacaine) elimination of drug depends upon hepatic enzyme activity and is independent of hepatic blood flow.[2]

2. ***Renal clearance:*** It is a function of glomerular filtration, secretion from peritubular capillaries to the nephron and reabsorption from nephron back to peritubular capillaries.

Clearance = glomerular filtration + tubular secretion – tubular reabsorption

Clearance is influenced by plasma concentration and reabsorption of drug by renal tubule. Reabsorption depends upon lipid solubility of drug and concentration gradient in tubular fluid. As water is absorbed from tubule, drug concentration in tubular fluid raises establishing concentration gradient and reabsorption of drug occurs. Drugs which are strong acids exist in urine in ionized form and are poorly absorbed. Drugs which are weak acids, e.g. barbital, which exist in non-ionized form in urine are almost all reabsorbed.[2]

PHARMACOKINETICS IN PAEDIATRIC POPULATION

Absorption

For a drug to exert its pharmacological effect it should bind to a receptor. Availability of drug to receptor site depends on concentration of drug in plasma. Absorption of drug into systemic circulation varies as per the route of administration.

Various routes of administration are as follows:

Oral

More acceptable route in children. The pH and volume of gastric fluid determines the absorption characteristics and hence the bioavailability of drug. Gastric pH reaches to adult value by 6 months to 3 years of age resulting in variable absorption of drug.[2,5] Small, lipid soluble, unionized molecules with favourable dissolution characteristics in gastric juice are better absorbed than larger ionized molecules.[1] An acidic drug such as penicillin, salicylate becomes less ionized as pH is reduced. Premedication with atropine and glycopyrrolate raises the pH of gastric contents.[2] Neonates have less gastric and bile acid secretion with variable gastric emptying. Gastric emptying is further slowed by increase in caloric density following neonatal formula feeds thus delaying the drug absorption.[2,5] Problems with oral route are emesis, degradation due to gastric juices, interference in absorption due to food or other drugs and first pass metabolism.[5]

Intramuscular and Subcutaneous

Absorption depends on lipophilicity of drug, local circulation and site of injection. Drug uptake is less in patients with shock, hypothermia and acidosis due to compromised local circulation.[2,5] Reduced skeletal muscle blood flow due to low arterial blood pressure and less muscular activity may reduce drug absorption in neonates.[5] Infants have dense capillary plexus in skeletal muscle which results in rapid drug uptake.[5] Drugs injected at upper extremity are rapidly absorbed than at lower extremity. Drugs with high pH like midazolam, phenobarbital is associated with tissue necrosis, pain and sterile abscess following intramuscular injection.[2]

Transdermal

Absorption is directly proportional to skin blood flow and indirectly proportional to thickness of stratum corneum.[2,5] Transdermal patch of NTG, clonidine, fentanyl and EMLA cream is available.[2] It provides sustained therapeutic plasma concentration as skin act

as a reservoir for drug and also absorption continue for many hours after removal of patch.

Intravenous

Preferred route as it avoids problems with uptake. Onset is rapid and immediate.[1] Bioavailability is 100%. Problems with this route are adsorption of drug to plastic or glass tubing, hence with slow rate of infusion large amount of drug is adhered to tubing which gives incorrect conclusion regarding patients requirement.[2]

Rectal

Preferred route in emesis and upper gastrointestinal pathology. Small surface area of rectal mucosa results in slow and erratic absorption of drug.[2] Uptake depends upon formulation of drug and metabolism by gut wall and intestinal flora.[2,5] Drugs deposited below anorectal line escapes first pass metabolism and circulated to brain and heart before they reach liver results in increase bioavailability of drug.[2,5] Drugs use per rectally are diazepam, thiopentone, methohexitone, paracetamol, midazolam, ketamine and atropine.[2]

Transmucosal

Drugs administered via oral transmucosal or nasal mucosal route bypass the hepatic first pass metabolism.[5] Therefore, they have a higher bioavailability, e.g. bioavailability of nasal midazolam is 57%, whereas of oral midazolam it is 30%. Sublingual NTG, ketamine spray and fentanyl lollypops are the available preparations.

Distribution

Distribution of drug in body depends upon the following factors.

Body Composition

Ageing is associated with decrease in total body water content and increase in fat and muscle content which affects drug deposition in paediatric patient (Table 10.1).

Increase in total body water and extracellular fluid results in higher distribution of water soluble drug.

Table 10.1 Body composition in paediatric age group[3]

Body compartment	Premature infant 1.5 kg	Full term infant 3.5 kg	Adult 70 kg
TBW (% body weight)	83	73	60
ECF (% body weight)	62	44	20
Muscle mass (% body weight)	15	20	50
Fat (% body weight)	3	12	18

Hence neonates may require larger loading dose compared to older children to achieve same effects, e.g. succinyl choline and theophylline. Larger dose may increase the store of drug and prolongs drugs half-life.[2]

Less volume of muscle and fat accounts for less uptake and thus smaller reservoir for fat soluble drug.[3,6]

Plasma Protein Binding

Drugs with reduced plasma protein binding have increased volume of distribution, e.g. ampicillin, theophylline, barbiturate, bupivacaine, lignocaine and diazepam.[2] Free fraction of drug binds to receptor and responsible for pharmacological effect and clearance of drug. Protein bound drug is reservoir that helps in maintaining concentration of free drug in plasma and tissues. Acidic drugs (salicylate) mainly bind to albumin and basic drug (local anesthetics, opioid, and diazepam) binds to $\alpha_1$acid glycoprotein and to lesser extent to globulin and lipoprotein.[2,3,5] Renal disease, liver disease, CCF and malignancies decrease albumin production. Trauma (including surgery), infection, pain increases α_1 acid glycoprotein. Neonates have low serum albumin level (increase to adult level by 5 months of age), their albumin has low binding capacity as well as affinity for drugs and substance found in plasma of neonate like FFA, bilirubin, maternal steroid and sulphonamide decreases protein binding of drugs.[2] It is of particular importance in highly protein bound drugs such as phenytoin, diazepam, bupivacaine, barbiturates, antibiotics and theophylline. α_1 acid glycoprotein levels are low in both neonates and infants.[6]

Cardiac Output and Regional Blood Flow

On intravenous administration initial drug uptake occurs primarily in well perfused tissues like heart, brain, liver, kidney and later in less well perfused tissues like fat and muscle.[2] Therefore, concentration of drug in CNS rises quickly and remains high for long time as brain receives higher cardiac output compared to adult. Due to less fat and muscle drug that depends upon redistribution into them for termination of its action will have longer clinical effect like thiopentone and fentanyl.[2]

Tissue Membrane Permeability

Immature blood–brain barrier in neonate and infant coupled with incomplete myelination results in entry of drug in CNS and prolonged clinical effect with drugs like barbiturate and morphine.[2,3,5]

Blood Tissue Partition Coefficient

It depends upon binding of drug in blood and tissue and lipid solubility of drug.[2,3]

Metabolism

Liver is principal site of metabolism and is dependent on hepatic blood flow.[6] Hepatic blood flow is low at birth and increases during infancy.

Enzyme systems involved in drug metabolism matures at different rate. Enzymes of phase I metabolism matures by 6 months of age and some phase II reactions (sulfonation) are mature at birth and some (acetylation, glycination, glucuronidation) are not. All becomes mature by 1 year of age.[2] Both these reactions are decreased in neonates but can be induced by barbiturate.[2] Drugs undergoing phase I metabolism are metabolized by cytochrome p450 system, e.g. CYP3A4 is responsible for metabolism of midazolam, diazepam and paracetamol. Paracetamol is conjugated by both glucuronidation and sulfonation, hence elimination half life is similar in neonates and adult (3.5 hrs).

Excretion

Elimination of drug and its metabolite depends upon GFR, tubular secretion and tubular reabsorption.[3,6] All of them are decreased in neonate and infant. GFR mature to adult level by 1 month and tubular function by 12–18 months as the renal blood flow improves.[2,3,6] Therefore, drugs reliant on glomerular and tubular function for elimination are particularly affected and results in prolonged half life, hence may require reduction in initial dose and increase dosing interval between subsequent doses.

Neonate exhibits delayed excretion due to large volume of distribution, immature renal and hepatic function and altered protein binding. Older children have mature renal and hepatic function with normal adult values for protein, fat and muscle content and high cardiac output to liver and kidney, hence excretion is less affected.[7]

Table 10.2 Pathway for drug metabolism[4]

Reactions	Drug
Phase I reaction	
Oxidation	Thiopental
Aliphatic hydroxylation	Pentazocine, ketamine
Aromatic hydroxylation	Lignocaine, bupivacaine, fentanyl, propranolol
O-dealkylation	Pancuronium, vecuronium
N-dealkylation	Morphine, fentanyl, diazepam, ketamine, atropine
N-oxidation	Morphine
Oxidative deamination	Epinephrine
Desulfuration	Thiopentone
Dehalogenation	Halogenated anesthetics
Ester hydrolysis	Succinyl choline
Phase II reaction	
Glucuronide	Morphine, fentanyl, naloxone
Sulphate	Paracetamol, morphine
Glutathione	Paracetamol

PHARMACODYNAMICS OF INDIVIDUAL DRUGS

Intravenous Induction Agent

Propofol

It belongs to alkyl phenol group and available as emulsion containing soyabean oil, glycerol and egg lecithin,[4] high lipid solubility results in rapid onset of action. Dose required in young children (2.9 mg/kg) is high compared to older child (2.2 mg/kg) and adult (2 mg/kg) due to increase volume of distribution and clearance.[2,4,7] Pharmacokinetic study in children shows 50% greater central volume of distribution and 25% greater clearance than adult for maintenance.[6] It undergoes extensive hepatic and extrahepatic clearance. Side effects are reduction in MAP, SVR and cardiac index with variable change in heart rate.[3,6] Apnoea, suppression of airway reflex, involuntary movement and pain on IV injection.[6] Use of propofol infusion for long term sedation in critically ill child is associated with lactic acidosis, rhabdomyolysis, cardiac and renal failure.[2,4,7]

Thiopentone

It is a sodium salt of barbiturate with high alkalinity (pH of 2.5% solution is >10). High lipid solubility and non-ionized fraction is responsible for maximal uptake in brain in spite of high protein binding.[4] Dose requirement in infant (7 mg/kg) is higher than older children and adult (4–5 mg/kg) due to large volume of distribution.[3,4] In neonate drug requirement is less (3–4 mg/kg) due to decrease protein binding and impaired clearance.[4,7] Large dose increase store in body and cause delay awakening.[5] Termination of action is due to redistribution of drug in muscle and fat.[7] Side effects are decrease in BP, increase in heart rate, depression of ventilation, and decrease in intraocular and intracranial pressure.

Ketamine

It is a cyclohexidine derivative. It produces dissociative anaesthesia by blocking the afferent impulses in diencephalon and associated pathway of cortex, sparing the reticular formation of brain stem[3] because of its analgesic property it is preferred for procedural sedation. High doses are required for induction in younger patient due to increase in volume of distribution (2–3 mg/kg).[2] Patient loses consciousness in 10 seconds and duration is 10–15 minutes[2] gag and cough reflex is maintained[2] clearance is reduced in neonates and infant due to reduced metabolism and excretion resulting in prolonged recovery.[2,5] It is used for sedation, induction and maintenance of anaesthesia. It is metabolized by liver; norketamine is principal metabolite which has 30% activity of parent compound. Problems are increase secretion, vomiting, dreaming, hallucination. Contraindications are URTI, raised ICT, open globe injury, psychiatric and seizure disorder; preservative free ketamine is used in epidural space because preservative causes neurotoxicity.[3,8]

Inhalational Anaesthetic Agent

Neonates, infants and young children have relatively higher alveolar ventilation and lower FRC compared with older children and adults. This higher minute ventilation to FRC ratio (5 : 1 in infant and 1.4 : 1 in adult) with relatively higher blood flow to VRG (Vessel rich group is 18% of body weight in infant compared to 8% in adult) and decrease in fat and muscle content results in rapid rise in alveolar anesthetic concentration and speeds inhalational induction. Blood gas coefficient is lower in neonates than adults thus allows faster induction. MAC is higher in infants than neonates and adult for halogenated agent except Sevoflurane which has same MAC in neonates and infants.[3,4,6,7] Cardiovascular system of neonates and infants is more sensitive to volatile agents because of not fully developed compensatory mechanism, e.g. vasoconstriction and tachycardia and immature myocardium is sensitive to myocardial depression.[2–4]

Table 10.3 Dose of ketamine[4]

Route of administration	Sedation dose (ml/kg)	Induction dose (ml/kg)
Per oral	6–10	—
Intravascular	0.5–1	2–3
Intramuscular	2–3	6–10
Per rectal	—	10

The MAC for almost all anesthetic agents is less in neonates than in infants. Typically MAC value peak at 1–6 months of age before decreasing to adult values.[3,8]

Sevoflurane

Pleasant smell and blood gas solubility coefficient 0.68 allows rapid induction and recovery, hence preferred in nonpremedicated children.[6] It is cardio stable (less tachycardia, myocardial depression and less sensitization of myocardium to catecholamine), causes dose dependent depression in tidal volume and respiratory rate with minimal airway irritation.[6] Breathholding, coughing, laryngospasm, desaturation during induction is infrequent, epileptiform and slowing of heart rate is reported.[3]

High incidence of excitement during emergence (33%) is noted.[7] It is not related to pain, inversely related to age, frequent in less than 5 years and low incidence with premedication.[7] Possible risk of exothermic reaction with dry dessicant and compound A formation if fresh gas flow is less than one liter.[7]

Isoflurane

It is not preferred for induction in paediatric patient due to irritation of airway and pungent smell. Wash in and wash out is slower due to high solubility in blood and tissue.[3,7] It causes less myocardial depression than halothane with a little change in heart rate. It causes

Table 10.4 Age related estimates of gas and tissue volume and blood flow[3]

Tissue volume	Gas and tissue volume (mL/kg)		Tissue blood flow % cardiac output	
	Adult	Infant	Adult	Infant
Tidal volume	7	7	—	—
FRC	40	20	—	—
Blood volume	70	90	—	—
Viscera	88	175	73	80
Muscle	425	180	11	10
Fat	150	100	6	5
Poorly perfused tissue	270	70	10	5

Table 10.5 MAC in paediatric patient[4]

MAC	Neonate	Infant	Child	Adult
Halothane	0.87	1.1–1.2	0.87	0.75
Sevoflurane	3.3	3.2	2.5	2
Isoflurane	1.6	1.8–1.9	1.3–1.6	1.2
Desflurane	8.9	9–10	7–8	6

greater reduction in $CMRO_2$ which is beneficial in anaesthesia for raised ICT patient.

Halothane

It causes potent myocardial depression. Sensitize the myocardium to catecholamine in presence of hypercapnia or inadequate depth.[3,7]

Desflurane

Its wash in and wash out is extremely fast but still induction is not recommended because triggering of upper airway reflex (50% breath holding and 40% laryngospasm).[3] Maintain cardiovascular homeostasis except for tachycardia.

Neuromuscular Blocking Agent

Immature neuromuscular junction and small reserve of acetylcholine makes neonate three times more sensitive to non-depolarizing muscle relaxant than adult. But this sensitivity is balanced by almost identical increase in volume of distribution so required dose is unaffected.[5,6] They also exhibits prolonged duration of action of neuromuscular blocking agent due to decreased hepatic and renal clearance, hence dose of additional relaxant should be reduced and given less frequently.[5,7]

Depolarizing Muscle Relaxant

Succinyl choline: It is available depolarizing muscle relaxant. It binds to acetyl choline receptor causing membrane ionic channel to open in the same fashion as acetylcholine. Molecule remains bound to receptor for extended period because they are not metabolized by acetyl cholinesterase and their concentration in synaptic cleft do not fall rapidly. This results in prolonged depolarization of muscle end plate.[3,4] With prolonged and repetitive exposure succinyl choline induced block begins to assume characteristics of nondepolarising block.[3] Dose required is high in neonates and infant (2–3 mg/kg IV) than in older children (1–2 mg/kg IV, 2–4 mg IM) and adult (1–1.5 mg/kg IV) [3] and duration is 3–10 minutes.[2,3] Difference in butyryl cholinesterase activity, receptor sensitivity and volume of distribution explains age related difference in succinyl choline requirement.[3] Patient should receive vagolytic doses of atropine prior to its administration. It has potential for rhabdomyolysis, hyperkalemia, masseter spasm and malignant hyperthermia.[4,7]

Non-depolarizing Muscle Relaxant

They act as a competitive antagonist. All non-depolarizing agents produce neuromuscular blockade by competition with acetylcholine for its binding sites on the α_1 subunits of the postsynaptic cholinergic receptor.[4]

Atracurium: It is a muscle relaxant of intermediate duration, metabolized by nonspecific ester and Hofmann degradation[3] onset of block and recovery time is same for all group but in neonate dose is influenced by time and temperature. Neonates less than 48 hours require less dose and duration is long in temperature less than 36°C.[2] Infants exhibits shorter duration of action due to large volume of distribution, rapid clearance and short half-life.[3]

Vecuronium: Sensitivity to Vecuronium is same in neonates, infants and children. Longer duration and prolonged recovery is seen in neonate due to large volume of distribution and delayed clearance.[2] Children recover rapidly than adults. Volume of distribution and mean residence time were greater in infants due to large volume of distribution and fixed clearance which results in prolongation of neuromuscular block.[3] Duration of effect (time from injection to 90% recovery) was longest in infant (73 min), children (35 min) and adult (53 min).[3] Infusion of 2.4 mcg/kg/min is required to maintain 95% of block in children during nitrous and narcotic anaesthesia which is higher than adults (0.9 mcg/kg/min)[3] in patients with renal and hepatic impairment duration is prolonged.[3]

Rocuronium: It is a muscle relaxant of intermediate duration with rapid onset (60–90 seconds). It is similar to Vecuronium but with one-tenth the potency[3] induction. Dose is 1 to 1.5 mg/kg.[2] With IV use of 0.6 mg/kg (increase heart rate by 15 beats), it produces complete neuromuscular block in infants and children at 50 and 80 seconds. In children if increase to 0.8 mg/kg neuromuscular block results in 30 seconds. Recovery is (0.6 mg/kg) twice longer in infant than children[3] thus infant exhibits potentiation of effect.

Opioid

Pharmacokinetics of opioid in younger children[4,8]

1. Increased free drug concentration due to decreased plasma protein binding (low levels of albumin and α_1 acid glycoprotein)
2. Easy entry of drug across brain due to immature blood–brain barrier.
3. Decrease metabolizing and excretory capacity due to immature hepatic and renal function.
4. Increased sensitivity to respiratory centre, hence susceptible to respiratory depression.

Table 10.6 Comparison of non-depolarizing neuromuscular blocking agents

Agent	Onset time (in sec)	Duration of action (in min)	Side effects	Clinical use	Refrigeration Storage
Atracurium	90	30 min or less	Hypotension, transiently, by release of histamine Toxic metabolite called laudanosine, greater accumulation in individuals with renal failure	Widely	Yes
Cisatracurium	90	60–80	Does not cause release of histamine	—	Yes
Vecuronium	60	30–40	Few, may cause prolonged paralysis and promote muscarinic block	Widely	No
Rocuronium	75	45–70	May promote muscarinic block	Widely	No
Pancuronium	90	180 or more	Tachycardia (slight) (no hypotension)	Widely	No

Morphine

It is 30–35% protein bound in adult and 18–22% in neonates. It has high hepatic extraction ratio, hence metabolism is improved with increase in hepatic blood flow.[3,4] It is metabolized by N-demethylation, glucuronidation and sulfonation. Patients with renal impairment are sensitive to its effect due to its decrease metabolism and delayed clearance.[3] Patients with hepatic impairment have prolonged half-life and delayed clearance.[3] Volume of distribution is large in children than adult and clearance increases with age.[6]

Hydromorphone

It is a synthetic derivative of morphine and five times more potent than morphine.[3,9] Pharmacokinetic profile is almost similar in adult and children with elimination half-life of 3–4 hours and duration of action 4–6 hours.[3,9]

Codeine

It is a derivative of morphine. Analgesic action is due to morphine which is the metabolite product from demethylation in liver.[2,9] Bioavailability is 60% following oral route. Onset is 20 min and peak at 1–2 hours. Elimination half life is 2.5 to 3 hours. It is administered with paracetamol for moderate painful procedure.[9] Recommended dose is 15 mg/kg of paracetamol with 0.5 mg/kg of codeine.

Fentanyl

It has high hepatic extraction and pulmonary intake. Mean elimination half life, total body clearance, volume of distribution was larger in paediatric age group compared to adults. Clearance is markedly reduced in premature infants and half life was reported as 6–32 hours.[3] In infants and children fentanyl plasma concentration were less than those in adults after similarly administered IV dose.[3] Fentanyl pharmacokinetics after continous infusion for less than 24 hours in critically ill children have shown increase steady state volume of distribution, increase terminal elimination half life and normal clearance.[3] It can be administered by various route like oral, transmucosal, intravenous, intranasal, transdermal. With oral transmucosal route (10–15 mcg/kg), it shows peak plasma concentration at 5–20 minutes with 50% bioavailability. Side effects are PONV, respiratory depression, sedation and itching.[8] Following transdermal route, it takes 18–66 hours to reach peak plasma concentration.

Table 10.7 Dose of hydromorphone in infants and children[9]

Route	Dose
Oral	40–80 mcg/kg every 4 hourly
IV Bolus	10–20 mcg/kg every 3–4 hourly
IV Infusion	3–5 mcg/kg/hr
Epidural infusion	1–3 mcg/kg/hr

Remifentanil

It has been used for maintenance of anaesthesia intraoperatively in infant and children. It is an ultra-short acting opioid with elimination half-life of 3.4 to 5.7 minutes.[3] Infant exhibits rapid clearance though elimination half life is same in all age group.[3] It gives stable conditions intraoperatively and associated with less incidence of PONV. Analgesic supplementation is required during extubation and recovery due to its

Table 10.8 Continuous IV infusion for infants <4 months (intense monitoring and nursing observation recommended) dose is in mg/kg.[8]

Drug	Bolus dose	Infusion dose
Morphine	0.02–0.05 mg/kg	0.02–0.05 mg/kg/hr
Fentanyl	1–2 mcg/kg	2–4 mcg/kg/hr

Table 10.9 Dose of fentanyl[4]

Route	Dose in mL/kg/hr
Intravenous (analgesia)	1–2 mcg/kg
Intranasal (analgesia)	2 mcg/kg
Intravenous (anaesthesia adjunct)	1–5 mcg/kg
Intravenous (induction)	50–100 mcg/kg
Intravenous (maintenance infusion)	2–4 mcg/kg/hr

ultra-short action.[3] It has been used in dose of 0.25 mcg/kg during general anaesthesia as IV infusion.[3]

NSAIDS

Non-opioid analgesic used to control mild to moderate pain of surgery. They act by blocking prostaglandin synthesis.

Diclofenac

It is recommended in children more than one year in dose of 1 mg/kg 8 hourly via oral route.[3] Single dose of 0.3 mg/kg for intravenous, 0.5 mg/kg for suppositories and 1 mg/kg for oral Diclofenac in children aged 1–12 years are recommended as they yield a similar AUC to 50 mg in adults.[10] It should be avoided in infants less than 6 months, hypovolemia, asthma, deranged renal function, patients with single kidney, peptic ulcer disease, etc.

Paracetamol

It is a weak inhibitor of prostaglandin synthesis. Analgesic action is probably due to activation of descending serotonergic pathway. Oral dose is 10–15 mg/kg 6 hourly.[2,8] Per rectal initial loading dose of 35–40 mg/kg followed by 20 mg/kg with dosing interval of 6 hours for first 24 hours.[2] Maximum dose does not exceed 100 mg/kg in children, 75 mg/kg in neonates and 40 mg/kg in premature infants less than 32 weeks.[2]

Ibuprofen

Dose is 5–10 mg/kg 6 to 8 hourly for 3 days.[2,8] Side effects are antiplatelet activity, gastritis, interstitial nephritis, hepatic toxicity.[8]

Ketorolac

Dose is 0.5 mg/kg 6 hourly IV/IM or 10 mg/kg 6 hourly PO for 3 days.

Local Anaesthetics

Pharmacokinetics of LA in children[2,8]

1. Decrease concentration of serum albumin and α_1 acid glycoprotein in neonate and infant less than 2 months leads to high concentration of free drug, hence prone to toxicity.
2. Infants less than 6 months of age have low levels of plasma cholinesterase.
3. Metabolism of amide group of local anesthetic is slow in newborn and adult value reaches by 3–6 months. Hence continuous infusion of local anaesthetic can lead to toxicity.
4. Infants in comparison with adults have slow elimination, less duration of block and require larger dose to achieve block, hence have a low therapeutic index.
5. Children have a low threshold for seizure.

They are of two types, Ester (tetracaine, chloroprocaine, procaine) and Amide (lignocaine, bupivacaine, ropivacaine).[3] They act by blocking voltage gated sodium channels. Ester compound is metabolized by plasma cholinesterase and amide compound is degraded in liver. Toxicity following local anesthetic administration is of two types. Local toxicity involves spinal cord or peripheral nerve and occurs at site of injection.[3] Systemic toxicity preferentially involves central nervous system and cardiovascular system. It depends upon the dose and rapidity of injection.[3]

Ropivacaine

It is a long acting amide with less cardiac and CNS side effects. It produces less motor blockade.[3] In comparative study of caudal ropivacaine vs bupivacaine quality and duration of post-operative pain relief, motor and sensory effect, time to first micturition were similar.[3] Pharmacokinetics of ropivacaine after caudal block is similar to bupivacaine with regards to onset, time, efficacy, duration and incidence of motor block[3] infants have shorter clearance than children with epidural use of ropivacaine (1.7 mg/kg).[3] It has low hepatic extraction ratio. Ropivacaine duration can be prolonged with neostigmine, clonidine and ketamine.[3]

In practical experience Ropivacaine and Levo bupivacaine used in caudal block is much more safer than bupivacaine.

Lignocaine

Neonates have longer elimination half life (3.2 hrs) compared to adult (1.8 hrs) via epidural route. Free drug concentration of lignocaine is 30–40%.[3] It has a high hepatic extraction ratio.[3] Lignocaine has longer elimination half life and larger volume of distribution in children than adult after caudal anaesthesia.[3] Maximum dose of plain lignocaine is 4 mg/kg and lignocaine

with adrenaline is 5 mg/kg, maximum infusion in neonates should not exceed 0.8 mg/kg/hr.[2]

Bupivacaine

It binds to α_1 acid glycoprotein which is low at birth and increases 3–5 times in first year of life, hence more free drug is found in plasma of neonate than older child.[6] In neonates clearance of bupivacaine is 10 mL/kg/min (adult—3 mL/kg/min), volume of distribution is 4.5 lit/kg (adult—1.2 lit/kg), elimination half life is 7 hours (adult—3 hrs) and also drug can easily cross brain due to immature blood–brain barrier (BBB). Hence they have more potential for toxicity than adult.[6] It has a low hepatic extraction ratio and it is highly protein bound. Free drug concentration for both ropivacaine and bupivacaine is 4–7%.[3] Drug clearance is low at birth but increases throughout life.[3] Infusion in neonates and infants less than 3 months should not exceed 0.2 mg/kg/hr and in infant more than 3 months and older children should not exceed 0.4 mg/kg/hr.[2]

Paediatric Anaesthesiology Pearl

The anaesthesiologist must recognize that there appears to be a plateau effect in dosing epidural local anesthetics. After some quantity of the local anesthetic has been injected, additional local anesthetic does not significantly increase block height.

Benzodiazepine

Diazepam

It is metabolized by hydroxylation and demethylation in liver and both these process are reduced in neonates (more marked in premature neonates), hence they have prolonged half-life.[2] Half-life of diazepam is 75 ± 38 hrs in preterm infants, whereas 18 ± 3 in children.[5] It produces good preoperative sedation with minimal cardiorespiratory side effects.[3,8] Dose is 0.1 to 0.3 mg/kg IV, IM or oral.[3,5,7] Onset is slow and at 30–90 minutes[7,8] t½ 80 hrs[5,7] IV injection is painful.

Midazolam

It is a short acting benzodiazepine. It exhibits pH-dependent ring phenomenon. At pH 4 diazepine rings open which makes drug more water soluble and at physiologic pH ring closes which makes drug more lipid soluble.[3] It has rapid onset of action.[2] It is preferred in paediatric age group due to mild cardiorespiratory depression, less pain on IV injection, short duration of action, decrease in separation anxiety and amnesia.[3] It is highly protein bound with 3–6% free drug concentration.[3] Metabolism is by hydroxylation in liver.[3] Some patients show postoperative problems like fearfulness, nightmare and food rejection seen after premedication with midazolam.[3] Problems with oral route are that it is bitter in taste, hence has to be mixed with flavor concentrate and bioavailability is 30 %, peak serum level is achieved after 45 minute and 85% shows peaceful separation[5] problems with nasal route is irritation of nasal mucosa, loss of volume, peak serum level in 10 minutes and animal study reveals neurotoxicity after topical application. Sublingual is 0.2–0.3 mg/kg as effective as 0.2 mg/kg intranasal (IN), rectal is 0.35 to 1 mg/kg, elimination half life is 2 hours.[7] If we used with narcotics it causes respiratory depression.[7] In neonate half-life is prolonged to 6–12 hrs.[7]

Fluid therapy in perioperative period

Fluid management is different in paediatric and adult patients because of the following reasons.[2,7,9]

I. Water requirement is more in young child due to high metabolic rate.
II. Greater evaporative loss due to high ratio of body surface area to body weight.
III. Thin stratum corneum allows greater evaporative loss especially in premature neonate.
IV. Insensible loss via respiration is greater as they have high minute ventilation.
V. Babies kept under overhead radiant heater often have increase loss of water and energy.
VI. Infants and child with renal insufficiency are not able to produce concentrated urine in presence of hypovolemia.

Fluid requirement is calculated based on the following methods[2,7,9]

1. **Calorie expenditure method:** Holliday Segar demonstrated that water requirement equals the

Table 10.10 Epidural infusion of bupivacaine in infants and children[2]

Age	Drug	Rate (mL/kg/hr)
>2–3 months	Bupivacaine 0.1% with fentanyl 2 mcg/cc	0.2–0.4
<2–3 months	Bupivacaine 0.1% with fentanyl 0.5 mcg/cc	0.1–0.2

Table 10.11 Dose of midazolam[3,4]

Intranasal	0.2–0.3 mg/kg	Onset–10 min
Per oral	0.5 mg/kg	15–30 min
Intramuscular	0.1 to 0.15 mg/kg	10 min
Per rectal	0.4 to 1 mg/kg	10 min
Oral transmucosal	0.2 mg/kg	10 min

total energy expenditure at rest in children. He has proposed the following formula to estimate the water requirement for maintenance. It does not include loss due to fluid deficit in preoperative period, third space loss, blood loss, increase requirement due to hyperthermia, etc.

2. **Body surface area:** This method requires weight and height of the child. It ignores the variations in metabolic rate and thus the fluid requirement and also prone to errors.[2,11]

Fluid requirement in neonates[7]

Newborn has high extracellular fluid volume. In initial few days of life they often excrete excess water hence has decrease fluid requirement for the first week. Volume required in neonate is shown in Table 10.13.

Perioperative fluid in paediatric patients should include replacement for preoperative deficit, ongoing maintenance requirement, surgical blood loss and postoperative requirement.

Preoperative deficit: It includes loss due to starvation in preoperative period, medical conditions like diarrhoea, fever, burns and surgical conditions like intestinal obstruction, intestinal perforation, trauma, etc. Starvation fluid is calculated by multiplying the hours of starvation with maintenance fluid requirement per hour. 50% of volume is replaced with isotonic fluid (isotonic saline or ringer lactate) in first hour and 25% each in the next two hours.[9]

Deficit due to starvation can be minimized by allowing clear liquid two hours prior to surgery. Intake of clear liquid has no effect on residual gastric volume and pH, it decreases the irritability due to thirst and hunger, decreases incidence of hypovolemia at induction and decreases the incidence of postoperative nausea and vomiting.[2,7] Patients with loss due to medical and surgical conditions should be assessed for severity of fluid deficit with the help of clinical parameters, urine output and acid–base status. Such patients needs aggressive resuscitation with crystalloid and if required colloid and blood depending upon the type of deficit in preoperative period.[2]

Table 10.12 Holliday-Segar formula[7]

Body weight	Requirement of maintenance fluid per hour
<10 kg	4 mL/kg/hr
10–20 kg	40 mL + 2 mL/kg/hr for each kg for >10 kg
>20 kg	60 mL + 1 mL/kg/hr for each kg for >20 kg

Table 10.13 Fluid requirement in neonate[7]

Day of life	Volume required per day
Day 1	70 mL/kg
Day 3	80 mL/kg
Day 5	90 mL/kg
Day 7	120 mL/kg

Intraoperative loss: It includes third space loss, fluid loss through RT aspirate, drains, ongoing maintenance requirement and surgical blood loss.[9]

Third space loss: Refers to transfer of relatively isotonic fluid from extracellular volume space to interstitial space. It should be replaced with isotonic (ringer lactate), non-glucose containing fluid.[9] Replacement of loss depends on severity of surgical trauma.[10]

Fluid loss with gastrointestinal secretions—ileostomy drain output is rich in K^+ and HCO_3, whereas pancreatic secretions are rich in Cl^-, hence replacing such loss with balance salt solution is preferred.[11]

Table 10.14 Estimation of fluid loss in neonates and infant[11]

Signs and symptoms	Mild	Moderate	Severe
Weight loss	3–5%	6–9%	>10%
General condition	Alert, restless	Thirsty, lethargic	Cold, sweaty, limp
Pulse	Normal rate, volume	Rapid, weak	Rapid, feeble
Respiration	Normal	Deep, rapid	Deep, rapid
Anterior fontanelle	Normal	Sunken	Very sunken
Systolic BP	Normal	Normal or low	Low or recordable
Skin turgor	Normal	Decreased	Markedly decreased
Eyes	Normal	Sunken, dry	Grossly sunken
Mucous membrane	Moist	Dry	Very dry
Urine output	Adequate	Less, dark colour	Oliguria, anuria
Capillary refill time	Normal	<2 seconds	>3 seconds
Estimated deficit	30–50 mL/kg	60–90 mL/kg	100 mL/kg

Table 10.15 Replacement of third space loss[11]

Surgical trauma	Type of surgery	Fluid replacement
Minimal	Inguinal hernia repair	1–2 mL/kg/hr
Moderate	Ureter implantation	4 mL/kg/hr
Major	Bowel obstruction	>6 mL/kg/hr

Maintenance requirement: It includes the loss due to evaporation, loss through skin and lungs and loss through stool and urine. Evaporative loss is dependent on gestational age, exposed surface area and ambient temperature and humidity.[11] Infants have greater fluid loss through respiration due to high minute ventilation. They can be minimized by providing humidified gases for ventilation. Skin wrap with plastic drape or cotton should be done to prevent evaporative loss.[2] Requirement of fluid is calculated by Holliday-Segar formula.[11]

Surgical blood loss: Maximal allowable blood loss (MABL) should be calculated for child undergoing surgery. It takes into consideration age, weight and starting haematocrit of child.[7] Target haematocrit is considered 40% in neonates and 30% in older children. It is calculated by following formula.[7]

$$\text{MABL} = \frac{\text{EBV} \times \text{Pre-blood loss haematocrit} - \text{Target haematocrit}}{\text{Pre-blood loss haematocrit}}$$

While replacing MABL, each mL of blood is replaced with 3 mL of crystalloid or 1 mL of colloid.[9,11] If blood loss is less than MABL there is no need for transfusion of PRBCs. If blood loss exceed MABL, Transfusion of blood is indicated.[7] Healthy children usually tolerate anaemia with adequate replacement of intravascular volume deficits. Preterm infants, term newborns, children with cyanotic congenital heart disease or those with respiratory failure in need of high oxygen-carrying capacity may not tolerate anaemia well and require early transfusion.[7] Incidence of apnoea is higher in neonates and preterm infants who have haematocrit values below 30%.

Table 10.16 Estimated blood volume (EBV) in Paediatric patients [7]

Age of child	Blood volume
Preterm neonate	100–120 mL/kg
Full term neonate	90 mL/kg
Infant	80 mL/kg
Child more than 1 year	70 mL/kg

Use of dextrose containing fluid in intraoperative period

Perioperative hypoglycemia is infrequent in healthy children even after prolonged fasting.[2,9,11]

1. Perioperative hyperglycemic stress response
2. Decrease glucose uptake by muscle
3. Ineffective utilization of glucose due to impaired effectiveness of insulin.

Problems with dextrose containing fluid are osmotic diuresis with rapid IV administration, impaired wound healing and increased susceptibility for damage to brain, heart and intestine during ischemic events.[2,9] Hence healthy children do not need glucose intraoperatively.[11] Children who receive clonidine in preoperative period and neuraxial block prior to surgery may not develop intraoperative hyperglycemic stress response, hence they require blood glucose monitoring at regular interval and if required dextrose containing fluid.[9] Use of 1–2% dextrose containing fluid may provide balance between risk of developing hypoglycemia or hyperglycemia during procedure.[11]

Children at risk for hypoglycemia are[2,9]

1. Premature neonate
2. Infant of diabetic mother
3. Sick children with chronic illness
4. Children on total parenteral nutrition
5. Children with inborn error of metabolism
6. Intolerance to oral feed

Such children have high requirement of intraoperative glucose (5–10%) and should be supplemented. It should be supplemented at maintenance rate with avoidance of bolus doses. Blood sugar monitoring should be done at regular interval.

Post-operative period: Tissues often retain excess water due to elevated ADH secondary to surgical trauma, pain, etc.[2] Hence replacement should be done with isotonic fluid and not hypotonic fluids as the latter cause hyponatremia and its clinical effects.

Colloid administration in paediatric patient

Replacement of fluid deficit should begin with crystalloid due to their low cost, lack of effect on coagulation, no risk of anaphylaxis and transmission of infection.[7,12] Bolus of 15–20 mL/kg of ringer lactate or isotonic saline over 15 to 20 minutes helps in maintaining cardiovascular stability.[12] Administration of colloid is indicated after 30–50 mL/kg of crystalloid infusion.[12]

Colloid in clinical use are albumin, hydroxy ethyl starch, gelatin and dextran.

Albumin: Albumin 5% is osmotically equivalent to plasma thus helps in expanding intravascular volume. It has been found harmful in children with traumatic brain injury and with increased intravascular permeability due to worsening of oedema.[12]

Hydroxyethyl starch: It is synthetic colloid derived from polysaccharide.[2,12] Dose should not exceed >20 mL/kg/day.[2] It is relatively safe in neonate and infant for plasma volume replacement.[12] Complications like coagulation abnormality (affects the activity of vWF, factor VIII, platelet), renal dysfunction (renal tubule cell swelling) and pruritus (accumulation in skin) are common with high molecular weight substance.[2,12] Newer generations are available with less side effects and prolonged volume expansion (4–6 hrs).

Gelatin: It is a polypeptide obtained from degradation of bovine collagen.[12] Effects are less on coagulation profile, allergic reaction and renal function following its administration.[2,12] Recent study has revealed risk of necrotizing enterocolitis in preterm infant and worsening of capillary leak in septic newborn with use of gelatin.[12]

Dextran: It is a glucose polymer synthesized by specific bacteria from sucrose.[2,12] Dose should not exceed 20 mL/kg/day.[12] It improves microvascular flow. Problems with use of dextran are interference with cross matching, platelet dysfunction, elevation of blood glucose and anaphylaxis.[2,12]

Take Home Message

1. There are many pharmacokinetic and pharmacodynamic changes occur as a child develops.
2. In general, caution is particularly needed in the premature and term neonate to avoid pharmacological errors.
3. The pharmacological variation amongst neonates and infants emphasize the need to titrate many drugs to effect.
4. Physiological and pathological factors can alter drug handling.
5. Enzyme systems in the developing child are variable and complex. This gives reduced predictability of how a drug will affect a young child.
6. The paediatric patient's ability to clear a drug changes rapidly in the first few months of life; often a child can clear drugs faster than an adult.
7. Anaphylaxis is rare in children. If it seems to be anaphylactic reaction, it probably is. Treat immediately starting with use of adrenaline.

Contd...

Take Home Message *(Contd...)*

8. Do not inject any pharmacological product that you did not draw up and label or have seen being done with your own eyes.
9. Perioperative fluid therapy should include preoperative fluid deficits, intraoperative loss due to surgery, third space loss, evaporative loss and postoperative requirement.
10. Majority of intraoperative loss is replaced with isotonic fluid (ringer lactate, isotonic normal saline).
11. Majority of healthy children do not require dextrose containing fluid in perioperative period. But children at risk of hypoglycemia should receive dextrose containing fluid.
12. Fluid therapy should be monitored by clinical parameters, input–output charting, acid–base status and serum electrolytes.

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11

CPCR in Paediatrics

Minal Harde and Rakesh Bhadade

ABSTRACT

Cardiopulmonary arrest is the most serious emergency in the medical practice and treatment must start without a second's delay. Cardiopulmonary cerebral resuscitation (CPCR) is an attempt to restart the heart and restore the brain functioning after cardiac arrest. Paediatric cardiopulmonary arrest is a unique from adult with respect to causes, pathophysiology and management.

American Heart Association (AHA) Guidelines for Cardiopulmonary Resuscitation (CPR) and Emergency Cardiovascular Care (ECC) completed 50 years of modern CPR in 2010.

This chapter describes essential elements of CPR based on most recent guidelines by AHA, key changes in CPCR guidelines in 2010 and the latest algorithms for paediatric and neonatal resuscitation.

Recognition of arrest and prompt action by the rescuer continue to be priorities for the 2010 AHA Guidelines for CPR and ECC. High quality CPR with monitoring is highly emphasized. Algorithms and the use and timing of drugs have been simplified.

Prevention of cardiac arrest situation is the most important step in paediatrics. Anticipation, extreme vigilance, early recognition, adequate preparation, prompt basic life support (BLS), and rapid paediatric advanced life support (PALS) are essential for survival and best quality of life.

INTRODUCTION

Cardiac arrest (CA) is cessation of cardiac mechanical activity. Paediatric cardiopulmonary arrest is a unique from adult CA as asphyxia is the commonest cause for CA.[1]

Approximately 16,000 children suffer a cardiac arrest each year in America.[2] Incidence in India is unknown. Overall outcome in-hospital resuscitation are better with survival of 27% as compared to an out-of-hospital arrest with survival of only 6%.[1,2] This can be improved by timely bystander CPR.[3,4] Children are more likely to survive in-hospital arrests than adults, and infants have a higher survival rate than children.[4,5]

The essential components of paediatric cardiopulmonary resuscitation (CPR) are:

- Prevention of cardiac arrest situation,
- Recognition of cardiac arrest and early CPR and basic life support (BLS),

Fig. 11.1 Paediatric chain of survival
Source: Part 13—Paediatric Basic Life Support 2010, American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

- Prompt access to the emergency response system
- Paediatric advanced life support (PALS), followed by
- Integrated post-cardiac arrest care.

The above 5 links form the American Heart Association (AHA) Chain of Survival for paediatric patients, the first 3 links of which constitute paediatric BLS (Fig. 11.1).[1]

CAUSES OF PAEDIATRIC CARDIOPULMONARY ARRESTS

Neonates and children have very unique causes of cardiac arrest. Most paediatric cardiac arrests occur in children younger than one year of age and 90% are respiratory arrest. In infants, the leading causes of death are congenital malformations, complications of prematurity, and sudden infant death syndrome (SIDS). In children over 1 year of age, injury is the leading cause of death. In hospital and perioperative causes of CA are unique.

Causes of CA in children can be categorised as follows:[3, 7–11]

- **Respiratory**
  1. Foreign body obstruction
  2. Trauma
  3. Drowning
  4. Poisoning
  5. Bronchial Asthma exacerbation
  6. Infection
     - Supraglottitis
     - Bronchiolitis
     - Pneumonia
- **Circulatory disturbances leading to CA**
  1. Sepsis
  2. Metabolic disorders
  3. Electrolyte distubances
  4. Drug toxicity
  5. Haemorrhage

Sudden cardiac arrest syndrome

In cases of sudden collapse in older paediatric patients and patients with congenital heart disease, a primary cardiac cause should be considered. It can be structural/functional:

1. Cardiomyopathy (Hypertrophic/dilated/restrictive)
2. Coronary artery anomalies
3. Aortic rupture/Marfan syndrome
4. Myocarditis
5. Left ventricular outflow tract obstruction
6. Mitral valve prolapse
7. Coronary artery atherosclerotic disease
8. Arrhythmogenic right ventricular cardiomyopathy
9. Congenital heart disease
10. Primary pulmonary hypertension

Electrical

1. LQTS
2. Wolff-Parkinson-White syndrome
3. Brugada syndrome
4. Catecholaminergic polymorphic ventricular tachycardia
5. Short QT syndrome
6. Complete heart block

- **Perioperative causes of CA**
  1. Cardiovascular depression from the inhaled agents.
  2. Hypovolemia (often from hemorrhage)
  3. Complications of massive transfusion (usually hyperkalemia)
  4. ASA Physical Status 3–5
  5. Procedure related complications
  6. Local anaesthetic agent toxicity
  7. Respiratory events
     - difficult intubation, malpositioned endotracheal tube, inadvertent extubation
     - airway obstruction, laryngospasm, bronchospasm
     - equipment failure
     - cardiac tamponade
     - pneumothorax

Phases

There are four phases of CA: Pre-arrest, no-flow, low flow and post-resuscitation, with distinct pathology and management.[2,11–15]

The pre-arrest phase consists of events leading to CA and prevention is the goal.

- Reduced SIDS with "Back to sleep"
- Implementation of swimming safety norms to reduce drowning.
- Use of child passenger safety seats.

In the pre-hospital and hospital settings, this is achieved by the education of health care providers by early recognition of paediatric pathology leading to CA: respiratory and cardiovascular failure. Identifying patients at risk for cardiopulmonary arrest are as important as providing good CPR. This requires constant clinical evaluation and identification of risk

factors. Critically ill patients are often at increased risk for cardiac arrest during airway manipulation, change in therapy, or manipulation of the patient or bed and when doctors and nurses change shifts.[15] Nearly 20% of anaesthesia-related paediatric cardiopulmonary arrests (CPAs) occur during emergence or recovery emphasizing the importance of extreme vigilance.[16]

The no-flow phase represents untreated CA prior to recognition by a lay bystander in the community or a medical provider in the hospital setting. The no-flow phase is longer in out-of hospital paediatric CA as compared to in-hospital CA.

The low-flow phase begins at the initiation of CPR. Chest compressions combined with ventilation provide coronary and cerebral perfusion. High-quality CPR with early ACLS will improve the chances of survival.[12]

The post-resuscitation phase begins with return of spontaneous circulation (ROSC). While ROSC is the initial therapeutic goal in CA and is a measure of the initial success, post-resuscitation care must be focused on reducing neuronal injury.

The Classification of Recommendations (COR) and Level of Evidence (LOE)

The American College of Cardiology Foundation (ACCF), the American Heart Association (AHA), International Liaison Committee on Resuscitation (ILCOR) and AHA Task Force on Practice Guidelines apply COR by developing, updating, and revising practice guidelines for cardiovascular diseases and procedures.[17,18] Writing committees assess the evidence with literature review; weigh the strength of evidence and update, or revise recommendations for clinical practice. Class and level of evidence is mentioned for tests, treatments, or procedures done during paediatric CPR. The Classification of Recommendations (COR) and Level of Evidence (LOE) is summarized in Table 11.1.

GUIDELINES IN PAEDIATRIC CARDIOPULMONARY RESUSCITATION (CPCR)

Cardiopulmonary resuscitation is a series of life-saving actions that improve the chance of survival following cardiac arrest. Recognition of arrest and prompt action by the rescuer continue to be priorities for the 2010 AHA Guidelines for CPR and ECC.

Recommended sequence of CPR has previously been known by the initials "ABC": Airway, Breathing/ventilation, and Chest compressions (or Circulation).

The 2010 AHA Guidelines for CPR and ECC recommend a "CAB" sequence (except for newly born) for the following reasons.

- During CPR, perfusing the heart and brain are the priorities and oxygen delivery is limited by blood flow rather than by arterial oxygen content, hence circulate the blood by starting ECC.
- Compressions can be initiated almost immediately, while positioning the head and attaining a seal for mouth-to-mouth or a bag-mask apparatus for rescue breathing take time and delays the initiation of chest compressions.
- AHA recommends CAB sequence for paediatric resuscitation in order to simplify training and more victims of sudden cardiac arrest will receive bystander CPR. It also offers the advantage of consistency in teaching rescuers, whether their patients are infants, children, or adults. However, for asphyxial cardiac arrest which is more common in infants and children, ventilations are also important in paediatric resuscitation. A recent large paediatric study shows that resuscitation results for asphyxial arrest are better with a combination of ventilations and chest compressions.[4]

Key Note:
The 2010 AHA Guidelines for CPR and ECC recommend a CAB sequence for paediatric resuscitation.

Table 11.1 Applying Classification of Recommendations (COR) and Level of Evidence (LOE)

Level of Evidence	Class I Benefit >>> Risk	Class IIa Benefit >> Risk	Class IIb Benefit ≥ Risk	Class III No Benefit, No Risk
A Data from multiple randomised controlled trials	Useful, effective, should be used	Useful, effective, reasonable to use	Useful, effective, may be considered	May not be useful, may be harmful
B Single or randomised controlled trials Non-randomised controlled trials	Useful, effective, should be used	Useful, effective, reasonable to use	Useful, effective, may be considered	Useful, effective, may be considered
C Only consensus opinion of experts, case studies	Useful, effective, should be used	Useful, effective, reasonable to use	Useful, effective, may be considered	Useful, effective, may be considered

Paediatrics BLS Algorithm (Fig. 11.2)

Activate (AHA) paediatric chain of survival. Safety of rescuer and victim is very important in field situations. If the infant or child is unresponsive and not breathing or only gasping (gasps do not count as breathing), health care providers may take up to 10 seconds to check for a pulse preferably brachial in an infant and carotid or femoral in a child (Class IIa, LOE C). CPR is not harmful but inaction, hence start CPR when in doubt about CA.

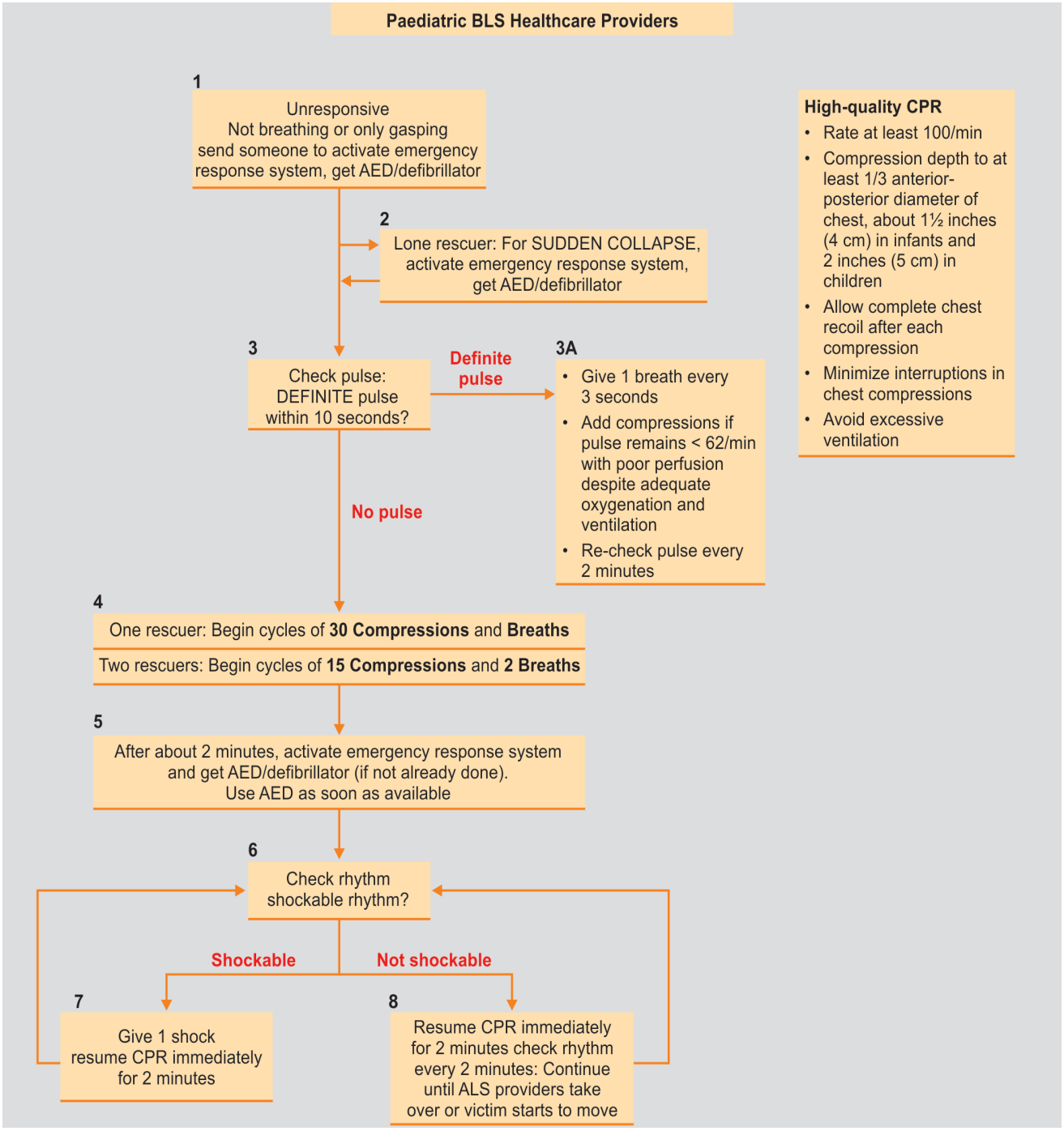

Fig. 11.2 Paediatric BLS Algorithm

Source: Part 13—Paediatric Basic Life Support 2010, American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

Key Notes: Diagnosis of CA and need for CPR

1. Unresponsive
2. Not breathing/gasps
3. No pulse (only health care providers up to 10 seconds)

Chest Compressions

During cardiac arrest, high-quality chest compressions generate blood flow to vital organs and increase the chances of ROSC. Give 30 chest compressions on a firm surface.[1,19] For an infant, compressions can be given by 2 fingers placed just below the intermammary line or the 2-thumb–encircling hands technique (Figs 11.3 and 11.4).

The 2-thumb–encircling hands technique is preferred over the 2-finger technique because it produces higher coronary artery perfusion pressure, results more consistently in appropriate depth or force of compression, and may generate higher systolic and diastolic pressures.[19–21] For a child, compress the lower half of the sternum with the heel of 1 or 2 hands. Do not press on the xiphoid or the ribs.[1,22]

The characteristics of high-quality CPR and the reason for key changes in 2010 guidelines are as follows:

- ***"Push fast"***: Push at a rate of at least 100 compressions per minute from up to 100/minute.

  "Push hard": Push with sufficient force to depress at least one third the anterior-posterior (AP) diameter of the chest or approximately 1½ inches (4 cm) in infants and 2 inches (5 cm) in children (Class I, LOE C). Chest compressions of appropriate rate and depth are essential for effective CPR.

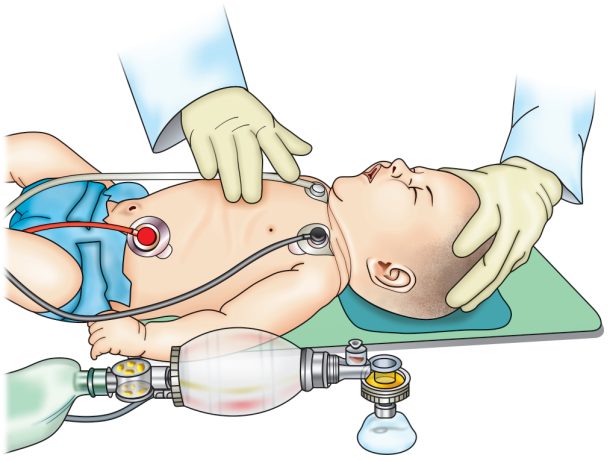

Fig. 11.3 Two finger technique ECM in infant
Source: Part 13—Paediatric Basic Life Support 2010, American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

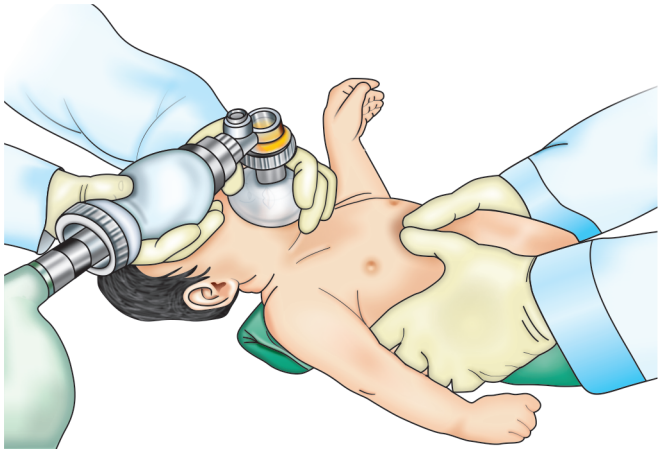

Fig. 11.4 Two thumb-encircling technique ECM in infants and newborns with bag and mask ventilation (2 rescuers)
Source: Part 13—Paediatric Basic Life Support 2010, American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

- ***Maintain compression: Relaxation Ratio: 1:1*** and allow complete chest recoil after each compression to allow the heart to refill with blood, thereby improving blood flow to the vital organs during CPR (Class IIb, LOE B).
- ***Minimize interruptions of chest compressions*** as after interruption when chest compressions are resumed, several chest compressions are needed to restore coronary perfusion pressure. Thus, interruptions of chest compressions prolong the duration of low coronary perfusion pressure and flow.
- ***Avoid excessive ventilation*** as it increases intrathoracic pressure, which impedes venous return, thus reducing cardiac output and cerebral and coronary blood flow (Class III, LOE C).

Rescuers should rotate the compressor role approximately every 2 minutes to prevent compressor fatigue and deterioration in quality and rate of chest compressions.[23] Resuscitation outcomes in infants and children are best if chest compressions are combined with ventilations.

Airway and Breathing

Maintaining a patent airway and providing adequate ventilation is extremely important in paediatric CPR. After the initial set of 30 compressions, open the airway and give 2 breaths. In an unresponsive infant or child, the tongue may obstruct the airway and interfere with ventilations. Look, Listen and Feel for breathing is no longer recommended in 2010 AHA Guidelines for CPR,

as precious time is lost in this process. Open the airway using a head tilt-chin lift manoeuvre and use only jaw thrust if there is evidence of trauma suggesting spinal injury (Class I, LOE B).[1]

To give breaths to an infant, use a mouth-to-mouth or mouth-to-nose technique; to give breaths to a child, use a mouth-to mouth technique (Class IIb, LOE C).[1] Each breath should be given over 1 second and observe the chest rise for effective breaths. In mouth-to-mouth technique, pinch the nose closed and in mouth-to-nose technique, close the mouth. Barrier devices can be used, however, they have not reduced the low risk of transmission of infection and some may increase resistance to airflow.[24] Bag-mask ventilation technique can be used by health care providers.

Coordination of Chest Compressions and Breathing is recommended with compression-to-ventilation ratio of 30:2 for single rescuers. Deliver ventilations with minimal interruptions in chest compressions (Class IIa, LOE C). Optimal CPR in infants and children includes both compressions and ventilations, but compressions alone are preferable to no CPR. If child returns to spontaneous circulation turn the child to one side (recovery position), which helps maintain a patent airway and decreases risk of aspiration. Optimal CPR in infants and children includes both compressions and ventilations, but compressions alone are preferable to no CPR (Class I LOE B).

High-quality CPR is very important because effective paediatric advanced life support (PALS) depends on good BLS.

Key Notes: High-quality CPR

1. Rate of chest compressions should be at least 100 compressions per minute.
2. "Push fast" and "Push hard"
3. Push at least 4 cm in infants and 5 cm in children.
4. Allow complete chest recoil after each compression.
5. Minimize interruptions in chest compressions.
6. Avoid excessive ventilation.
7. Maintain high-quality CPR.

ELECTRICAL INTERVENTIONS IN CARDIAC ARREST

Defibrillation

The 2010 AHA Guidelines for CPR and ECC recommend rapid defibrillation and Integrated Automated External Defibrillator (AED) in the Chain of Survival in BLS outside hospitals. The term defibrillation (shock success) is defined as termination of VF for at least 5 seconds following the shock.[25] Shock temporarily depolarizes or stuns an irregularly beating heart terminating fatal arrhythmia for at least 5 seconds and allows more coordinated contractile activity to resume. Children with sudden witnessed cardiac arrest are likely to have ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT) and need immediate CPR and rapid defibrillation. VF and pulseless VT are referred to as "shockable rhythms" because they respond to defibrillation. (Class I, LOE B)

Defibrillators

Defibrillators are either manual or automated, with monophasic or biphasic waveforms. AEDs are sophisticated, computerized devices that guides for safe defibrillation by using voice and visual prompts. For infants a manual defibrillator is preferred but if not available AED with a paediatric dose attenuator can be used (Class IIa, LOE C).[26] If neither is available, an AED without a dose attenuator can be used.

Universal steps of AED operation:

- Step 1: Power ON the AED and attach electrode pads
- Step 2: 'Clear' the patient and ANALYSE the rhythm
- Step 3: PRESS the SHOCK button if shock is indicated

Manual defibrillators have adult (8–10 cm) and infant (4–5 cm) hand-held paddles or self-adhesive pads also can be used. Pads should be pressed firmly on the chest so that the gel on the pad completely touches the child's chest. Place manual paddles over the right infraclavicular area and the apex of the heart so the heart is between the two paddles (Figs 11.5A and B).

Energy dose: The recommended first energy dose for defibrillation is biphasic 2 J/kg followed by 4 J/kg, higher energy may be considered but not beyond 10 J/kg (Class IIb, LOE C).

Integration of Defibrillation with Resuscitation

Rescuers should coordinate chest compressions and shock delivery to minimize interruptions in chest compressions. Resume CPR, beginning with compressions, immediately after shock. No pulse check is recommended after defibrillation. Give 2 minutes of uninterrupted CPR and limit interruptions to <10 seconds; interrupt only during intubation and when you are ready to deliver a shock.

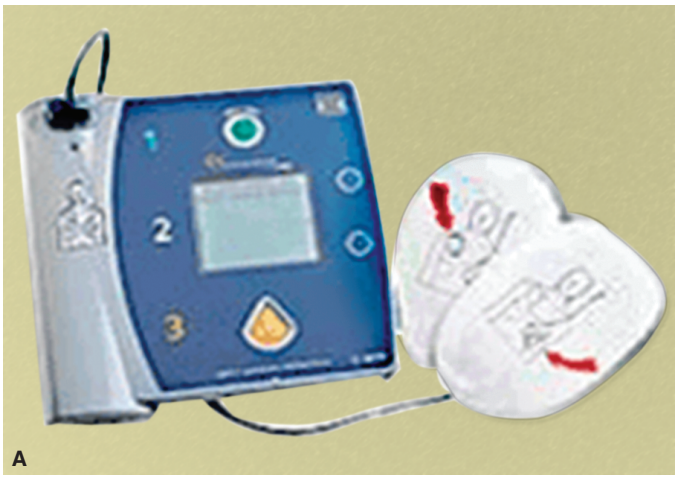

Fig 11.5A and B Defibrillator—**(A)** AED with adhesive pads (*From NET*) and **(B)** Pediatric paddles in conventional defibrillator

PAEDIATRIC ADVANCED LIFE SUPPORT

Paediatric advanced life support (PALS) is the organized response in an advanced healthcare environment where coordinated actions are performed simultaneously by a team. Organization of the rescuers into an efficient team for successful resuscitation is important.[27]

Chest compressions should be immediately started by one rescuer, while a second rescuer prepares to start ventilations with a bag and mask and other rescuers should obtain a monitor defibrillator, establish vascular access and calculate and prepare the anticipated medications. Ventilation is extremely important in paediatrics because of the large percentage of asphyxial arrests in which best results are obtained by a combination of chest compressions and ventilations.[4] Ventilations are sometimes delayed because equipment (bag, mask, oxygen and airway) must be mobilized. Therefore, start CPR with chest compressions immediately, while a second rescuer prepares to provide ventilations (Class I, LOE C). The effectiveness of PALS is dependent on high-quality CPR (Fig. 11.6).

Airway

After doing triple manoeuvre to open the airway, oropharyngeal and nasopharyngeal airways help maintain an open airway by displacing the tongue or soft palate from the pharyngeal air passages. Bag-mask ventilation should be done with a correct mask size, maintaining an open airway, providing a tight seal between mask and face (Class IIb, LOE C). Supraglottic devices like Laryngeal Mask Airway (LMA) can be used (Class IIa, LOE C).[28]

Use only the force and tidal volume needed to just make the chest rise visibly, avoid delivering excessive ventilation. Excessive ventilation during cardiac arrest increases intrathoracic pressure, which impedes venous return, thus reducing cardiac output and cerebral and coronary blood flow. It also increases the risk of stomach inflation, regurgitation and aspiration. Gastric inflation may interfere with effective ventilation and cause regurgitation, aspiration of stomach contents, and further ventilatory compromise.[29] These can be decreased by avoiding excessive peak inspiratory pressures, applying cricoid pressure or passing a nasogastric or orogastric tube to relieve gastric inflation (Class IIa, LOE B). Cricoid pressure is not routinely recommended as interferes with ventilation or the speed or ease of intubation.[29]

Endotracheal Intubation

Endotracheal intubation is the gold standard. Both cuffed and uncuffed endotracheal tubes (ETT) are acceptable for intubating infants and children but 2010 AHA Guidelines for CPR and ECC emphasize for use of appropriately sized cuffed ETT.[30] Verification of tube placement should be done by direct visualisation, clinical signs or the presence of water vapour in the tube and confirmed by End-Tidal CO_2 ($PETCO_2$) (Class I, LOE B).[31] During cardiac arrest, if exhaled CO_2 is not detected, confirm tube position with direct laryngoscopy because the absence of CO_2 may reflect very low pulmonary blood flow rather than tube misplacement.

After intubation, secure the tube and ventilate with an inspiratory time of approximately 1 second and at a

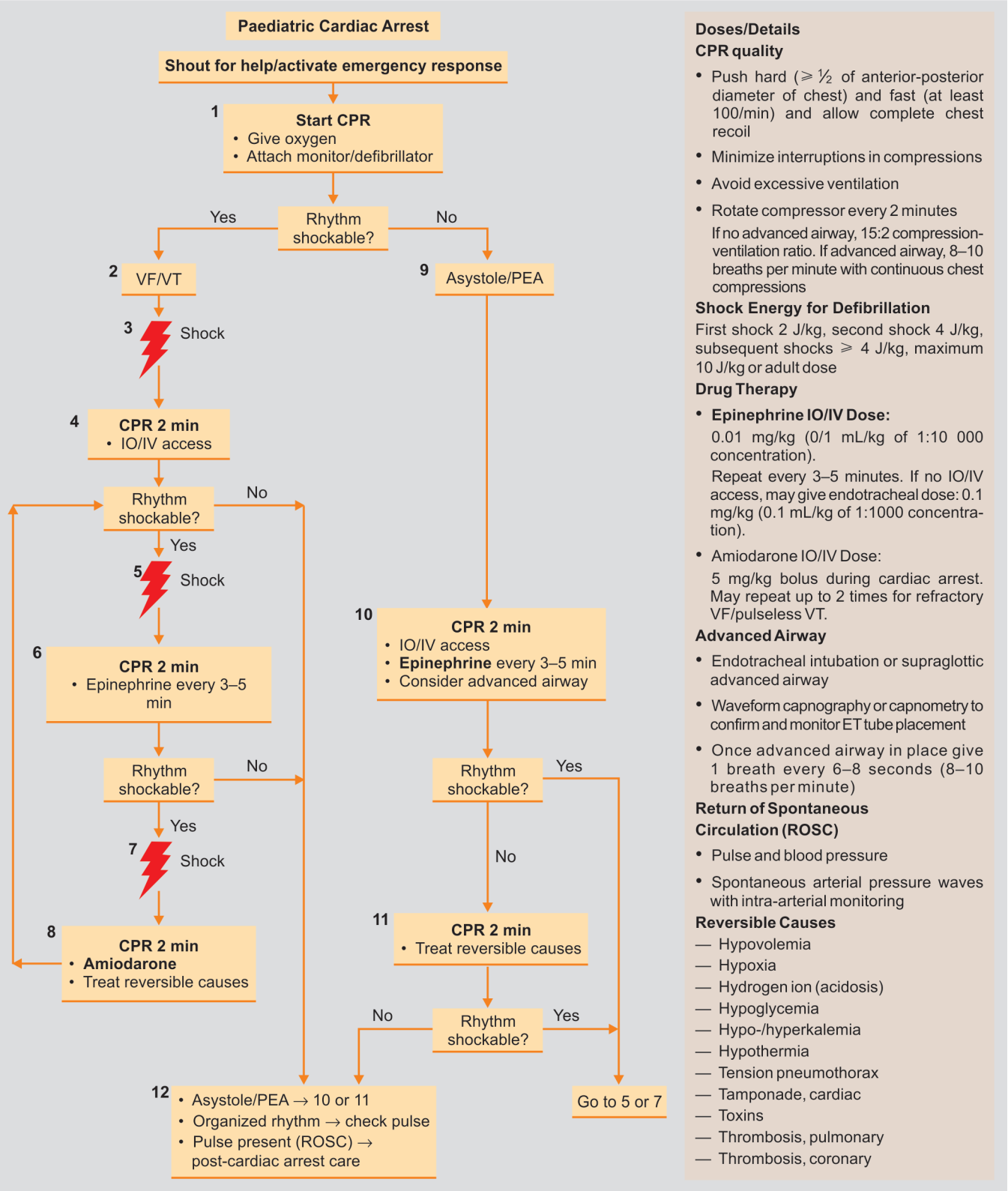

Fig. 11.6 Paediatric advanced life support (PALS) algorithm
Source: Part 14—Paediatric Advanced Life Support 2010, American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

rate of about 8 to 10 per minute without interrupting chest compressions (Class I, LOE C).

Oxygen

Ventilate with 100% oxygen during CPR once ROSC is achieved; adjust the FiO_2 to the minimum concentration needed to achieve arterial oxyhemoglobin saturation at least 94%, with the goal of avoiding hyperoxia while ensuring adequate oxygen delivery (Class IIb, LOE C).[27]

VASCULAR ACCESS

Vascular access is essential for administering medications and fluids. Peripheral venous access is preferred but can be difficult in children during an emergency.

Venous Access: Peripheral IV access is acceptable and can be placed rapidly, but placement may be difficult in a critically ill child. A central venous catheter (CVC) placement is time consuming and requires training and experience. If both central and peripheral accesses are available, administering medications like sympathomimetics and antiarrythmics are preffered through CVC.[32]

Intraosseous (IO) access can be quickly established with minimal complications. IO access is a rapid, safe, effective, and acceptable route for vascular access in children (Class I, LOE C). Proximal tibia is the preferred site in children as it has a broad flat surface and the cortex, abundant marrow content and is easy to penetrate. Insertion site is the anteromedial surface of the tibia, 1–3 cms below the tibial tuberosity (Fig. 11.7).

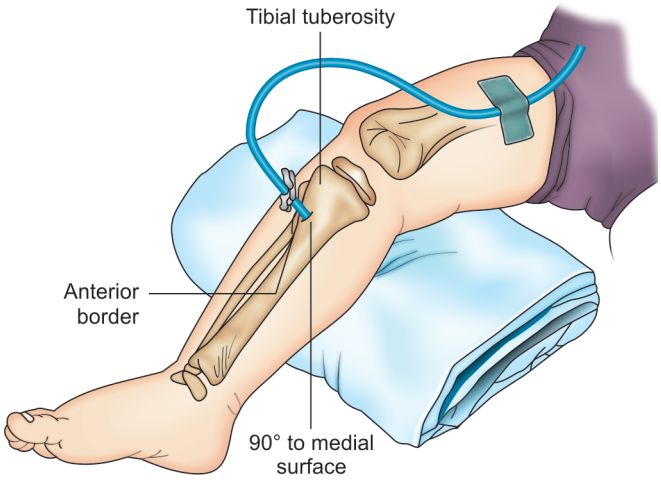

Fig. 11.7 Interosseous
Source: Critical Care Medicine Paediatric and Neonatal Intensive Care (Sec.-5;Ch-73-net)

All intravenous medications can be administered intraosseously and drug doses and fluid rates are the same as for intravenous route. Onset of action and drug levels for most drugs are comparable to venous administration.[32, 33] Each medication should be flushed with a saline bolus for prompt entry into the central circulation.

Endotracheal Drug Administration

The preferred method for drug delivery during CPR are IO or IV, but if it is not possible, lipid-soluble drugs, such as lidocaine, epinephrine, atropine, and naloxone can be administered via an endotracheal tube. After administering the drug through endotracheal tube flush 5 mL of normal saline and 5 consecutive positive-pressure ventilations. Exact endotracheal doses of medications are unknown. Recommended doses are double or triple the dose of lidocaine, atropine or naloxone. For epinephrine, a dose ten times the intravenous dose (0.1 mg/kg or 0.1 mL/kg of 1 : 1000 concentration) is recommended.

Key Note:
Drugs can be administered by endotracheal route are: **A**tropine, **l**idocaine, **o**xygen, **n**aloxone, and **e**pinephrine (mnemonic "ALONE").

PHARMACOLOGY OF RESUSCITATION (Table 11.2)

In the 2010 AHA Guidelines for CPR and ECC, the use and timing of drugs have been simplified and the following changes are made.

- Atropine is not recommended for routine use in the management of PEA/asystole.
- High-dose epinephrine is not routinely recommended.
- Adenosine is the drug of choice for supraventricular tachycardia and for management of stable undifferentiated regular monomorphic wide-complex tachycardia.
- Calcium, sodabicarbonate, magnesium are not indicated unless specific indications.

MONITORING

Electrocardiography

Continuous monitoring of cardiac rhythm is necessary for diagnosis of abnormal rhythm as well as to follow response to treatment and changes in clinical condition.[48]

Table 11.2 Pharmacology of CPR

Drug	Dose/Route	Action	Comments
Adenosine	0.1 mg/kg (maximum 6 mg) IV or IO followed by a rapid saline flush can be repeated as 0.2 mg/kg (maximum 12 mg). It should be preferably administered through the central line with continuous ECG monitoring.	Adenosine causes a temporary atrioventricular (AV) nodal conduction block and interrupts reentry circuits that involve the AV node. Pharmacologic cardioversion[34,35]	Adenosine is the drug of choice for supraventricular tachycardia. In 2010 AHA Guidelines recommended for management of stable undifferentiated regular monomorphic wide-complex tachycardia
Amiodarone[36, 37] (Class IIb, LOE C)	5 mg/kg IV/IO can be repeated twice up to 15 mg/kg with continuous monitoring of ECG and blood pressure. Maximum single dose 300 mg	Amiodarone slows AV conduction, prolongs the AV refractory period and QT interval, and slows ventricular conduction (widens the QRS).	It can given IV push during cardiac arrest but slowly with perfusing rhythm. Caution when administering with other drugs that prolong QT
Atropine	0.02 mg/kg IV/IO, small doses of atropine < 0.1 mg can produce paradoxical bradycardia because of its central effect. Maximum single dose is 0.5 mg	Parasympatholytic drug that accelerates sinus or atrial pacemakers and increases the speed of AV conduction	*In 2010 AHA guidelines* atropine not recommended for management of PEA/asystole. Indicated only in bradyarrythmia. Higher doses in organophosphate poisoning.[27]
Calcium chloride (Class III, LOE B)	Calcium chloride (10%) 20 mg/kg IV/IO Calcium gluconate 100 mg/kg over 5–10 minutes	Calcium chloride may be preferred because it results in a greater increase in ionized calcium but is more irritating to the vein	Indicated only in hypocalcemia, calcium channel blocker overdose, hypermagnesemia, or hyperkalemia.[38,39]
Epinephrine (Class I, LOE B)	0.01 mg/kg (0.1 ml/kg 1:10,000) IV/IO 0.1 mg/kg (0.1 mL/kg 1:1000) through endotrachael route and can be repeated every 3–5 minutes.	The α adrenergic-mediated vasoconstriction. Increases aortic diastolic pressure and coronary perfusion pressure. Redistribution of blood flow to vital organs.	High-dose epinephrine is recommended only for beta blocker overdose.[27,40,41] Do not administer catecholamines and sodium bicarbonate simultaneously
Glucose (Class I, LOE C)	(D25W) administered as 0.5–1 g/kg IV/IO (2–4 mL/kg)	Infants have a high glucose requirement and low glycogen stores, hence hypoglycaemia may develop when energy requirements increase.	Blood glucose concentration should be checked during the resuscitation and hypoglycemia to be treated promptly.[27,42]
Lidocaine	1 mg/kg IV/IO bolus, followed by infusion of 20–50 mcg/kg/minute.	Lidocaine decreases automatically and suppresses ventricular arrhythmias.[36,37]	It can be used in VF refractory to shocks and epinephrine
Magnesium sulfate	25–50 mg/kg IV/IO over 10–20 minutes can be administered rapidly in torsades de pointes and maximum single dose is 2 gm		Indicated in documented hypomagnesemia or for torsades de pointes.[43]
Naloxone	0.1 mg/kg		Indicated in the infant for reversal of respiratory depression, secondary to maternal opioids, given four hrs before delivery.
Procainamide	15 mg/kg IV/IO slowly with continuous monitoring of ECG and blood pressure.	Procainamide prolongs the refractory period of the atria and ventricles and depresses conduction velocity.	There is a limited clinical data on using procainamide in infants and children.[44]

Contd...

Table 11.2 Pharmacology of CPR *(Contd...)*

Drug	Dose/Route	Action	Comments
Sodium Bicarbonate (Class III, LOE B)	1 mEq/kg per dose IV/IO slowly after adequate ventilation.	To be administered with caution as may cause hypokalemia, hypocalcemia, hypernatremia, and hyperosmolality; decrease the VF threshld and impair cardiac function.	Indicated for treatment of hyperkalemic cardiac arrest, documented acidosis.[45]
Vasopressin	Vasopressin: 0.4 U/kg Terlipressin: 10–20 U/kg	Effective as a rescue therapy in refractory prolonged cardiac arrest when standard treatment fails.[46,47]	There is insufficient evidence for or against the routine use of vasopressin during paediatric CPR

Echocardiography may be considered to identify patients with potentially treatable causes of the arrest, particularly pericardial tamponade and inadequate ventricular filling (Class IIb, LOE C).[49,50] Minimize interruption of CPR while performing echocardiography.

End-Tidal CO_2 ($PETCO_2$)

The 2010 AHA Guidelines for CPR recommend monitoring quality CPR by continuous capnography for effectiveness of chest compressions. For high quality CPR maintain $PETCO_2$ consistently above 10–15 mmHg. (Class IIa,LOE C). There is a strong correlation between $PETCO_2$ and interventions that increase cardiac output during CPR or shock.[27,51] $PETCO_2$ must be interpreted with caution for 1 to 2 minutes after administration of epinephrine or other vasoconstrictive medications because these medications may decrease the end-tidal CO_2 level by reducing pulmonary blood flow. An abrupt and sustained rise in $PETCO_2$ is observed just prior to clinical identification of ROSC.[52]

Whenever feasible, monitoring of arterial pressure during the relaxation phase of chest compressions or central venous oxygen saturation ($ScvO_2$) are recommended.

ARREST RHYTHMS

The arrest pulse less rhythm is either "shockable" (e.g. VF or rapid VT) or "not shockable" (e.g. asystole or PEA). It may be necessary to momentarily interrupt chest compressions to determine the child's rhythm. Asystole and bradycardia with a wide QRS are most common in asphyxial arrest. VF is commomner in older children with sudden arrest.[1,27]

"Nonshockable Rhythm": Asystole/PEA

PEA is an organized electric activity slow, wide QRS complex without palpable pulse. This rhythm may be more reversible than asystole.

For asystole and PEA throughout resuscitation, emphasis should be on provision of high-quality CPR. During CPR administer epinephrine, 0.01 mg/kg (0.1 mL/kg of 1 : 10 000 solution) maximum of 1 mg (10 mL) repeated every 3 to 5 minutes. Check rhythm every 2 min with minimal interruptions in chest compressions.

If at any time the rhythm becomes "shockable," give a shock and resume chest compressions. If the rhythm is "nonshockable" continue with cycles of CPR and epinephrine administration until there is evidence of ROSC or termination of the effort. At this time treat the cause and not only the condition. Search for and treat reversible causes of CA which can be summerised as 6 Hs and 6 Ts (Table 11.3).

In case of bradycardia unresponsive to standard CPR and if associated with congenital or acquired heart disease, emergency transcutaneous pacing may be lifesaving (Class IIb, LOE C).[27]

"Shockable Rhythm" VF or Rapid Pulseless VT

Provide high quality CPR until the defibrillator is ready to deliver a shock; after shock delivery (2 J/kg), immediately resume CPR for 2 minutes, beginning with chest compressions. Minimize interruptions of chest compressions as defibrillation is successful after a period of effective chest compressions.[51] CPR may provide coronary perfusion, increasing the likelihood of defibrillation with a subsequent shock. If a "shockable" rhythm persists, give another shock (4 J/kg) and continue CPR, give epinephrine 0.01 mg/kg every 3 to 5 minutes.

Table 11.3 Differential diagnosis of cardiac arrest–6Hs and 6Ts

Hypoxia	Tablets (drug overdose)
Hypovolemia	Tamponade (cardiac)
Hydrogen ion (acidosis)	Tension pneumothorax
Hyperkalemia/Hypokalemia	Thrombosis-heart (AMI)
Hypothermia	Thrombosis-lungs (pulmonary embolus)
Hypoglycemia	Trauma

Check rhythm every 2 minutes with minimal interruptions in chest compressions. Outcome of shock delivery is best if the time between last compression and shock delivery is minimized.

During prolong VF, the myocardium is depleted of oxygen and other metabolic substrates. Chest compressions can deliver oxygen and energy substrates, increasing the chances of shock success and thus terminating VF and a perfusing rhythm may return.[53]

There is no upper limit to the number of shocks you can give as shockable rhythms have better prognosis and as long as the myocardium has energy to produce VF, it has energy to revert to normal sinus rhythm. However, high quality CPR to be maintained and rhythm appropriate medications as discussed in PALS to be administered. If the rhythm turns "nonshockable" continue with cycles of CPR and epinephrine administration until there is evidence of ROSC or termination of the efforts to declare death.

Extracorporeal Life Support (ECLS)

Extracorporeal life support (ECLS) is a modified form of cardiopulmonary bypass used to provide prolonged delivery of oxygen to tissues. ECLS should be considered for cardiac arrest occurring in ICU and which are refractory to standard resuscitation attempts, with a potentially reversible cause of arrest (Class IIa, LOE C). The expertise and equipment availability is limiting factor.[54]

With underlying cardiac disease, long-term survival when ECLS is initiated in a critical-care setting has been reported even after 50 minutes of standard CPR.

RECENT GUIDELINES IN NEONATAL RESUSCITATION (Fig. 11.8)

CPR recommendations are different for infants and for the newly born.[55–57] The aetiology of neonatal arrests is nearly always asphyxia, hence the A-B-C sequence has been retained for resuscitation. Resuscitation guidelines have been modified and C-A-B sequence is recommended for neonates with congenital heart disease, with single-ventricle anatomy, Fontan or hemi-Fontan/bidirectional Glenn physiology and pulmonary hypertension.[55]

Assessment of the foetus at birth using the Apgar score is a simple, useful guide to neonatal well-being and resuscitation. It is evaluated at 1 and 5 minutes[15,56] (Table 11.4) .

"**The Golden Minute**" The first minute is very important during which the following steps should be completed.

- Rapid evaluation
- Assessment of Apgar score
- The initial steps of resuscitation:
  1. To provide warmth by covering the baby in plastic wrapping (Class I, LOE A) or placing under a radiant heat source
  2. Positioning the head in a "sniffing" position to open the airway
  3. Clearing the airway, if necessary, however the role of peripartum suctioning has been deemphasized in active babies even in the presence of meconium
  4. Drying the baby and stimulating breathing

Oxygen saturations (SpO_2) monitoring is recommended when resuscitation is anticipated, with the probe attached to the right upper extremity. It guides for any need of supplementary oxygen, when cyanosis is persistent and when assisted ventilation is needed (Class I, LOE B).

For babies born at term, it is recommended to begin resuscitation with room air as hyperoxia can be toxic. If oxygen administered should be blended with air and SpO_2 monitored to guide titration of the blend delivered.[55]

Table 11.4 Relation of age, height, and weight to body surface area (BSA)

Sign	Score*		
	0	1	2
Heart rate	Absent	Less than 100/min	More than 100/min
Respiratory effort	Absent	Slow, irregular	Good, crying
Color	Blue, pale	Body pink, extremities blue (acrocyanosis)	Completely pink
Reflex irritability (response to insertion of a nasal catheter)	Absent	Grimace	Cough, sneeze
Muscle tone	Limp	Some flexion of extremities	Active motion

*Each variable is evaluated individually and scored from 0 to 2 in an infant at 1 and 5 minutes of age. The total score at each time is the sum of the scores of the individual variables. A total score of 10 is perfect.

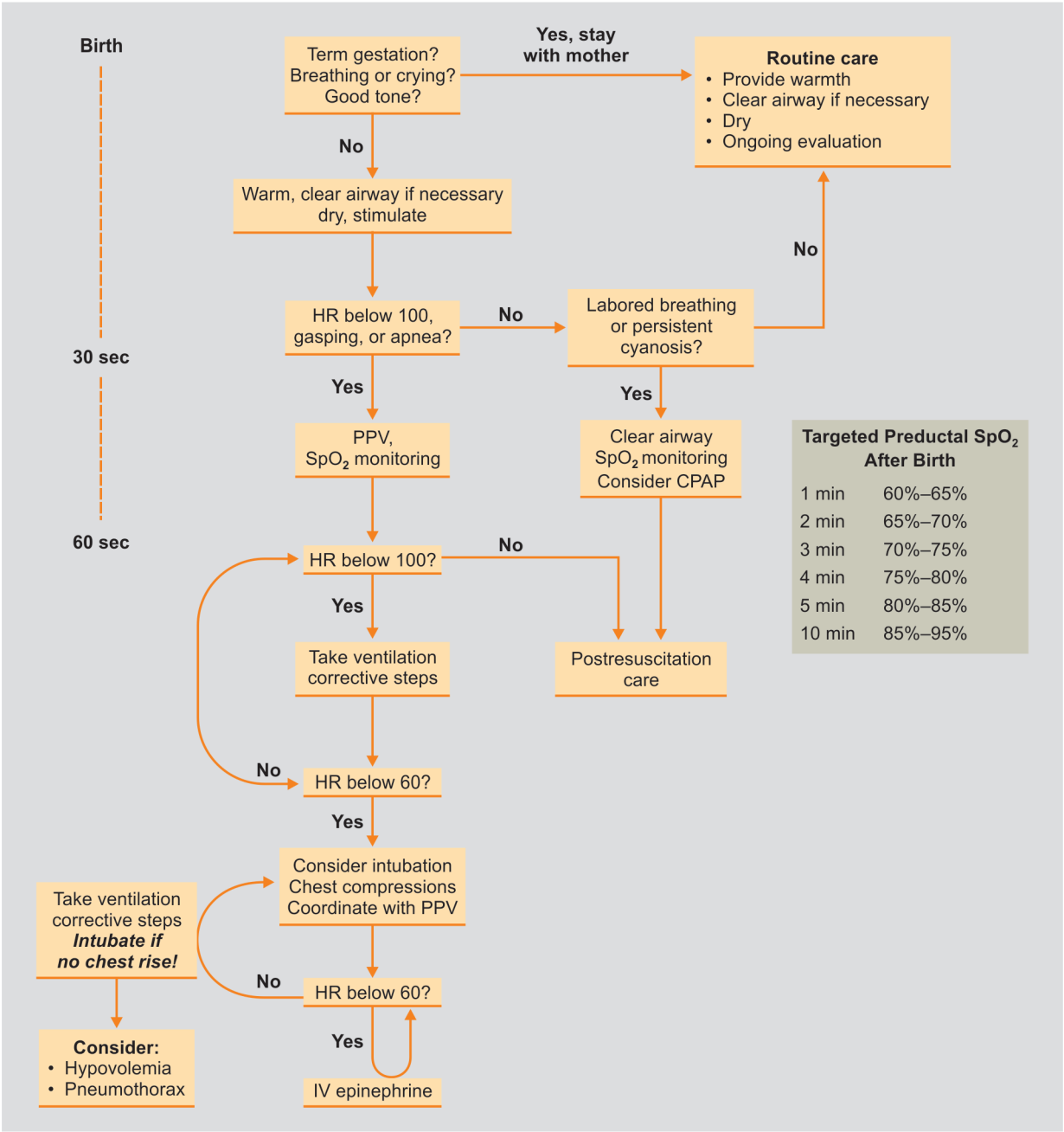

Fig. 11.8 Recent guidelines in neonatal resuscitation
Source: Part 14—Paediatric Advanced Life Support 2010, American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

Spontaneously breathing preterm infants with respiratory distress may be supported with CPAP or with intubation and mechanical ventilation (Class IIb, LOE B).

Laryngeal mask airway (LMA) is effective for ventilating newborns weighing more than 2000 g (Class IIb, LOE B). LMA can be used during resuscitation if face-mask ventilation is unsuccessful and tracheal intubation is unsuccessful or not feasible.[55,57] (Class IIa, LOE B).

Indications of endotracheal intubation during neonatal resuscitation:

- Initial endotracheal suctioning revealing meconium
- Bag and mask ventilation is ineffective or prolonged

- When chest compressions are performed
- Congenital diaphragmatic hernia or extremely low birth weight neonate.

Exhaled CO_2 detection is recommended as a quick confirmation of the accurate position of the endotracheal tube in neonates (Class IIa, LOE B).

Ventilation is most effective in neonatal resuscitation and assisted ventilation should be delivered optimally before starting chest compressions.

Chest Compressions in new born should be on the lower third of the sternum to a depth of approximately one-third of the anterior-posterior diameter of the chest. The 2-thumb–encircling hands technique may generate higher peak systolic and coronary perfusion pressure than the 2-finger technique, hence are recommended in newly born infants[55, 58] (Class IIb, LOE C) (Fig. 11.4).

The chest should re-expand fully during relaxation, but the rescuer's thumbs should not leave the chest.

Ratio of 3:1 compressions to ventilations with 90 compressions and 30 breaths to achieve approximately 120 events per minute should be maintained. Assess heart rate, and oxygenation periodically avoiding frequent interruptions of compressions and continue CPR until the spontaneous heart rate is more than 60 per minute.

Pharmacology of neonatal resuscitation

The recommended IV dose of epinephrine is 0.01 to 0.03 mg/kg (Class IIb, LOE C). An isotonic crystalloid solution or blood can be used for volume expansion. The recommended dose is 10 mL/kg, which can be repeated. In premature infants, rapid infusions of large volumes may cause intraventricular haemorrhage. (Class IIb, LOE C).[55,57,59,60]

Glucose infusion should be given as soon as after resuscitation, to avoid hypoglycemia (Class IIb, LOE C).

Calcium, buffers or vasopressors are rarely indicated during CPR but may be useful after resuscitation.

Therapeutic hypothermia is recommended for babies born near term with evolving moderate to severe hypoxic-ischemic encephalopathy.

Key Points:

- Apnoea or gasping start ventilation at a rate of 40 to 60 breaths per minute.
- Heart rate is less than 60 per minute, then Start Chest compressions.
- The 2-thumb–encircling hands technique
- Ratio of 3:1 compressions to ventilations with 90 compressions and 30 breaths.

Discontinuing Resuscitative Efforts

In a newly born baby with no detectable heart rate for 10 minutes, discontinuing resuscitation can be considered[55] (Class IIb, LOEC). When extreme prematurity, birth weight < 400 g or congenital anomalies such as an encephaly, and major chromosomal abnormalities like trisomy 13 are associated with almost certain early death or unacceptably high morbidity, resuscitation is not indicated (Class IIb, LOE C).

FOREIGN-BODY AIRWAY OBSTRUCTION (CHOKING)

Foreign-body airway obstruction (FBAO) in children < 5 years of age is one of the commonest and potentially treatable cause of cardiac arrest. Sudden onset of respiratory distress with coughing, gagging, stridor, or wheezing in the absence of fever suggests FBAO.[1,61,62] Key to successful outcome is early recognition as signs are obvious but often fatal if undiagnosed and untreated.

Causes of FBAO

- Liquids are the most common cause of choking in infants
- Large, poorly chewed pieces of food
- Balloons, small toys
- Foods (e.g. round candies, nuts, and grapes)
- Loose teeth.

FBAO can be partial and presents with wheezing, cough and stridor or complete which presents with inability to speak, breathe or cough. Child Clutches neck and turns blue (Universal chocking sign).

Precautions to prevent FBAO

- Food cut into small pieces
- Slow and thorough chewing
- Avoiding laughing and talking during swallowing
- Safe toys for children

Management of FBAO (Figs 11.9A to C)

Chest Thrusts

- Used instead of Heimlich Maneuver in infants and children up to 8 years as abdominal thrusts may damage the infant's relatively large and unprotected liver.
- Give up to 5 upward chest thrusts with a fist of one hand positioned over the lower half of sternum.
- It should simulate artificial cough.

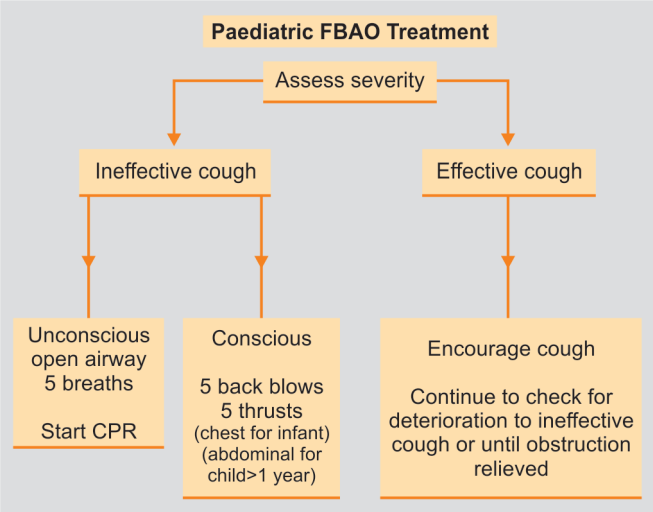

Fig. 11.9A Paediatric FBAO algorithm

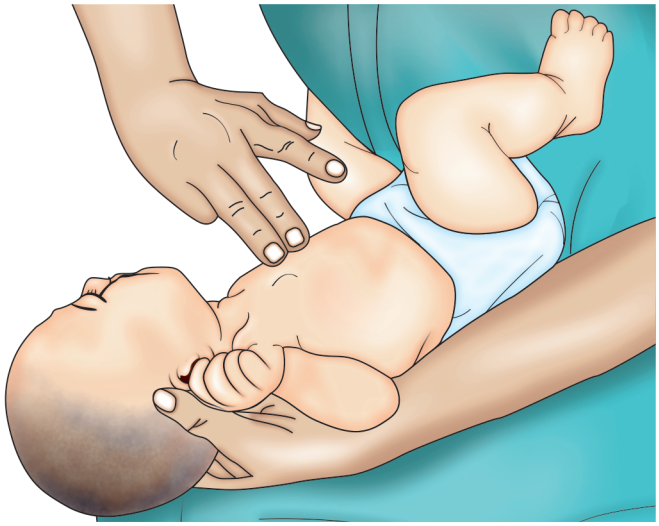

Fig. 11.9B Chest thrust in infant

Back Blows

- Infant: Prone, head low, supported between 2 forearms and on the thigh of rescuer.
- Deliver 5 back blows forcefully between shoulder blades with heel of hand ensuring an open mouth

If the child becomes unresponsive, start CPR with chest compressions. If foreign body is visible, remove it but do not perform blind finger sweeps. Attempt to give 2 breaths and continue with cycles of chest compressions and ventilations until the object is expelled.

Drowning

Drowning is one of the common causes of CA in children and preventon by implementation of swimming safety

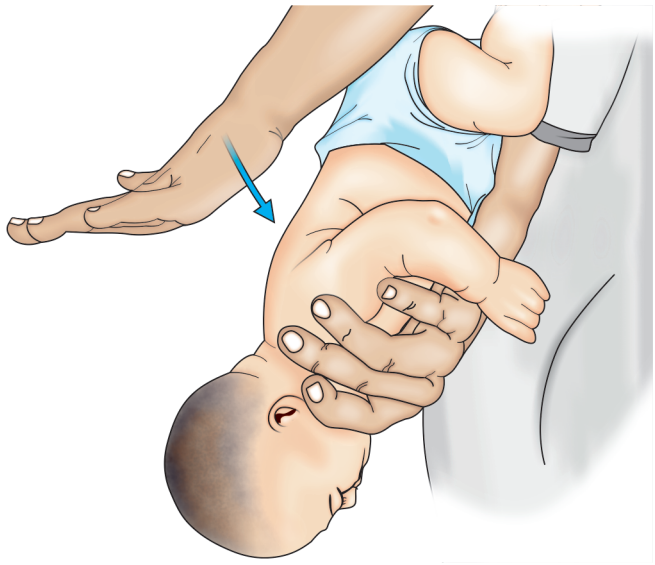

Fig. 11.9C Back blow in infants

norms is must.[1,2] Outcome depends on the duration of submersion, the water temperature, and prompt and effective CPR.[63] Start resuscitation by safely removing the child from the water as rapidly as possible. Prompt initiation of rescue breathing is very essential and can be started in the water by trained person. Mouth-to-nose ventilation may be preferred. Chest compressions should be given outside the water. Routine stabilization of cervical spine in the absence of a spinal injury is not recommended. Do not attempt to remove water from lungs but remove visible foreign material from mouth. Hypothermia is suspected if submerged for long time, rewarm slowly.

Key Points:

- Do not attempt CPR in water.
- Begin rescue breathing as soon as possible
- Begin with 5 cycles (about 2 minutes) of CPR, then activate emergency response system

POST-CA SYNDROME

If ROSC is achieved quickly after the recognition of CA and initiation of treatment, a pathological post-resuscitation phase may not occur. Children have increased cerebral blood flow and higher metabolic needs as compared with adults, and undergo neuronal maturation and synaptogenesis at the time of the insult.[11]

Brain injury includes impaired cerebrovascular autoregulation, cerebral oedema and post-ischemic neurodegeneration. Clinically child may have seizures,

cognitive dysfunction, myoclonus, signs of stroke, coma, persistent vegetative state and brain death.[64]

Myocardial dysfunction after paediatric CA is a reversible characterised by global myocardial hypokinesia, low cardiac output, with normal coronary blood flow. Clinically, it can manifest as hypotension, dysrhythmias and cardiovascular collapse which is usually normalized by 72 hours.

Systemic ischaemia/reperfusion response in CA is secondary to inadequate tissue oxygenation followed by reperfusion which may lead to increased coagulation, impaired vasoregulation, adrenal suppression and increased susceptibility to infection. Clinical manifestations include fever, hypotension, hyperglycemia and infection that may precipitate multiorgan failure.[64]

IATROGENIC COMPLICATIONS OF CPCR

Iatrogenic complications of CPCR are rare in infants and children. Clinically significant iatrogenic injuries occur in approximately 3% of cases.[65] Commonest complications are rib fractures, sternal fracture followed by pneumothorax, pneumoperitoneum, haemorrhage, retinal haemorrhages, etc.

Burns to the patients can occur due to poor contact between defibrillator paddles and patient's chest, hence proper use of conduction gel or self-adhesive pads are recommended. Fire in the oxygen rich environment can occur with sparking from defibrillator, hence resuscitation bag or ventilator should be left connected to endotracheal tube.

POST RESUSCITATION CARE

The 2010 AHA Guidelines for CPR and ECC emphasize increased importance of post-cardiac arrest care and bundled goal-oriented management.[27,66]

Objectives of post cardiac arrest care are:

- ***To optimize systemic perfusion***, restore metabolic homeostasis and support organ function.

  Monitor vital signs at frequent intervals and step up monitoring and secure central venous line and arterial line. Arterial lactate and central venous oxygen saturation to assess the adequacy of tissue oxygen delivery should be monitored.

  Vasoactive drugs administered to improve myocardial function and organ perfusion. Epinephrine or norepinephrine (0.1–0.5 mcg/kg/min) may be preferable to dopamine (5–10 mcg/kg/min) in infants with marked circulatory instability and decompensated shock. Dobutamine (5–10 mcg/kg/min) is preferred in children with poor myocardial function.

- ***Optimize mechanical ventilation to minimize lung injury***

  Goal is to reduce the risk of oxidative injury while maintaining adequate oxygen delivery.

  Keep lowest inspired oxygen concentration that will maintain the arterial oxyhemoglobin saturation around 94%. Monitor with blood gases and $PETCO_2$. Appropriate analgesia and sedation may improve ventilation and child comfort.

- ***Reduce the risk of renal and multiorgan injury***

  Avoid dehydration, nephrotoxic medications. Maintain systemic perfusion and urine output 0.5–1 mL/kg per hour in children.

- ***To preserve neurologic function, prevent secondary organ injury***

  A primary goal of resuscitation is to preserve brain function and avoid secondary damage.

  Interventions to reduce secondary brain injury, such as therapeutic hypothermia, can improve survival and neurological recovery.[66, 67]

Targeted Temperature Management

Therapeutic hypothermia is recommended for neonate born near term with evolving moderate to severe hypoxic-ischemic encephalopathy and children who do not awaken after ROSC.[67] Not indicated in patients with major bleeding.

Cooling should be initiated in neonatal intensive care facilities and body temperature is reduced to 32–34°C immediately after ROSC. Commonly used methods are surface cooling and endovascular cooling. Favourable neurological outcome is documented by a few studies. Associated complications are shivering, bradycardia, hypotension, diueresis, hypokalemia, infections.[66,67]

TERMINATION OF RESUSCITATIVE EFFORTS AND ETHICAL ISSUES

There are no specific predictors of outcome to guide when to terminate resuscitative efforts in paediatrics.[27] In 2010 AHA Guidelines for CPR and ECC. The duration of resuscitation was reviewed. In a newly born baby with no detectable heart rate for 10 minutes, stopping resuscitation can be considered. When certain early death and an unacceptably high morbidity are known with gestation, birth weight, or congenital anomalies, resuscitation is not indicated.

Certain clinical variables associated with survival are length of CPR, number of doses of epinephrine, age, witnessed versus unwitnessed cardiac arrest, and the first and subsequent rhythm.[68] None of the above factor, however, predict outcome. Witnessed collapse, by-stander CPR and prolonged in-hospital resuscitation improve the chances of a successful resuscitation.[1,27,68]

The death of the child is very devastating for the family. Family guilt is overwhelmed hence emotional support is essential. Whenever possible, provide family members with the option of being present during resuscitation of an infant or child.[69] (Class I, LOE B)

Prevention, anticipation, adequate preparation, extreme vigilance, accurate evaluation, and prompt initiation of CPR are critical for successful paediatric resuscitation.

Pearls

- Time is crucial
- Follow all steps of resuscitation well
- Treat the cause and not the condition
- Resuscitate the heart and restore the brain
- Emphasize importance of high quality CPR
- Follow simplified cardiac arrest algorithms
- Re-start the heart and keep it restarted

Take Home Message

CPR is not harmful; inaction is, hence start CPR when in doubt.

FAQs with Answers

Q. What constitutes Paediatric Chain of Survival?

A. Prevention of cardiac arrest, immediate recognition, early BLS, Prompt access to the emergency response system, PALS, Integrated post-cardiac arrest care.

Q. What are characteristics of High-quality CPR?

A. "Push fast" and "Push hard", complete chest recoil after each compression, minimize interruptions in chest compressions, avoid excessive ventilation, monitor quality CPR.

Q. What is the recommended energy dose for defibrillation in paediatrics?

A. The recommended first energy dose for defibrillation is biphasic 2 J/kg followed by 4 J/kg, higher energy may be considered but not beyond 10 J/kg

Q. What are different arrest rhythms?

A. The arrest pulse less rhythm is either "shockable" (e.g. VF or rapid VT) or "not shockable" (e.g. asystole or PEA).

Q. Which drugs can be administered by endotracheal route?

A. Atropine, lidocaine, oxygen, naloxone, epinephrine (ALONE) can be administered via endotracheal route

Q. What are signs of ROSC?

A. An abrupt and sustained rise in $PETCO_2$ occurs prior to clinical signs of ROSC like return of central pulsation.

Q. What are the key changes made in 2010 AHA Guidelines for CPR and ECC?

A. "CAB" sequence, high quality CPR with monitoring continuous capnography. BLS, PALS and neonatal algorithms and the use and timing of drugs have been simplified.

Q. What is the target temperature for therapeutic hypothermia?

A. For therapeutic hypothermia body temperature is reduced to 32–34ºC immediately after ROSC.

Q. How do you monitor CPR quality?

A. For high quality CPR maintain $PETCO_2$ consistently above 10–15 mm Hg.

BLS

C - Closed Chest Compression ECM A- Open Airway (Jaw Thrust, Chin Lift and Head Tilt)
B - Positive Pressure Ventilation Expired Air/Resuscitation Bag
D - Defibrillation (Pulseless Patient with VT or VF)

ACLS

D - Defibrillation (Pulseless Patient with VT or VF)
A - Airway with ET Tube
B - Assess Adequacy of Ventilation
C - Closed Chest Compression ECM IV Access for Fluids and Drugs
D - Diagnosis: Treat and Reverse Cause of Arrest

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