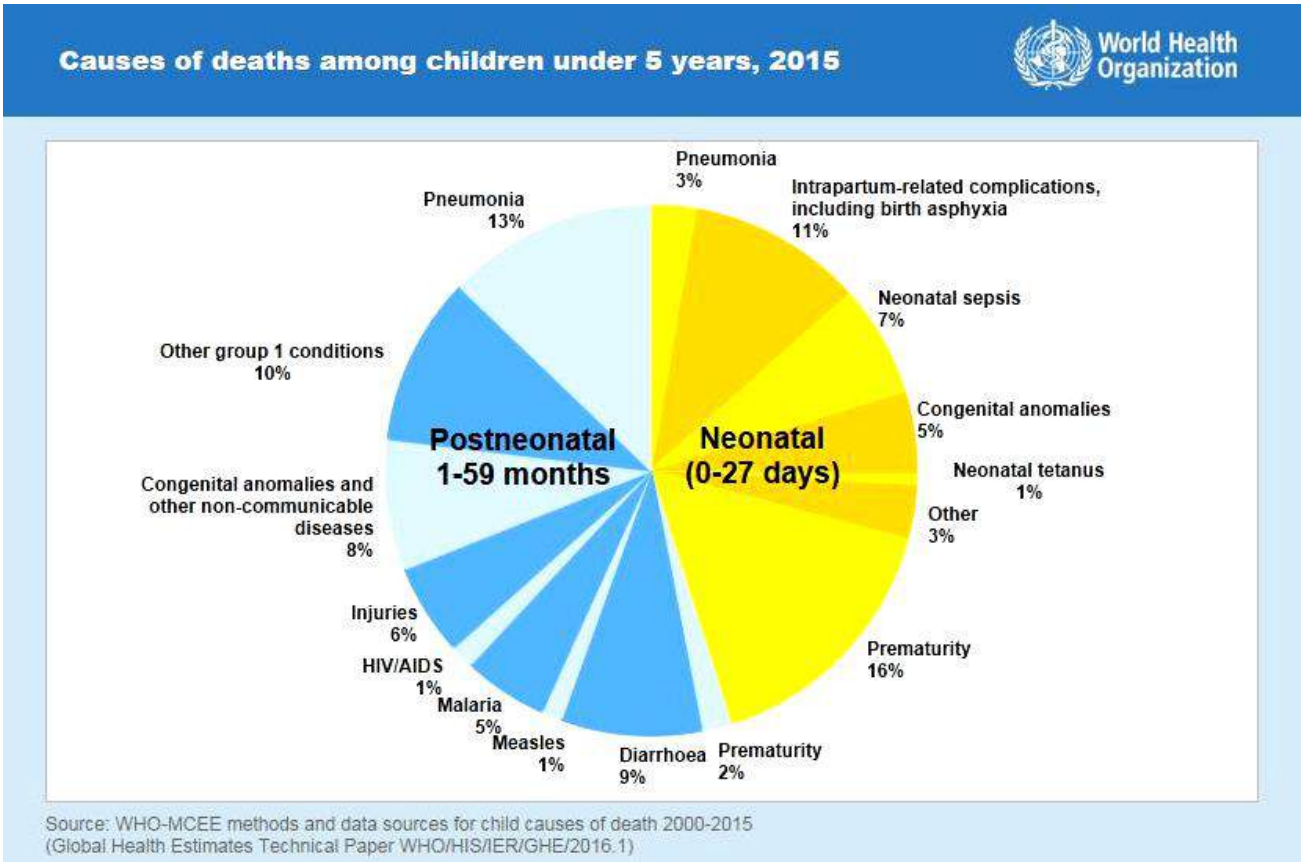
Introduction to Pediatrics

Pediatrics (paediatrics) is a branch of medicine that deals with the medical care of infants, children and adolescents.
According to UNICEF definition, the age limit of childhood ranges from birth up to 18.
Children are considered "national wealth" and hence pediatric care has its implication on the ultimate progress of the nation.

"Children's health should be defined as the extent to which individual children or groups of children are able or enabled to (a) develop and realize their potential, (b) satisfy their needs, and (c) develop the capacities to allow them to interact successfully with their biological, physical, and social environments." [National Research Council and Institute of Medicine. Children's Health, the Nation's Wealth: Assessing and Improving Child Health. Washington, DC: National Academies Press; 2004].

The key health dangers for children and adolescents

- 5.9 million children under the age of 5 died in 2015. 75% (4.5 million) of all under-five deaths occurred within the first year of life.
- More than half of these early child deaths are due to conditions that could be prevented or treated with access to simple, affordable interventions.
- Children in sub-Saharan Africa are about over 14 times more likely to die before the age of five than children in developed regions.



The risk of death is highest in the first month of life. Preterm birth, birth asphyxia and infections cause most newborn deaths.

Health risks to newborns are minimized by:

- quality care during pregnancy;

- safe delivery by a skilled birth attendant; and

- strong neonatal care: immediate attention to breathing and warmth, hygienic cord and skin care, and early initiation of exclusive breastfeeding.

From one month to five years of age, the main causes of death are pneumonia, diarrhoea, malaria, measles, congenital anomalies, injuries.

* For some of the most deadly childhood diseases, such as **measles**, vaccines are available and timely completion of immunization protects a child from this illness and death.

* **Pneumonia** is the prime cause of death in children under five years of age. Addressing the major risk factors –including malnutrition and indoor air pollution – is essential to preventing pneumonia, as are vaccination and breastfeeding. Antibiotics and oxygen are vital tools for effectively managing the illness.

* **Diarrhoeal diseases** are a leading cause of sickness and death among children in developing countries. Breastfeeding helps prevent diarrhoea among young children. Treatment for sick children with Oral Rehydration Solutions (ORS) combined with zinc supplements is safe, cost-effective, and saves lives.

* One child dies every minute from **malaria**. Insecticide-treated nets prevent transmission and increase child survival.

* Over 90% of children with **HIV** are infected through mother-to-child transmission; this can be prevented with antiretrovirals, as well as safer delivery and feeding practices.

* **Malnutrition** is estimated to contribute to more than one third of all child deaths.

Worldwide, about 20% of deaths among children under-five could be avoided if feeding guidelines are followed. WHO recommends exclusive breastfeeding for six months, introducing age-appropriate and safe complementary foods at six months, and continuing breastfeeding for up to two years or beyond.

Adolescents – young people between the ages of 10 and 19 years – are often thought of as a healthy group. Nevertheless, many adolescents do die prematurely due to accidents, suicide, violence, pregnancy related complications and other illnesses that are either preventable or treatable. Many more suffer chronic ill-health and disability. In addition, many serious diseases in adulthood have their roots in adolescence. For example, tobacco use, sexually transmitted infections including HIV, poor eating and exercise habits, obesity lead to illness (hypertension, coronary heart disease, diabetes mellitus, osteoporosis etc.) or premature death later in life.

Indicators of infant and child health

Infant and child mortality rates are leading indicators of the level of child health and overall development in countries.

- **Infant mortality rate (IMR)** *is the number of deaths of children less than one year of age per 1000 live births in a given year.*

$$IMR = \frac{\textbf{Number of deaths of infants under one year old in a given year}}{\textbf{Total number of live births in the same year}} x\ 1000$$

- **Neonatal mortality rate (NMR)** *is the number of neonatal deaths per 1000 live births in a given year.*

$$NMR = \frac{\textbf{Number of neonatal deaths } 0-28 \textbf{ days in a given year}}{\textbf{Total number of live births in the same year}} x\ 1000$$

- **Under-five mortality rate (U5MR)** *is the number of deaths of children under 5 years of age per 1000 live births in a given year.*

$$U5MR = \frac{\textbf{Number of deaths of children under 5 years in a given year}}{\textbf{Total number of live births in the same year}} x\ 1000$$

- **Perinatal mortality rate (PMR)** *is the number of perinatal deaths per 1000 total births in a given year.*

$$PMR = \frac{\textbf{Number of perinatal deaths in a given year}}{\textbf{Total births in the same year}} x\ 1000$$

The World Health Organization defines perinatal mortality as the "number of stillbirths and deaths in the first week of life per 1,000 total births, the perinatal period commences at 22 completed weeks (154 days) of gestation and ends seven completed days after birth", but other definitions have been used*.

* *Wanda D. Barfield and COMMITTEE ON FETUS AND NEWBORN.* ***Standard Terminology for Fetal, Infant, and Perinatal Deaths.*** *Pediatrics 2016;137.*

"Children are not little adults"

Major physiological characteristics of children are their **intense growth and development**. Their needs for energy, water and oxygen are higher, because they go through an intense anabolic process. At the same time, these characteristics put children at greater risk of damage during differentiation and maturation of organs and systems.

1 UNIQUE EXPOSURE PATHWAYS

- They can be exposed in utero to toxic environmental agents that cross the placenta. Such exposures can be chemical (pollutants and pharmaceuticals), physical agents (radiation, heat) and biological (viral, parasitic). They can also be exposed, after birth, to pollutants that pass into their mother's milk. Neither of these routes of exposure occur in adults or older children.
- Children also have pathways of exposure that differ from those of adults due to their size and developmental stage. For example, young children engage in normal exploratory behaviours including hand-to-mouth and object-to-mouth behaviours, and non-nutritive ingestion which may dramatically increase exposure over that in adults.
- Children's physical differences also cause them to reside in a different location in the world, i.e. closer to the ground. Pollutants such as mercury, solvents, pesticides are concentrated in their breathing zone and deliberate applications of pesticides and cleaning solutions make them more readily accessible to small children. Because they are small, they have a high surface area to volume ratio and can have dramatically higher absorption through dermal contact than adults.
- And, they may have much more limited ability to understand and move out of danger, both from toxic agents and dangerous situations which could result in injury. This characteristic is obvious in the pre-ambulatory phase, but persists through exploratory toddler behaviour and even into the high-risk behaviours seen in adolescence.

2 DYNAMIC DEVELOPMENTAL PHYSIOLOGY

Children have a dynamic physiology that is not only turned up to "high" because of growth demands, but also vulnerable to damage during differentiation and maturation of organs and systems.
They inhale and ingest larger quantities of potentially contaminated air, food, and water for their weight than do adults; they absorb toxins more readily because of increased skin permeability and greater proportionate body-surface area; they are smaller in size, stature, and muscle mass than adults; they have less fluid reserve.

3 LONGER LIIFE EXPECTANCY

Children, ideally, are around longer in the world than adults. Not only do they live longer, allowing more time in which to develop diseases with long latency, but they also have longer to live with disabilities. In addition, they inherit the world we are creating, with all its problems and promises.

4 POLITICALLY POWERLESS

Children are defenceless. With no political standing of their own, they must rely on adults to protect them from toxic environmental agents.

Childhood Periods

The main feature of the child's body is that it grows and develops.
Isolation of developmental stages and age periods with their anatomical and physiological features, allows us a differentiated approach to the child. There are intrauterine (gestational, prenatal) and extrauterine (postnatal) stages of human development.

Prenatal stage

On average, this stage lasts 280 days (40 weeks).
The gestational age is expressed in completed weeks.

Prenatal stage of development consists of three periods:

1. **Initial period (first 2 weeks)** - includes fertilization, cleavage, and implantation.
Pathology seen in this period is called **blastopathy.**

2. Embryonic period (3-8 weeks) – organogenesis of almost all organs occurs.
Pathology seen in this period is called **embryopathy.**

3. Fetal period (from the 9th week to the birth) – formation of placenta occurs, and the organs mature to the stage of development, which will allow the infant to survive outside the womb.
Pathology seen in this period is called **fetopathy.**

Postnatal stage

After ligation of the umbilical cord postnatal stage or actual childhood begins.

1. Early childhood – 0-5 years – includes the following periods:

- **Infant — birth to 1 year.**
This includes the **neonatal period (from birth to the 28th day).**
Early neonatal period refers to the period before 7 days of age*. Late neonatal period refers to the period from completion of 7 days up to 28 days of life.

Newborn classification based on gestational age:
- ***Preterm (premature)*** — gestational age of less than 37 completed weeks
- ***Term*** — gestational age of 37 to less than 42 completed weeks
- ***Post-term (postmature)*** — gestational age of 42 completed weeks or more

- **Toddler** — age 1 to 3 years
- **Preschool age** — 3(1) to 5 years

2. School-age — 5 to 10 years

3. Adolescence — 10 to 18 (19) years

** The perinatal period*

The perinatal period commences at 22 completed weeks (154 days) of gestation and ends seven completed days after birth. Perinatal health and maternal health are closely linked.

Clinical Assessment of Children

'I've learned that people will forget what you said, people will forget what you did, but people will never forget how you made them feel.'

Maya Angelou

I. Conduct a Patient/Parent/Caretaker Interview

HELLO

Children are quick to assess adults, and often very accurate. Approach the child with courtesy, a smile and a friendly greeting.

INTRODUCE YOURSELF

Introduce yourself and find out to whom you are speaking. What does the child like to be called?

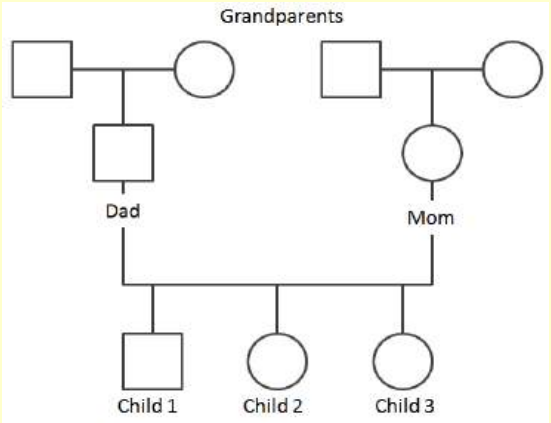
OBTAIN A HISTORY FROM A SECOND PARTY (PARENT), AS WELL AS DIRECTLY FROM THE PATIENT

➢ **Principles**

- At all times the doctor must show genuine concern and interest when speaking with parents. The parents/caretakers and the child must feel that the doctor has the time, interest and competence to help them.
- Use different styles of questioning - **open ended**, directed, follow-up and summary.

  Close-ended questions are those which can be answered by a simple "yes" or "no," while open-ended questions are those which require more thought and more than a simple one-word answer.
- Communicate information to parents/patients.
  - Insure that both the child and the parent understand the diagnosis and treatment, and have an opportunity to ask questions.
  - Incorporate anticipatory guidance as a part of health supervision visits and discharge from the nursery.
  - Direct an interview and exam for an acute specific complaint, or for a specific purpose (e.g., evaluation of heart disease, preschool physical and pre-sport physical, etc).

➢ What to ask about when taking a history?

Presenting complaint	Record the main problems in the family's own words as they describe them
Temporal profile of the present illness	Try to get an exact chronology from the time the child was last completely well. Allow the family to describe events themselves, using questions to direct them, and probe for specific information. Try to use open ended questions: ' Tell me about the cough ' rather than ' Is the cough worse in the mornings? '
Epidemiology	Recent infections; contacts; trips; environmental factors
Social history	Which school or nursery does the child attend? Ask about jobs and smoking, and try to get a feel for the financial situation at home. The social context of illness is very important in paediatrics
Family history	Who is in the family and who lives at home? Ask about consanguinity, as cousin marriages increase the risk of genetic disorders. Ask if there are any illnesses that run in the family. Does anyone have a disability, and have there been any deaths in childhood? Draw up a family tree 
Past medical history	In young children and infants this should start from the pregnancy and include birthweight and details of the delivery and neonatal period, including any feeding or breathing problems Ask about all illnesses, hospital attendances including accidents and admissions, and immunizations
Drugs and allergies	What drugs is the child taking and are there any allergies?
Dietary history	Feeding; appetite; weight changes
Developmental history	Ask about milestones and school performance. Are there any areas of concern?
Elinimation	Ask about voiding and defecation
Dailty activity and sleep	What does the child do during a day? How many hours does he/she sleep?

II. Perform a physical exam (PE)

This includes:

General appearance	Vital signs (VS) and body measurements	Examination of individual body parts and organs
▪ First impressions ▪ Conciousness/awakeness Behavior (calm, irritable) Crying (loudly, weak) ▪ Respiratory effort ▪ Posture at rest ▪ Movements ▪ Deformations and malformations ▪ Assessment of color	▪ ***VS:*** temperature (T); respiratory rate (RR); heart rate (HR); capillary refill time (CRT); blood pressure (BP); oxygen saturation (SpO2) ▪ ***Anthropometry:*** weight; length; head circumference (HC); chest circumference	· skin · skull · ears, eyes, nose and mouth · neck · chest and heart sounds · abdomen · genitalia · extremities · spine · neurological status

ADAPTATION OF THE EXAMINATION TO THE CHILD

The examination must be adapted to the child, his/her temperament, and developmental level. This requires knowing the characteristics of different age groups.

CHILDHOOD PERIODS	AGE SPECIFIC EXAM SKILLS
NEONATAL PERIOD ***is characterized by:*** **1. Adaptive processes –** the newborn adapts to extrauterine life conditions, the fetal type of physiological functions transfers to the post-natal type: formation of pulmonary function with an effective gas exchange, the complete "inclusion" of the pulmonary circulation, closing of the fetal communications (foramen ovale, ductus arteriosus), the commencement of enteral nutrition, the establishment of renal homeostatic functions *etc.* **2. Transient events –** transitional physiological changes that manifest as pathological features, and do not require any therapy. These include: - *Physiological weight loss* 3-9%. Within 10 days to two weeks, the baby should have regained enough weight so that he weighs at least what he did at birth. - *Physiological jaundice* – appears between the 2nd and 5th days of life in most newborns, and disappears by 1 to 2 weeks of age. - *Benign skin lesions, e.g.:* - *toxic erythema* – small (1–3 mm), firm, yellow or white raised bumps filled with pus on top of a red area of skin (resolves over 1–4 weeks); - *sebaceous gland hyperplasia* – pinpoint yellow papules on the nose, cheeks, upper lip and forehead (resolves during the first few months of life).	○ Assess the stability of vital functions, e.g. respirations, heart rate, temperature, feeding and stooling ○ Assess and interpret APGAR scores ○ Assess infant maturity ○ Elicit newborn reflexes

MAJOR PHYSIOLOGICAL PARAMETERS OF THE NEWBORN

Parameter	Reference range	Parameter	Reference range
Body Temperature (T)	*36.5^{0}C - 37.5^{0}C*	Micturitions	*20-24 times daily*
Respiratory Rate (RR)	*40-60 per minute*	Defecations	*3-5 times daily*
Heart Rate (HR)	*100-160 per minute*	Sleep	*17-18 hours/day*

CHILDHOOD PERIODS	AGE SPECIFIC EXAM SKILLS

INFANCY ***is characterized by rapid growth and development.***

During the first year of life body length increases by 50%, while the body weight is tripled.

Their growth and needs for energy, water and oxygen are higher, because they go through an intense anabolic process.

- Infants primarily communicate through nonverbal vocalization and crying and respond to nonverbal communication behaviors of adults such as holding, rocking, and patting. It is useful to observe the parent's or caregiver's interpretation of the infant's nonverbal cues and the nonverbal communications of the parents.
- Young infants respond well to gentle physical contact with any adult, but older infants can demonstrate strong separation and stranger anxieties.
- Although infants younger than 6 months usually tolerate lying on the examining table, older infants and toddlers are more comfortable when held or sitting in the parent's or caregiver's lap.

TODDLER ***years are characterized by great cognitive, emotional and social development.***

The word is derived from "to toddle", which means to walk unsteadily, like a child of this age.

- Use techniques for building rapport with children who have stranger anxiety.
  Their communication is rich with expressive nonverbal gestures and simple verbal communications. Toddlers accept the verbal communications of others literally. Toddlers have the beginnings of memory and imagination, but they are unable to understand abstractions and become frustrated and frightened by phrases that seem ordinary to adults.

  Communication with toddlers requires that the physician use short, concrete terms. Explanations and descriptions need to be repeated several times. Visual aids such as puppets and dolls assist explanations. Children of this age attribute magical qualities to inanimate objects, so it is useful to allow them to handle instruments and to tell them exactly, in concrete terms, what the instrument does and how it feels.
- Assess motor, language, and social development.

PRESCHOOL AGE ***is characterized by:***

- Rapidly improving motor skills
- Development of the intellectual sphere and language
- High rates of growth, although it is lower than in the first year of life
- Increased periods of wakefulness (1.5 year-old children sleep 3 hours during the day and 11 hours at night)
- Formation of hygiene practices: toilet training

- Many of the guidelines for communicating with toddlers apply to preschoolers as well.
- The older preschooler, in particular, likes to conform, knows most external body parts, and might be interested in the purpose of various parts of the assessment.
- Allowing the preschooler to handle the equipment eases fears and helps answer questions about how the equipment is used.
- Preschool-age children are often very modest. They should be exposed minimally during examination and requested to undress themselves. They need to know exactly what is being examined and benefit from opportunities for questions. Parental proximity is still important for this age group.

CHILDHOOD PERIODS	AGE SPECIFIC EXAM SKILLS
SCHOOL-AGE *is characterized by:* • Rapidly evolving intelligence, improved memory, development of complex coordination of movements of the small muscles. • Eruption of the permanent teeth begins between 5 and 7 years and usually finishes by 13 to 14 years of age.	○ School-age children think in concrete terms but at a more sophisticated level. Generally they have had enough contact with health care personnel that they can rely on past experiences to guide them. Depending on the quality of their past experiences, they might appear shy or reticent during health assessment. Children might fear injury or embarrassment. Allowing time for composure and privacy (perhaps even from parents) aids in communication. Reassurance and third-person speech are helpful in eliciting worries and anxieties and in allowing the child to express fear or pain. ○ The purpose of the health assessment should be related to the child's condition. It is useful to determine what the child already knows about the health contact and to proceed from there. Simple medical diagrams and teaching dolls are useful in explaining the assessment process. Specific information should be given about body parts affected by the assessment. ○ Children of this age are often curious about the function of equipment and its usefulness.
ADOLESCENCE *is characterized by* • Pubertal growth spurt (after 11-12 years) • Pronounced reorganization of the endocrine system, the intense sexual maturation, the formation of the reproductive system and sexual behavior of the individual. Normal puberty begins at about 9-14 years in boys, and about 8-12 years in girls.	○ There are several methods that might be used to elicit both health information and psychosocial information. One approach that was developed at Childrens Hospital of Los Angeles is to obtain psychosocial information using the HEADS interview. This includes the topics of H – Home (living arrangement, family relationships, support) E – Education (school issues, study habits, achievement, expectations) A – Activities (recreation, friends, exercise, employment) D – Drugs (alcohol, tobacco, marijuana, cocaine, pills, etc.) Depression S – Sexuality (sexual activity, sexual orientation) Self-esteem (body image) Safety (abuse, intimate partner violence, risk of self-harm) Suicidality  ○ Asess and stage secondary sexual characteristic. ○ Communicating with adolescents can feel more difficult than communicating with a parent of a young child, but similar interviewing techniques can be used. Open-ended answers require engagement between the patient and provider.

QUIZ

2 year old girl becomes distressed when you attempt to palpate her abdomen. You know the abdominal findings are important to your ability to establish a diagnosis in this case. You should:

(A) Enlist the assistance of a parent or nurse to restrain her for the examination
(B) Omit the abdominal examination
(C) Sedate her to enable an adequate examination
(D) Explain the purpose of the examination and obtain her cooperation
(E) Return to examine the abdomen later

Three Main Approaches to Patient Assessment

Rapid initial assessment in emergencies (eg. ABC DE approach)	Focused assessment	Comprehensive Assessment
• Airway • Breathing • Circulation • Disability (deficiency of cerebral function) • Exposure	Detailed assessment of specific body system(s) relating to the presenting problem or current concern(s) of the patient. This may involve one or more body system	This includes both clinical and psycho-social-cultural assessment of the child and the family

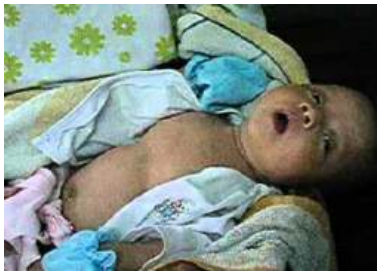
CLINICAL MANIFESTATIONS OF DISEASE

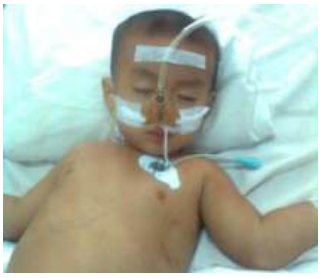
Symptoms	Signs
Something the patient feels or observes which is abnormal, e.g. pain, vomiting, loss of function. A good history provides a clue to the diagnosis in 80% of patients.	Physical or functional abnormalities detected by examination: inspection, palpation, percussion, auscultation, laboratory and instrumental investigations.

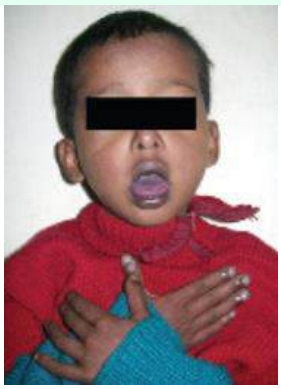
Emergency signs include:

■ severe respiratory distress
■ central cyanosis
■ signs of shock (cold hands, capillary refill time longer than 3 s, high heart rate with weak pulse, and low or unmeasurable blood pressure)
■ coma (or seriously reduced level of consciousness)
■ convulsions
■ signs of severe dehydration in a child with diarrhoea (lethargy, sunken eyes, very slow return after pinching the skin or any two of these).

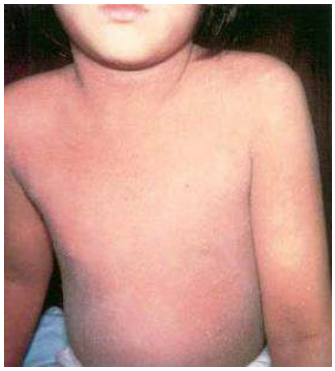
Children with these signs require immediate emergency treatment to avert death.

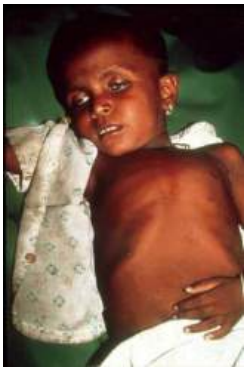

A 1-year-old baby with severe respiratory distress


A 22-month-old child with coma


A three-year-old boy with central cyanosis


Opisthotonus in a child with meningitis


Diffuse scarlatiniform eruption in a child with staphylococcal toxic shock syndrome


Hypovolemic shock in a child with diarrhea and severe dehydration

Psycho-Social-Cultural Assessment of the Child and the Family

Pediatricians live and work in a multicultural world. Among the world's 7 billion people residing in >200 countries, >6,000 languages are spoken.

➢ FAMILY ASSESSMENT

The family and community provide the foundation for the growth and development of a pediatric patient. Understanding the basic concepts of family and community dynamics helps the physician to provide comprehensive care to the pediatric patient and family.

A family consists of two or more members who interact and are dependent upon one another socially, financially, and emotionally. There are several types of families:

_ **Nuclear family:** Husband (usually the provider), wife (usually homemaker although frequently works also), and child/children.

_ **Reconstituted/binuclear/blended family:** Child or children and one parent in one home and another parent in a different home. A stepparent and step-siblings may be present in one or both homes, reconstituting two families into one and resulting in two blended nuclear families.

_ **Cohabitation family:** A man and woman who live together with a child or children without being married.

_ **Single-parent family:** A man or woman living with one or more children.

_ **Gay/lesbian family:** Two men or two women who live together as parents to one or more biological or adopted children.

_ **Extended family:** Multigenerational groups consisting of parents and children with other relatives (i.e., grandparents, aunts, uncles, cousins, grandchildren).

A nuclear family (mother, father, child or children)

An extended family may have three generations of a family living together

This nontraditional family represents the diversity in family types

Guidelines for Communicating with Families

■ Display a sincere sense of warmth, caring, and encouragement.
■ Demonstrate neutrality; perceptions of partiality toward particular family members can interfere with assessment and assistance.
■ Use active and reflective listening.
■ Convey a sense of cooperation and partnership with the family.
■ Promote participatory decision making.
■ Promote the competencies of the family.
■ Encourage the family's use of natural support networks.

Table. Assessment of the Family

ASSESSMENT	FINDINGS
Family Composition Refers to everyone in the household. Ask who is in the family.	Extended families and multigenerational households are common among many cultures such as Vietnamese, Chinese, and South Asians. **Clinical Alert** Losses or additions to families can result in crisis.
Rank Order Refers to the arrangement of children according to age and gender.	Family position is thought to influence relationships and even careers. Eldest children are considered more conscientious, perfectionistic; middle children are sometimes considered nonconformist, and to have many friends; and youngest children are sometimes seen as precocious, less responsible with resources, and playful. **Clinical Alert** Frequent references to rank order ("She's the eldest") might signify a role assignment that is uncomfortable for the individual who is involved. The first child can be at increased risk for abuse in abusive families.
Subsystems The parents and children are part of subsystems within a larger family system. The family should be viewed as interacting, complex elements. Studying a child and a parent as separate units does not constitute family assessment because it neglects observation of interactions. It is important to remain open to the multiple interpretations of reality within a family, recognizing that family members might not fully realize how their behavior affects others or how others affect them.	Ask if the family has special smaller groups. Mothers who are highly involved with their infants and who form tight subsystems with the infants can unintentionally push the father to an outside position. This can exacerbate marital dissatisfaction and conflict. Behavior is reciprocal; each family member's behavior influences the others. If mother responds angrily to her toddler because he turned on the hot water tap while her infant was in the tub, the toddler reciprocates with a response that further influences the mother. **Clinical Alert** A child acting as a parent surrogate might signify family dysfunction or abuse.
Boundaries Refers to who is part of what system or subsystem. Need to consider if family boundaries and subsystems are closed, open, rigid, or permeable. Knowledge of the family's boundaries can help the physician predict the level of social support that the family might perceive and receive.	Strength of boundaries might be influenced by culture. East Indian families, for example, tend to be close-knit and highly interdependent. Cambodians and Laotians consider family problems very personal, private, and off limits to outsiders. **Clinical Alert** Families with rigid, closed boundaries might have few contacts with the community suprasystem and might require tremendous assistance to network appropriately for help. Conversely, families with very **loose, permeable boundaries** might be caught between many opinions as they seek to make health-related decisions. Members within family systems might similarly experience extremely closed or permeable boundaries. In enmeshed families, boundaries between parent and child subsystems might be blurred to the extent that children adopt inappropriate parental roles. In more rigid families, the boundaries between adult and child subsystems might be so closed that the developing child is unable to assume more mature roles.

Table. Assessment of the Family *(continued)*

<table>
<tr><th>ASSESSMENT</th><th>FINDINGS</th></tr>
<tr><td>Culture
- Way of life for a group.
Ask if other languages are spoken.
Ask how long family has lived in area/country.
Ask if family identifies with a particular ethnic group.
Ask how ethnic background influences their lifestyle.
Ask what they believe causes health/illness.
Ask what they do to prevent/treat illness.</td><td>Medical care is significantly affected by ethnicity.
For example, cultural norms in muslims:
<table>
<tr><th>Description of Norm</th><th>Consequences of Failure to Appreciate</th></tr>
<tr><td>Fasting during the holy month of Ramadan</td><td>Inappropriate therapy; will not take medicines during daytime misinterpreted as noncompliance; misdiagnosed</td></tr>
<tr><td>Modesty: Women's body including hair, body, arms, and legs not to be seen by men other than in immediate family. Female chaperone and/or husband must be present during exam and only that part of the body being examined should be uncovered</td><td>Deep personal outrage, seeking alternative care</td></tr>
<tr><td>Touch: Forbidden to touch members of the opposite sex other than close family. Even a handshake may be inappropriate</td><td>Patient discomfort, seeking care elsewhere</td></tr>
<tr><td>God's will: God causes all to happen for a reason, and only God can bring about healing</td><td>Allopathic medicine will be rejected if it conflicts with religious beliefs, family may not seek healthcare</td></tr>
<tr><td>Patriarchal, extended family: Older male typically is head of household, and family may defer to him for decision making</td><td>Child's mother or even both parents may not be able to make decisions about child's care; emergency decisions may require additional time</td></tr>
</table></td></tr>
<tr><td>Religion
Influences family values and beliefs. Might affect care of the infant/ child.
Ask if family is involved in a church or if they identify with a particular religious group.</td><td>In families who are Jehovah's Witnesses, blood transfusions are not allowed. Christian Scientists believe that healing is a religious function and oppose drugs, blood transfusions, and extensive physical examinations.
Buddhists might be reluctant to consent to treatments on holy days.
Families who are Black Muslim prefer vegan diets and might refuse pork-base medicines.
Islamic families might refuse narcotics and any other medicines that are deemed addictive or to have an alcohol base.
Hindu families might refuse beefbased medical products.</td></tr>
<tr><td>Social Class Status and Mobility
Mold family values.
Inquire about work moves, satisfaction, and aspirations.</td><td>Clinical Alert
Family dysfunction might be associated with job instability.
Migrancy can result in social isolation and lack of health care.</td></tr>
<tr><td>Environment
Refers to home, neighborhood, and community.</td><td>Clinical Alert
Chipped paint, heavy street traffic, uncertain water supplies, and sanitation can all affect family health. Temporary shelters or lack of dwelling might indicate homelessness of family, related to physical or substance abuse, job layoffs, domestic conflicts, parental illness, or other crisis.</td></tr>
</table>

Table. Assessment of the Family *(continued)*

ASSESSMENT	FINDINGS
Family Development Like individuals, families experience a developmental sequence, which can be divided into eight distinct stages. *Stage One: Marriage (Joining of Families)* *Stage Two: Families with Infants* *Stage Three: Families with Preschoolers* *Stage Four: Families with School-Age Children* *Stage Five: Families with Teenagers* *Stage Six: Families as Launching Centers* *Stage Seven: Middle-Age Families* *Stage Eight: Aging Families*	**Clinical Alert** A family that resists change might become stuck in a stage. The adolescent, for example, might be treated the as a young child, producing great distress. Family breakdown and divorce affect the family differently depending on the timing in the family cycle.
Expressive Functioning Refers to the affective issues and is useful in delineating functional families and those families who are experiencing distress and who would benefit from intervention or referral.	**Clinical Alert** A family might refuse to show emotion appropriately or allow members to do so, which can suggest dysfunction. In alcoholic families, for example, members might show an unusually bland response to extremes in circumstances or behavior. Expression of emotions might be influenced by culture. In some cultures (e.g., Japanese), expression of emotions might be restrained.
Problem Solving Refers to ability of family to solve own problems. Ask who first notices problems, how decisions are made, who makes decisions.	Decision making is culturally influenced. In many cultures (e.g., Hispanic, Vietnamese, Puerto Rican) the father is the main family decision maker. **Clinical Alert** Dysfunctional families might tend to employ a narrow range of strategies, consistently apply inappropriate strategies, or fail to adapt strategies to needs and stages of family members.
Adaptation to changes Families attempt to maintain balances between change and stability.	The crisis of illness might temporarily produce a state of great change within a family. Efforts at stability, such as emphatic attempts at maintenance of usual feeding routines during the illness of an infant, might seem paradoxical to the period of change; however, both change and stability can and do coexist in family systems. Overwhelming change or rigid equilibrium can contribute to and be symptomatic of severe family dysfunction. Sustained change usually produces a new level of balance as the family regroups and reorganizes to cope with the change.

Supporting the Grieving Child and Family

Virtually all children experience the death of a family member or friend. Pediatricians and other pediatric health care providers can play a vital role by building on their preexisting relationship with the child and family to ensure that the child understands accurately what has occurred, provide advice to families on how to help promote adjustment and coping, identify misconceptions and reactions (eg, unwarranted fears, guilt, somatization, depression) that would benefit from clarification or additional services, and assist the child and family in identifying supportive resources within the community.

Adjustment requires that the children first understand what has occurred and its implications. **There are four basic concepts about death that children must come to understand: (1)** death is irreversible—very young children may equate death with separation and await the deceased's return; **(2)** all life functions end completely at the time of death (termed nonfunctionality or finality)—if this is not understood, children may worry about the physical suffering of the deceased; **(3)** all living things eventually die—if children do not understand the inevitability of death, they may question what the deceased individual or the child himself or herself did that was responsible for this person being selected to die; and **(4)** a realistic understanding of the cause of death, which helps to minimize the attribution of the cause to unrelated thoughts or actions of the victim or the child. While most children, on average, come to learn these concepts by the age of 5 to 7 years, personal experience and educational interventions can accelerate comprehension. For this reason, children with a terminal condition generally have a precocious understanding of these concepts and an appreciation of their own mortality.

Pediatricians can begin by creating an environment where children and adolescents feel it is safe and welcome to discuss their thoughts and feelings related to the death. Physicians often worry, though, that they do not know what to say that will be helpful and do not wish to make matters worse by raising the topic. **Approaches to initiate discussion by adults that may be less helpful include** (1) trying to "cheer up" those who are actively grieving (eg, "I'm sure you will feel better soon" or "At least your father is no longer in pain"); (2) encouraging people to be strong or to hide or minimize their expressions of distress (eg, "You don't want to have your son see you cry" or "You are the man of the house now that your father has died"); and (3) telling people how they should or do feel rather than asking them about their own feelings (eg, "You must be angry" is often not helpful, whereas stating "I have the sense you may be angry —is that the case?" or "I wonder if you are angry" is more likely to be well received). Much can be accomplished by a genuine and empathic statement of concern (eg, "I'm sorry to hear that your brother died"), a willingness to be with the individual who is actively grieving without trying to change his or her feelings immediately, active listening, and an offer to provide assistance now and in the future.

Professional Conduct and Attitudes

Knowledge, skills, clinical reasoning, and informed decision making while crucial to a physician's practice of medicine, are insufficient to guarantee successful clinical interactions. A physician must have well-developed interpersonal skills that facilitate communication, and must also demonstrate attitudes, behaviors and beliefs that serve to promote the patient's best interest. Students can learn to be professional, at least to a certain degree, in the abstract, but will acquire professional characteristics most effectively through contact with physicians chosen to serve as role models. Historically the most privileged professions have depended on their legitimacy for serving the public interest. The public trust of physicians is based on the physician's commitment to altruism. Many medical schools include variations on the traditional Hippocratic Oath as part of the commencement ceremonies as a recognition of a physician's responsibility to put the interest of others ahead of self-interest.

The American Academy of Pediatrics (AAP), the American Board of Pediatrics (ABP), the American Board of Internal Medicine, the LCME, the Medical School Objectives Project of the Association of American Medical Colleges, and the ACGME Outcome Project have called for increasing attention to professionalism in the practice of medicine and in the education of physicians.

PROFESSIONAL STANDARDS IN THE PRACTICE OF PEDIATRICS (ABP 2000; AAP 2007)

- **Honesty/integrity** is the consistent regard for the highest standards of behavior and the refusal to violate one's personal and professional codes. Maintaining integrity requires awareness of situations that may result in conflict of interest or that may result in personal gain at the expense of the best interest of the patient.
- **Reliability/responsibility** includes accountability to one's patients and their families, to society to ensure that the public's needs are addressed, and to the profession to ensure that the ethical precepts of practice are upheld. Inherent in this responsibility is reliability in completing assigned duties or fulfilling commitments. There also must be a willingness to accept responsibility for errors.
- **Respect for others** is the essence of humanism. The pediatrician must treat all persons with respect and regard for their individual worth and dignity; be aware of emotional, personal, family, and cultural influences on a patient's well being, rights, and choices of medical care; and respect appropriate patient confidentiality.
- **Compassion/empathy** is a crucial component of medical practice. The pediatrician must listen attentively, respond humanely to the concerns of patients and family members, and provide appropriate empathy for and relief of pain, discomfort, and anxiety as part of daily practice.
- **Self-improvement** is the pursuit of and commitment to providing the highest quality of health care through lifelong learning and education. The pediatrician must seek to learn from errors and aspire to excellence through self-evaluation and acceptance of the critiques of others.
- **Self-awareness/knowledge of limits** includes recognition of the need for guidance and supervision when faced with new or complex responsibilities. The pediatrician also must be insightful regarding the impact of his or her behavior on others and cognizant of appropriate professional boundaries.
- **Communication/collaboration** is crucial to providing the best care for patients. Pediatricians must work cooperatively and communicate effectively with patients and their families and with all health care providers involved in the care of their patients.
- **Altruism/advocacy** refers to unselfish regard for and devotion to the welfare of others. It is a key element of professionalism. Self-interest or the interests of other parties should not interfere with the care of one's patients and their families.

Examples of professional attitudes and corresponding behaviors for medical students

Attitude	Behavior
Honesty	Behaviors that demonstrate honesty and trustworthines
Accountability	Takes responsibility for actions
Caring	Volunteering
Desire for self-improvement	Continued learning Self-instruction
Respect	Dresses appropriately Punctual Maintains confidentiality
Open-minded	Increased receptiveness to new ideas
Resposibility to learn	Comes to class prepared Actively participates in class activities, such es engages in discussion
Team player	Engages in constructive peer assessment Accepts and applies constructive critique
Values of experiences	Desire to seek out and take on new challenges

QUESTIONS

1. In a crowded elevator a fellow medical student begins discussing a fascinating patient that he had seen earlier in the day. How would you respond?

2. While on attending rounds with the Pediatric Clerkship director (who assigns the final grade for the rotation), you are asked if one of your patients has been febrile during the past 24 hours. You cannot remember if the patient has been afebrile or not. What should you tell the attending?

3. You and two other students are alone waiting for attending rounds to begin. One of the students makes a racist remark about a patient he had seen earlier in the day. What should your response be?

4. During a routine health care supervision visit, a sixteen-year old girl confides to you confidentiallythat she has been sexually active, has tried marijuana, and on a few occasions snorted cocaine. That evening her mother calls you. She is very concerned about her daughter's behavior and demands to know if the daughter is using drugs or having sex. What are your ethical and legal obligations? What would you tell the mother?

5. The mother of a six-year-old boy is upset that you examined his testicles and penis during a well-child examination. She feels that this part of the examination is private and best left to family discussions. What would you say to her?

6. Brothers aged 10 and 16 present for a routine health care supervision visit with their mother. How would you interview these patients? How would your interview strategy or questions differ?

7. After informing the mother of a two-year-old infant that the child has a viral infection, the mother demands antibiotic for the child. How would you respond?

8. A previously healthy 16 year-old girl presents for a routine health care supervision visit with her mother. When you ask the mother to leave the room, she refuses. How would you approach this situation?

9. The clerkship director has scheduled a mandatory meeting with all the students on the rotation to discuss the final examination. Just before the meeting time, a sixteen-year old girl with cystic fibrosis whom you have been following on the ward says that she needs to talk with you right away and begins to cry. What should you do?

10. During bedside attending rounds, a girl admitted the previous night with a diagnosis of cellulitis isdiagnosed with pernio. The mother requests more information about this topic. What would you do? What resources are available?

ANSWERS

1. Consider the patient's privacy and confidentiality. Suggest to your colleague that he wait until the two of you are in a more private setting before discussing the case. Never use/discuss a patient's name or anyother identifying information in public areas of medical facilities such as elevators, cafeterias or hallways.
2. Be honest with the attending and let him/her know that you do not remember. Reporting false information can potentially result in harm to the patient.
3. Pull your colleague aside and inform him/her that the comment was not only inappropriate and unprofessional, but disrespectful as well. If this behavior continues, bring it to the attention of your teamleader.
4. The healthcare provider is ethically and legally obligated to maintain confidentiality unless the pt. threatens to harm self or others. Suggest to the mother that she ask her daughter about what's been going on, and to try having a discussion with her daughter about her behavior and her concerns regarding the behavior.
5. Explain to the mother that as a healthcare provider you are responsible for evaluating each of your patients from head to toe and documenting all that is normal and abnormal. It may be helpful to describe the importance of evaluating growth and symmetry of the male genitalia, as well as potential pathological processes that can involve male genitalia in the pediatric age group (i.e. signs of child abuse, infection, etc.)
6. The ten year old can be interviewed and examined with his mother in the room. The sixteen year old should be interviewed (especially for questions involving HEADS) and examined in a separate room. Consider asking the mother if she has any concerns regarding development or behavior of the sixteen year old before interviewing him so that those issues can be addressed when you do interview him.
7. Explain to the mother that infections can be caused by viruses and bacteria. Bacteria are living microorganisms whereas viruses are not. Antibiotics only fight living bugs (i.e. bacteria). It may be helpful to educate the mother about breeding resistance to antibiotics. Giving him unnecessary antibiotics jeopardizes the future usefulness in treating bacterial diseases.
8. Inform the mother that in order to provide optimal care for her daughter, you, as the healthcare provider,need her daughter to be completely honest and open with you. Explain that adolescents are often reluctant to answer certain questions, or answer them untruthfully when a parent/guardian is present in the room because of multiple reasons such as shame, guilt, or fear of being reprimanded. Explain to the mother that you would like her daughter to feel as comfortable as possible during the examination in order to develop a trusting patient-physician relationship.
9. Address the patient's concerns. Report the encounter to a team leader. Explain situation to clerkship director and have the team leader address clerkship director on your behalf if necessary.
10. Inform the mother of educational websites, and books online that she can visit for more info. If she doesnot feel comfortable doing this, offer to retrieve an article from the web for her. Make sure the article iswritten to be understood by patients rather than physicians. The physician may have pamphlets with more info as well.

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Growth

COMPETENCIES

You must…

Know	Be able to	Appreciate
• When a child's growth is of concern • How to diagnose the common and important conditions responsible for poor growth in infants and children, and the principles of managing them • The causes of poor weight gain in young children and babies • How to advise a child who is suffering from obesity	• Plot measures on a growth chart • Weigh and measure a baby and child accurately and correct for prematurity • Calculate BMI	• The stress and anxiety of having a child with weight faltering (FTT), especially if there are eating difficulties

Growth is the progressive increase in the size of a child or parts of a child.

The assessment of growth is very helpful in finding out the state of health and nutrition of a child. Continuous normal growth and development indicate a good state of health and nutrition of a child. Abnormal growth or growth failure is a sign of disease. Hence, measurement of growth is an essential component of the physical examination.

Factors affecting growth and development

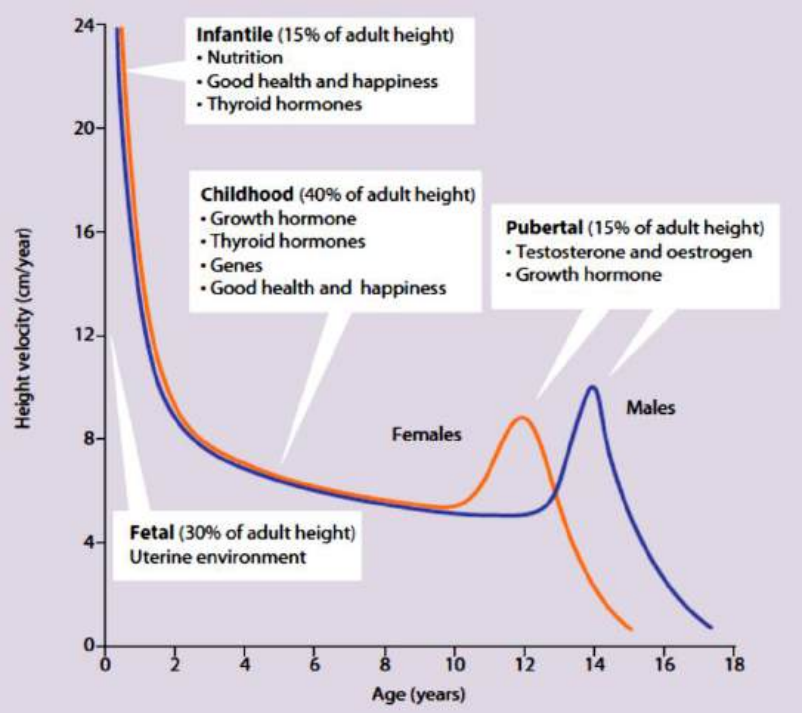
Each child's path or pattern of growth and development is determined by genetic and environmental factors. The genetic factors determine the potential and limitations of growth. If favourable, the environmental factors, such as adequate nutrition, facilitate the achievement of the genetic potential of growth. Unfavourable factors, acting singly or in combination, slow or stop growth. Some of the unfavourable factors are ***malnutrition, infections, congenital malformations, hormonal disturbances, disability, lack of emotional support, lack of play, and lack of language training.*** To promote optimum growth, these environmental factors can be removed or minimized. Once they are removed, there follows a period of **catch up growth**. During this period the growth rate is greater than normal. This growth rate continues until the previous growth pattern is reached. Then the growth rate is reduced to the normal rate determined by the individual's genetic factors. A child genetically determined to be tall grows slightly more rapidly than a child genetically determined to be short.

Phases of human growth

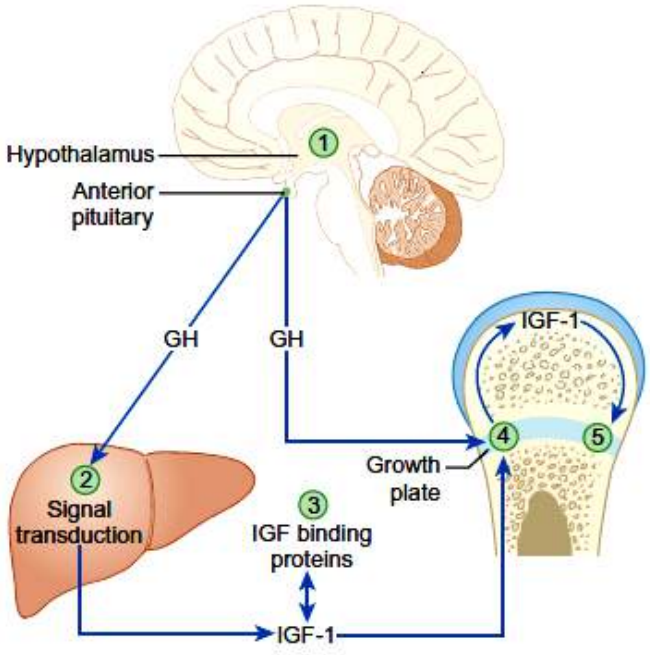
Growth phase		Growth rate	Main determinants of growth
1	***Fetal (intrauterine) phase***	- the fastest period of growth, accounting for about 30% of eventual height	- Mother's size and nutrition - Placental circulation and nutrient supply
2	***Infancy phase***	- the fastest period of postnatal growth, accounting for about 15% of eventual height	- Adequate nutrition - Normal thyroid function * *An inadequate rate of weight gain during this period is called* ***'failure to thrive'.***
3	***Childhood phase***	- a slow, steady but prolonged period of growth that contributes 40% of final height	- Hormones: growth hormone (GH), thyroxine and insulin
4	***Pubertal growth spurt***	- occurs from the onset of puberty to fusion of the epiphyses. This adds 15% to final height	- Growth hormone and sex hormones (androgens and oestrogens) * *The same sex hormones cause fusion of the epiphyseal growth plates and a cessation of growth. If puberty is early, which is not uncommon in girls, the final height is reduced because of early fusion of the epiphyses.*

Sex differences in growth

- Growth spurt starts in early puberty but maximal velocity does not occur untill middle puberty.
- Puberty begins 2 years later in males than in females. The growth spurt can last 2 to 3 years, but occurs earlier in females, and their peak height velocity (PHV) is less, so their adult height is usually shorter than males.
- The peak height velocity occurs at a mean of 13.5 years in boys and 11.5 years in girls. The weight gain follows the height gain a few months later.
- Adult males are taller than females as they have a longer childhood growth phase, their peak height velocity is higher and their growth ceases later.



Endocrine regulation of growth



Growth hormone (GH) exerts the major influence on postnatal growth. GH stimulates the synthesis from the liver and a number of other organs of insulin-like growth factors (IGF-1 and IGF-2), which share a degree of structural homology with proinsulin and may exert weak insulinlike effects. IGF-1 is thought to be a major regulator of GH action. It circulates bound to IGF binding protein-3 (IGFBP-3), whose concentrations are also regulated by GH. This complex associates with another GH-dependent glycoprotein known as acid-labile subunit, the combination forming a ternary complex.

Fig. The growth hormone/IGF-1 axis*. Cytokines act on (1) appetite centres in the brain affecting appetite and calorie intake; (2) growth hormone signal transduction in the hepatocyte; (3) proteolysis of IGFBP-3; (4) IGF-1 expression in the growth plate; (5) proliferation of growth plate chondrocytes.*

Genetic mutations associated with pituitary hormone deficiencies

• *PROP1* gene – the most common, autosomal recessive inheritance, associated with deficiencies of GH (growth hormone), TSH (thyroid-stimulating hormone), LH (luteinizing hormone), FSH (follicle-stimulating hormone), ACTH (adrenocorticotrophic hormone) and prolactin.
• *POU1F1* (previously known as *PIT1*) – autosomal dominant or recessive, causes deficiencies of GH, prolactin and the β-subunit of TSH.
• *HESX1* – autosomal dominant or recessive, is expressed in the oral ectoderm that gives rise to Rathke's pouch, causes GH deficiency in association with septo-optic dysplasia.
• *LHX3* and *LHX4* – regulate the proliferation and differentiation of pituitary specific cell lineages, associated with combined pituitary hormone deficiencies.

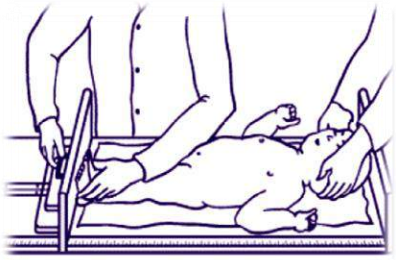
Major parameters of physical growth. Anthropometry

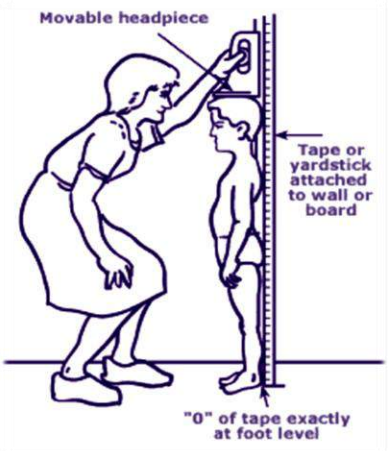
1. Body weight

- Weigh babies naked (a wet nappy could change their weight significantly)
- Weigh older children in only their underwear
- Make sure that the scales you are using have been properly calibrated

2. Length/height

Before 2 years of age





Length

- If a child is less than 2 years old you should measure their length instead of their height.
- You need a special piece of equipment and two people in order to do this properly
- This can be really tricky to do well and often best to have an experienced person help you if length needs to be measured

Height

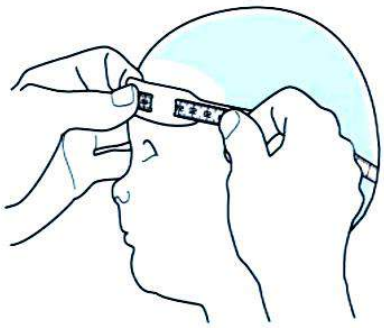
- From 2 years onwards you can measure a child's height
- Measure the child's height with no shoes on
- Make sure that their knees and heels are flat against the wall or back of the measuring frame
- Use a proper standing frame to measure the child's height
- Lift slightly at the child's head to encourage them to stand straight but make sure they keep their feet flat on the floor

3. Calculation of body mass index (BMI)

— *is accepted as best clinical indicator for measure of under- and overweight*

$$\frac{\text{weight in kilograms}}{(\text{height in meters})\times(\text{height in meters})}\times 10{,}000$$

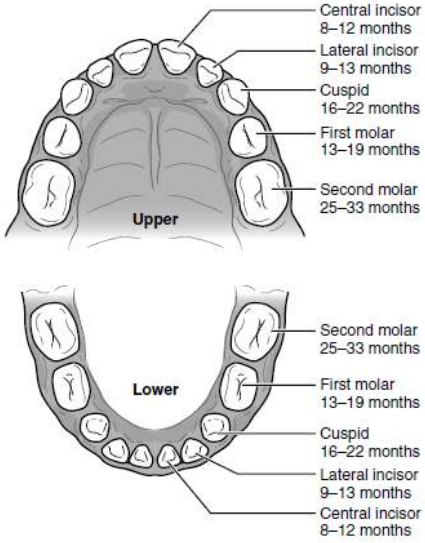
4. Head circumference



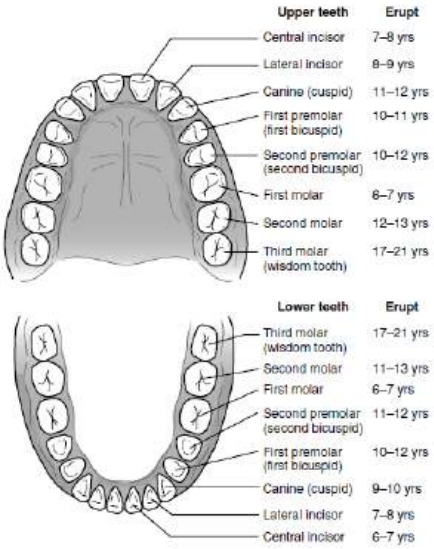
- Use a tape measure which is not stretchy! Most units have disposable paper versions
- Measure around most prominent part of the occiput to the most prominent part of the forehead
- Take the tape off and reposition to take three measurements
- Record the largest of the three measurements as the head circumference

5. Dentition

The normal sequence of primary tooth eruption



The normal sequence of permanent tooth eruption



6. Bone age

The bone age of a child indicates his/her level of biological and structural maturity better than the chronological age calculated from the date of birth. Radiography of the hand & wrist is the commonest modality used to calculate bone age (see "The musculoskeletal system").

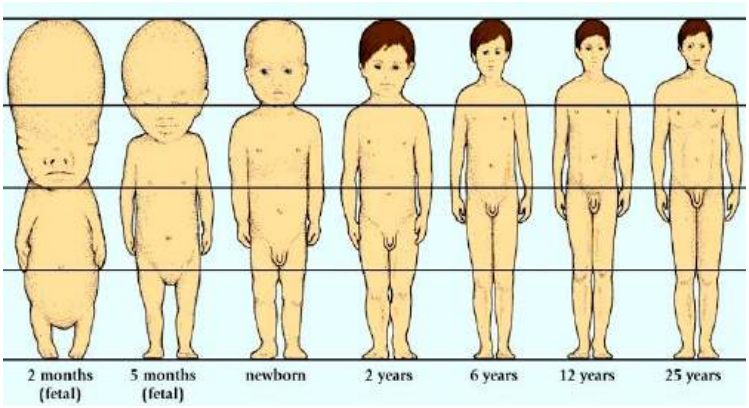
7. Mid upper arm circumference (MUAC)

MUAC is the circumference of the left upper arm, measured at the mid-point between the tip of the shoulder and the tip of the elbow (olecranon process and the acromium). In children, MUAC is useful for the **assessment of nutritional status**. For children aged 6 to 60 months, values below the cut-offs of 125 mm and 115 mm are used to define moderate and severe acute malnutrition, respectively (WHO).

8. Body proportions

Proportionality can be assessed by measuring the lower body segment, defined as the length from the symphysis pubis to the floor, and the upper body segment, defined as the height minus the lower body segment. The ratio of upper body segment divided by lower body segment (**U/L ratio**) equals approximately 1.7 at birth, 1.3 at 3 yr of age, and 1.0 after 7 yr of age. Higher U/L ratios are characteristic of short-limb dwarfism or bone disorders such as rickets.

As stature and weight increase, the individual's proportions also change, from the relatively large head and small torso and limbs of the neonate, to the adult's relatively small head and long torso and limbs.



CASE STUDY **A mother brings in her 7-day-old, full-term newborn with concerns that the infant's current weight is 10% less than birth weight. What is the next step?**

Average growth measurements of normal children

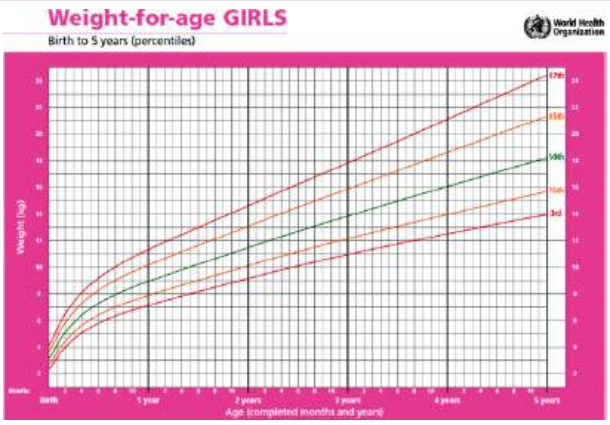
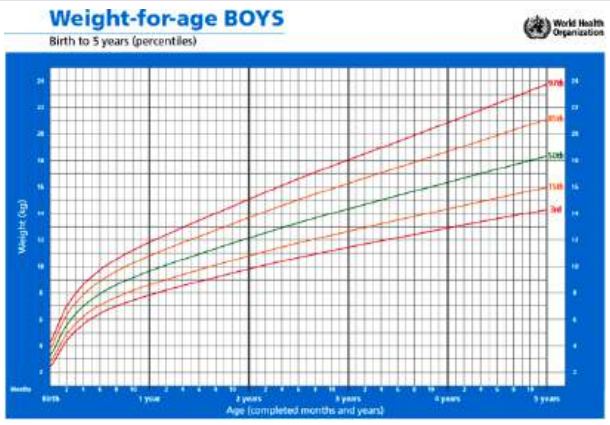
Age	Weight	Length/height	Head circumference
Birth	3 kg	50 cm	35 cm
6 Months	7.0 kg		
1 year	10.0 kg	75 cm	46 cm
2 years	12.0 kg		
3 years	14.0 kg		
4 years	16.0 kg	100 cm	
5 years	18.0 kg		50 cm

- Newborn infants can lose up to 10% of their birth weight soon after birth, which is due to loss of extracellular water. The infant should stop losing weight by 5 to 7 days and regain birth weight by 10 to 14 days.
- The average infant doubles their birth weight by 5 to 6 months of age and triples their birth weight by 12 months. Birth height increases 50% by 1 year, doubles by 4 years, and triples by 13 years.

CENTILE CHARTS AND ASSESSING GROWTH

There is ample evidence that the growth (height and weight) of well-fed, healthy children from different ethnic backgrounds and different continents is remarkably similar, at least up to six years of age.
The most powerful tool in growth assessment is the **growth chart**.
Growth in children is typically assessed by plotting a child's measurement and age on a gender-specific growth curve. Growth curves allow clinicians to compare a child's measurements with those of other children of the same age and to evaluate patterns in an individual child's growth if measurements from multiple points in time are plotted on the same curve.
There are two standard forms commonly used:
- the Centers for Disease Control and Prevention (CDC) charts published in 2000 based on data from multiple national cross-sectional studies including both healthy children and those with medical problem; the charts consist of **seven centile lines** (3rd, 10th, 25th , 50th 75th, 97th).
- the World Health Organization (WHO) charts published in 2006 based on a prospective longitudinal study of healthy, breastfed children on six continents; the charts consist of **five centile lines** (3rd, 15th, 50th, 85th, 97th).

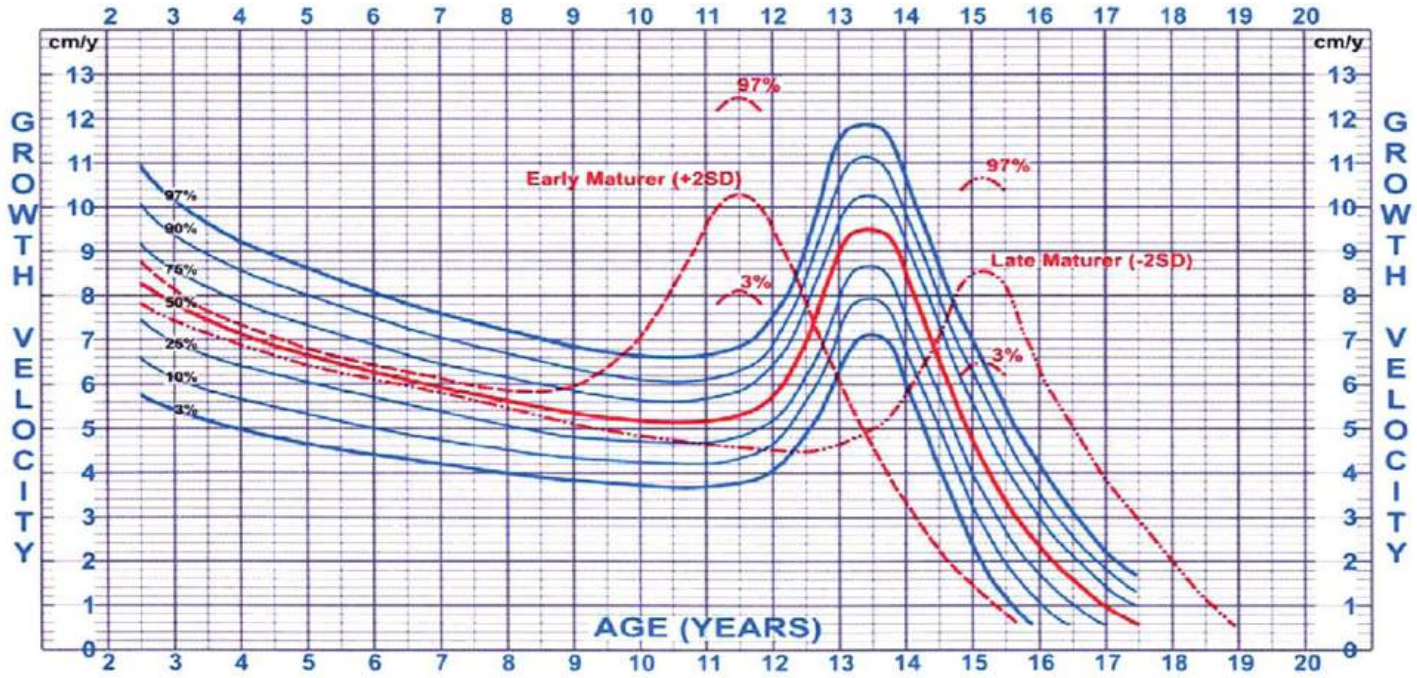
Growth indicators	The growth measurements are presented in **five standard charts**: *- Length/height-for-age* *- Weight-for-age* *- Weight-for-length/height* *- Body mass index-for-age (BMI, kg/m²)* *- Head circumference*

Gender	*Girls – pink charts*	*Boys – blue charts*
		

- *Because centile charts are usually used to assess a parameter over time, they are normally presented graphically. The parameter is shown on the y axis and the age on the x-axis.*
- *Each chart is composed of five or seven percentile curves, representing the distribution of weight, length, stature, or head circumference values at each age.*
- *The percentile curve indicates the percentage of children at a given age on the x-axis whose measured value falls below the corresponding value on the y-axis.*
- *By definition, the 50th percentile is the median. It is also termed the standard value.*
- *The weight-for-height charts are constructed in an analogous fashion, with length or stature in place of age on the x-axis.*
- ***Centile charts show the position of a measured parameter within a statistical distribution. They do not show if that parameter is normal or abnormal.*** *They merely show how it compares with that measurement in other individuals. If a parameter such as height is on the 3rd centile, this means that for every 100 children of that age, 3% would be expected to be shorter and 97% - taller. On the 97th centile, 97% would be shorter and 3% - taller.*
- *Specialized charts have also been developed for children with various conditions, including Down, Turner, and Klinefelter syndromes and achondroplasia.*

Growth monitoring	Centile charts are very useful for assessing growth velocity over time.

- Growth velocity varies during childhood and adolescence, being the fastest during the first year of life, approximately 25 cm. The rate of growth then decreases, averaging 5 cm/year after age 6 until puberty.
- Child is genetically programmed to stay on one to two growth curves after age 2 yrs and any deviation should prompt further assessment of growth abnormalities.
- Height percentile at 2 years of age correlates with final adult height percentile.



Final height and target height

Final height is the height reached after the completion of puberty and is estimated to be achieved when growth velocity has slowed to <2.0cm/year. This can be confirmed by finding epiphyseal fusion of the small bones of the hand and wrist on assessing the bone age X-ray.

Final height is largely genetically determined. A target height range can be estimated in each individual from their parent's heights, first calculating the mid-parental height (MPH).This is calculated using:

MPH (boys) = [(Mother's height (cm) + Father's height (cm))/2] + 6.5cm

MPH (girls) = [(Mother's height (cm) + Father's height (cm))/2] – 6.5cm

Target height range = MPH ± 10cm

Use of *Z*-scores in anthropometry

Z-scores (also known as standard deviation scores, or 'SD' scores) are a measure of the distance between the child's value and the expected value of the reference population.

SDS (Z-score) = (observed value - median reference value) / z-score of the reference population

Z-scores allow more precision in describing anthropometric status than does the customary placement "near" or "below" a certain percentile curve. For example, the phrase "below the 3rd percentile" does not distinguish between a child just below this point (whose z-score may be -2.1) from one with severe growth faltering (whose z-score may be -3.5 or lower)

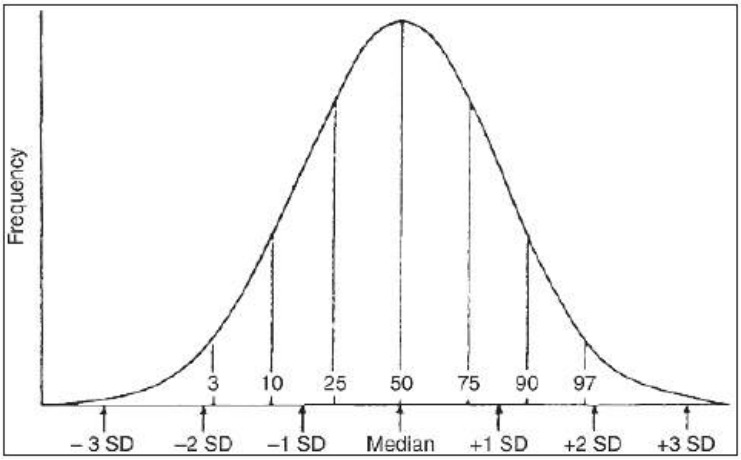


Fig. Comparison of per-centiles vs. standard deviation or z-scores. Two SDs below (or above) the mean corresponds to the 3rd (or 97th) percentile.

Expressing anthropometric measures in terms of z-scores is recommended by the World Health Organization (WHO), especially when describing groups of subjects.
There are CDC computer programs that calculate anthropometric data such as weight for height for age and weight for height (http://www.cdc.gov/growthcharts/computer_programs.htm); these are expressed as percentiles, z-scores, and percentage of the median without making recourse to plotting points by hand. Software for palm-based computers is also available.

Quick Quiz

1.A newborn presents with weight, length, and head circumference significantly below age-matched norms. What is the most likely cause?

2. A newborn presents with weight and length below average and head circumference within normal limits. What are some possible causes?

3. **A newborn presents with weight significantly below average with sparing of the height and head circumference. What are some possible causes?**

4. A 1-year-old boy is failing to meet expected norms for weight and height and is noted to have loss of subcutaneous fat, loss of muscle mass, edema, distended abdomen, and hair loss. These signs are a characteristic of which condition?

Growth Disorders

I knew a little elfman once
Down where the lilies blow.
I asked him why he was so small,
And why he didn't grow
He slightly frowned, and with his eyes
He looked me through and through:
'I'm quite as big for me,' he said,
'As you are big for you.'

John Kendrick Bangs
(1862 – 1922)

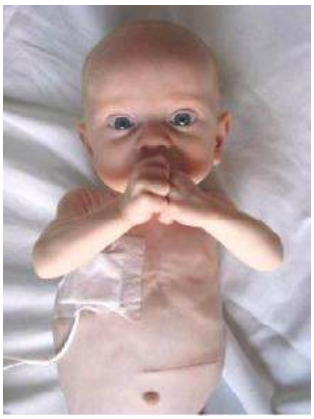
ASSESSING GROWTH DISORDERS BY CENTILE CHARTS

Growth disorder		Parameters	
1. Body weight changes	Underweight	weight-for-age, weight-for length/height, BMI-for-age	<3rd centile
	Overweight		>85th centile
	Obesity		>97th centile
2. Length/height changes	Short stature (stunted growth)	length-for-age, height-for-age	<3rd centile
	Tall stature		>97th centile
3. Head circumference changes	Microcephaly	head circumference	<3rd centile
	Macrocephaly		>97th centile

ASSESSING GROWTH DISORDERS BY Z-SCORES

Z-score	Growth indicators			
	Length/height for-age	Weight-for age	Weight-for length/height	BMI-for-age
Above 3	Very tall	A child whose weight-for-age falls in this range may have a growth problem, but this is better assessed from weight-for-length/height or BMI-for-age.	Obese	Obese
Above 2			Overweight	Overweight
Above 1			Possible risk of overweight	Possible risk of overweight
0 (median)				
Below -1				
Below -2	Stunted	Underweight	Wasted	Wasted
Below -3	Severily stunted	Severily underweight	Severily wasted	Severily wasted

Failure to thrive (FTT) or faltering growth



This applies to a young child who is not growing well, usually for weight gain. In practice, this means:

- *weight is below the 3rd or 5th percentile for age on more than one consecutive occasion*
- *weight drops down two major percentile lines**
- *weight is less than 80% of the ideal weight for age*
- *a child who is below the 3rd or 5th percentile on the weight-for-length curve*
- *body mass index (BMI) for age less than the 3rd or 5th percentile*
- *weight velocity less than the 3rd or 5th percentile*

* Unfortunately, no standard uniform approach exists to identify reliably each child who has FTT solely by use of growth curves. Based on strong research evidence, infants and young children may cross major percentile lines on growth curves during a normal course of growth.

> *Mei and associates described shifts in growth curves during the first 60 months of age in a cohort of 10,844 children. Between birth and 6 months of age, 39% of healthy children crossed two major percentile lines (up or down) on the weight-for-age curve, as did 6% to 15% of children between 6 and 24 months of age. Similar shifts occurred with the length-for-age curve. Strikingly, on the weight-for-height curve, 62% of children between birth and 6 months and 20% to 27% of children between 6 and 24 months crossed two major percentile lines.*

Therefore, documentation of weights or lengths falling off of growth channels is not, by itself, proof of FTT.

FTT is a physical sign of undernutrition, NOT a diagnosis!

In nutritional insufficiency, **weight** is generally the first to be affected, and the weight for height is low. But with prolonged duration of malnourishment, length and head circumference may also adversely be affected. The head circumference declines only in severe FTT.

Nutritional insufficiency must be differentiated from congenital, constitutional, familial, and endocrine causes of decreased linear growth. In the latter cases, the length declines first or at the same time as the weight; weight for height is normal or elevated.

Major causes of undernutrition

Illness-related	Non-illness-related
▪ Malabsorbtive diseases, e.g., celiac disease, cystic fibrosis ▪ Congenital heart defects (CHD) ▪ Gastroesophageal reflux disease (GERD) ▪ Neurologic disorders ▪ Metabolic disease	▪ Poverty and neglect are important issues to consider in the evaluation of a child with failure to thrive.

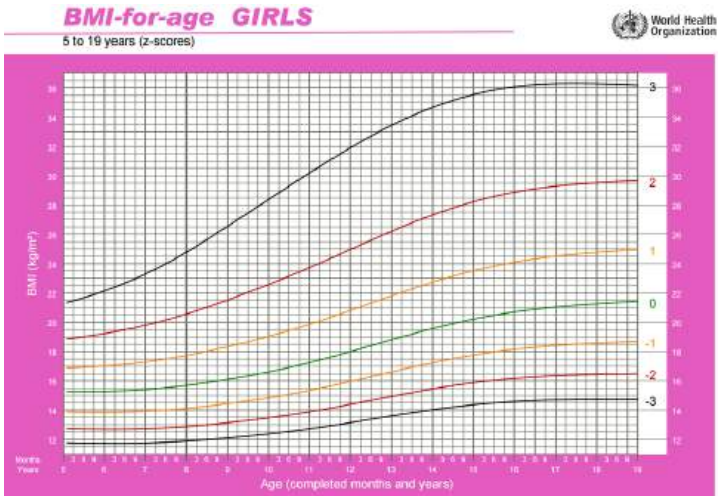
Overweight and obesity

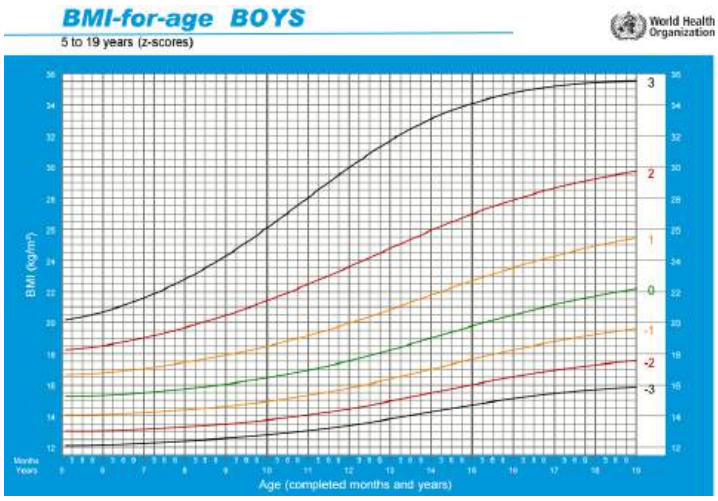
Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health.

Body mass index (BMI) is a simple index of weight-for-height that is commonly used to classify overweight and obesity in adults. It is defined as a person's weight in kilograms divided by the square of his height in meters (kg/m2).

WHO defines overweight and obesity as follows:

	OVERWEIGHT	OBESITY
For adults	BMI greater than or equal to 25	BMI greater than or equal to 30
For children under 5 years of age	Weight-for-height greater than 2 standard deviations above WHO Child Growth Standards median	Weight-for-height greater than 3 standard deviations above the WHO Child Growth Standards median
For children aged between 5–19 years:	BMI-for-age greater than 1 standard deviation above the WHO Growth Reference median	BMI-for-age greater than 2 standard deviation above the WHO Growth Reference median





High BMI correlates with excess body fat in all age groups and in both genders, with the exception of persons with very high muscle mass (e.g., "body builders").

Key facts

- Worldwide obesity has more than doubled since 1980.
- In 2014, more than 1.9 billion adults, 18 years and older, were overweight. Of these over 600 million were obese.
- 39% of adults aged 18 years and over were overweight in 2014, and 13% were obese.
- Most of the world's population live in countries where overweight and obesity kills more people than underweight. Once considered a high-income country problem, overweight and obesity are now on the rise in low- and middle-income countries, particularly in urban settings.
- 41 million children under the age of 5 were overweight or obese in 2014.
- Obesity is preventable.

Common health consequences of overweight and obesity

Raised BMI is a major risk factor for noncommunicable diseases such as:

- cardiovascular diseases (mainly heart disease and stroke), which were the leading cause of death in 2012;
- diabetes;
- musculoskeletal disorders (especially osteoarthritis – a highly disabling degenerative disease of the joints);
- some cancers (including endometrial, breast, ovarian, prostate, liver, gallbladder, kidney, and colon).

The risk for these noncommunicable diseases increases, with increases in BMI.

Childhood obesity is associated with a higher chance of obesity, premature death and disability in adulthood. But in addition to increased future risks, obese children experience breathing difficulties, increased risk of fractures, hypertension, early markers of cardiovascular disease, insulin resistance and psychological effects.

Short stature (stunted growth)

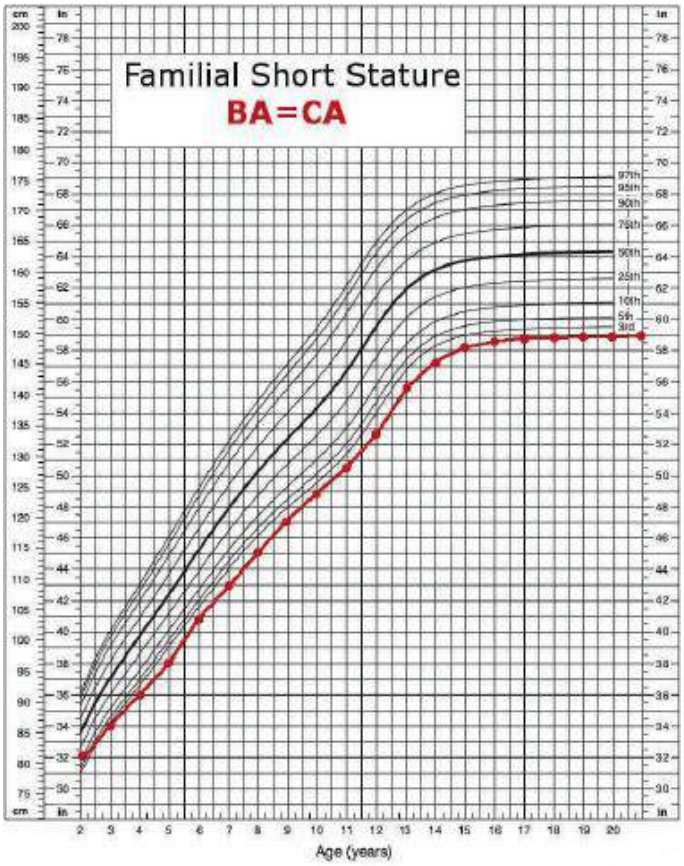
Because height is a continuous variable, the definition of “short” involves a selected cutoff; a height that is more than 2 standard deviations (SD) below the mean for age and sex is the most commonly accepted threshold.

MAJOR CATEGORIES OF CAUSES OF SHORT STATURE

	Normal growth variants	Abnormal growth variants
Bone age = Chronologic age	Familial short stature	Genetic syndromes associated with short stature
Bone age < Chronologic age	Constitutional delay of growth and puberty	Chronic illness Nutritional deficiencies Endocrine disorders

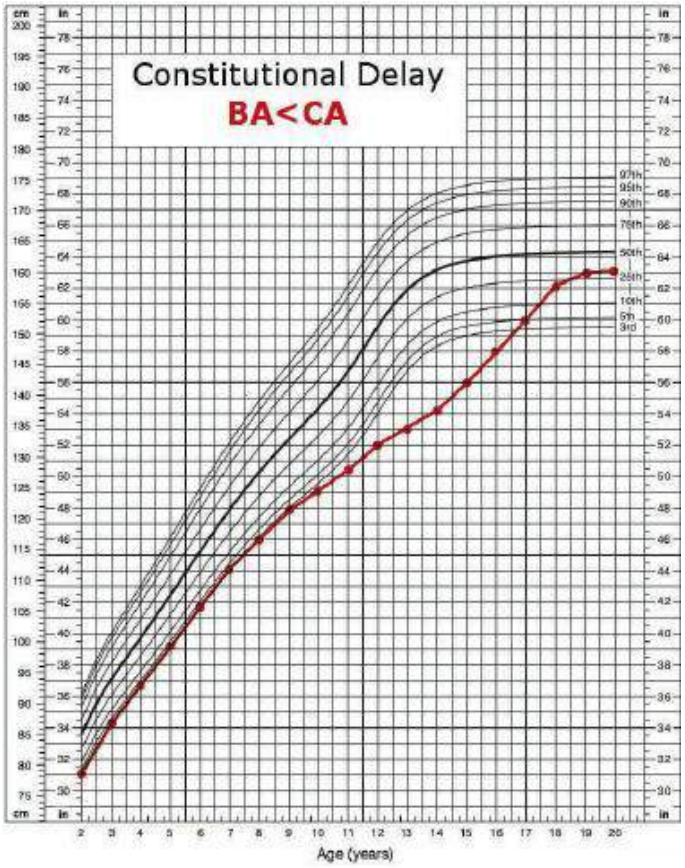
Normal variants of short stature

Familial short stature (FSS)



- The child's pattern of growth is consistent with that of his/her parents (and often siblings, too).
- The child's growth velocity is usually normal, so that the growth curve is low, but parallel to the normal lines. As skeletal growth is not delayed, the bone age should be within the normal range (BA=CA).
- The predicted adult height is in keeping with midparental target height.
- In the absence of a family history of delayed puberty, the timing of puberty is usually average.

Constitutional delay of growth and puberty (CDGP)

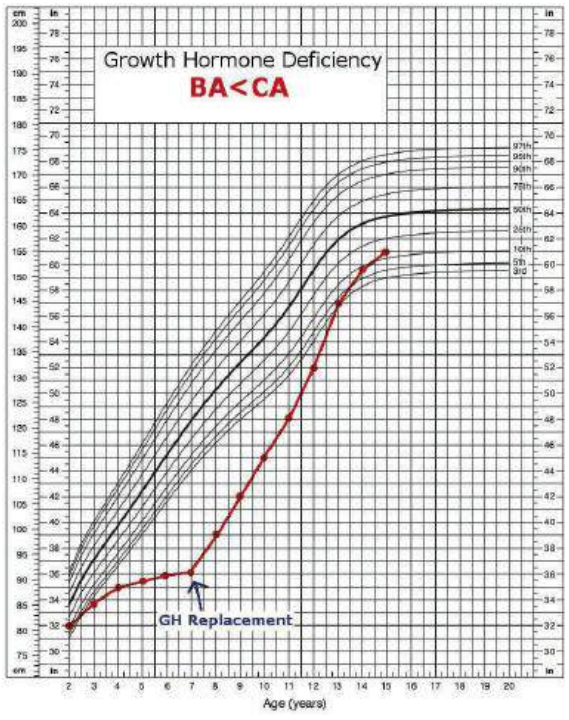
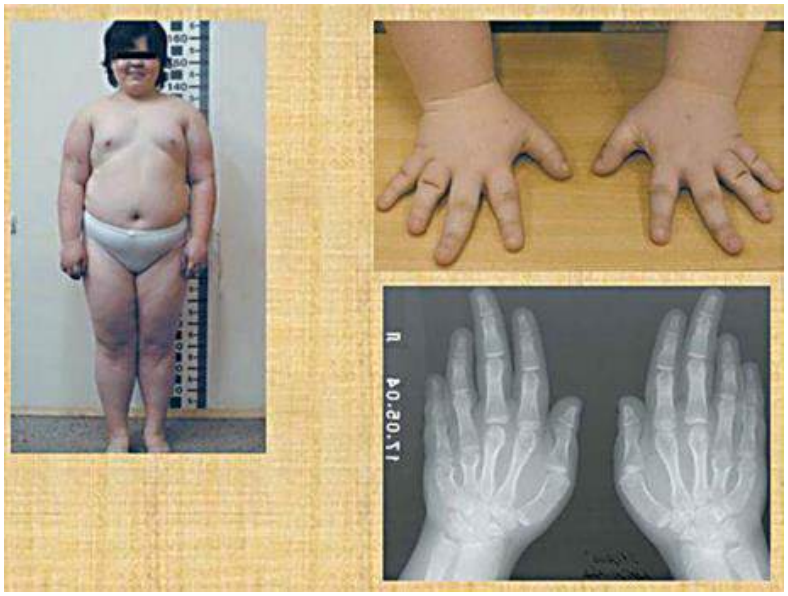


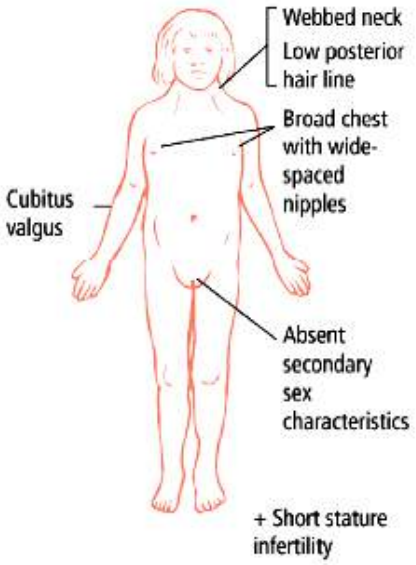
- **Delayed puberty** - the absence of pubertal development by 14 years of age in females and 15 years in males.
- Pubertal growth spurt is also delayed, and these children continue to grow at the prepubertal rate of 4 to 6 cm/year while their peers' height velocity increases, resulting in a gap between the heights of children with CDGP and the heights of age-matched peers — **a transient relative short stature.**

These children usually have a normal birth length, begin to cross height percentiles early in life, and settle in the lower percentiles by the age of 2 years. Between the ages of 2 years and the onset of puberty in their peers, the children's height velocity usually places them along the lower margins of the growth curve (around or sometimes below the 5th to 10th percentile). Then, as their peers begin the pubertal growth spurt and the growth curve slope increases, the children with CDGP commonly fall further below the fifth percentile.

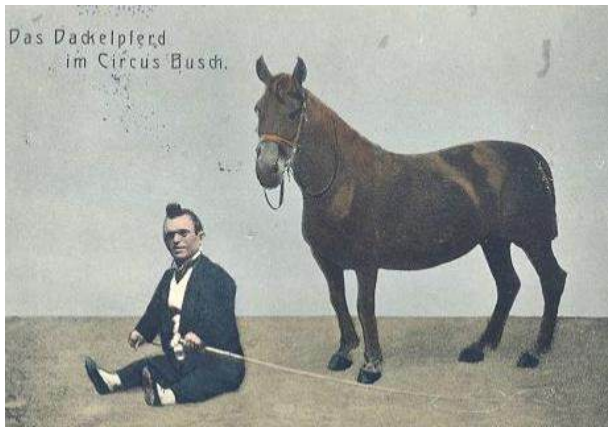
Pathologic variants of short stature

Endocrine disorders	• Hypothyroidism (congenital/autoimmune thyroiditis) • Growth hormone deficiency (possibly secondary craniopharyngioma affecting pituitary), • Corticosteroid excess = Cushing syndrome (usually iatrogenic) • Pseudohypoparathyroidism
Intrauterine growth retardation (IUGR)	33% of infants with severe IUGR/extremely premature infants remain short.
Nutritional/chronic illness	Relatively common cause; children short and underweight secondary to malnutrition from insufficient food intake, unbalanced diets or anorexia associated with a underlying chronic disease (coeliac disease, Crohn.s disease, chronic renal failure, cystic fibrosis, congestive cardiac failure and chronic hypoxia).
Psychological	Emotional deprivation/neglect
Chromosomal disorders	Trisomy 21, Turner syndrome (45XO), Noonan syndrome …
Disproportion	• Skeletal dysplasias (e.g., achondroplasia, chondrodystrophy) • Mucopolysaccharidoses

Growth hormone deficiency	Albright hereditary osteodystrophy
Growth hormone deficiency that appears during the first year of life is associated with hypoglycemia; after the age of 5 years, it is associated with short stature.	A type of pseudohypoparathyroidism, is characterized by short stature, obesity, developmental delay, and brachydactyly, specifically a shortening of the fourth and fifth metacarpals.
	



Turner syndrome (45XO)



Chondrodystrophy

Pituitary dwarfism

Detailed evaluation for short stature warranted when:

- *Severe height deficit (*<1st percentile for age)
- Abnormally slow growth rate (<10th percentile for bone age)
- Predicted height is significantly different from midparental height
- Body proportions are abnormal

Extensive laboratory tests are generally not indicated unless the growth velocity is abnormally low. Laboratory testing may include any or all of the following: *complete blood count, urinalysis, chemistry panel, sedimentation rate, thyroxine, thyroid-stimulating hormone, insulin-like growth factor-1 (IGF-1), and IGF-binding protein-3 (IGFBP-3).*

- Depending on the ethnic background of the child or the clinical history, testing might also be done for celiac disease, inflammatory bowel disease, renal tubular acidosis, or other occult conditions.

- Random growth hormone levels are of little value because they are generally low in the daytime, even in children of average height.

- IGF-1 mediates the anabolic effects of growth hormone, and levels correlate well with growth hormone status. However, IGF-1 can also be low in nonendocrine conditions (e.g., malnutrition, liver disease).

- IGFBP-3, which is the major binding protein for IGF-1 in serum, is also regulated by growth hormone. IGFBP-3 levels generally indicate growth hormone status and are less affected by nutritional factors than IGF-1. Most endocrinologists now use IGF-1 and IGFBP-3 as their initial screening tests for growth hormone deficiency.

Tall stature

• Tall stature is defined as height beyond 97th. percentile (i.e., over 2 standard deviations) of mean for age and sex.
• Bone age ≥ Chronologic age
– Normal growth variant: familial tall stature, obesity
– Abnormal growth variant: genetic syndromes, endocrine disorders, CNS lesions

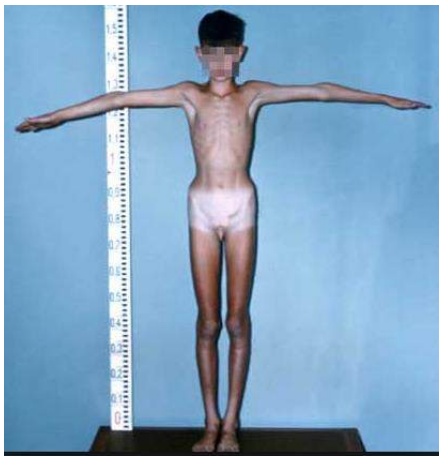
Children who are growing above the 97th percentile should be examined carefully for signs of precocious puberty or adrenal androgen excess.

1. Most children have **familial tall stature**. Occasionally, girls in early adolescence who have familial tall stature may request treatment to reduce final adult stature. High-dose estrogen may induce premature epiphyseal fusion and reduce final height.

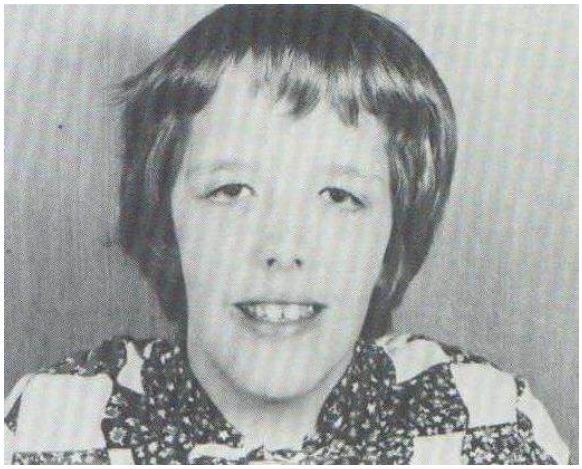
2. Rare causes of tall stature are:

- *GH excess (causing acromegaly and gigantism)*
- *Marfan syndrome*
- *Homocystinuria*
- *Klinefelter syndrome (XXY)*
- *Beckwith-Wiedemann syndrome*
- *Cerebral gigantism (Sotos syndrome)*
- *Fragile X syndrome*

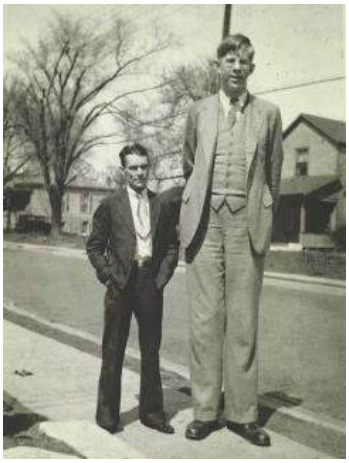
etc.



Klinefelter syndrome (XXY)



Facial appearance of patient with cerebral gigantism (Sotos syndrome)



Excess GH secretion

Abnormal head growth

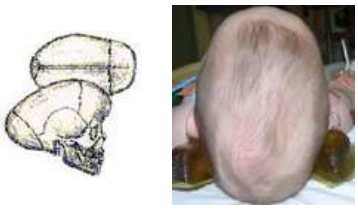
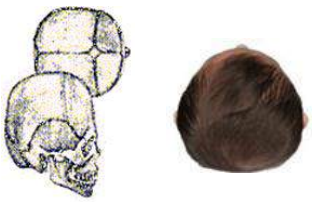
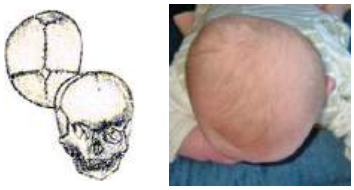
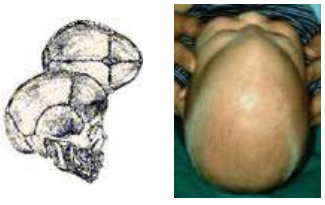
Normal head circumferences (HC) in term infants range from 32 to 38 cm. Head circumference is an important indicator of brain development and should be monitored over time, especially if a fontanel closes early. Bright Futures recommendations state that head circumference measurements should be obtained at each health supervision visit from birth to 24 months of age, but the Centers for Disease Control and Prevention growth charts extend to 36 months.

- **Abnormalities in Head Size**

Microcephaly	Macrocephaly
 HC > 2 standard deviations (SDs) below the mean for age or roughly less than the 2nd percentile	 HC > 2 SD above the mean for age on the standard curve or greater than the 98th percentile
In the newborn, this generally reflects abnormal growth due to genetic, infectious, or teratogenic forces. It is often, but not always, associated with developmental delay. Normal genetic variants may also occur (e.g. in pygmies and dwarfs).	It is important to determine HC of both parents in order to interpret this finding. A common etiology is **benign familial macrocephaly**. However, one must also consider the possibility of pathologic conditions such as hydrocephalus, intracranial cysts, arteriovenous malformation.

- **Abnormalities in Head Shape due to Craniosynostosis**

Craniosynostosis is the premature fusion of one or more cranial sutures, typically resulting in an abnormal head shape.

Scaphocephaly:	*Brachycephaly:*	*Plagiocephaly:*	*Trigonocephaly:*
Condition in which the head is elongated from front to back in the sagittal plane; most normal skulls are scaphocephalic	Condition in which head shape is shortened from front to back along the sagittal plane; the skull is rounder than normal	Condition in which head shape is asymmetric in the sagittal or coronal planes; can result from asymmetry in suture closure or from asymmetry of brain growth	Condition in which head shape is triangular due to premature fusion of the metopic suture
			

Growth Charts Quiz

Test your ability to identify growth charts. They are all Girls: Birth to 36 Month CDC US Growth Charts.

Which of the following explanations is the most likely description of the growth charts below?

a) Normal catch up growth pattern
b) Constitutional short stature
c) Overweight due to excessive cereal mixed with the formula
d) Benign familial megalocephaly
e) Environmental failure to thrive
f) Growth hormone deficiency
g) Hydrocephalus
h) Normal breast fed baby

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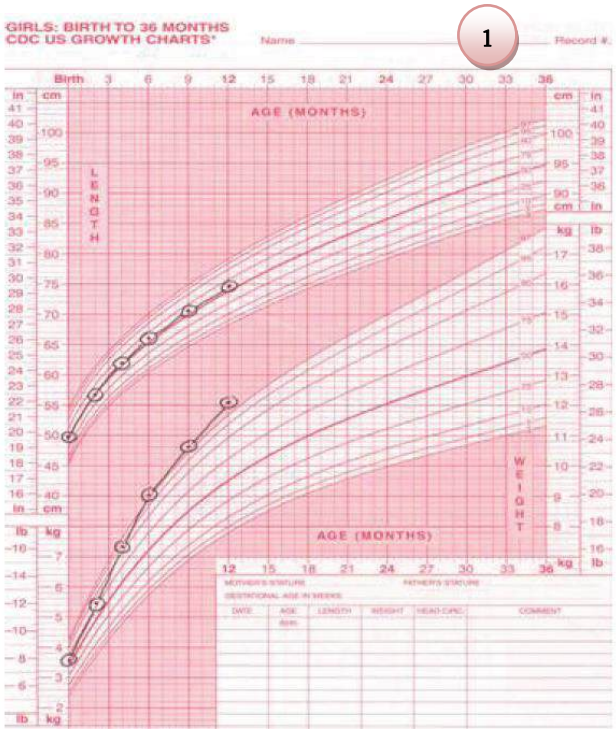

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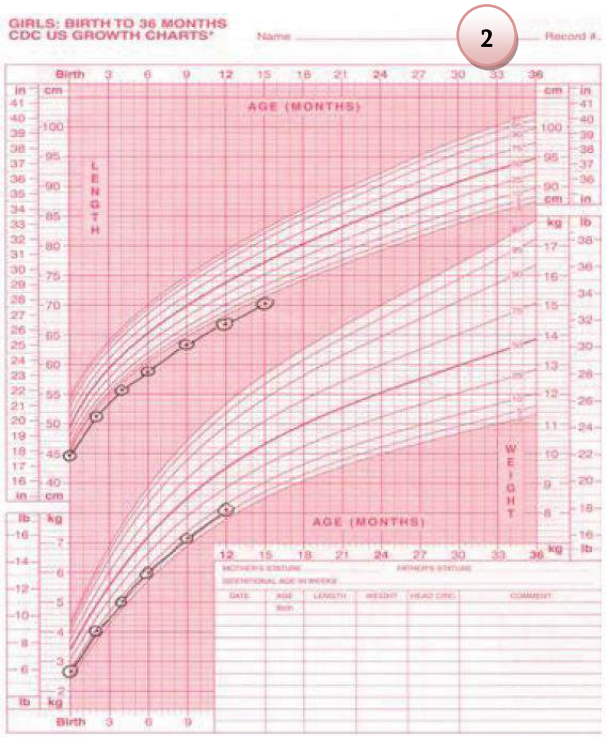

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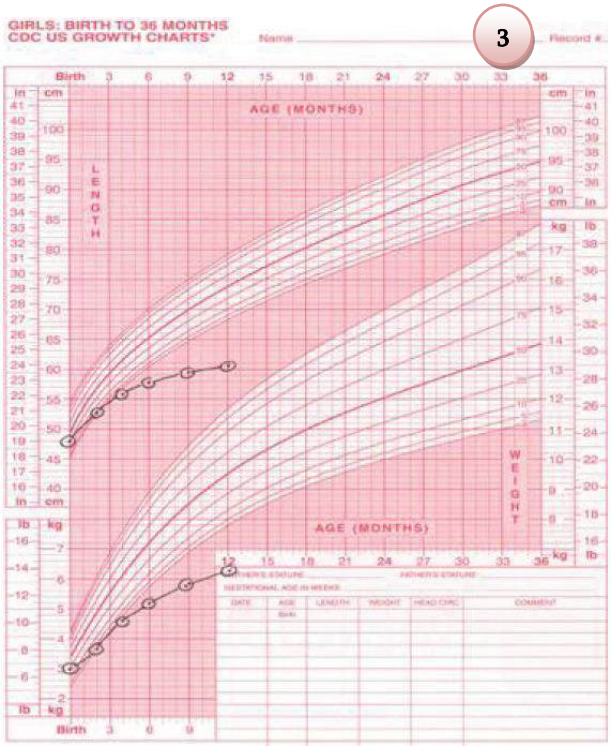

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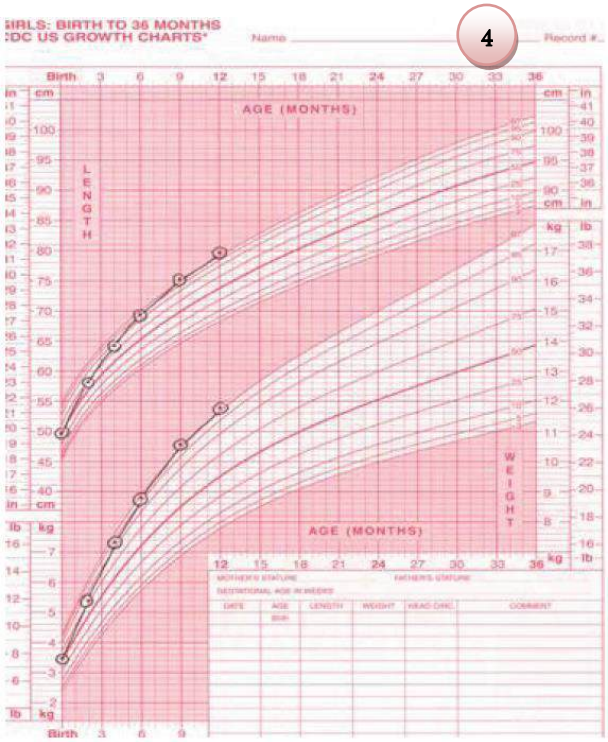

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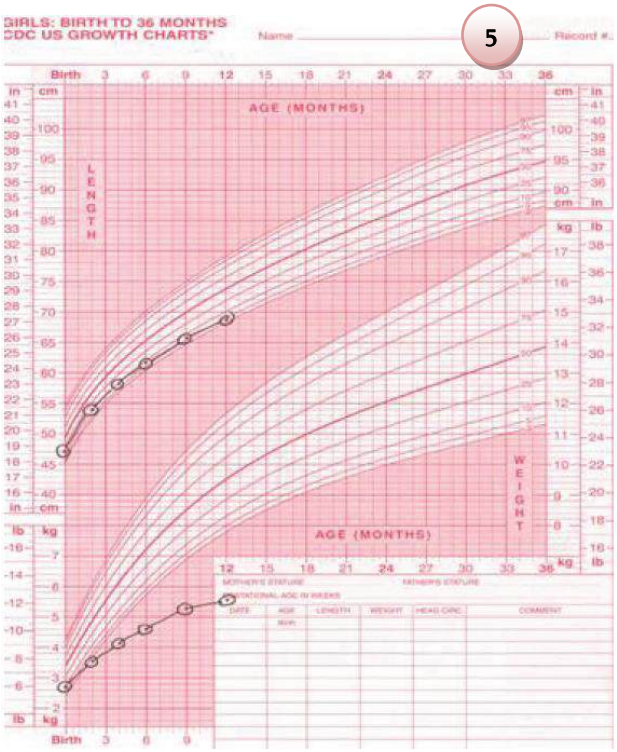
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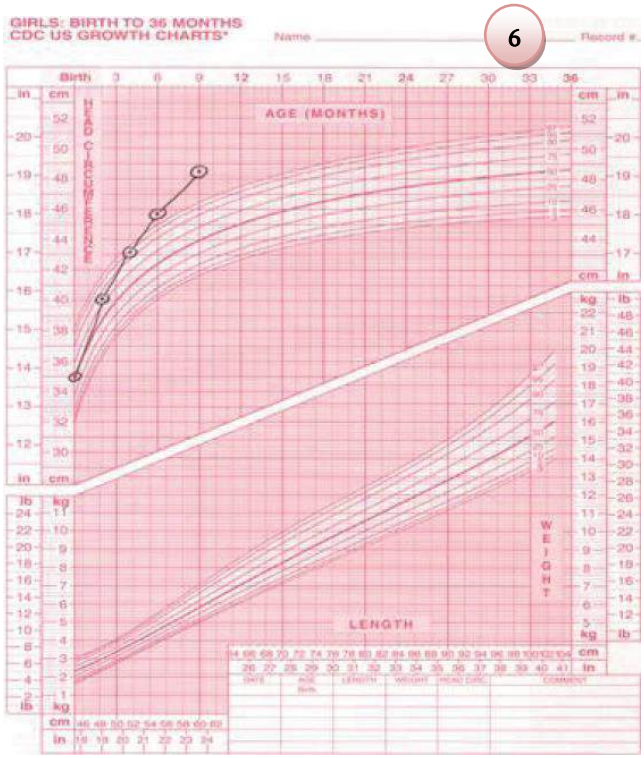
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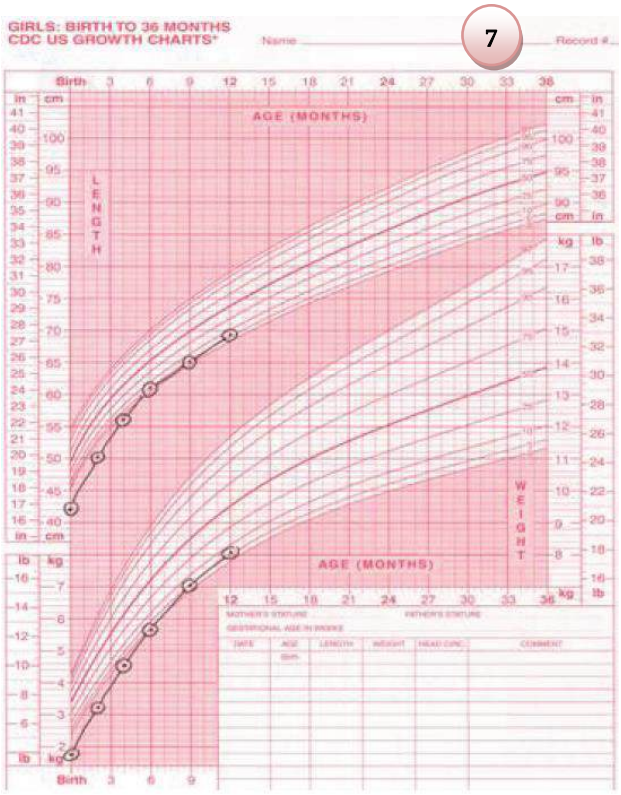
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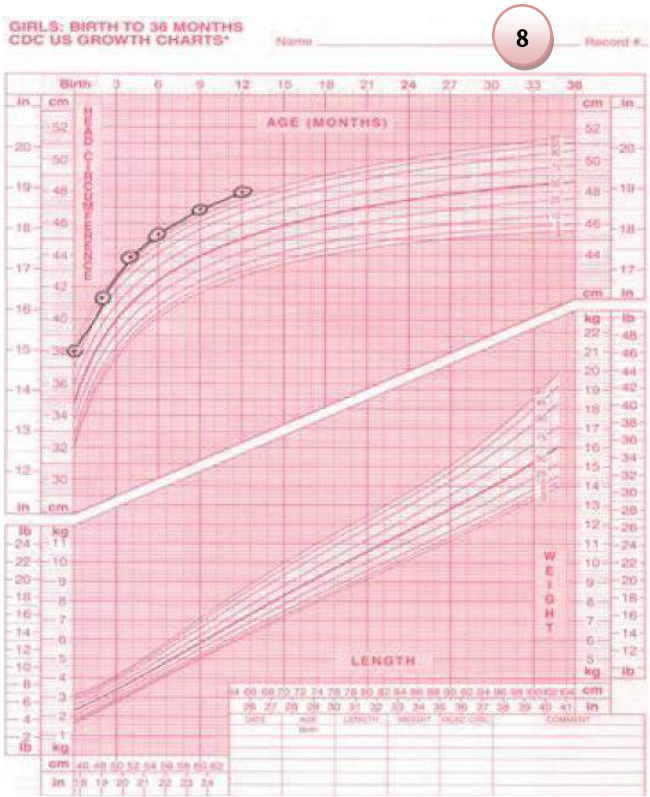
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HEAD CIRCUMFERENCE
WEIGHT
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ANSWERS TO QUESTIONS on page 9

1. An intrauterine insult or genetic abnormality is most likely responsible when multiple growth parameters are below average at birth.

2. Likely causes include constitutional growth delay, genetic short stature, or endocrine causes of growth failure.

3. Likely causes include insufficient caloric intake or a hypermetabolic state.

4. This child is presenting with failure to thrive (FTT), defined as weight, height, or head circumference below the third to fifth percentile, falling off the growth curve by crossing two major percentiles, or weight less than 80% of ideal body weight for age. It is not a diagnosis; it is a sign of an underlying organic or non-organic disorder.

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DEVELOPMENTAL AND BEHAVIORAL PEDIATRICS

CASE STUDY

The parents of a 12-month-old are concerned that she is not walking yet. They report that she sat independently at 7 months and began crawling at 8 months. She can pull herself up to stand while holding on to furniture but is not cruising. Her birth and medical history are unremarkable. The physical examination is within normal limits, and review of your records reveals no concerns on a developmental screening test administered at 9 months of age.

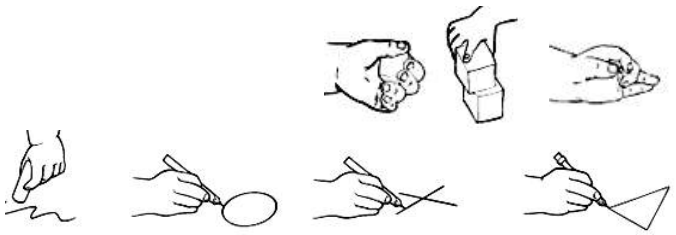
Questions 1. What are the major areas in which development is assessed? 2. What are the gross motor, fine motor, and personal/ social milestones for a 12-month-old? 3. What developmental screening tests could you administer to further assess her development? 4. How is developmental delay in children defined?

Developmental assessment and screening

- **Development** refers to the acquisition of functional skills during childhood. Monitoring the growth and development of children is an integral part of the assessment of pediatric patients.
- For ease of monitoring, these developmental milestones may be divided into 5 major domains or areas: gross motor, fine motor, language, social, and self-help.

1. **Gross motor skills** are overall movements of large muscles (eg, sitting, crawling, walking, running).

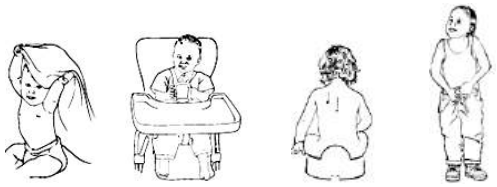
2. **Fine motor skills** involve use of the small muscles of the hands, the ability to manipulate small objects, problem-solving skills, and eye-hand coordination (e.g. holding an object, drawing a shape).



3. **Language skills** include hearing, understanding, and use of language.

4. **Social skills** involve socialization and ability to care for personal needs.

5. **Self-help skills** (e.g. washing hands, feeding with spoon, dressing and undressing without help, toilet training)



CHILD DEVELOPMENT CHART (by Harold Ireton) outlines the normal pattern of development for each of these skills. The chart lists the average age of attainment of these skills.

Child Development Chart – First Five Years

Harold Ireton, Ph.D.

	SOCIAL	SELF-HELP	GROSS MOTOR	FINE MOTOR	LANGUAGE	
5-0 yrs.	Shows leadership among children.	Goes to the toilet without help.	Swings on swing, pumping by self.	Prints first name (four letters).	When asked, for example, "What is an orange?" answers, "A fruit."	5-0 yrs.
4-6	Follows simple rules in board or card games.	Usually looks both ways before crossing street.	Skips or makes running "broad jumps."	Draws a person that has at least three parts - head, eyes, nose, mouth, etc.	Reads a few letters (five+).	4-6
		Buttons one or more buttons.	Hops around on one foot, without support.	Draws recognizable pictures.	Prints a few letters or numbers. Counts ten or more objects.	
4-0 yrs.	Protective toward younger children.	Dresses and undresses without help, except for tying shoelaces.			Follows a series of three simple instructions in order.	4-0 yrs.
3-6	Plays cooperatively with minimum conflict and supervision.	Washes face without help.	Hops on one foot without support. 	Cuts across paper with small scissors.	Talks in long, complex sentences (10 or more words). Answers questions like, "What do you do with your eyes? ears?"	3-6
	Gives directions to other children.	Toilet trained.	Rides around on tricycle, using pedals.	Draws or copies a complete circle.	Identifies at least four colors by name correctly. Asks questions beginning with "Why? When? How?"	
3-0 yrs.	Plays games like tag, hide and seek.	Dresses self with help.	Walks up and down stairs - one foot per step.	Cuts with small scissors.	Answers questions like, "What do you do with a cracker? a hat?"	3-0 yrs.
2-6	Plays a role in "pretend" games like house or school - mom, dad, teacher.	Washes and dries hands.	Stands on one foot without support.	Draws or copies vertical (|) lines.	Speaks clearly - is understandable most of the time.	2-6
	Plays with other children-cars, dolls, building.				Talks in sentences at least four words long.	
2-0 yrs.	"Helps" with simple household tasks.	Opens door by turning knob.	Climbs on play equipment - ladders, slides.	Scribbles with circular motion.	Has a vocabulary of at least 20 words.	2-0 yrs.
	Usually responds to correction - stops.	Takes off open coat or shirt without help.	Walks up and down stairs alone.	Turns pages of picture books, one at a time.	Follows two-part instructions.	
	Shows sympathy to other children, tries to comfort them.	Eats with spoon, spilling little.	Runs well, seldom falls.		Names a few familiar objects in picture books.	
	Sometimes says "No" when interfered with.	Eats with fork.	Kicks a ball forward.	Builds towers of four or more blocks.	Asks for a drink or food, using words or sounds. Uses at least ten words.	
18 mos.	Greets people with "Hi" or similar.		Runs. 	Scribbles with crayon.		18 mos.
	Gives kisses or hugs.	Feeds self with spoon. Insists on doing things by self such as feeding.	Walks without help.	Picks up two small toys in one hand.	Talks in single words.	
12 mos.		Lifts cup to mouth and drinks.	Stands without support.	Stacks two or more blocks.	Says "Mama" or "Dada" for parent, or similar.	12 mos.
	Waves "Bye-bye."	Picks up a spoon by the handle. 	Walks around furniture or crib while holding on.	Picks up small objects - precise thumb and finger grasp.	Understands phrases like "No-no" and "All gone."	
9 mos.	Plays social games, "peek-a-boo," "patty-cake."		Crawls around on hands and knees.			9 mos.
	Pushes things away he/she doesn't want.		Sits alone . . . steady, without support.	Uses two hands to pick up large objects.	Makes sounds like da-da, ma-ma, ba-ba.	
	Reaches for familiar people.	Feeds self cracker.	Rolls over from back to stomach.	Transfers toy from one hand to the other.	Responds to name - turns and looks. Babbles.	
6 mos.	Distinguishes mother from others.	Comforts self with thumb or pacifier.	Turns around when lying on stomach.	Picks up toy with one hand.	Laughs out loud.	6 mos.
					Makes sounds - ah, eh, ugh.	
	Social smile.	Reacts to sight of bottle or breast.	Lifts head and chest when lying on stomach.	Looks at and reaches for faces and toys.	Cries in a special way when hungry.	
Birth						Birth

Four principles apply to all aspects of development.

- First, motor development is a continuous process that proceeds in the cephalocaudal direction and parallels neuronal myelination; therefore, developmental milestones reflect the maturation of the nervous system.
- Second, the sequence of development is the same in all children, but the rate of development may vary from child to child (eg, all children must walk before they run, but the age at which children walk or run varies from child to child).
- Third, the rate of attainment of milestones in one area may not parallel that in another.
- Fourth, certain primitive reflexes must be lost before corresponding voluntary movements can be attained (eg, the asymmetric tonic neck reflex must disappear before children can roll over).

Development in Newborns and Infants

Normal, full-term newborns enter the world capable of responding to visual, auditory, olfactory, oral, and tactile stimuli. They can be quieted and can even soothe themselves. Newborns can signal needs (eg, crying when hungry or wet), but they have a limited ability to respond to caregivers, primarily exhibiting disorganized and seemingly purposeless movements when stimulated. The newborn's reflexive generalized symmetric movements (eg, arm waving and kicking) in response to environmental stimuli are eventually replaced by cortically mediated voluntary actions in older infants and children. Additionally, in newborns, certain primitive reflexes can be elicited by appropriate peripheral stimuli. Eventually, primitive reflexes are replaced by reactions that allow children to maintain postural stability in response to a variety of sensory inputs (proprioceptive, visual, and vestibular).

Primitive reflexes are mediated by the brain stem; they are involuntary motor responses that are elicited by appropriate peripheral stimuli and are present at birth but disappear during the first 6 months of life (Table 1). Normal motor development seems to be related to the suppression of these reflexes. Persistence or reappearance of these reflexes may indicate the presence of brain damage.

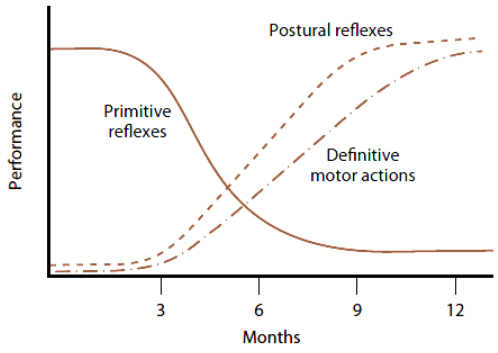


Figure 1. Primitive reflex profile (Capute AJ et al. 1978)

Postural reactions, which are ultimately smoothly integrated into adult motor function (Figure 1), appear between 2 and 9 months of age. These reactions help maintain the orientation of the body in space and the interrelationship of one body part to another (Table 2). The profile generated by combining primitive reflexes and postural reactions can be used to monitor the course of normal development and identify cases of problematic development. Persistence of primitive reflexes or failure of development of postural reactions can signal developmental problems.

Table 1. Selected Primitive Reflexes

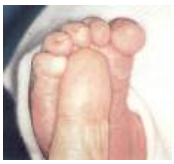
REFLEX	DESCRIPTION	AGE AT APPEARANCE	AGE AT DISAPPEARANCE
Moro	 Allowing the baby's head to drop back suddenly results in abduction and upward movement of the arms followed by adduction and flexion.	Birth	3-6 mo
Palmar Grasp	 Placing finger in infant's palm results in flexing of infant's fingers	Birth	6 mo
Plantar Grasp	 To elicit this, stroke the sole of the foot – the toes will curl to grasp the object	Birth	6-8 mo
Rooting	 Tactile stimulus about infant's mouth results in the mouth pursuing the stimulus	Birth	4-6 mo
Trunk incurvation (Gallant)	 Stroking the skin along the edge of vertebrae produces curvature of the spine with concavity on the side of the stroke	Birth	4 mo
Stepping	 Hold the baby in a standing position and slowly move the baby forwards with the toes touching the bed – the baby will lift the feet and place them in front of each other, as if walking.	Birth	3-4 mo
Asymmetrical tonic neck	 With infant supine, turning of the head results in ipsilateral extension of the arm and leg with flexion of opposite extremities in a "fencing" posture	Birth	3-4 mo
Babinski	 Stroking lateral aspect of sole from heel up results in dorsiflexion of the great toe and fanning of the remaining toes	Birth	12-18 mo

Table 2. Selected Postural Reactions

REACTION	DESCRIPTION	AGE AT APPEARANCE	AGE AT DISAPPEARANCE
Righting Reactions	These allow the body to maintain normal postural relationships of the head, trunk, and extremities during all activities. The different reactions appear at different ages, beginning shortly after birth and ranging up to 12 months of age.		Never
Protective Equilibrium Response	 When gently pushed toward one side while in a sitting position, infants increase trunk flexor tone toward that side to regain their center of gravity and extend the arm on the same side to protect against falling.	4-6 mo	Never
Parachute Refactions	 When held in ventral suspension and suddenly lowered (downward parachute), infants extend their arms as if to protect themselves from a fall; similar reactions are seen with forward and backward stimulation.	8–10 mo	Never

Gross Motor Skills

During the first year of life, the ultimate goal of gross motor development is **walking**. The first step toward this goal is head control. By 6 months of age, children are able to sit without support for a few seconds (Figure 2). At 9 to 10 months of age, children are able to pull themselves to a standing position, and by 12 to 17 months of age, they are able to walk. Children then learn to run, negotiate stairs, hop on one foot, and skip — in that order.

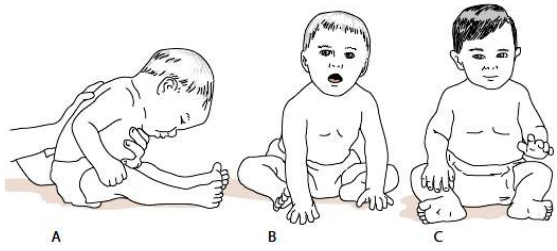


Figure 2. Stages in the development of sitting. A, Head control. B, "Tripod sitting." C, Head steady and back straight without support

Variation

There is wide variability in the 'normal ranges'. This is particularly so with walking – normal children may walk from 11–18 months (Figure 3). If they bottom shuffle (instead of crawling), they generally walk late as bottom shuffling is so efficient.

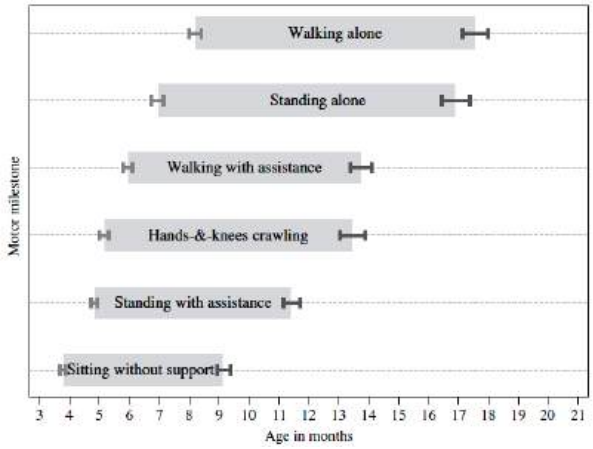


Figure 3. Windows of milestone achievement expressed in months
[WHO Motor Development Study. Acta Pædiatrica, 2006; Suppl 450: 86_ 95]

Fine Motor Skills

Development of **the 2-finger pincer grasp** is the major goal of fine motor development during the first year (Figure 4). The hands primarily remain in a fisted position until 3 months of age. Infants also discover the midline at this age, and shortly thereafter they may play with the hands in the midline. Four-month-olds begin reaching for desired objects; by 6 months of age, they are able to transfer objects from one hand to the other. By 7 months, they have a 3-finger pincer grasp, and by 9 to 10 months, they have developed the 2-finger grasp, which allows them to manipulate small objects such as raisins and pencils.

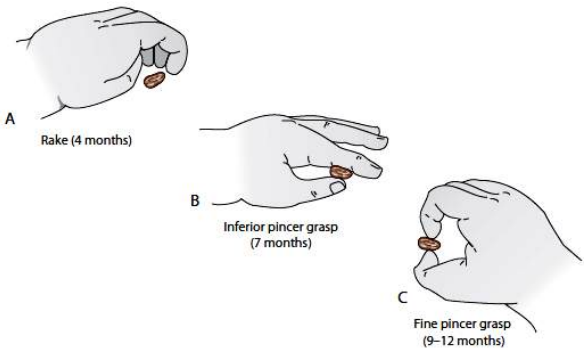


Figure 4. Development of the pincer grasp. A, Rake (4 months). B, Inferior pincer grasp (7 months). C, Fine pincer grasp (9–12 months).

By 14 months, they begin to scribble, and by 3 to 5 years, they are able to copy geometric shapes. Children with early preference for the use of one hand over another, especially prior to about 18 months of age, should be assessed for the presence of paresis or other neuromuscular problems. Handedness may develop by 3 years but often is not firmly established until the age of 4 to 5 years.

Social Skills

These skills enable children to **interact and respond to the surrounding world**. Deficits in the development of age-appropriate social skills/social relatedness (eg, social orienting, social referencing, joint attention, pretend play) are a defining feature of autism spectrum disorders (ASDs). For children within this spectrum, the development of social skills is characteristically “out of sync” with their overall level of functioning. Joint attention is the inclination to share enjoyment, interests, or achievement with other people, and like other developmental skills, it seems to develop in graduated stages (early skills include reciprocal smiling at the sight of a familiar person, followed by later emerging skills like the ability to isolate one’s index finger and point by 12–15 months of age). Lack of joint attention seems to be a core deficit in ASDs; it also seems to be specific to ASDs.

Toilet Training

This is also very variable. Bladder and bowel control is usually attained by 2 years of age in girls and by 3 years in boys. Nocturnal enuresis until 5 years is relatively common. Boys are notoriously slow.
The American Academy of Pediatrics (AAP) has outlined the following as indicating a toddler's readiness for toilet training: Child stays dry for at least 2 hours, has regular bowel movements, follows simple instructions, walks to and from bathroom and helps undress, is uncomfortable with dirty diapers, asks to use the toilet or potty, and asks to wear "big girl" or "big boY' underwear.

CASE RESOLUTION

The parents of the child described in the case history may be reassured that their child is developing normally for her age. Although most children begin walking at about 12 months of age, commencement of walking anywhere up to the age of 17 months is considered to be within normal limits. The American Academy of Pediatrics (AAP) recommends that standardized developmental screening should be performed when developmental surveillance identifies high risk factors and routinely at the 9-, 18-, and 24- or 30-month health maintenance visits. Administration of a formal screening tool is probably not necessary at this visit but can be considered again at the 15-month visit if there is a lack of progression in her gross motor skills or if any other risk factor is identified at that time.

Speech and Language Skills

CASE STUDY

The parents of a 3-year-old girl bring her to see you. They are concerned because their daughter has only an 8- to 10-word vocabulary and she does not put words together into phrases or sentences. They report that she seems to have no hearing problems; she responds to her name and follows directions well. In general, she has been in good health. Her development, aside from delayed speech, is normal. During the physical examination, which is also normal, the girl does not speak.

Questions 1. What language skills should children have at 1, 2, and 3 years? 2. Approximately how many words should 3-year-olds have in their vocabulary? 3. By what age should children's speech be intelligible to strangers at least 75% of the time? 4. What factors may be associated with delayed speech development? 5. What tests are used to assess children's hearing, speech, and language development?

The ability to communicate through language is a uniquely human skill. **Speech** refers to the production of sounds, whereas **language** involves comprehension and expression; it is the use of words, phrases, and gestures to convey intent. **Receptive language** refers to the ability to understand others, while **expressive language** is the ability to produce communication to convey meaning to others. Normal hearing is essential for the development of speech and language.

The left hemisphere of the brain is responsible for language skills in 94% of right-handed adults and approximately 75% of left-handed adults. Peripheral auditory stimuli are transmitted to the primary auditory areas in both temporal lobes. Sounds then undergo a series of analyses, primarily in 3 main areas in the left cerebral cortex: Wernicke area (or auditory association area), which is responsible for the comprehension of language; Broca motor speech (or motor encoding) area, which is responsible for the preliminary conversion of language into motor activity; and the primary and supplementary motor cortexes, which control the movements necessary for speech. This complex process is responsible for the comprehension and production of language.

Speech and language develop in a predictable, orderly sequence. Language skills can be receptive or expressive. Early receptive milestones refer to ability to hear and respond to sound, whereas later milestones reflect ability to understand spoken words. Early expressive milestones relate to speech production; later, children use language to convey their intent to others. In the first year of life, receptive skills are more advanced than expressive skills.

Children's language skills evolve primarily through parent-child interactions. Language begets language; children must first receive language before they are able to express themselves with language. Eye contact, social smiling, and ability to share attention with others, or joint attention (developed by 12–15 months of age), are children's first experiences with shared meaning, crucial for language development. Evidence exists that by the time a child is 4 years of age, the differences in word exposure between children living in higher socioeconomic environments as compared with those living in lower socioeconomic environments may be up to 30 million words. Research also suggests that expressive language vocabulary at age 3 predicts language and reading achievement up to 9 to 10 years of age.

Knowledge of normal receptive and expressive language skills (Table 3) is essential to recognition and identification of developmental delays.

Table 3. Receptive and Expressive Language Milestones (Birth to 3 Years)

Skill	***Mean Age***	***Normal Range***
Receptive Milestones		
Alerts to sound	Newborn	
Orients to sound/turns to voice	4 mo	3–6 mo
Responds to name	4 mo	4–9 mo
Understands “no”	10 mo	9–18 mo
Follows 1-step command with gesture	12 mo	10–16 mo
Follows 1-step command without gesture	15 mo	12–20 mo
Points to several body parts	18 mo	12–24 mo
Follows 2-step command with gesture	24 mo	22–30 mo
Expressive Milestones		
Cooing (vowel sounds)	3 mo	1–4 mo
Laughs	4 mo	3–6 mo
Babbling (consonants added to vowel sounds)	6 mo	5–9 mo
Dada/Mama nonspecifically	8 mo	6–10 mo
Dada/Mama specifically	10 mo	9–14 mo
3- to 5-word vocabulary	12 mo	
Immature jargoning (gibberish with inflection)	13 mo	10–18 mo
Mature jargoning (gibberish with occasional word)	18 mo	16–24 mo
50-word vocabulary	24 mo	
2-word phrases	24 mo	20–30 mo
Uses pronouns indiscriminately	24 mo	22–30 mo
States first name	34 mo	30–40 mo
Uses pronouns appropriately	36 mo	30–42 mo
250-word vocabulary	36 mo	
75% of speech intelligible to strangers	36 mo	

DEVELOPMENTAL DISORDERS. BEHAVIORAL AND PSYCHOSOCIAL ISSUES IN CHILDREN

Concerning signs in early development

- No social smiling by 2 months
- Not sitting alone by 9 months
- Not crawling by 1 year
- Not walking by 18 months
- No speech by 18 months
- Hand preference development < 1 year (this usually develops at 18–24 months)

➢ DEVELOPMENTAL DELAY

Children are said to be developmentally delayed if they fail to reach developmental milestones at the expected age. This age ranges widely because of the wide variation among normal children. Individual children may be delayed in one area or several areas of development.

Transient developmental delay

Some children have a transient delay in their development. For example, some extremely premature babies may show a delay in the area of sitting, crawling and walking but then progress on at a normal rate. Other causes of transient delay may be related to physical illness and prolonged hospitalisation, immaturity, family stress or lack of opportunities to learn.

Persistent developmental delay

Disorders which cause persistent developmental delay are often termed **developmental disabilities**. Examples are cerebral palsy, muscle disorders, language disorders, autism, emotional problems and disorders of vision and hearing. All these conditions can cause developmental delay. However, one of the most common causes is an **intellectual disability** (formerly **mental retardation**).
Intellectual disability (ID) is defined as significantly subaverage intellectual functioning existing concurrently with deficits in adaptive behavior (e.g., communication, self-care, self-direction) and manifested during the developmental period.

Differential diagnosis

Three factors are involved in the differential diagnosis of children with developmental delays:

- *determination of the area or areas of development in which delay is apparent;*
- *if motor delay is evident, determination of whether the condition is progressive or nonprogressive;*
- *assessment to see if developmental milestones previously achieved are lost or if age-appropriate milestones were achieved at all.*

Children with an early history of normal development who subsequently experience a slowing of developmental progression, often associated with cognitive delays or seizures, may have a **metabolic defect**. Children who attain developmental milestones and subsequently lose them may have a neurodegenerative disease (eg, multiple sclerosis, adrenoleukodystrophy) or a lesion of the spinal cord or brain. The presence of habitual rhythmic body movements (eg, body rocking, head banging) may be a sign of a pervasive developmental disorder such as ASDs.

Cerebral palsy, the classic example of nonprogressive motor abnormality, is a form of static encephalopathy characterized by abnormal movement and posture. The type of cerebral palsy depends on which area of the brain is injured. Spastic cerebral palsy, seen most commonly, is secondary to upper motor neuron injury. The ataxic form of the disease is related to lesions of the cerebellum or its pathways. Dyskinetic cerebral palsy manifests as uncontrolled and purposeless movements that often result from a basal ganglia lesion (eg, athetosis following bilirubin deposition in the basal ganglia). Onset of symptoms is in infancy or early childhood. The key factor in making the diagnosis is establishing that the motor deficits are static and not progressing.

Autism spectrum disorders (ASDs) are characterized by profound impairment in social interaction (e.g., lack of eye contact, poor peer relationships); restricted, repetitive, and stereotyped patterns of behavior (e.g., unusual preoccupations, inflexibility, stereotyped motor movements); and altered communication (verbal and nonverbal) ranging from nospeech to jargon, echolalia, and "pedantic speech."

CAUSES OF DEVELOPMENTAL DELAY

Motor

- Normal, e.g. delay in walking in commando crawlers or bottom shufflers
- Neurological disorder, e.g. cerebral palsy
- Neuromuscular disorder, e.g. Duchenne muscular dystrophy
- Any cause of global developmental delay

Communication (speech, language and non-verbal)

- Hearing disorder
- Visual disorder
- Lack of stimulation
- Articulation defect – neuromuscular disorder, physical abnormality, e.g. cleft palate
- General developmental delay
- Autism
- Communication is also affected by general intelligence and motor function

Global

- Genetic low intelligence
- Lack of stimulation
- Chronic illness
- Psychological upset
- Genetic disorder or syndrome, e.g. Down syndrome; metabolic disorder, e.g. phenylketonuria; brain abnormality, e.g. hydrocephalus
- Antenatal disorder – congenital infection; teratogens
- Birth asphyxia
- Prematurity
- Hypothyroidism
- Neurological insult – head trauma; meningitis, encephalitis; metabolic, e.g. hypoglycaemia

➢ COMMON BEHAVIORAL AND PSYCHOSOCIAL PROBLEMS

Infants	**Colic** • A late afternoon, early evening fussy period is very common in many babies between 2 weeks and 3 to 4 months of life. Generally these babies respond to soothing by the parent. • Colic can be defined as > 3 hours of crying per day for more than 3 days in a week. This can be viewed as an exaggerated form of the normal fussy period described above. In colic, the crying episodes are more intense, of longer duration, and less responsive to the parent's attempt to soothe. The age interval tends to be the same (2 weeks to 3 or 4 months). • History and physical exam should rule out feeding problems (under- or overfeeding), medical conditions (e.g., gastroesophageal reflux), or other causes of pain (e.g., hair tourniquet).
Toddlers	**Feeding problems** • Parental concerns about decreased food intake in toddlers is extremely common. • Power struggles over feeding reflect the toddler's emerging mastery (desire to feed self) and autonomy (having control over what foods he or she will accept). **Temper tantrums** • Tantrums are normative behavior in the toddler age range. They include crying, screaming, hitting, kicking, and throwing self to floor. Tantrums are an expression of acute frustration, often in response to a parental "no" or the child's inability to master a specific skill or task. • Some potential "**red flags**" that tantrums are beyond the normative range include: – *Frequent, prolonged tantrums (more than three times a day or longer than 15 minutes)* – *Occurring before 1 year of age or after age 4* – *Excessive emotional response (e.g., anger, guilt) by parent to the tantrums* – *Injury to self or others (parents should remove child to a safe location and not allow child to hit the parent or anyone else)*
Preschool years	**Lying** at this age is generally not a cause for concern, as the preschooler does not yet have a firm grasp on the distinction between fantasy and reality. **Aggression**, which is normative in the 18-month-old toddler, should be greatly diminished in the preschool years. Persistent aggressive behavior in a preschooler is an indication for both behavioral and developmental assessment.
School-age years	Behavioral concerns in the school-aged child can present as academic difficulties (e.g., due to attentional weakness), social concerns, and/or disruptive behaviors. **Depression and anxiety disorders** are important psychiatric concerns confronting the schoolage children. They have different clinical presentations than seen in older adolescents and adults. For example, symptoms of inattention and overactivity can be seen in children with anxiety, depression, or both. Such children are at risk for being mistakenly diagnosed and treated for ADHD. **Attention deficit hyperactivity disorder (ADHD)** (Table 4) is a behavioral syndrome characterized by inadequate attention span, impulsivity, and hyperactivity. The syndrome gives rise to challenges in academic performance, behavior, and social functioning. Boys are affected more frequently than girls.

Table 4. Selected Symptoms Associated with Attention Deficit Hyperactivity Disorder

Symptoms Associated with Inattention	Symptoms Associated with Hyperactivity/Impulsivity
• Often makes careless mistakes	• Often fidgets, squirms, or is out of seat
• Problems sustaining attention in school and at play	• Often "on the go" and frequently running
• Problems Mth organization and forgetfulness	• Excessive talking
• Lack of follow-through on schoolwork and chores	• Often blurts out answers or interrupts others
• Easily distracted	• Problems awaiting a tum

CASE RESOLUTION

The child described in the case history has delayed development of expressive language skills. At the age of 3 years, she should have a 250-word vocabulary and speak in 3-word sentences; in addition, her speech should be primarily intelligible to strangers. Because of the delay, she should be referred immediately for a hearing assessment and speech and language evaluation. Hearing loss is an important diagnosis to rule out. Simply because her parents report no hearing problems does not mean she does not have a deficit. She may have learned to respond to nonverbal cues, or she may hear only some things.

Danger Signals in Language Development

- **Inconsistent or lack of response to auditory stimuli at any age**
- **No babbling by 9 months**
- **No intelligible speech by 18 months**
- **Inability to respond to simple directions or commands (eg, “sit down,” “come here”) by 24 months**
- **Speech predominantly unintelligible at 36 months**
- **Dysfluency (stuttering) of speech noticeable after 5 years**
- **Hypernasality; inappropriate vocal quality, pitch, or intensity at any age**

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Child's Nervous System

Quick Quiz

1. A pregnant woman is found to have an elevated alpha-fetoprotein (AFP) at her 16-week obstetrics visit. An ultrasound done at the visit shows that the fetus is anencephalic. What supplements should this mother have taken in early pregnancy to decrease the chance of this defect from occurring?

2. A baby suffers from meconium aspiration with presumed hypoxic damage to her brain. She is hypotonic for several months but then develops bilateral hypertonicity, especially in her lower extremities. Is this condition progressive?

3. A baby is born with a "port-wine" stain in the distribution of the first branch of cranial nerve V. What syndrome must you consider and what sequelae of the disease should the parents anticipate in the coming years?

4. A 10-month-old boy is seen in a paediatric outpatient clinic because the health visitor has agreed with the mother that he is not yet sitting properly and is not particularly interested in his surroundings. On pulling to sit he has a tendency to be pulled along the examination couch and fall backwards. He will not support his own weight on supported standing. His asymmetrical tonic neck reflex is pronounced to the right and not present to the left. He has a flexed posture of his left upper limb at rest and does not seem to move this arm.
A) What is the most likely neurological diagnosis?
B) What should be done?
He has also had significant problems in establishing feeding and will only take milk from a bottle in small amounts with a number of aspiration-like events. His weight and length are therefore progressing poorly and he is moving downwards across the centiles.
C) What nutritional approach might be recommended, which would also protect his airway?

EMBRYOLOGY AND DEVELOPMENT

I. Neurulation: complete by three weeks

The nervous system develops from a group of ectodermal cells extending the entire length of the embryo along the dorsal midline. The central core of this 'neural plate' folds inwards to form a tube – the basic neuraxis – while the more laterally placed 'neural crest' cells migrate inwards to form the main sensory elements of the central, peripheral and autonomic nervous systems. The remainder of the central nervous system (CNS) and the motor elements of the peripheral nervous system develop from the neural tube.

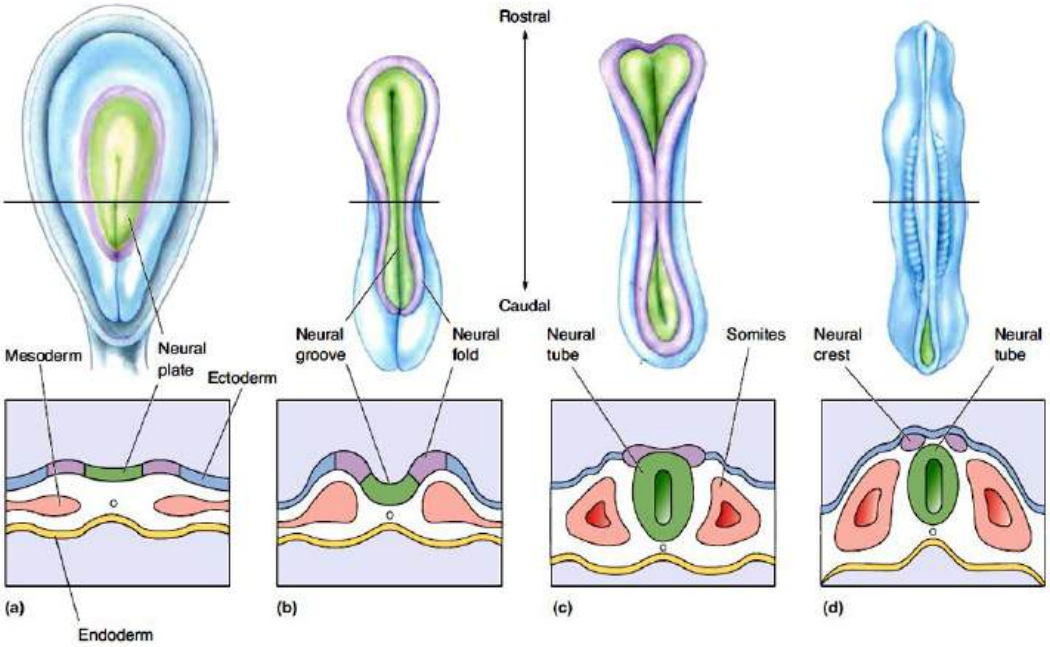


Fig. Formation of the neural tube and neural crest
(a) The primitive embryonic CNS begins as a thin sheet of ectoderm.
(b) The first important step in the development of the nervous system is the formation of the neural groove.
(c) The walls of the groove, called neural folds, come together and fuse, forming the neural tube.
(d) The bits of neural ectoderm that are pinched off when the tube rolls up is called the neural crest, from which the PNS will develop.

Failure of normal neurulation gives rise to spina bifida (spinal dysraphism) and, in extreme cases, anencephaly.
A recent discovery of enormous public health importance is that many neural tube defects can be traced to a deficiency of the vitamin folic acid (or folate) in the maternal diet during the weeks immediately after conception. It has been estimated that dietary supplementation of folic acid during this period could reduce the incidence of neural tube defects by 90%.

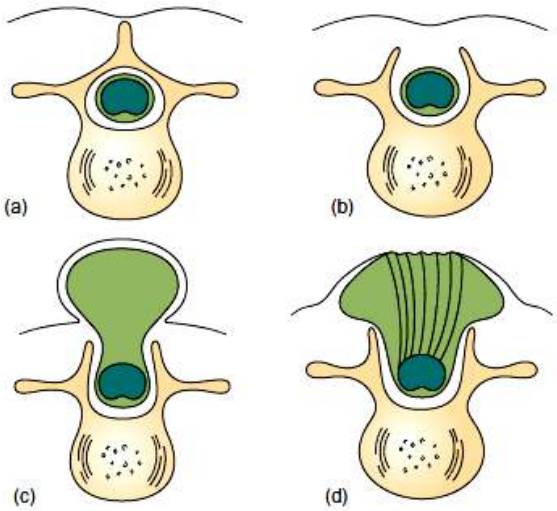
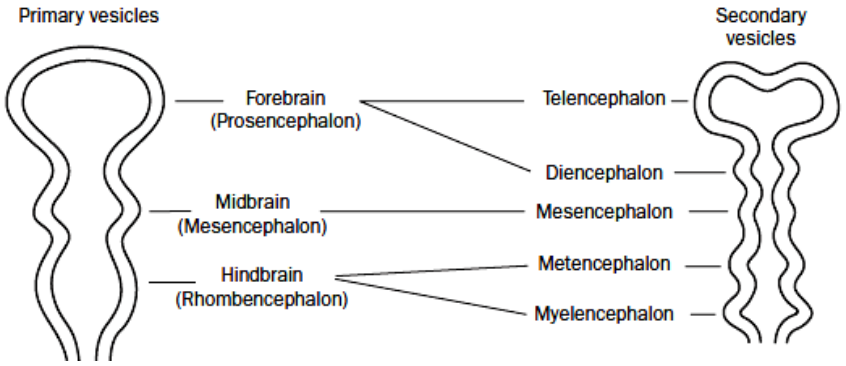


Fig. Spina bifida
(A) normal,
(B) spina bifida occulta (failure of complete mesodermal closure),
(C) meningocele (failure of mesodermal and ectodermal closure) and
(D) myelocele (failure of complete neural tube closure)

II. Encephalization: complete by five weeks

The rostral end of the primitive neuraxis undergoes a process of enlargement and organization to form pairs of vesicles from which the main structures of the mature brain will develop.



Failure of encephalization results in incomplete development of the cerebral hemispheres (holoprosencephaly) and a variable degree of associated motor and cognitive disability. Facial dysmorphism and hypothalamic/ pituitary dysfunction may also be present.

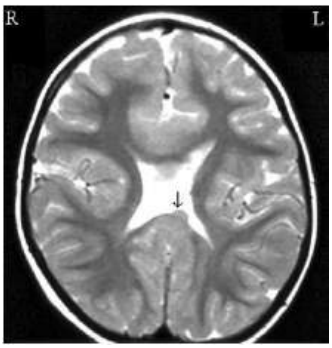


Fig. Magnetic resonance image – holoprosencephaly*. Note the unusually shaped (fused) lateral ventricles, and the continuous band of cortex crossing the midline anteriorly. Note also the small nodule of heterotopic grey matter (arrow) – a neural migration defect*

III. Proliferation and migration: complete by 20 weeks

Neural stem cells surrounding the primitive ventricles divide and differentiate to form neurones and glial cells. The number of cells is greatly in excess of that which will be needed in the mature brain. Simultaneously, neuronal migration begins and continues for some time after proliferation is complete. Oligodendrocytes begin this process, leaving behind 'glial tubes' which guide the following neurones and will eventually form the myelin sheaths of the developing axons. By this process neurones become concentrated in the cortex and central grey matter while their interconnecting axons form the commissures and tracts of the white matter. The characteristic 'wrinkled' appearance of the mature cortex is a consequence of this migration and subsequent growth and branching of cortical neurones. Involution of redundant neurones takes place throughout subsequent brain development – a process that is influenced by environmental and early learning processes.

Disorders of neuronal proliferation and migration are among the most common prenatal causes of learning disability, particularly when associated with severe epilepsy. The underlying cause may be genetic (for example tuberous sclerosis) or environmental (as in fetal alcohol effects) but is frequently unknown. In severe cases it is readily apparent on brain imaging (heterotopias or abnormal gyral patterns). In less severe or more diffuse cases imaging may be normal. Abnormal head size in a child with severe learning disability and epilepsy may be an important clue.

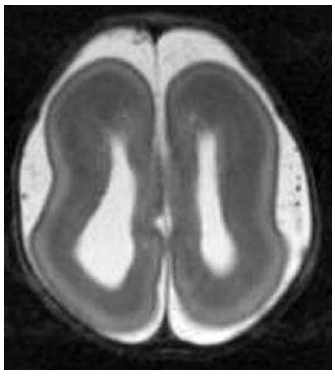
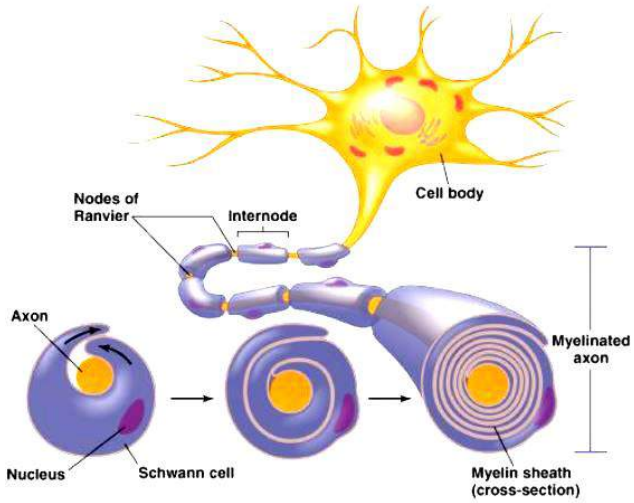


Fig. Magnetic resonance image – lissencephaly*. Note the complete absence of gyri, a consequence of severe disruption to neuronal migration with greatly reduced numbers of cortical neurones.*

IV. Myelination: complete by 7 years

Most myelination takes place in postnatal life but prenatal events can have a profound influence on its rate and extent of completion. Having blazed a trail for its migrating neurone, each oligodendrocyte remains with its axon processes which it will later invest with its myelin sheath. Oligodendrocytes, being metabolically more active, are vulnerable, particularly to ischaemia or hypoxia. Delayed and incomplete myelination are non-specific effects of a variety of prenatal and postnatal insults.



Because of the vulnerability of oligodendrocytes during prenatal development, disorders of myelination may originate many months before myelination should normally commence. A common example of this is periventricular leukomalacia (PVL) – the most frequent cause of diplegic cerebral palsy – which most often results from an insult sustained between five and eight months post conception. The corticospinal tracts do not myelinate until the end of the first year of postnatal life – the time when diplegia is most often first apparent.

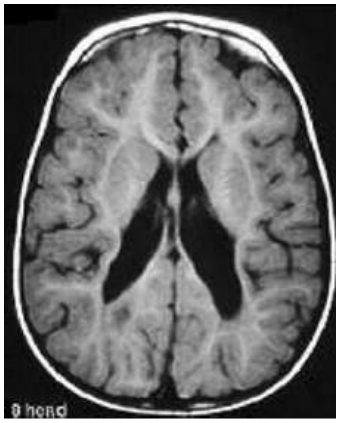


Fig. Magnetic resonance image – periventricular leukomalacia*. Note the selective, ex-vacuo dilatation of the posterior horns of the lateral ventricles and the marked reduction in white matter volume posteriorly*

V. Dendritic branching and neuronal pruning: complete by 7 years

For much of early childhood two further processes shape ongoing brain development. Neurones that are not used involute, while those which are, grow and increase in complexity. Axonal growth occurs to a limited extent but extensive growth and branching of dendrites results in the increasing 'connectivity' which underpins brain function.

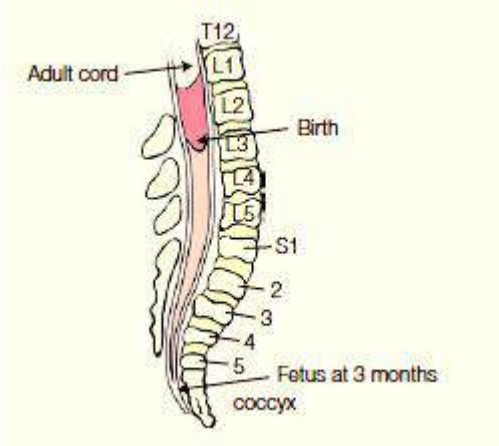
Dendritic branching and neuronal pruning are examples of early 'learning' processes. Common examples of the effect of experience and environment on brain development include visual and motor development. An infant denied normal visual input (for example because of untreated cataracts) will never develop good visual function unless visual input is provided before three months. An infant who sustains a brachial plexus injury will never acquire full function of the affected arm, even if nerve recovery is complete, unless nerve recovery has occurred before six months. In both these illustrations, failure to utilize central neural connections within a critical timescale results in irreversible axonal loss and permanent functional deficit.

POSTNATAL DEVELOPMENT OF THE NERVOUS SYSTEM

- The neurologic system is anatomically complete at birth; however, since it is **not fully myelinated**, it is functionally immature; myelination is rapid in the first 2 years of life and is completed by approximately age 7 years. Nerve impulses do not travel as quickly down unmyelinated nerves; these impulses are slower and less predictable. Myelination occurs cephalocaudally and proximodistally and corresponding advances in gross and fine motor function are seen, as evidenced by more localized stimulus response, increasing sphincter control, and better balance, memory, and comprehension; most actions in newborns are primitive reflexes.

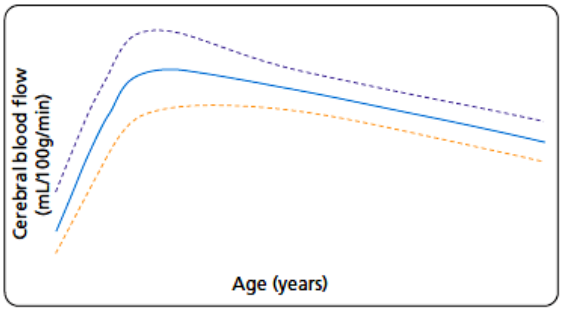
- **The brain** weighs approximately 12–20% of the newborn's body weight in comparison with an adult, where the brain comprises only 2% of the total body weight. Neurogenesis, the formation of new neurones, continues after birth, doubling the size of the brain in the first year of life. To accommodate this initial growth within the rigid skull, the anterior fontanelle closes slowly over a period of 18 months. A 2-year-old child's brain is 75% of its future adult brain weight, increasing to 90% by the age of 6, reaching adult size by the age of 10 (MacGregor, 2008).
  The brain volume is reflected in head circumference measured at the greatest circumference from the top of the eyebrows and pinna of the ears to the occipital prominence of the skull. The head circumference increases by 8–9 cm in the first year of life. It is an important measurement of brain development.

- Vertebral column growth exceeds spinal column growth, resulting in ascension of the conus medullaris from the L3 vertebral segment at birth to the adult level of L1–L2 by age 8 years.
  This necessitates altered approach for lumbar puncture and epidural anesthesia in children younger than 8 years.

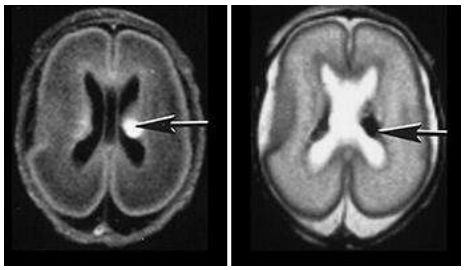


- **Developmental changes in cerebral blood flow**

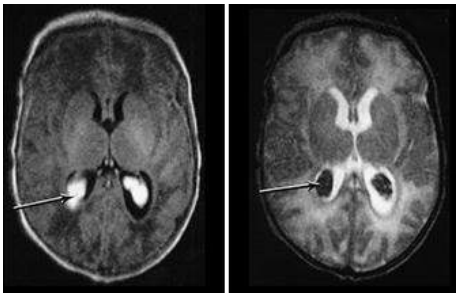
  At birth, blood flow to the brain is low compared with adult levels of cerebral blood flow. During the first years of life, blood flow rates increase sharply to a peak at 4 years of age and then taper off during adolescence to adult values.



When an infant is born prematurely, especially at the limits of viability near the beginning of the third trimester, **residual germinal matrix** is present in the caudothalamic groove adjacent to the lateral ventricles. This ongoing germinal activity is accompanied by a transient network of fragile vascular overgrowth, and is a site of hemorrhage in the premature neonate.



In term infants the germinal layer has largely involuted and intraventricular hemorrhage in the term infant usually originates from the **choroid plexus**.

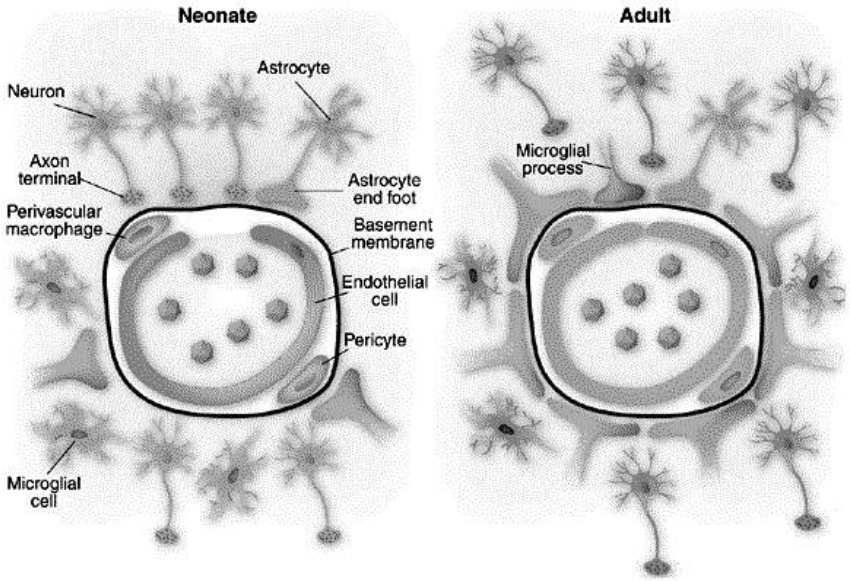


Blood–brain barrier (BBB)

– Astrocytes wrap around synaptic endings of neurones and blood capillaries. They mediate the permeability of endothelial cells in the blood capillaries which form the blood–brain barrier. This prevents potentially harmful substances such as bacteria and toxic agents entering the CNS by limiting the free diffusion of substances. They provide nutrients to neurones, maintain extracellular ion balance and provide structural support in both the grey and white matter of the brain.

– Ependymal cells line the fluid-filled spaces in the brain and spinal cord. They assist with cerebrospinal fluid (CSF) circulation and are part of the blood–brain barrier.

– In the fetus and newborn the blood–brain barrier is indiscriminately permeable, allowing passage of protein and other large and small molecules to pass freely between the cerebral vessels and the brain. Conditions such as hypertension, hypercapnia, hypoxia and acidosis cause cerebral vasodilation and disrupt the blood–brain barrier.

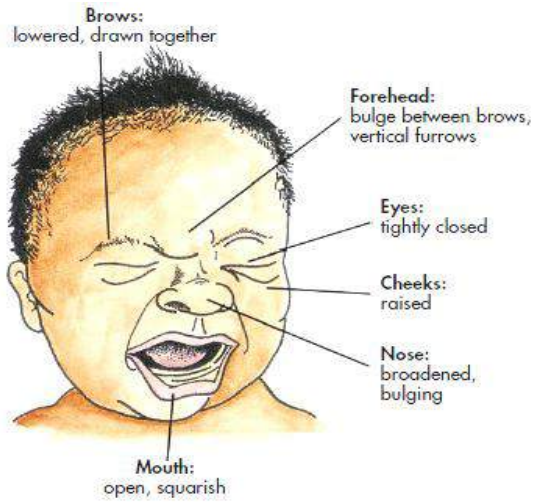


More permeable BBB allows passage of large, lipid-soluble molecules (e.g., bilirubin) and some drugs (e.g., some antibiotics, barbiturates, opioids), causing some drugs to have an increased and variable central nervous system effect or unpredictable duration of action.

Perception of pain

The nociceptor system is functional in fetuses by 20 to 24 weeks of gestation although the cortical experience may be minimal. Repetitive, painful experiences and prolonged exposure to analgesic drugs in infants, in children, and during the neonatal period may permanently alter synaptic and neuronal organization and fetal pain may have an enduring effect on behavior and pain perception.

- Facial expression, crying, body movements, and lack of consolability are the most consistent expressions of pain in infants. The painful facial expression includes lowered brows drawn together; presence of a vertical bulge and furrows in the forehead between the brows; broadened nasal root; tightly closed, scourged eye fissures; and angular, tongue cupping, squarish mouth and chin quiver. Physiologic responses include increases in heart rate, blood pressure, and respiratory rate although these measures lack sensitivity and specificity. There may be flushing or pallor, sweating, and decreased oxygen saturation.



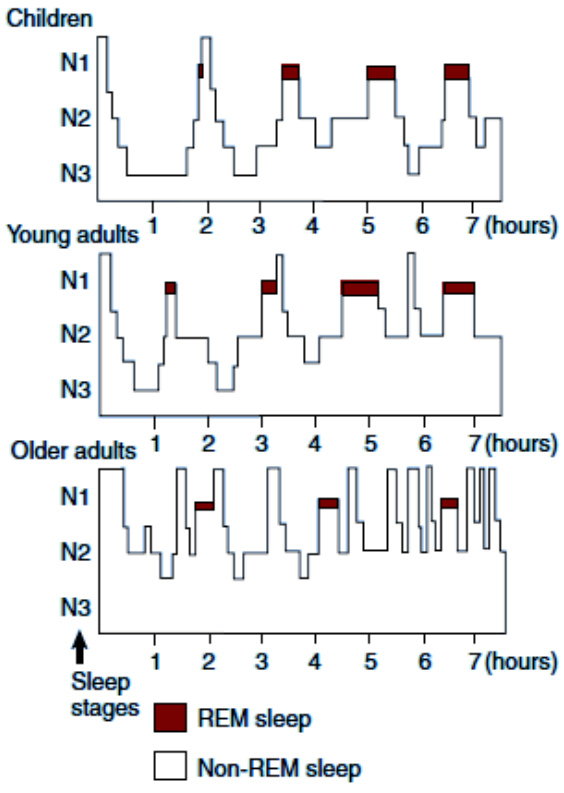
- Toddlers also express pain with crying, facial expression, and body language (tensed body, guarding, and hands holding body).
- Older children, between ages 5 and 18 years, tend to have a lower pain threshold than do adults. Children, like adults, have highly individual responses to pain. Any behavioral and physiologic indicators of pain must be carefully and accurately assessed and adequately treated for children of all ages.

Sleep patterns

Newborns sleep about 16 to 18 hours per day. About 53% of that time is spent in active sleep (REM sleep), 23% in quiet sleep (NREM sleep), and the remainder in an indeterminate phase. The infant sleep cycle is approximately 50 to 60 minutes long, with 20 minutes of NREM sleep and 10 to 45 minutes of REM sleep, in contrast to the adult sleep cycle. Newborns enter REM sleep immediately on falling asleep. At about 1 year of age, an infant spends approximately 45% of total sleep time in quiet sleep and 41% in REM sleep. Total sleep time decreases slightly from birth to 1 year. In the young child, the sleep cycle length is 45 to 60 minutes, in contrast to 90 to 100 minutes in the adult.

The child assumes the adult sleep pattern at some point during the first 2 to 5 years of life.

Sleep for infants and children is important for growth and neurocognitive development. Sleep disorders are common in children and include insomnia and obstructive sleep apnea syndrome (OSAS). OSAS is related to adenotonsillar inflammation (i.e., enlargement of the adenoids and tonsils) or to obesity.



GENERAL PRINCIPLES OF PEDIATRIC NEUROLOGIC DIAGNOSIS

The common neurologic conditions seen in the ambulatory setting include (a) headaches; (b) abnormal development (motor, cognitive, language); (c) seizures; and (d) movement disorders (tics).

History

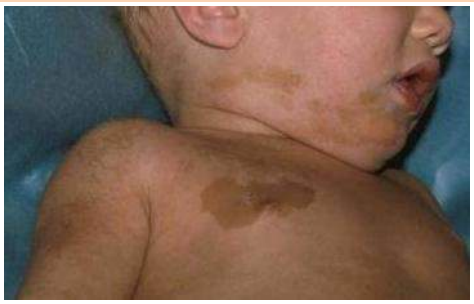
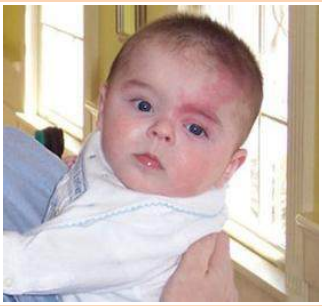
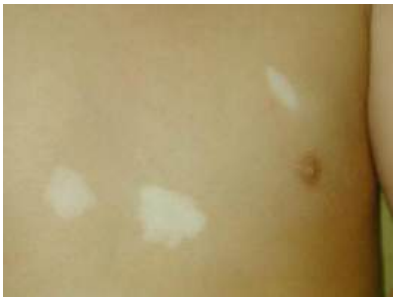
1. A well-performed history should emphasize whether the neurologic problem being analyzed is:
    a. Focal or diffuse
    b. Acute or insidious
    c. Static or progressive
2. An attempt should be made to obtain eyewitness accounts of "spells" or suspect behaviors. Special attention should be given to the developmental history and school function.

Physical examination

- Special aspects of the pediatric neurologic examination include evaluation of the developmental reflexes and postural reactions, measurement of head circumference, assessment of developmental milestones (see "DEVELOPMENTAL AND BEHAVIORAL PEDIATRICS"), and search for birthmarks (neurocutaneous markers), which can signal a neurologic defect.
- Assessment of meningeal irritation should be done in cases of CNS irritation, infection, or with intracranial hemorrhage. If the provider suspects any of these conditions, he or she should begin by assessing for general signs of meningeal irritation, such as irritability, lethargy, severe headache, or photophobia. With bacterial meningitis, fever, nausea, and vomiting may also accompany these signs.

Neurocutaneous markers

Neurocutaneous markers are specific lesions or appearances of the skin that are associated with neurological disease.

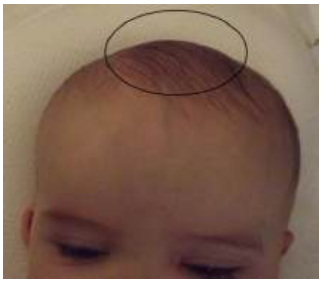
Café-au-lait spot	Port-wine stain	Ash leaf macule
Large, flat freckles	Purple-red birthmark across the face	Ash-leaf shaped flat area of depigmentation, often over the sacrum
		
Numerous conditions, including neurofibromatosis	Sturge–Weber syndrome	Tuberous sclerosis

Syndrome of increased intracranial pressure (ICP) in children

Presentation of the infant with increased ICP

- Bulging scalp veins and fontanels, but *it is normal for the fontanel to bulge with crying*
- Cranial sutures separation (diastasis)
- High pitched cry

The large cranium of a child with hydrocephalus



Bulging anterior fontanelle and scalp veins

Sunsetting eyes

The infant with **hydrocephalus** typically has suture separation (diastasis) and a bulging fontanel. The child typically has signs and symptoms of increased intracranial pressure and a cranial vault that is large in proportion to the face. Common causes of *congenital hydrocephalus* include aqueductal stenosis (CSF obstruction at the cerebral aqueduct), Dandy–Walker malformation (obstruction of the outlet of the 4th ventricle with cerebellar hypoplasia), and Chiari II (small posterior fossa with cerebellar tonsils and medulla well below the foreman magnum and associated with myelomeningocele). Chiari III is associated with occipital encephalocele. *Acquired hydrocephalus* can result from any disease process that obstructs the CSF pathways including tumor, meningitis, and subarachnoid hemorrhage.

Assessment of meningeal irritation in children

- Neonates and infants 2 months of age and younger are not able to localize infection, so meningeal irritation may not be recognized until late stages, for example, when a bulging anterior fontanelle is visible.

Opisthotonos, or severe arching of the back, is a sign of meningeal irritation but can also occur with tetanus, subarachnoid hemorrhage, brain tumor, and severe head injury. Opisthotonos is more common in infants and children than in adults because of their immature neurologic systems.

Signs of meningeal irritation also include Kernig sign and Brudzinski sign.

(A) **Kernig sign** is tested by flexing legs at the hip and knee *(A1),* then extending the knee *(A2).* A positive report of pain along the vertebral column is a positive sign and indicates irritation of meninges. *(B)* **Brudzinski sign** is tested by the child lying supine with the neck flexed *(B1).* A positive sign occurs if resistance or pain is met (**nuchal rigidity**). The child may also passively flex hip and knees in reaction, indicating meningeal irritation *(B2).*

SPECIAL DIAGNOSTIC PROCEDURES

Useful procedures, depending on the clinical problem, can include:

1. Lumbar puncture and cerebrospinal fluid (CSF) examination (e.g., for infectious, metabolic, and degenerative diseases)

2. Electroencephalography (EEG) (for epilepsy)

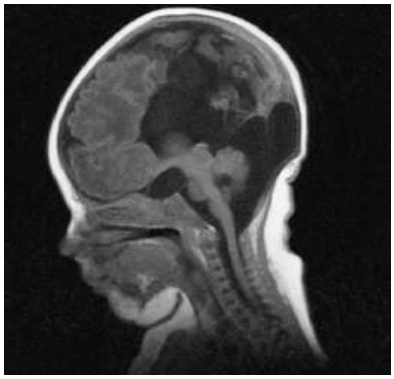
3. Electromyography (EMG) and nerve conduction studies (for motor unit diseases)

4. Measurement of cortical evoked potentials (for assessment of central nervous system [CNS] function)

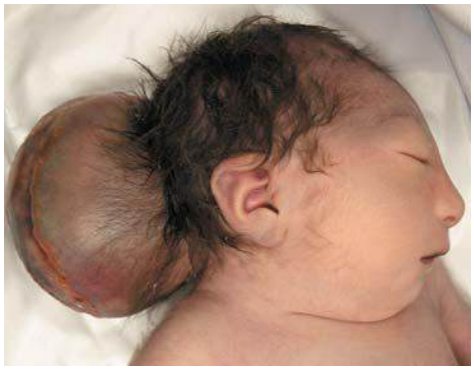
5. Neuroimaging studies

a. Skull radiography (e.g., for depressed skull fracture)
b. Computed tomography (CT) scan (useful in emergencies and detection of calcification and blood or bony abnormalities)
c. Magnetic resonance imaging (MRI) scan (for evaluating anatomic abnormalities, especially in the midline structures; optimal for assessing gliosis or other abnormalities of gray and white matter; new techniques [magnetic resonance angiography] also permit assessment of the cerebral vasculature)
d. Arteriography (for vascular disease)
e. Positron emission tomography (PET) scan (research tool for assessment of brain metabolism)

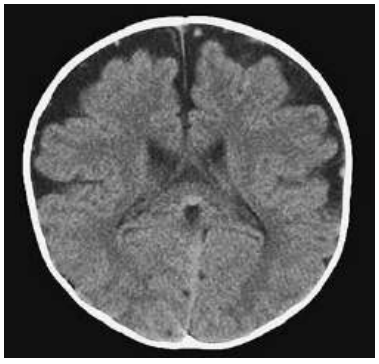
6. Biopsies of muscle, peripheral nerve, skin, liver, bone marrow, rectal mucosa, and, rarely, brain (for evaluation of a degenerative disease)



Sagittal T1-weighted MRI showing the characteristic features of Dandy–Walker malformation. The arrow denotes the large, retrocerebellar CSF collection (cyst). This child also has agenesis of the corpus callosum



An infant with a large occipital encephalocele



Noncontrast CT showing benign extra-axial fluid collections of infancy — *a common condition associated with macrocrania, can sometimes be confused with chronic subdural hematomas or hygromas*

ANSWERS TO QUIZZES

1. This baby has a neural tube defect (NTD) that results in elevated AFP levels in the amniotic fluid andmaternal serum. NTD appears to be associated with a combination of genetic and environmental factors. Folic acid fortification for women 3 months before as well as during pregnancy is necessary to reduce NTD.

2. Cerebral palsy (CP) is a nonprogressive, static disorder affecting motor activity and posture. Physical and occupational therapy will be extremely important for maximizing independent skill.

3. Sturge-Weber must be considered. The parents should be aware of the possible development of ophthalmologic disease, such as glaucoma, as well as neurological sequelae such as seizures, hemiparesis, and mental retardation.

4. A) The most likely diagnosis is right hemiparesis with possible diplegia accounting for the increased lower limb tone. B) Referral to multidisciplinary developmental team. C) The use of PEG (percutaneous endoscopic gastrostomy).

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Basics of Adolescent Health

Dr Sergey Sargsyan

Who is an adolescent?

According to WHO definitions

- Adolescents are persons from 10 to 19 years

- Early adolescence: 10 -13
- Middle: 14-16
- Late: 16 and upper

Why it's important

- 20% of all world population are adolescents
- Timeframe of establishing behaviors which affect all life
- 70% of all adults' mortality and morbidity are related to the behaviors or health problems of adolescence period

Definitions

WHO, 1974

Adolescent period is timeframe, when:

- Pubertal maturation is going on since developing secondary signs until full maturity
- Child behavioral and psychology changes to the type of psychology and behavioral, typical for adult
- From period of complete social and economical dependence a person become relatively independent

What changes happen in adolescent

- Pubertal
- Physical / somatic
- Cognitive and moral
- Identity formation
- Family
- Sexual
- Peers
- Relationship to society

Physical growth

- Just before puberty period, physical growth retards, with puberty – accelerates
- In girls the peak is at age of 11.5 years with average annual growth 8.3 cm; stops ate age of 16 years
- In boys, the peak is at age of 13.5 years with average growth 9.5 cm; stops at age of 18 years
- Assessment according to the national or NCHS percentile curves (from 3^{rd} to 97^{th})

Physiological changes in adolescents

- Significantly increased activity of autonomic neural system, but with higher risk for dysfunctions
- Rapid endocrine changes
- Connective tissue: more sensitive; results in susceptibility to arthritis
- There is some discrepancy in growth of bones and muscles ; bones growth earlier under STG effects until age of 15 years in girls and 18 years in boys
- CVS : changes in pulse, blood pressure. In result of neural, endocrine changes is very unstable
- Respiratory system: in boys lung volume intensively increases
- GIT: functional instability
- Immune system: due to androgen effects, the humoral system activates and cell immunity depresses. It results in higher susceptibility to autoimmune diseases

Pubertal development

- Include appearance of the secondary sexual characteristics, increase to adult size, and development of reproductive capacity.
- Adrenal production of androgen may occur as early as 6 yr of age
- Levels of luteinizing hormone and follicle-stimulating hormone rise progressively throughout middle childhood
- Rapid pubertal changes begin with increased sensitivity of the pituitary to gonadotropin-releasing hormone (GnRH); pulsatile release of GnRH, LH, and FSH during sleep; and corresponding increases in gonadal androgens and estrogens
- The triggers for these changes are incompletely understood

Pubertal development

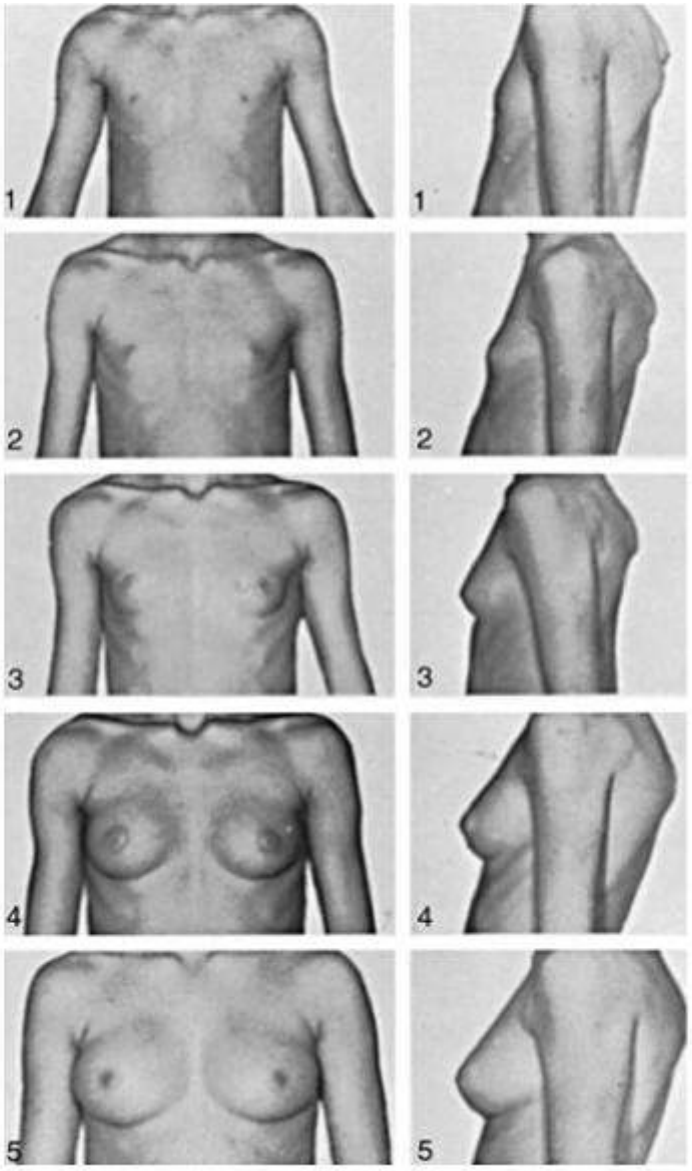
- Normally starts between ages of 8-12 years in girls and 9- 14 in boys
- *Telarche:* increasing sizes of breasts is the first sign in girls
- *Adrenarche:* androgen-dependant signs at pubic areas in girls and boys
- Testicular enlargement is the first sign in boys, which in average is late for 6 mo
- *Menarche* takes place at ages 11-13 in average (with variations from 10 to 15), usually after 1-3 years of initial signs of maturation; it becomes regular in 2-2.5 years, but girl acquires normal reproductive capacities in 1.5 - 5 years after menarche
- Nowadays sexual maturation is going on faster than before (for 6-12 mo) and depends on environment and racial factors20

Classification of Sex Maturity States in Girls (the Tanner Scale)

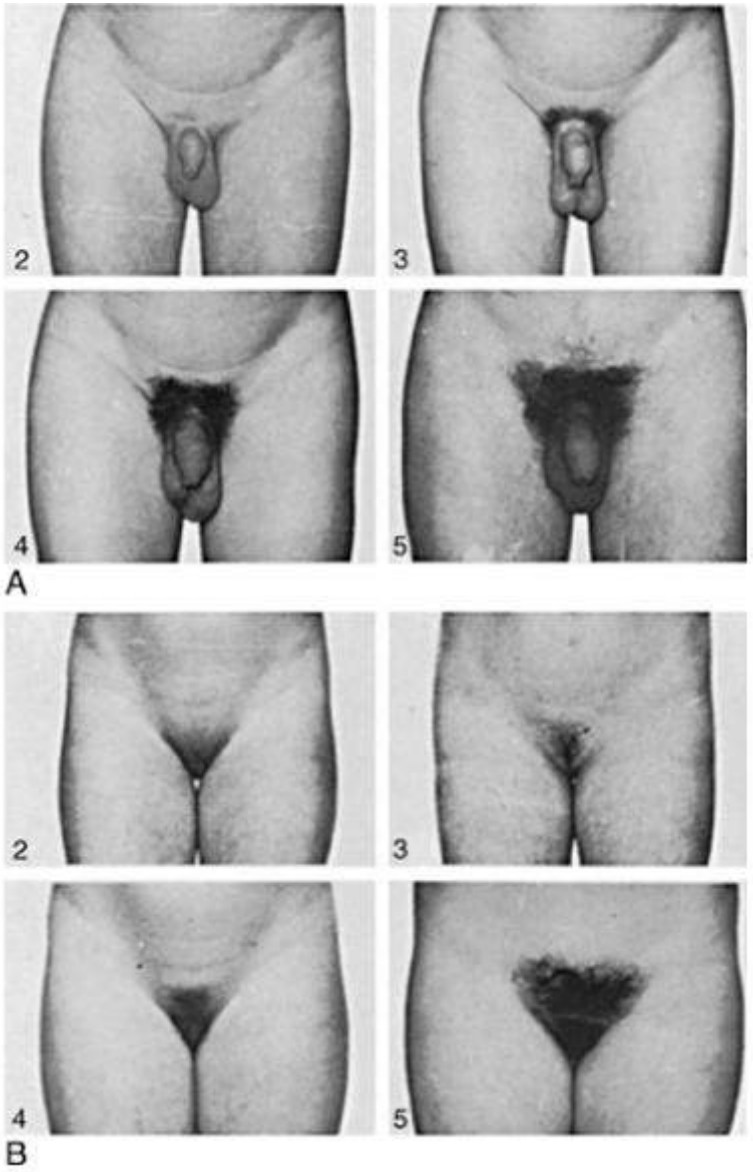
SMR STAGE	PUBIC HAIR	BREASTS
1	Preadolescent	Preadolescent
2	Sparse, lightly pigmented, straight, medial border of labia	Breast and papilla elevated as small mound; diameter of areola increased
3	Darker, beginning to curl, increased amount	Breast and areola enlarged, no contour separation
4	Coarse, curly, abundant, but less than in adult	Areola and papilla form secondary mound
5	Adult feminine triangle, spread to medial surface of thighs	Mature, nipple projects, areola part of general breast contour

Classification of Sex Maturity States in Boys (the Tanner Scale)

	Pubic hairs	Penis	Testes
1	None	Preadolescent	Preadolescent
2	Scanty, long, slightly pigmented	Minimal change/enlargement	Enlarged scrotum, pink, texture altered
3	Darker, starting to curl, small amount	Lengthens	Larger
4	Resembles adult type, but less quantity; coarse, curly	Larger; glans and breadth increase in size	Larger, scrotum dark
5	Adult distribution, spread to medial surface of thighs	Adult size	Adult size

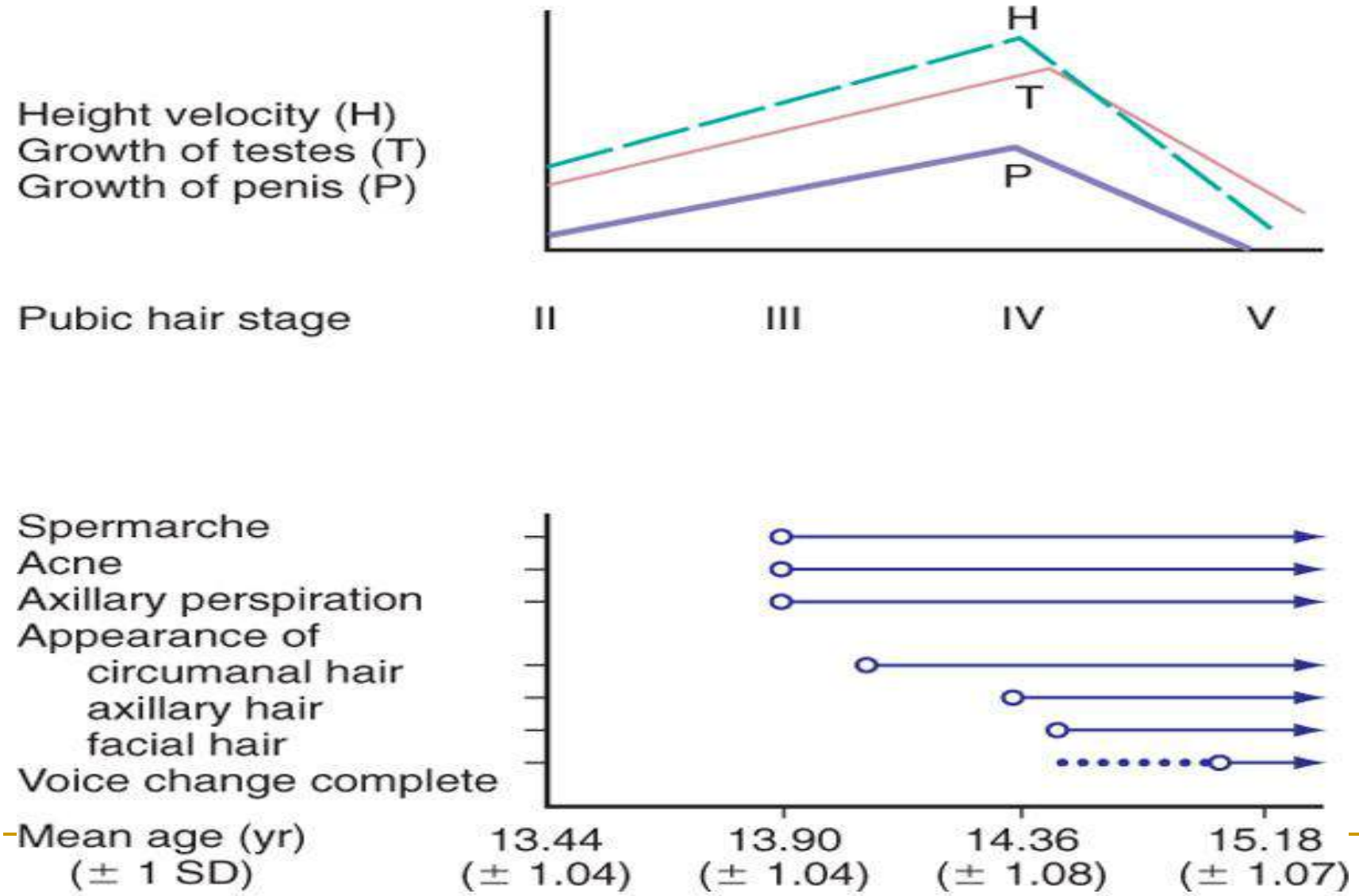


Sex maturity ratings (1 to 5) of breast changes in adolescent girls.

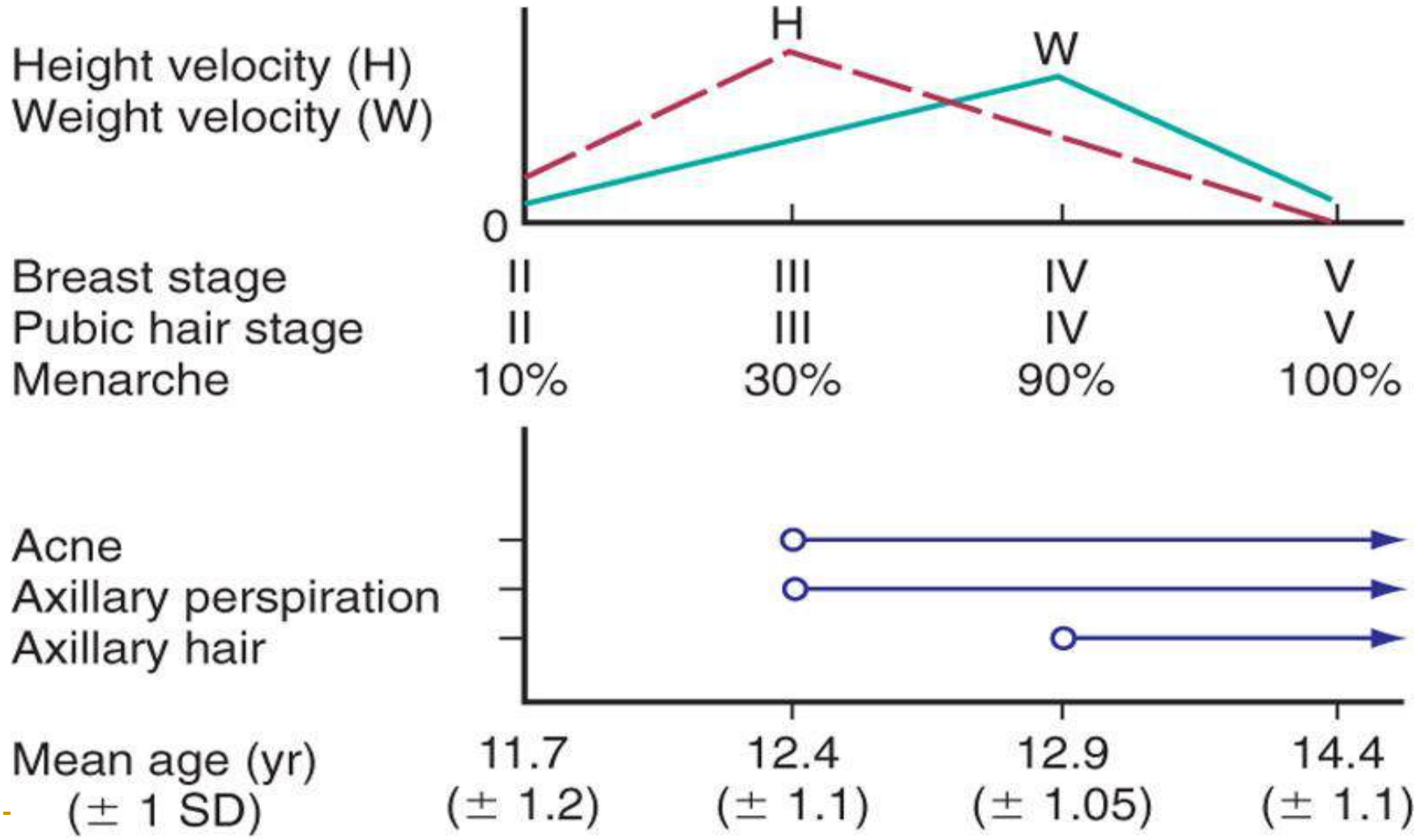


Sex maturity ratings (2 to 5) of pubic hair changes in adolescent boys and girls

Sequence of maturational events in boys.



Sequence of maturational events in girls



Psychological / cognitive changes

Early adolescence	Middle adolescence	Late adolescence
Concrete operations Unable to perceive long-term outcome of current decision-making Conventional morality	Emergence of abstract thought *(formal operations)* May perceive future implications, but may not apply in decision-making Questioning mores	Future-oriented with sense of perspective Idealism; absolutism Able to think things through independently

Self-concept/identity formation

Early adolescence	Middle adolescence	Late adolescence
Preoccupied with changing body Self-consciousness about appearance and attractiveness Fantasy and present-oriented	Concern with attractiveness Increasing introspection "Stereotypical adolescent"	More stable body image Attractiveness may still be of concern Emancipation complete Firmer identity

Family

Early adolescence	Middle adolescence	Late adolescence
Increased need for privacy Increased bid for independence	Conflicts over control and independence Struggle for acceptance of greater autonomy	Emotional and physical separation from family Increased autonomy

Peers

Early adolescence	Middle adolescence	Late adolescence
Seeks same-sex peer affiliation to counter instability	Intense peer group involvement Preoccupation with peer culture Peers provide behavioral example	Peer group and values recede in importance Intimacy/possible commitment takes precedence

Sexual

Early adolescence	Middle adolescence	Late adolescence
Increased interest in sexual anatomy Anxieties and questions about genital changes, size Limited dating and intimacy	Testing ability to attract partner Initiation of relationships and sexual activity Questions of sexual orientation	Consolidation of sexual identity Focus on intimacy and formation of stable relationships Planning for future and commitment

Social / relation to society

Early adolescence	Middle adolescence	Late adolescence
Middle school adjustment	Gauging skills and opportunities	Career decisions (e.g., college, work)

Health and health-related problems in adolescents

- Physical health problems
- Nutritional problems
- Substance use
- Psychological / psychiatric disorders
- Violence
- STDs / HIV

Main causes of mortality

- Unintentional injuries / road traffics
- Suicide
- Somatic diseases
- Homicides

Physical health problems

- Growth problems
- Excessive / low weight and / or height
- Specific / complicated course of many chronic diseases
- Related problem: lack of physical activity, time spend for watching TV and using computers

Nutritional and associated with nutrition problems

- Unhealthy eating behavior very common among masses of adolescents, including wrong regimen, avoiding of healthy food and use / overuse of fast-food, soft-drinks etc
- Prevalence of obesity is increasing year by year worldwide, up to 20% of adolescents in some developed countries. Obesity leads to developing metabolic syndrome (obesity, hyperlipidemia, hypertension, II type diabetus)

Nutritional and associated with nutrition problems

- Anorexia, is common especially in girls with frequency 1:100; male: female ratio is 1:10
- Leads to developing amenorrhea and fertile problems in the future

Psychological problems

- Lonely feeling
- Depression
- Suicide: one of main reasons of mortality in adolescents
- Causes problems with peers, family, school
- Related problem: violence, especially in schools

Violence / injuries

- Violence among adolescents is common worldwide
- Affect both physical health (traumas) and mental health (depression, suicides)
- Unintentional injuries are other leading cause of mortality and morbidity in this period

Risk taking behaviour

- Use of alcohol, tobacco, and illicit drugs and carrying a weapon
- Pregnancy rates among adolescents aged 13-19 have decreased since 1990
- Strong relationship between the age at onset of drinking and the risk of alcohol-related problems in both adolescence and adulthood.

Chronic diseases in adolescents

- Chronic diseases' / conditions prevalence in adolescents and school-aged children is on rise
- National Institute of Health (USA) estimates prevalence among school-aged children as high as from 20 to 30 %

Consequences of chronic diseases in adolescents

- Delay in physical and pubertal growth
- Psychological problems: depression, neurotics, infantilism, egocentrism
- Risky behaviors
- Family problem
- Educational problems
- Peer problems
- Compliance problems %

What are outcomes for clinicians?

- Any clinician, treating adolescents should be well familiar with specificity of this age and know principles of working with them
- Basic principles include; the concept of Adolescent Friendly Health Services and HEADSS approach

Adolescent Friendly Health Services;

Basic principles

- Confidentiality
- Privacy
- Accessibility, affordability
- Right to be informed
- Effective services
- Equal access for both sexes

HEEADSS approach

Harvey Berman, 1972, Eric Cohen, 1985

Psychosocial questionnaire, including:

- Home environment
- Education
- Employment
- Eating
- Activities (peer-related)
- Affect (mood)
- Drugs
- Sexuality
- Suicide
- Safety from violence and Injury

SKIN CHARACTERISTICS IN CHILDREN

COMPETENCIES

You must…

Know	Be able to	Appreciate
• Peculiarities of the skin and subcutaneous fat in children	• Differentiate and describe lesions of the skin	• The social consequences of having a chronic skin condition
• How to recognize acute and chronic skin rashes in childhood	• Identify the common childhood exanthems clinically	• The danger of excessive use of topical steroid creams
• How to recognize other systemic conditions presenting with rash	• Recognize common birth marks • Advise a parent about caring for a baby's nappy rash	• The significance of finding purpuric and petechial rashes

KEY POINTS

1. The skin is anatomically mature at birth but continues functional maturity during the first year of life.

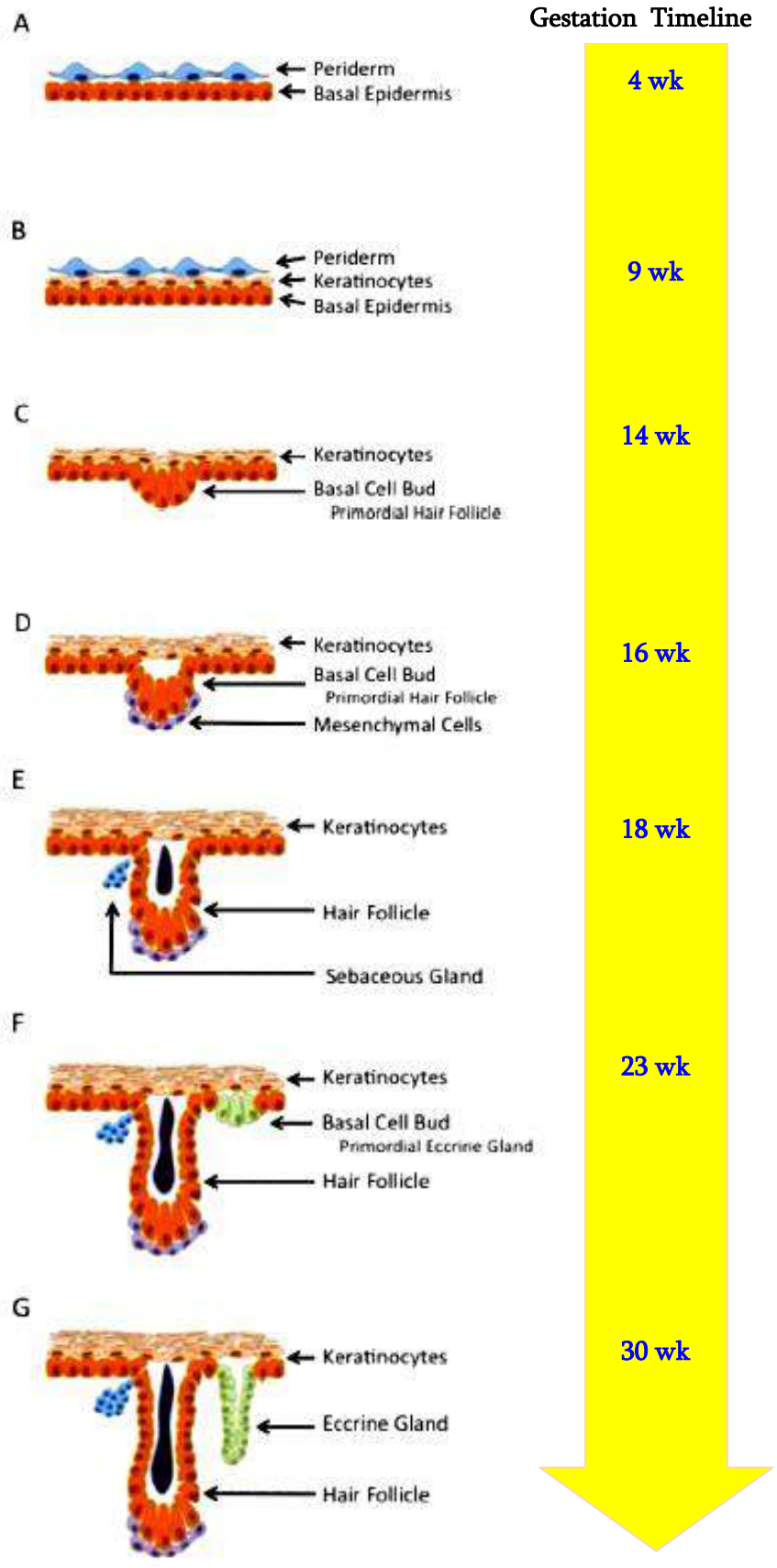
2. In contrast to adults, infant skin is in a constant state of flux with changes in transepidermal water loss, hydration, lipid content and skin acidity.

3. Mature barrier function is critical for maintenance of thermoregulation, hydration and protection against infection.

4. Impaired barrier function and skin desiccation increases risk of pathology including atopic or contact dermatitis, infection and, even, lethal excess water loss.

FETAL DEVELOPMENT OF THE SKIN

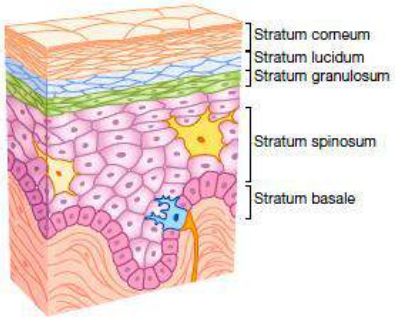
[From *Facial Plast Surg Clin North Am. 2013 February ; 21(1): 1–6]*



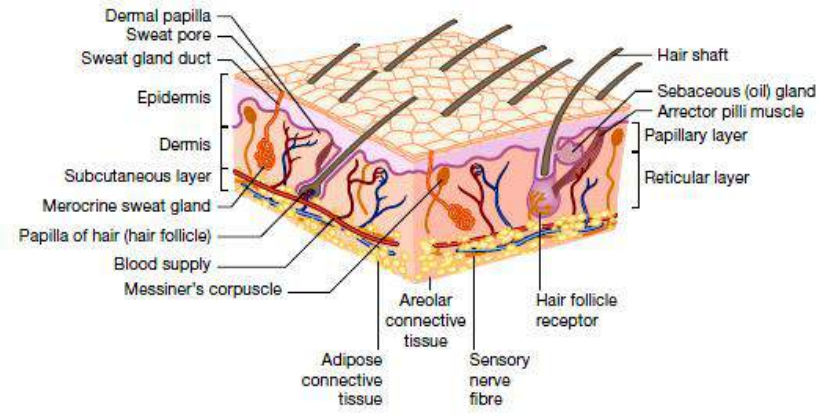
- *The skin is composed of two layers: the periderm and basal epidermis.*
- *Keratinization*
- *Stratification of the epidermal layer*
- *Budding of the basal layer and formation of primordial hair follicle*
- *Mesenchymal cells may be seen associated with the epidermal bud.*
- *Sebaceous glands become apparent, along with hair follicle elongation.*
- *The hair follicle continues to elongate while the basal layer bud to form primordial eccrine glands.*
- *The eccrine glands continue to elongate and coil.*

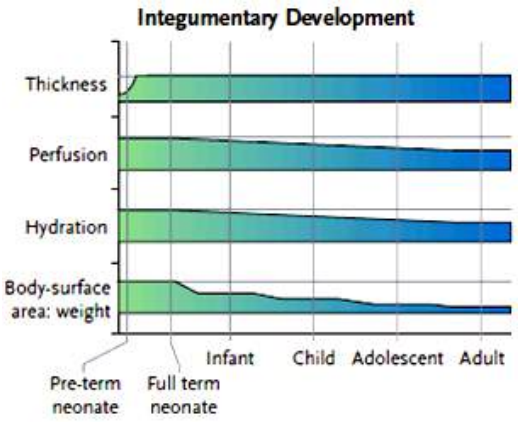
THE STRUCTURE OF THE SKIN

Frequently referred to as the largest organ in the body, the skin covers all of the body's external surfaces and is approximately 10% of the body mass. By adulthood the skin will be almost 2 m^2. The ratio of skin surface to body weight is highest at birth, and this will decline progressively during infancy. At birth the surface area is nearly three times greater than that of an older child, whereas at 37 weeks' gestation or less it is proportionally five times greater than that of a term baby (Wong, 1999).

Skin Layers	Pediatric Peculiarities	Clinical Impact
EPIDERMIS There are five distinct layers in the epidermis, all present at birth:  	The infant's epidermis is thinner and less waterproof (increased hydration); has alkaline or neutral pH at birth (protective "acid mantle" develops within 4 weeks of birth)	▪ Increased risk of skin maceration and damage ▪ Increased permeability to infective agents and topically applied drug
	Epidermis is loosely bound to the dermis	▪ Friction may easily cause separation of the layers, resulting in blistering or skin breakdown
	Epidermis is less pigmented than that of the adult (in all races)	▪ Increased risk of skin damage from ultraviolet radiation
DERMIS	Rich vascularization (increased perfusion)	▪ Increased resorption of topically applied drugs
	Prevalence of type III collagen (vs adult skin, which will only have 15% type III collagen and 85% type I collagen)	▪ Less tensill strength (less protection from direct injury)
	Collagen and elastin are produced more rapidly in children; as a result of this, granulation tissue forms more quickly.	▪ Rapid wound healing and scars formation
PANNICULUS (SUBCUTANEOUS FAT)	Decreased amount of subcutaneous fat, thus blood vessels lie closer to the surface	▪ The infant loses heat more readily through the skin's surface than the older child or adult does

*A specialized adipose tissue referred to as **brown fat** is found in the nape of the neck, posterior to the sternum and perineal area. This forms during the 17th–20th weeks of gestation. These cells have a high number of mitochondria. As the fatty acids break down, energy is released in the form of heat. This is essential for thermoregulation in the newborn.*

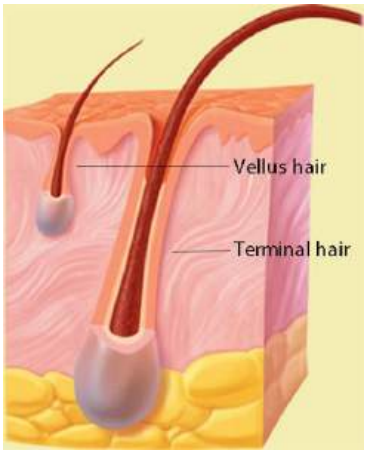




THE SKIN APPENDAGES

Hair

Very fine hairs appear at 20 weeks' gestation, first on the eyebrow, chin and upper lip, and then followed by appearance on the forehead and scalp. This fine downy unpigmented hair is referred to as **lanugo**, and by 26 weeks' gestation this is replaced by the **vellus hair (secondary hair)** which covers the entire body. The lanugo is shed both before and after birth, with the scalp, eyebrows and eyelashes shed last (England, 1996). At birth the newborn's hair lies flat and has a silky feel. Individual strands are identifiable.

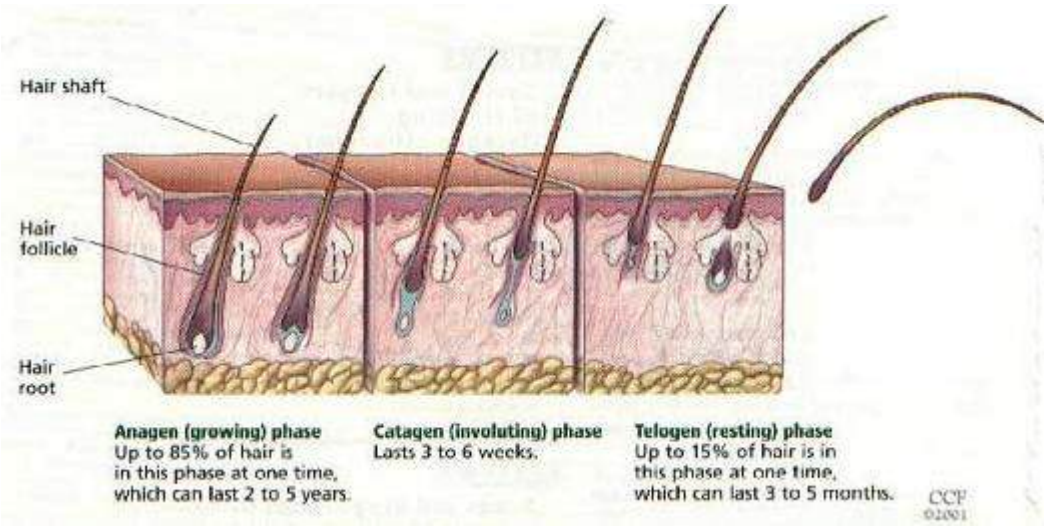


Lanugo

Terminal hair is the hair on the head, eyebrows and eyelashes; it remains present throughout the lifespan and is more deeply pigmented than vellus hair.

The vellus hair that is present in the axillae, pubic area and limbs remains there until puberty, but then the circulating sex hormones stimulate the hair follicles to produce terminal hair, which is often curly.

Human hair growth is cyclic, with alternate periods of growth (anagen), transition (catagen), and rest (telogen). The length of the anagen phase varies from months to years. At birth, all hairs are in the anagen phase. Subsequent generative activity lacks synchrony, so an overall random pattern of growth and shedding prevails. At any time, approximately 85% of hairs are in the anagen phase. Scalp hair usually grows about 1 cm per month.



The nails

The nail reaches the fingertip by 32 weeks' gestation and the top of the toe by 36 weeks' gestation, so nails not reaching the finger or toe tips indicate prematurity. Nail growth is more rapid in the infant and decreases with age. A newborn baby may be born with scratches on their face from their own nails.

An infant born after 42 weeks will have keratinized nails, which may also be long and stained green due to the passage of meconium in utero.

The glands in the dermis

Sebaceous glands function immaturely at birth. The sebum secreted serves to lubricate the skin and hair. Sebum production increases in the preadolescent and adolescent years, which is why acne develops at that time.

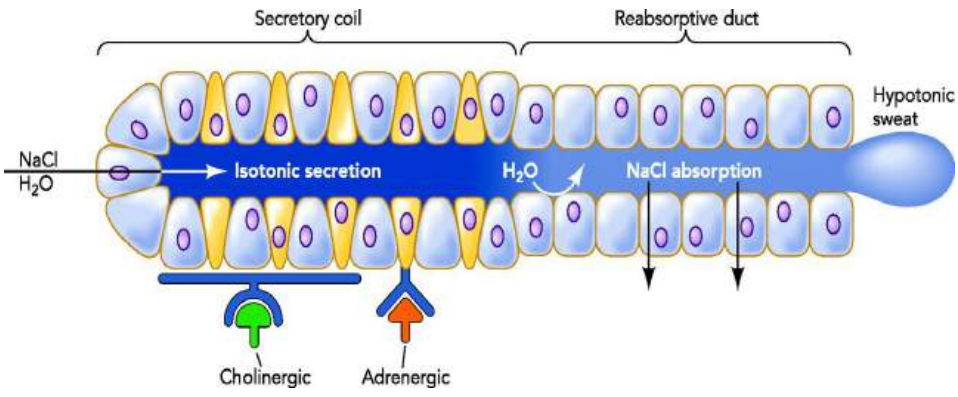
The infant's **eccrine sweat glands** are somewhat functional and will produce sweat as a response to emotional stimuli and heat. They become fully functional in the middle childhood years. Until that time, temperature regulation is less effective compared to older children and adults.

The apocrine sweat glands are small and nonfunctional in the infant. They mature during puberty, at which time body odor develops in response to the fluid secreted by these glands.

	Sweat Glands			*Sebaceous*
	Eccrine	*Apocrine*	*Apoeccrine*	
Distribution	Throughout the skin with the exception of nail beds, labia, glans penis and ear canal	Axilla, groin, areolae, ear canal, breast and eye lid	Axilla	Throughout the skin with the exception of palms of the hands and the soles of the feet
Location	Lies in the lower third of the dermis and may extend down to the subcutaneous fat layer; resurfaces at the surface of the epidermis	Mostly in the subcutaneous layer and the duct ends at the hair follicle	Not found in the axillae until puberty and develop from eccrine and apocrine glands	Associated with hair follicles generally, but located in areolae, nipples, labia and inner prepuce as free structures.
Secretion	Sweat – water, sodium chloride, urea, uric acid, ammonia, glucose, enzymes and lactic acid	Sweat, but also a lipid substance	Sweat	A lipid-rich secretion called sebum
Function	Thermoregulation	Scent gland	Sweat	Moisturize hair follicle and skin
Onset of function	Shortly after birth	Puberty	Puberty	Well developed at birth and active for a few months, after which they atrophy and then become active again at puberty

The sweat gland first secretes a primary fluid that is isotonic with the interstitial fluid. Along the way, the ductal cells modify the fluid (absorb NaCl) so that the final sweat is normally hypotonic to plasma.

In cystic fibrosis (CF) the process of NaCl absorption is characteristically impeded by the absence or malfunction of the mutated CF gene product, the CFTR Cl-channel, in the apical and basal membranes of the duct cells. Consequently, sweat emerges from these glands with the characteristically high salt concentration generally used in diagnosis (Quinton, 2007).



ASSESSMENT OF THE SKIN

ASSESSMENT	FINDINGS
1. Enquire about itching (pruritus)	Dermatological causes (eg, atopic dermatitis, urticaria, scabies) Systemic causes (eg, renal and liver diseases)
2. Observe for skin odor	The presence of odor can indicate poor hygiene or infection.
3. Observe for skin color	Overall skin color normally varies between and within races and affects assessment findings.
4. Palpate for skin moistness	The skin is normally slightly dry. Exposed areas normally feel dryer than body creases.
5. Palpate for skin temperature with the back of the hand	*Compare each side of the body with the other, and the upper with the lower extremities.*
6. Inspect and palpate for skin texture	An infant's or child's skin is normally smooth and even.
7.Palapate for skin turgor	*Palpate for turgor by grasping a fold on the upper arm or abdomen between the fingers and quickly releasing.* A skinfold that returns slowly to place or retains marks commonly indicates dehydration or malnutrition.
8. Inspect and palapte for edema, skin lesions and birthmarks	*Note the distribution, arrangement, shape, color, size, and consistency of the lesions and birthmarks.*

Determination of the primary lesion and secondary change is the cornerstone of dermatologic diagnosis.
A **primary lesion** is defined as the basic lesion that arises de novo and is most characteristic of the disease process.

PRIMARY SKIN LESIONS

- A **macule** represents an alteration in skin color but cannot be felt. When the lesion is >1 cm, the term **patch** is used.
- **Papules** are palpable solid lesions <1 cm.
- **Plaques** are palpable lesions >1 cm in size and have a flat surface.
- **Nodules** are palpable lesions >1 cm with a rounded surface. The word **tumor** may be used for a large nodule that is suspected to be neoplastic in origin.
- **Vesicles** are raised, fluid-filled lesions <1 cm in diameter; when larger, they are called **bullae**.
- **Pustules** contain purulent material.
- **Wheals** are flat-topped, palpable lesions of variable size, duration, and configuration that represent dermal collections of edema fluid.
- **Cysts** are circumscribed, thick-walled lesions; they are covered by a normal epidermis and contain fluid or semisolid material.

Primary lesions may change into secondary lesions, or secondary lesions may develop over time where no primary lesion existed.

SECONDARY SKIN LESIONS

- **Scales** consist of compressed layers of stratum corneum cells that are retained on the skin surface.
- **Purpura** are the result of bleeding into the skin and have a red-purple color; they may be flat or palpable.
- **Petechiae** are small purpura <2-3 mm.
- **Erosions** involve focal loss of the epidermis, and they heal without scarring.
- **Ulcers** extend into the dermis and tend to heal with scarring. Ulcerated lesions inflicted by scratching are often linear or angular in configuration and are called excoriations.
- **Fissures** are caused by splitting or cracking.
- **Crusts** consist of matted, retained accumulations of blood, serum, pus, and epithelial debris on the surface of a weeping lesion.
- **Scars** are end-stage lesions that can be thin, depressed, and atrophic; raised and hypertrophic; or flat and pliable.
- **Lichenification** is a thickening of skin with accentuation of normal skin lines that is caused by chronic irritation (rubbing, scratching) or inflammation.

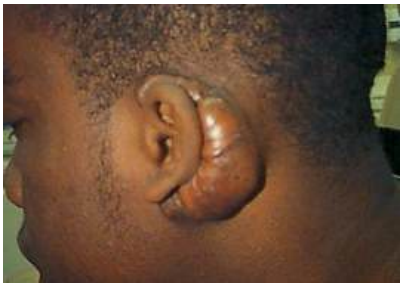
If the diagnosis is not clear after a thorough examination, 1 or more **diagnostic procedures** may be indicated: skin biopsy; Wood lamp; potassium hydroxide preparation (for rapid detection of fungi); immunofluorescence studies.

COLOR VARIATIONS IN LIGHT AND DARK SKIN

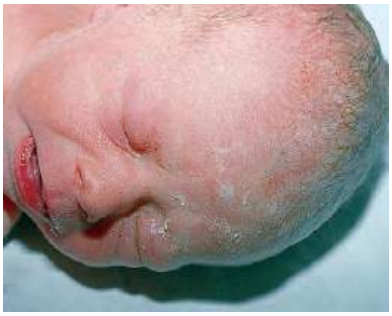
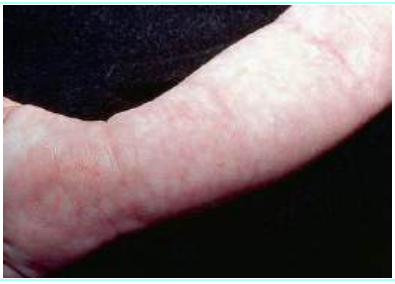
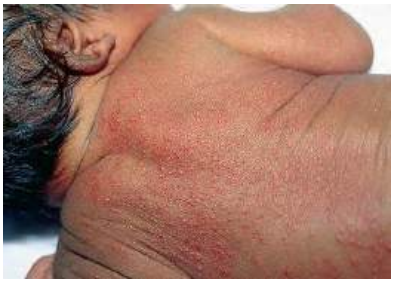
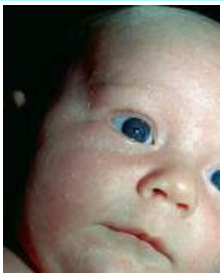
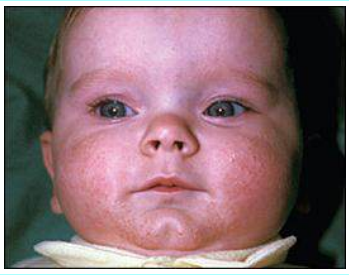
	Light skin appearance	Dark skin appearance
Cyanosis	Bluish tinge, especially in palpebral conjuctiva, nail beds, earlobes, lips oral membranes, soles, palms	Ashen gray lips and tongue
Pallor	Loss of rosy glow in skin, especially in the face	Ashen gray in black skin color; More yellowish brown color in brown skin
Erythema	Redness easily visible anywhere on the body	Much more difficult to assess; Rely on palpation for warmth or edema
Ecchymosis	Purplish to yellow-green areas; may be seen anywhere on the skin	Very difficult to see unless in mouth or conjuctiva
Petechia	Purplish pinpoint markings most easily seen anywhere on the skin.	Usually invisible except in oral mucosa, conjunctiva of eyelids, and conjuctiva covering eyeball
Jaundice	Yellow staining seen in sclera of eyes, skin, soles, palms, fingernails, oral mucosa.	Mostly reliably assessed in sclera, hard palate, palms and soles.

Differences in Dark-Skinned Children

Children with dark skin tend to have more pronounced cutaneous reactions compared to children with lighter skin. Hypopigmentation or hyperpigmentation in the affected area following healing of a dermatologic condition is common in dark-skinned children. This change in pigmentation may be temporary (a few months following a superficial skin disorder) or permanent (following a more involved skin condition). Dark-skinned children tend to have more prominent papules (rounded, nonpustular elevation on the skin), follicular responses, lichenification, and vesicular or bullous reactions than lighter-skinned children with the same disorder. Hypertrophic scarring and keloid formation (fig.) occur more often in dark-skinned children (Burns et al., 2009).



SKIN CHARACTERISTICS IN NEWBORNS

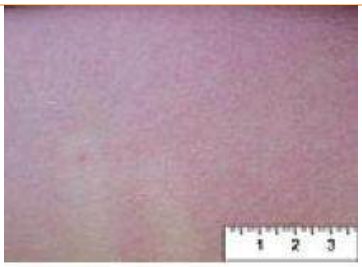
COMMON FINDINGS	DESCRIPTION	
Vernix caseosa	• Characteristic white to gray, greasy covering on the skin surface of the newborn at birth • Composed of shed epidermal cells, sebum and lanugo hairs • Sheds without therapy during the first week of life	
Cutis marmorata	• Caused by instability or immaturity of the nerve supply to the superficial capillary blood vessels in the skin. This causes the blood vessels in some regions of the skin to dilate, producing a red color of the skin, while other regions are contracting, producing pale skin. Typically resolves by 1 year • Persistent cases associated with Down syndrome, trisomy 18, hypothyroidism, congenital heart disease	
Erythema toxicum neonatorum	• Occurs in 40–70% of full-term infants (rarely affects preterm infants) on day 1–2 of life; not present at birth • Characteristic eruption with macular erythema and discrete, scattered yellow papules and pustules with surrounding erythematous wheals • Location: primarily face, trunk and extremities with sparing of the palms and soles • Self-limited course typically over 1–4 weeks	
Sebaceous gland hyperplasia	• Caused by maternal androgen stimulation of sebaceous glands that occurs in the final month of gestation • Characteristic pinpoint yellow papules with no surrounding erythema • Location: nose, cheeks, upper lip and forehead • Spontaneous resolution during the first few months of life	
Milia	• Keratinous cyst originating from vellus hair follicle • Results from retention of keratin within the lowest portion of the infundibulum of the pilosebaceous unit at the level of the sebaceous duct • 1–2 mm white, firm papules on the face, but can also occur on the trunk, extremities, genitalia and oral mucosa (known as Epstein's pearls when they occur in the oral cavity) • Typically resolves within weeks to months	
Acne neonatorum	• Consists of closed comedones on the forehead, nose, and cheeks, although other locations are possible • Results from stimulation of sebaceous glands by maternal or infant androgens. • Usually resolves spontaneously within four months without scarring. Treatment generally is not indicated, but infants can be treated with a 2.5% benzoyl peroxide lotion if lesions are extensive and persist for several months.	

COMMON PEDIATRIC RASHES

I. ERYTHEMATOUS MACULOPAPULAR LESIONS

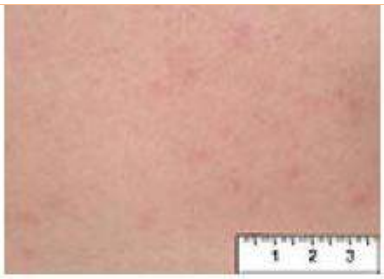
'Erythema' means redness, 'macules' are flat lesions, and 'papules' are raised lesions. Erythematous maculopapular rashes are therefore erythematous, the redness being due to inflammation, and they may be raised (papular), flat (macular) or a mixture of the two (maculopapular).

There are three major types of erythematous maculopapular rashes:



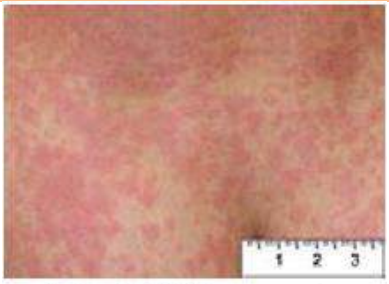
Scarlatiniform rash
(<1 mm)

- *presents as tiny, sometimes infiltrated macules converging rapidly to form broad expanses of bright or dark red skin with rare patches of healthy skin in between, particularly in the skin folds; it is rarely pruriginous*



Rubelliform rash
(1-3 mm)

- *pale pink, more or less widespread, tiny, flat macules separated by areas of healthy skin; it is not pruriginous*



Morbilliform rash
(3-5 mm)

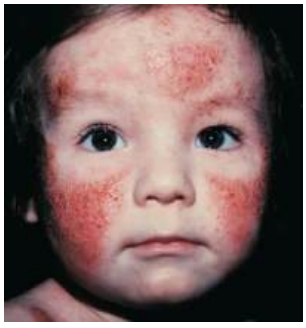
- *erythematous macules that tend to merge and are separated by patches of non pruriginous, healthy skin*

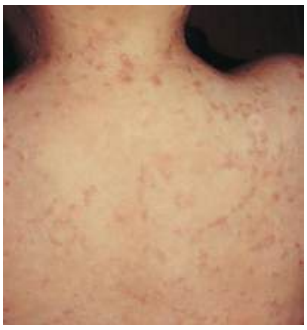
Key causes include:

- *eczema*
- *drug eruptions*
- *scarlet fever*
- *viral exanthems*
- *Kawasaki disease*
- *Still's rash in systemic-onset juvenile idiopathic arthritis*
- *malar rash (butterfly rash)*
- *erythema chronicum migrans in Lyme disease*
- *Gianotti-Crosti syndrome*
- *Napkin rashes*

It is important to stress that a single cause may give rise to a variety of rashes (for example, parvovirus B19) and that the same rash can be induced by different causes (for instance, Gianotti-Crosti syndrome).

Viral exanthems can be difficult to distinguish from a drug eruption. However, viral exanthems are more common in children, and drug eruptions tend to be more common in adults. A thorough history will aid in the diagnosis.





Eczema (atopic dermatitis)

The fundamental problem in eczema is skin dryness, which leads to the development of a scratch–itch cycle. This in turn leads to erythema, excoriation, bleeding and a risk of infection.

No itch? – then it's not eczema

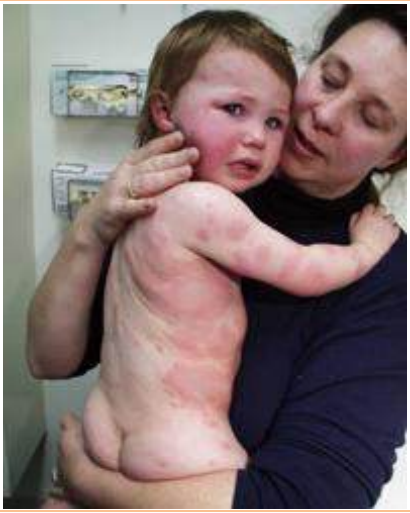
Drug eruptions

Immediate reactions: occur less than 1 hour of the last administered dose

- *Urticaria, angioedema, anaphylaxis*

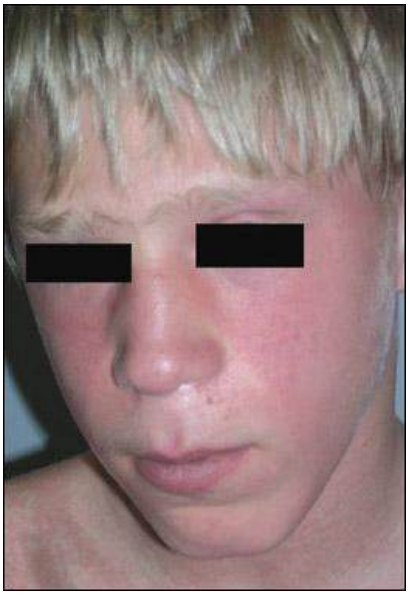
Delayed reactions: occur after 1 hour, but usually more than 6 hrs and occasionally weeks to months after the start of administration

- *Exanthematous eruptions (~90%)*
- *Systemic reactions, eg, drug-induced hypersensitivity sindrome (DIHS), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN)*
- *Vasculitis (may also be systemic)*

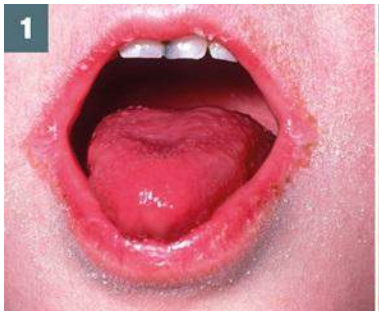


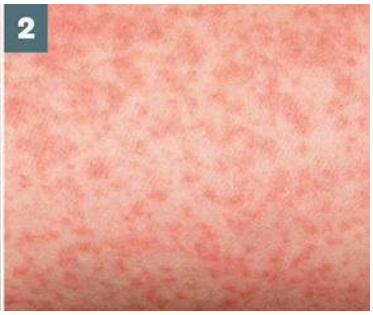
Erythematous raised skin lesion (Wheal) in acute urticaria

- Localised or generalised
- Well circumscribed but often coalescent
- May be intensely pruritic with excoriation
- Vary in size from tiny flat papules to large raised plaques
- Flat centre with raised erythematous edge



DIHS – (also known as drug reaction with eosinophilia and systemic symptoms - DRESS) is a severe, multiorgan reaction to oral antiepileptics that manifests as fever, rash, lymphadenopathy, and hepatitis.





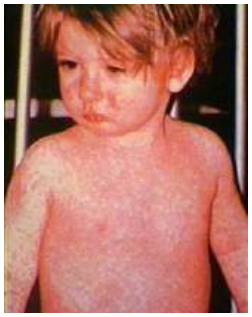
Scarlet fever is characterized by sore throat, fever, and a characteristic red rash:

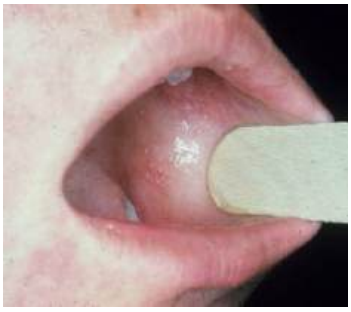
- is fine, red, and rough-textured
- on the face, often shows as red cheeks with a characteristic pale area around the mouth (circumoral pallor)
- is worse in the skin folds (so-called Pastia lines)

Classic Childhood Viral Exanthems

Historically, there were six childhood exanthems whose etiologies are now well-defined:

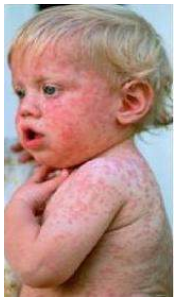
NUMBER	NAME	ETIOLOGY
First Disease	Measles (Rubeola)	Measles virus
Second Disease	Scarlet Fever	*Streptococcus pyogenes*
Third Disease	Rubella	Rubella virus
Fourth Disease	Duke's Disease	No longer accepted as a distinct disorder
Fifth Disease	Erythema Infectiosum	Parvovirus B19
Sixth Disease	Roseola Infantum	HHV-6 and HHV-7

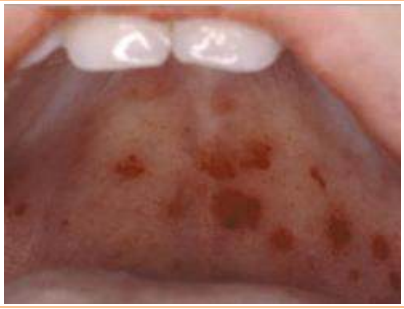




Measles (rubeola)

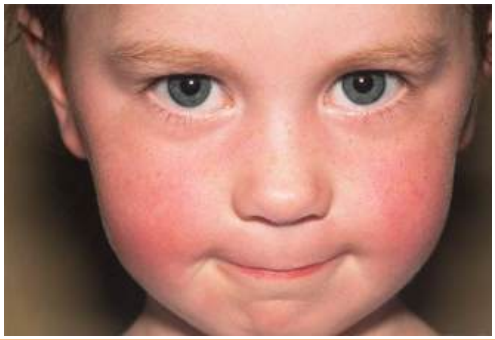
Erythematous macules and papules begin on the face and spread cephalocaudally and centrifugally, Koplik spots.





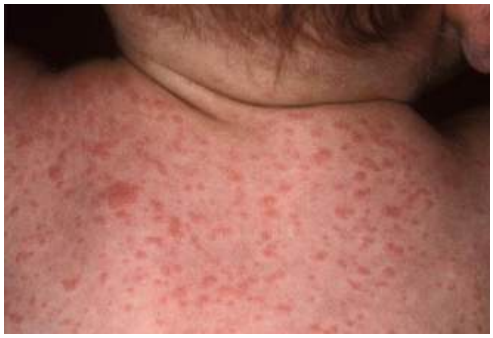
Rubella (german measles)

Pruritic, pink to red macules and papules which begin on the face and spread to neck, trunk and extremities over 24hrs, 20% with Forchheimer sign (petechial lesions on soft palate and uvula).



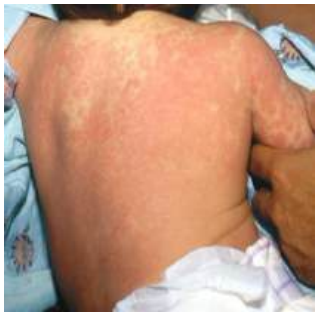
Erythema Infectiosum (fifth disease)

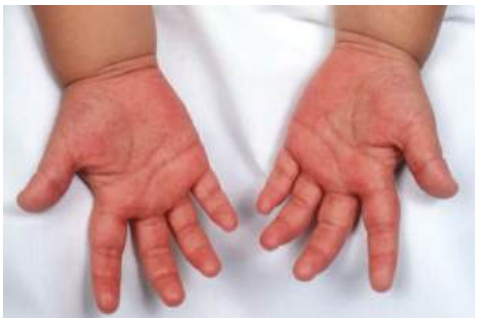
Begins with bright red cheeks and as the facial rash fades over 1-4 days, a symmetric, erythematous, reticular eruption appears on the trunk and extremities.



Roseola infantum (sixth disease)

Pink macules and papules surrounded by white halos. Begins on trunk, spreads to neck and proximal extremities.
This is caused by HHV 6 and HHV 7. Several other viruses – particularly the arboviruses and enteroviruses - can cause **roseoliform rashes**.

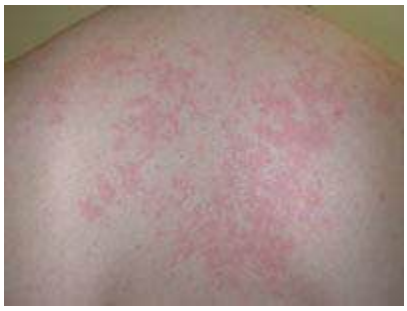




Kawasaki disease is a medium- and small-vessel vasculitis.

The rash of Kawasaki disease is non-specific, and diagnosis is made when the associated features are also present:

- red and swollen peripheries, with skin peeling
- fevers continuing for more than 5 days
- cervical lymphadenopathy
- bilateral non-purulent conjunctivitis
- redness or cracking of lips



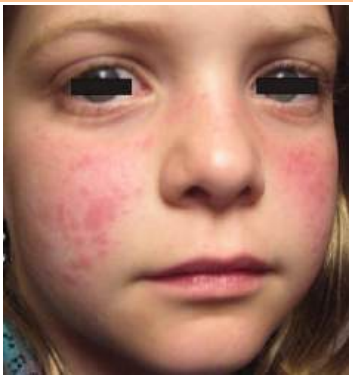
Still's rash in systemic-onset juvenile idiopathic arthritis

Skin rash that coincides with the fever develop in about of 95% of patients. Characteristics of the rash are:

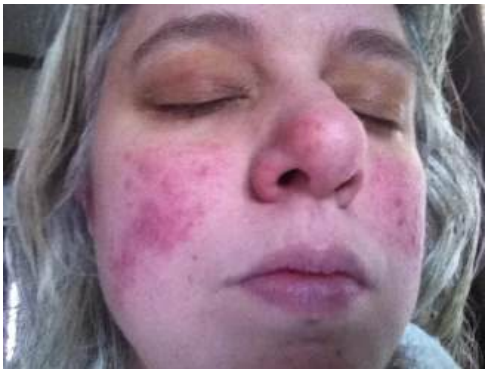
- small, non-itchy spots or patches up to 5cm in diameter
- salmon-pink coloured
- usually appear on the limbs and trunk, but may occur on the face or neck

Malar rash (butterfly rash)

It is often seen in lupus erythematosus (SLE) but is not pathognomonic - it is also seen in other diseases such as dermatomyositis (DM).



Malar rash in SLE



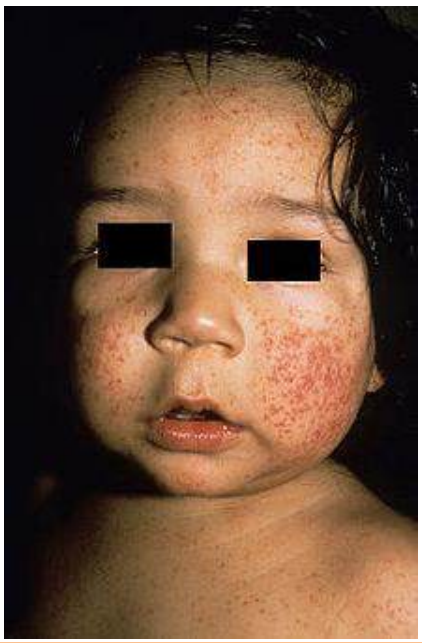
Malar rash in DM

Gianotti-Crosti syndrome

It is a characteristic response of the skin to viral infection in which there is a papular rash which lasts for several weeks. The specific viruses causing Gianotti-Crosti syndrome include:

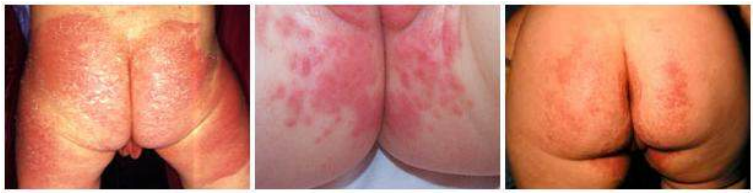
- Hepatitis B infection
- Epstein Barr virus (the cause of glandular fever)
- Enterovirus infections
- Echo viruses
- Respiratory syncytial virus

Gianotti-Crosti syndrome mainly affects children between the ages of 6 months and 12 years.



Napkin dermatitis (diaper rash)

Napkin rashes are common, although irritant reactions are much less of a problem with the widespread use of disposable nappies, as they are more absorbent.



Causes *of napkin rashes*

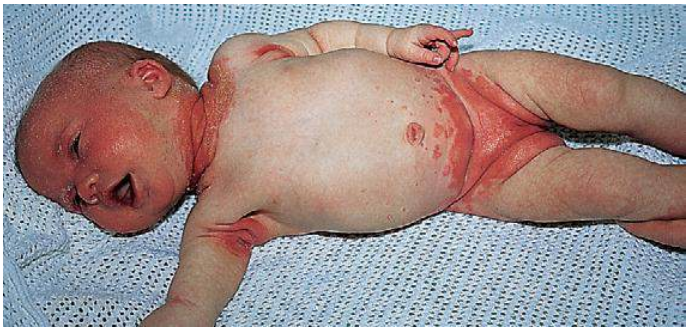
Common	*Rare*
• Irritant (contact) dermatitis • Infantile seborrhoeic dermatitis • Candida infection • Atopic dermatitis	• Acrodermatitis enteropathica • Langerhans cell histiocytosis

Irritant dermatitis, the most common napkin rash, may occur if nappies are not changed frequently enough or if the infant has diarrhoea. However, irritant dermatitis can occur even when the napkin area is cleaned regularly. The rash is due to the irritant effect of urine on the skin of susceptible infants. Urea-splitting organisms in faeces increase the alkalinity and likelihood of a rash. The irritant eruption affects the convex surfaces of the buttocks, perineal region, lower abdomen and top of thighs. Characteristically, the flexures are spared, which differentiates it from other causes of napkin rash. The rash is erythematous and may have a scalded appearance. More severe forms are associated with erosions and ulcer formation. Mild cases respond to the use of a protective emollient, whereas more severe cases may require mild topical corticosteroids. While leaving the child without a napkin will accelerate resolution, it is rarely practical at home.

Seborrhoeic dermatitis

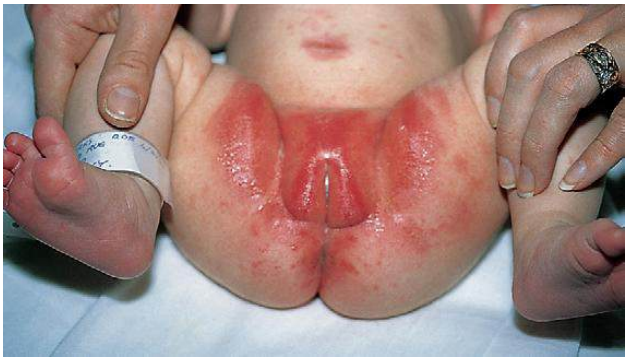
- Red moist rash with fine yellow scale
- Non-pruritic ± rash elsewhere and cradle cap

Cradle cap



Involvement of face, axillae and napkin area

Candida infection may cause and often complicates napkin rashes. The rash is erythematous, includes the skin flexures and there may be satellite lesions. Treatment is with a topical antifungal agent.



II. VESICULOBULLOUS LESIONS

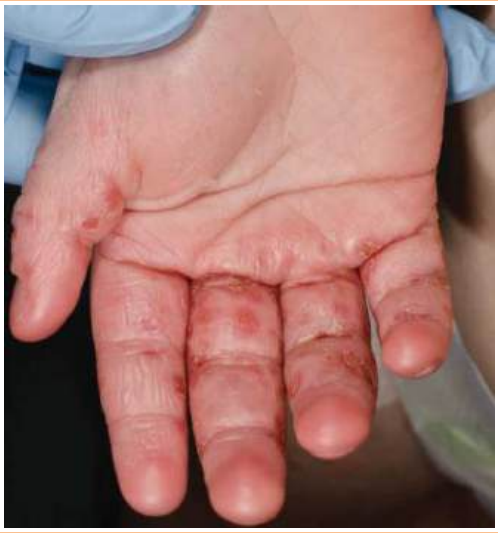
Vesicobullous lesions are rashes in which the lesions are small blisters (vesicles) or larger blisters (bullae).

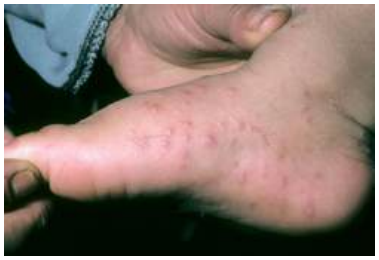
Key causes include:

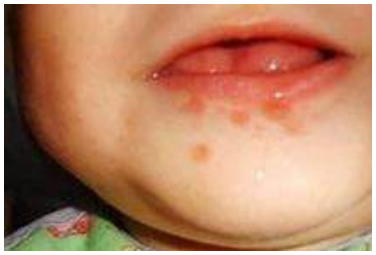
- *varicella*
- *shingles*
- *hand-foot-mouth disease (HFMD)*
- *eczema herpeticum*
- *bullous impetigo*
- *bullous pemphigoid*
- *Staphylococcal scalded skin syndrome (SSSS)*
- *Stevens–Johnson syndrome*

Varicella

Varicella is an acute infectious disease caused by varicella zoster virus (VZV). In primary infection (chickenpox) the rash is generalized and pruritic and progresses rapidly from macules to papules to vesicular lesions before crusting. The recurrent infection (herpes zoster, also known as shingles) occurs when latent VZV reactivates (mostly in adults).



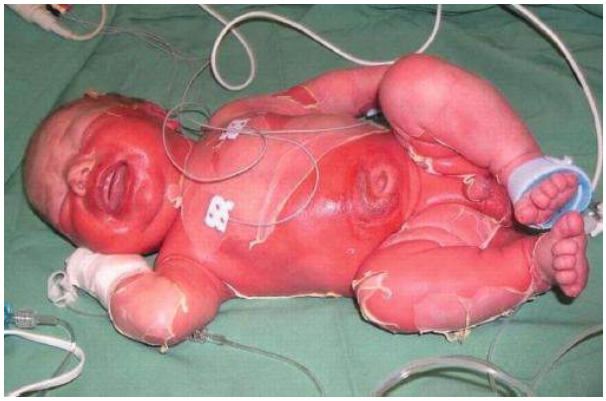




Hand-foot-mouth disease

This is a common childhood illness. It most frequently affects children younger than 5 years. It starts with a fever, followed by painful mouth sores and a non-itchy rash. The rash blisters on hands, feet, and sometimes buttocks and legs.

It is caused by one of several serotypes of enterovirus, typically coxsackievirus A16.

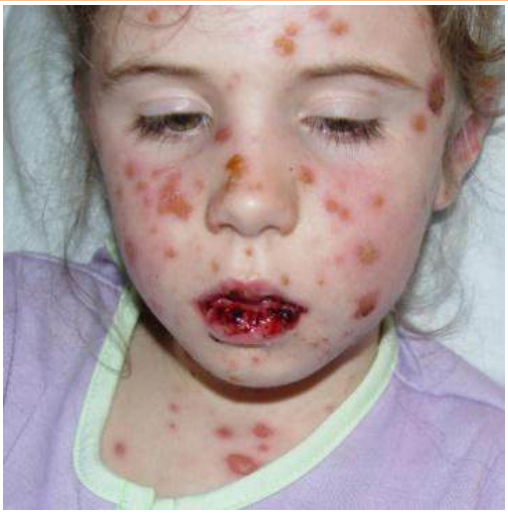


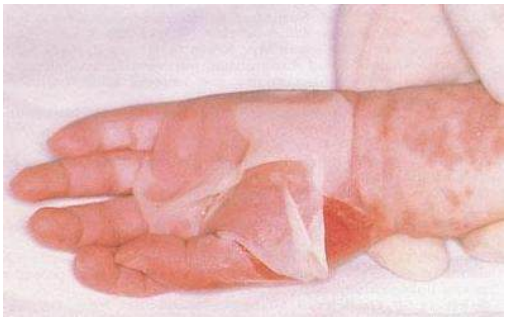
Staphylococcal scalded skin syndrome (SSSS)

- also known as Ritter disease (in newborns). SSSS is a generalized form of bullous impetigo. Children are more at risk because of lack of immunity and immature renal clearance capability (exfoliative toxins are renally excreted). Adults with SSSS are most often chronically ill, are immunocompromised, or have renal failure. SSSS can also appear in adults in cases with a high burden of staphylococcal infection where the quantity of exotoxin is significant.

Severe drug reactions

- *Stevens-Johnson syndrome (SJS),*
- *Toxic epidermal necrolysis (TEN)*





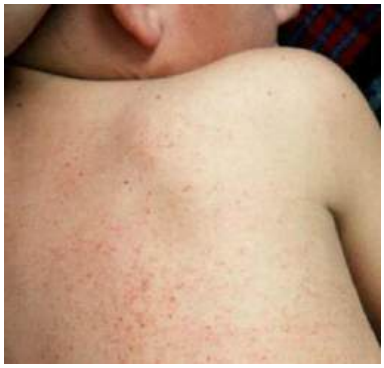
SJS and TEN are variants of a single hypersensitivity disorder. SJS is defined by epidermal detachment on less than 10% of the total body surface area; TEN is defined by epidermal detachment on more than 30% of the body surface area. Mucosal involvement is more common in SJS. In children, SJS is more common than TEN; however, both conditions have been described in all age-groups from neonates to adults.
Onset is within the first 8 weeks of exposure to the causative agent. The usual disease course is 1 month.

III. PURPURIC LESIONS

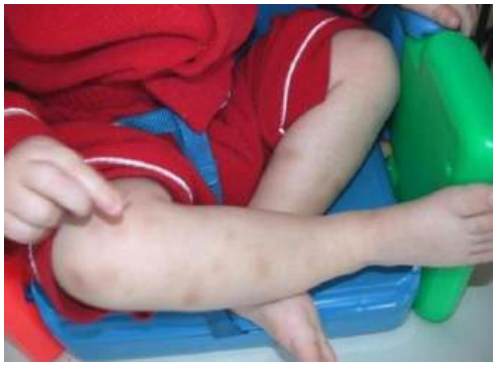
Purpura are small areas in which blood has extravasated into the skin. Pinprick-sized areas are called petechiae. Because the blood is outside the blood vessel, these lesions do not blanch on pressure (since the red blood cells are fixed in place).

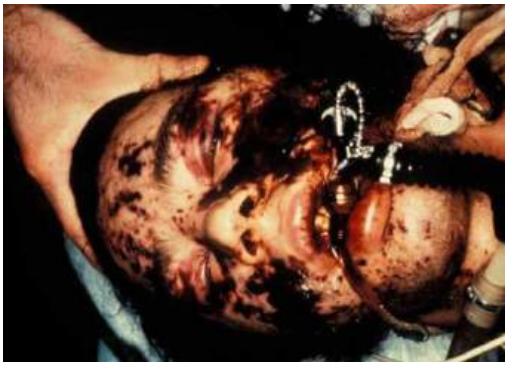
The key causes are:

- *Henoch–Schönlein purpura*
- *thrombocytopenia*
- *meningococcal septicaemia*



Petechiae - a small (1-2 mm) red or purple spot on the body, caused by a minor hemorrhage



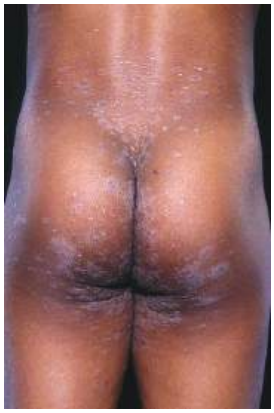
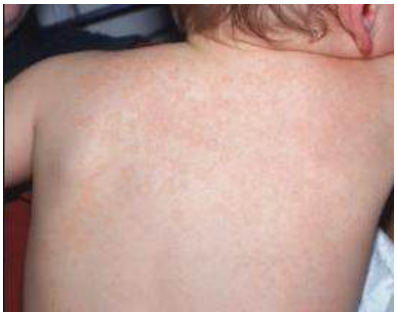
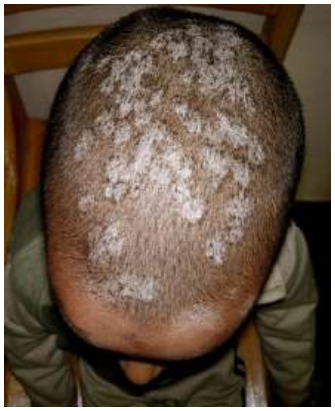
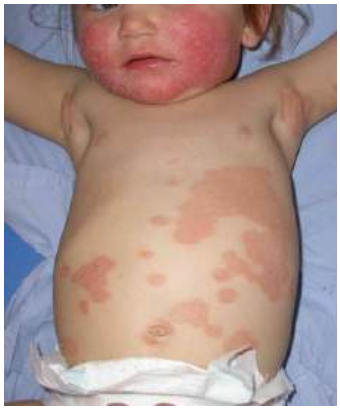


Ecchymosis - a subcutaneous purpura larger than 1 centimeter or a hematoma, commonly, but erroneously, called a bruise. That is, bruises are caused by trauma whereas ecchymoses, a type of purpura, are not caused by trauma

IV. SCALY LESIONS

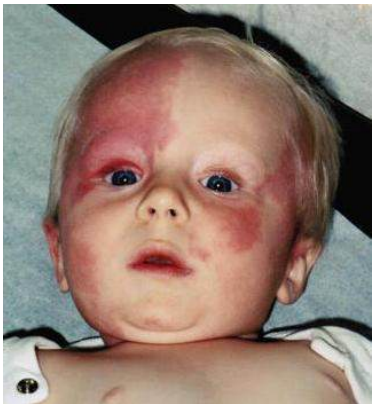
In some conditions, a scale may form on top of a rash.

Key causes of a scaly rash include:

Pityriasis rosea	Tinea versicolor	Tinea capitis	Psoriasis
			
There is a 'Christmas tree' distribution to the rash	▪ *is a fungal infection of the skin* ▪ *there are small circular areas of depigmentation*	▪ *is a fungal infection of the scalp* ▪ *localised area of hair loss or alopecia, with a scaly border*	▪ *the skin is thickened and inflamed, with a silvery, scaly appearance* ▪ *typically occurs in patches on extensor areas*

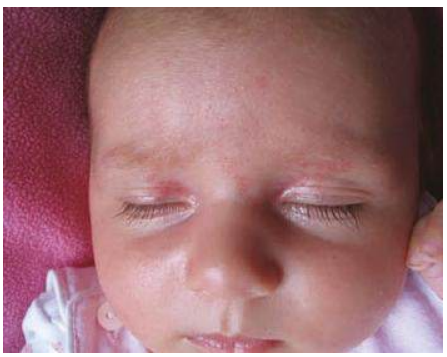
V. COMMON BIRTHMARKS

PORT-WINE STAIN (PWS) — is a flat red area due to ectatic dermal capillaries, i.e. a vascular anomaly. These are present from birth and remain throughout life. There may be associated eye and brain abnormalities:



Glaucoma	PWS of the face with eyelid involvement may be associated with glaucoma of the affected eye
Sturge–Weber syndrome	PWS of the face always including the area covered by the *ophthalmic branch of the trigeminal nerve*, and *Ipsilateral leptomeningeal vascular abnormality* with neurological symptoms, e.g. seizures, hemiplegia

SALMON PATCH

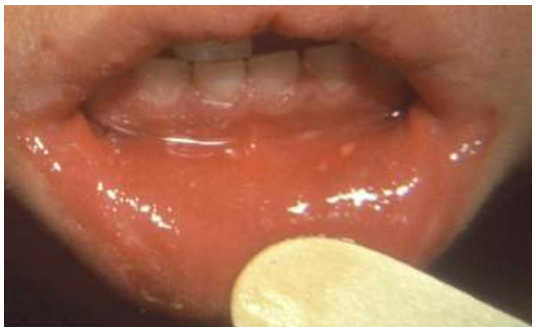


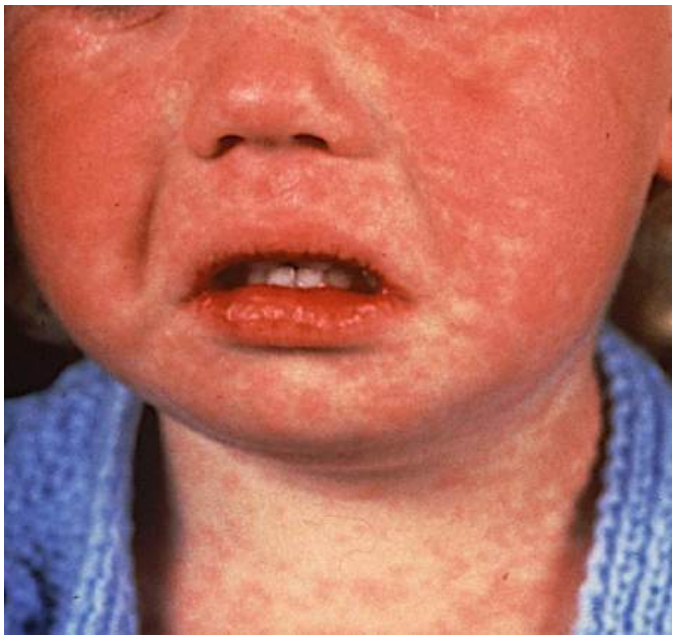
- Common pale pink vascular anomalies, present at birth on the face (eyelids, nose, forehead) or nape of the neck
- Generally fade during the first few weeks of life, except those on the nape of the neck (known popularly as a stork bite and present in around half of newborns) that usually persist for life

Case One

- Ana is 4-year-old previously healthy girl who presents with a 1 week history of cough, runny nose, fever, sore throat and red eyes. She went to her pediatrician 2 days ago and was prescribed Augmentin (amoxicillin and clavulanate) for presumed pharyngitis.
- Yesterday, Ana developed a red rash which started on her face and has spread to her trunk. Her mother would like to know if the rash is from her new medication.
- Upon further questioning you discover that Ana has never received vaccinations due to her mother's fear regarding autism.
- The augmentin was started 24 hours before the onset of her rash.
- You also discover that a close family member recently visited from the Netherlands, who also developed a similar rash.

- Ana is an ill-appearing child who presents with a morbilliform rash with erythematous macules and papules.
- Lesions have coalesced on the face and neck.
- Rash has spread to her trunk and extremities (not shown)
- Inspection of Ana's mouth reveals, bluish-white dots on the mucosal surface. These are called Koplik spots.





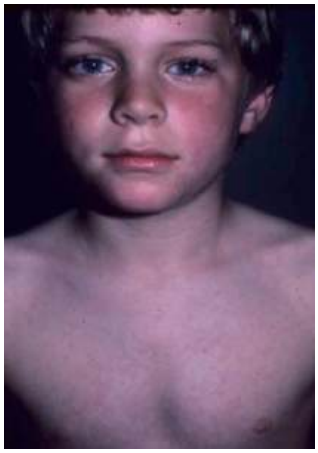
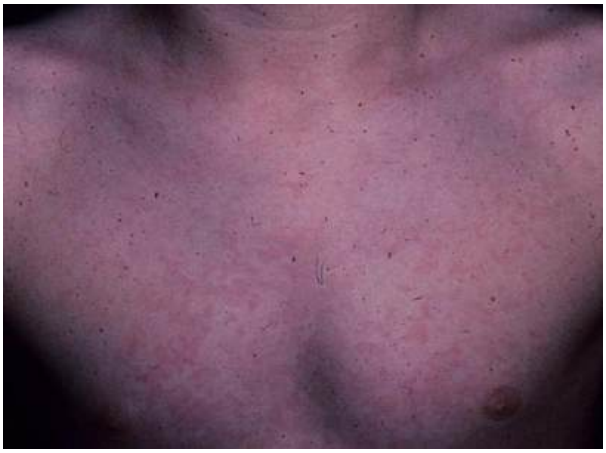
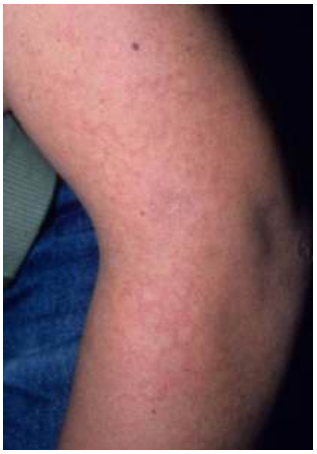
- **Based on the history and exam, what is the most likely diagnosis (differential diagnosis)?**

1. Drug Eruption	For exanthematous drug eruptions, the initiation of the medication is often 7-10 days before the rash
2. Erythema Infectiosum	Eruption begins with bright red cheeks followed by a reticular eruption on the trunk and extremities
3. Roseola	Tends to occur in younger children with high fevers preceding a sudden rash that begins on the trunk
4. Rubella	Rash tends to spread more quickly, covering the body in 24hrs
5. Measles	Rash tends to spread over a period of days

RIGHT ANSWER:

Case Two

- Keith is a 10-year-old boy who was brought to the pediatrician by his mother because he developed low grade fevers, red cheeks and a new rash on his body.
- Keith is up to date with his vaccinations.
- How would you describe Keith's rash?
  - Confluent, erythematous, edematous plaques on the malar eminences - "slapped cheeks."
  Erythematous reticular eruption on the trunk and extremities

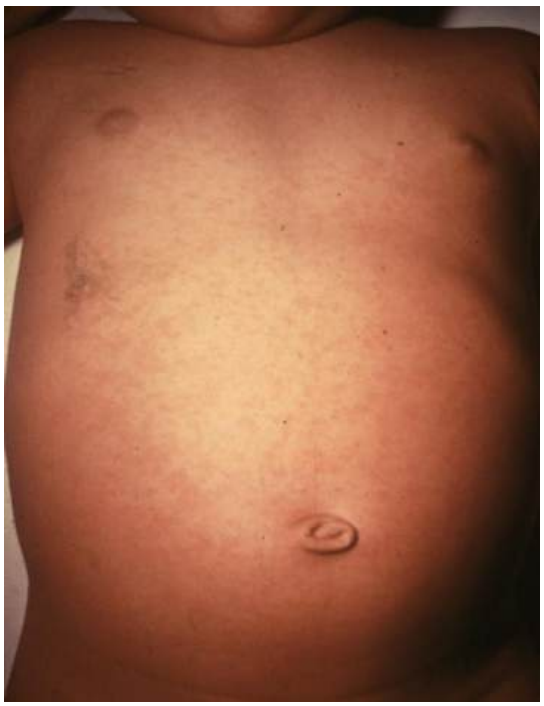




- **Based on the history and exam, what is the most likely diagnosis (differential diagnosis)?**

1. Drug Eruption. 2. Erythema Infectiosum. 3. Roseola. 4. Rubella. 5. Measles.

Case Three

- Caleb is a 9-month-old boy who presents for evaluation of fever and rash. His mother noted a fever of 40˚C two days ago. He appeared well and was eating and playing normally, so his mother was not alarmed. After the fever resolved, Caleb developed a red rash that progressed rapidly over the past 24 hours.



- **Based on the history and exam, what is the most likely diagnosis (differential diagnosis)?**
  1. Drug Eruption
  2. Erythema Infectiosum
  3. Roseola
  4. Rubella
  5. Measles

Nutrition in Children

Mother feeding baby is an art image symbolizing peace, kindness, happiness, joy of life. But how many women often thoughtlessly or willingly deprive themselves and the child of the gift of nature!

Kildiyarova RR

The 1,000 days between a woman's pregnancy and her child's 2nd birthday offer a unique window of opportunity to shape healthier and more prosperous futures. The right nutrition during this 1,000 day window can have a **profound impact on a child's ability to grow, learn, and rise out of poverty**. It can also shape a **society's long-term health, stability and prosperity**.

Worldwide, about 20% of deaths among children under-five could be avoided if feeding guidelines are followed.

WHO recommends:

- **exclusive breastfeeding for six months,**
- **introducing age-appropriate and safe complementary foods at six months,**
- **continuing breastfeeding for up to two years or beyond.**

➢ Advantages of breastfeeding (BF)

Breast milk

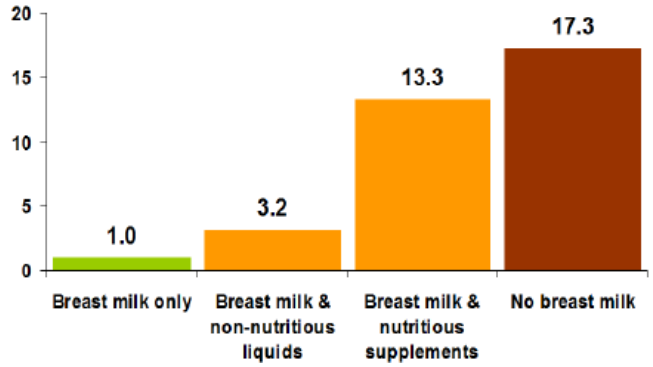
- Perfect nutrients
- Easily digested; efficiently used
- Protects against infection

Breastfeeding

- Helps bonding and development
- Helps delay a new pregnancy
- Protects mothers' health

- Costs less than artificial feeding

Fig. Risk of diarrhoea by feeding method, Philippines, infants aged 0-2 months [Popkin 1990]



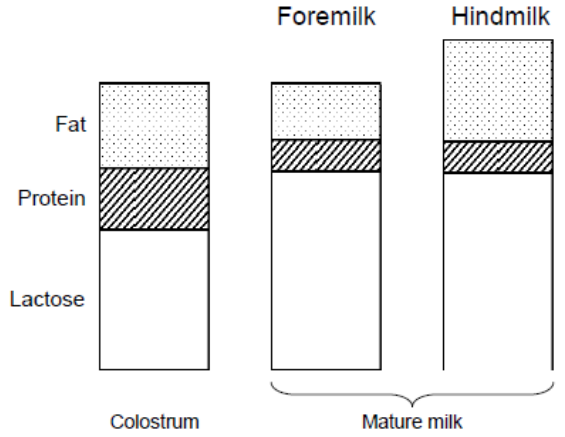
Benefits to baby:	Benefits to mother:
1. Decreases the incidence and/or severity of a lot of diseases: diarrhea, lower respiratory infection, otitis media, bacterial meningitis, botulism, urinary tract infection, necrotizing enterocolitis **2. Possible protective effect against:** sudden infant death syndrome, insulin-dependent diabetes mellitus, Crohn's disease, ulcerative colitis, lymphoma, allergic diseases, other chronic digestive diseases **3. Promotes:** childhood growth, cognitive development **4. The Influence on the *development* of the oral cavity:** * Breastfed babies have better jaw alignment and are less likely to need orthodontic work as they get older. The sucking action used to breastfeed involves complex motions of the facial muscles and tongue. This improves the development of facial muscles and the shape of the palate. The better jaw alignment associated with BF can even mean less snoring and a lowered risk for a condition known as obstructive sleep apnea–the blockage of air flow during sleep, which can disturb sleep patterns and lead to other health problems. * The action of BF also reduces the incidence of ear infections; assists with clear speech.	▪ Increases levels of oxytocin, resulting in less postpartum bleeding and more rapid uterine involution ▪ Less menstrual blood loss over the months after delivery ▪ Earlier return to pre-pregnant weight ▪ Delayed resumption of ovulation with increased child spacing ▪ Improved bone remineralization postpartum ▪ Reduction in hip fractures in the postmenopausal period ▪ Reduced risk of ovarian cancer/pre-menopausal breast cancer

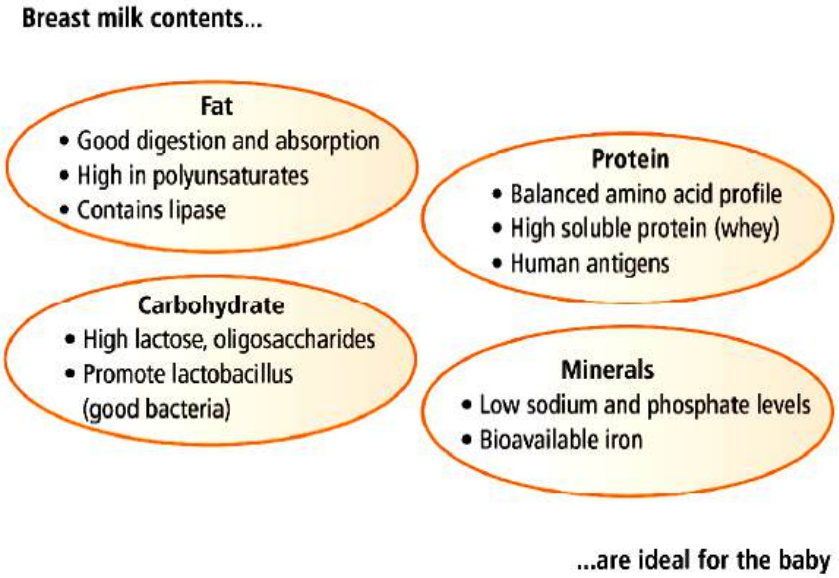
➢ Composition of breast milk

Breast milk contains all the nutrients that an infant needs in the first 6 months of life, including fat, carbohydrates, proteins, vitamins, minerals and water. It is easily digested and efficiently used. Breast milk also contains bioactive factors that augment the infant's immature immune system, providing protection against infection, and other factors that help digestion and absorption of nutrients.

Colostrum	Mature milk
During the first few days after delivery, the mother produces colostrum. This is a thin yellowish fluid that is the same fluid that sometimes leaks from the breasts during pregnancy. It is **rich in protein and antibodies that provide passive immunity to the baby** (the baby's immune system is not fully developed at birth). It contains **more white blood cells** than mature milk. Colostrum also helps the newborn's digestive system to grow and function properly. It has a **mild purgative effect**, which helps to clear the baby's gut of meconium (the first dark stools). This clears bilirubin from the gut, and helps to prevent jaundice from becoming severe. Colostrum is **rich in vitamin A** which helps to reduce the severity of any infections the baby might have.	Colostrum will gradually change to become mature milk. In the first 3–4 days it will appear thin and watery and will taste very sweet; later, the milk will be thicker and creamier. Human milk quenches the baby's thirst and hunger. In the 1980s and 1990s, lactation professionals (De Cleats) used to make a differentiation between **foremilk** and **hindmilk**. But this differentiation causes confusion as there are not two types of milk. Instead, as a baby breastfeeds, the fat content very gradually increases, with the milk becoming fattier and fattier over time.

Differences between colostrum and mature milk





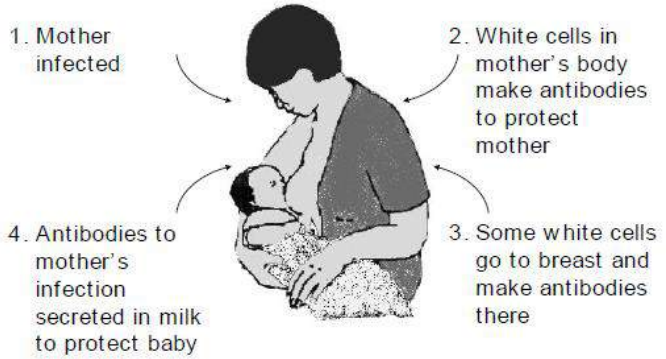
Anti-infective properties of breast milk

- **Sterile feed**
- **Maternal antibodies**
- **Macrophages, neutrophils, lymphocytes**
- **Complement, Lactoferrin, Lyzozyme**
- **Promotes colonization with laktobacilli and bifidobacter**

❖ Breast milk contains white blood cells, and a number of anti-infective factors, which help to protect a baby against many infections.

❖ Breast milk also contains antibodies against infections that the mother has had in the past.

The baby should not be separated from his mother when she has an infection, because her breast milk protects him against the infection!



Human milk after preterm delivery

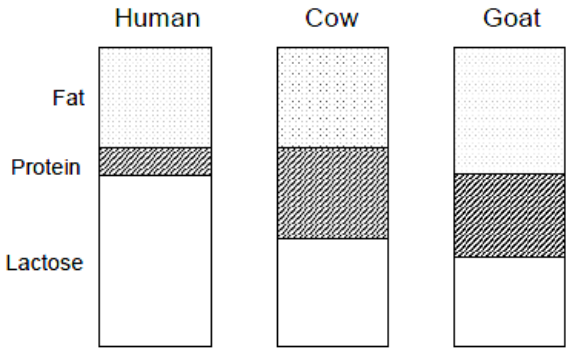
The composition of human milk for preterm infants differs from that for term infants in a number of ways. For every 100 mL, breast milk from women delivering preterm infants is higher in calories (67 to 72 kcal versus 62 to 68 kcal), higher in protein (1.7 to 2.1 g versus 1.2 to 1.7 g), higher in lipids (3.4 to 4.4 g versus 3.0 to 4.0 g), lower in carbohydrates, higher in multiple minerals and trace elements (especially sodium [Na], chloride [Cl], iron [Fe], Zinc [Zn], and copper [Cu]), and higher in vitamins (especially vitamins A and E). However, as breast milk becomes mature, many of these nutritional advantages are lost.

➢ Comparison of breast milk to cow milk

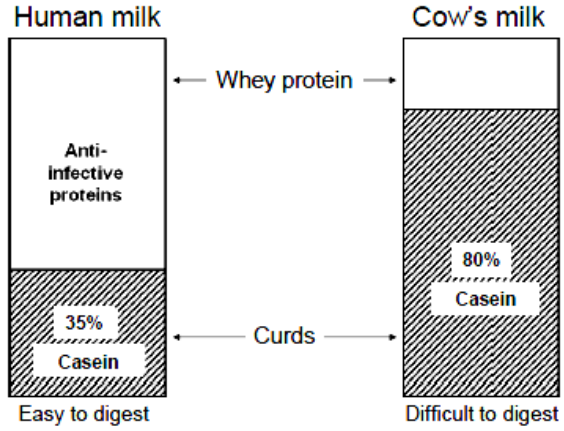
Component	Human Milk	Cow Milk
Water/solids	Same	Same
Calories	20 cal/oz	20 cal/oz
Protein	1–1.5% (whey dominant)	3.3% (casein dominant)
Carbohydrate	6.5–7% lactose	4.5% lactose
Fat	high in LCFAs	high in MCFAs
Minerals	Iron better absorbed	Low iron and copper
Vitamins	Diet dependent, low in K, D	Low in C, D
Digestibility	Faster emptying	Same after 45 days
Renal solute load	**Low** (aids in renal function)	Higher

Note
LCFAs – long chain fatty acids
MCFAs – medium chain fatty acids

Nutrients in human and animal milks



Quality of proteins in different milks



Summary of Major Differences Between Human Milk and Commercial Substitutes Marketed for Normal Term infants

	Human milk	Commercial Substitutes
Protein	Appropriate (species specific) quality/quantity, easier to digest	Corrected in quantity but not in quality (not species specific)
Fat	Appropriate quality/quantity of essential fatty acids, lipase present	Lipase absent
Vitamins	Adequate except for vitamins D and K in some situations (see text)	Vitamins added
Minerals	Correct amount	Partly corrected
Anti-infective properties	Present	Absent
Growth factors	Present	Absent
Digestive enzymes	Present	Absent
Hormones	Present	Absent

Adapted from WHO/CDR/93.6. and further modified, 2009

Physiology of Lactation

Some mothers think their breasts are too small to produce enough milk. What is the difference between large breasts and small breasts?

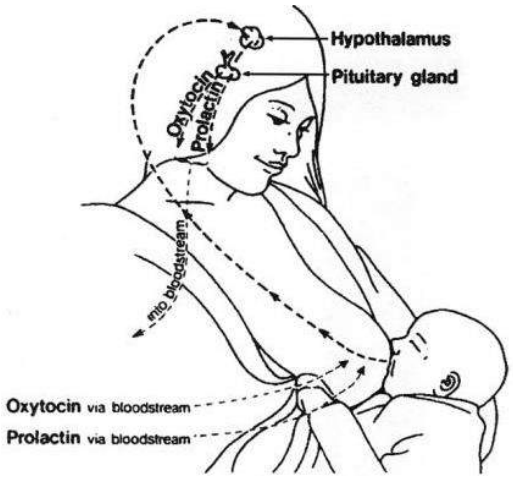
- *It is the fat and other tissue which gives the breast its shape, and which makes most of the difference between large and small breasts.*
- *Small breasts and large breasts both contain about the same amount of gland tissue, so they can both make plenty of milk.*

Lactation (milk production) occurs after childbirth and involves two components: milk secretion and milk removal.

1) **Milk secretion (synthesis and release)** is a continuous process, which is promoted by **PROLACTIN.** Prolactin secretion, in turn, increases by continued breastfeeding
2) **Milk removal or ejection ("let-down" refex)** is intermittent and triggered by **OXYTOCIN**.

Normal term infants are born with a number of reflexes and behaviors to help assure that the newborn survives the transition from intra to extra uterine life. These reflexes enable him to begin feeding immediately after birth (*see* "The digestive system").
Breastfeeding involves a set of reflexes and hormones that also drive the milk supply.

SUCKLING REFLEX



The stimulation of sensory nerves in the breast by the infant initiates the suckling reflex. Unlike ordinary reflexes with only neural components, the afferent arc of the suckling reflex is neural and the efferent arc is hormonal. The suckling reflex increases the release of prolactin, oxytocin, and ACTH and inhibits the secretion of gonadotropins.
Suckling on one breast causes milk flow not only in that breast but also in the opposite breast.

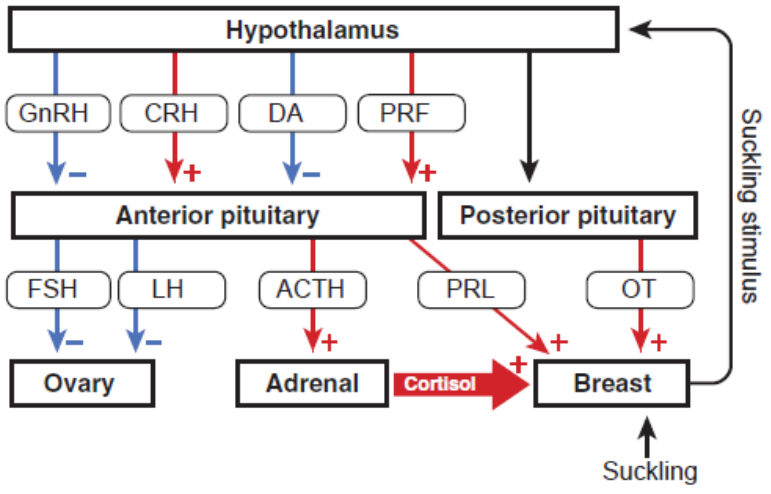
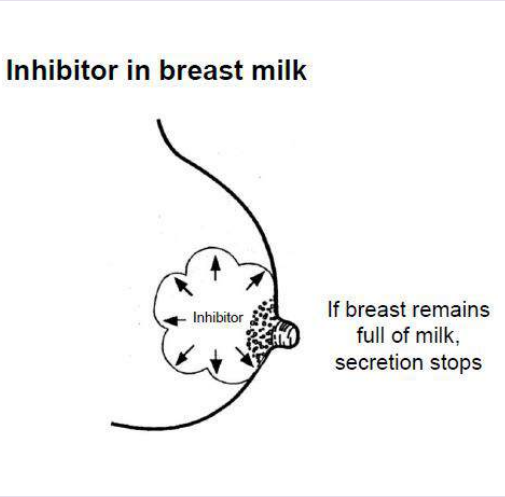


Fig. Effect of suckling on hypothalamic, pituitary, and adrenal hormones. GnRH, gonadotropinreleasing hormone; CRH, corticotropin-releasing hormone; DA, dopamine; PRF, prolactin-releasing factor; FSH, follicle-stimulating hormone; LH, luteinizing hormone; ACTH, adrenocorticotropic hormone; PRL, prolactin; OT, oxytocin.

"THE LAW OF DEMAND AND SUPPLY"

Milk production is influenced positively by early frequent and effective milk removal and negatively by late infrequent feeds or by the feeding the baby other liquids or foods before six months of age. The frequency of feeding regulates milk supply. The more often a baby removes the milk the greater the milk supply. Conversely, a baby who sleeps many hours at a time in the early weeks or feeds less than an average of eight times in 24 hours does not have the opportunity to stimulate the breast, causing the milk supply to drop. Because each breast responds to the amount of milk demanded by the infant, it is possible to exclusively breastfeed more than one baby at a time or to use only one breast. Initially, if the milk is not removed the breast becomes full and eventually engorged. At that point, a local factor known as the **feedback inhibitor of lactation (FIL)** begins to decrease milk secretion. The exact mechanism of FIL is still under study.



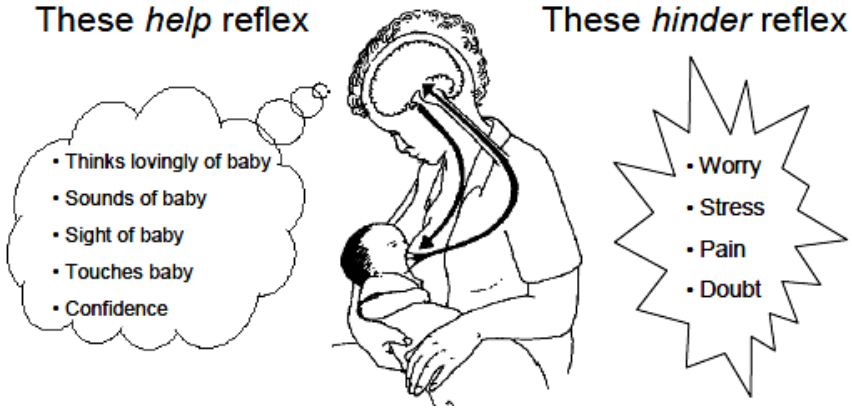
Sometimes people suggest that to make a mother produce more milk, we should give her more to eat, more to drink, more rest, or medicines. It is important for a mother to eat and drink enough, but these things do not help her to produce milk if her baby does not suckle.

Some special things to remember about prolactin are:

- The prolactin level is highest about 30 minutes after the beginning of the feed, so its most important effect is to make milk for the next feed. For this feed, the baby takes the milk which is already in the breast.
- More prolactin is produced at night; so breastfeeding at night is especially helpful for keeping up the milk supply.
- Hormones related to prolactin suppress ovulation so breastfeeding can help to delay a new pregnancy (**lactational amenorrhea**). Breastfeeding at night is important for this.

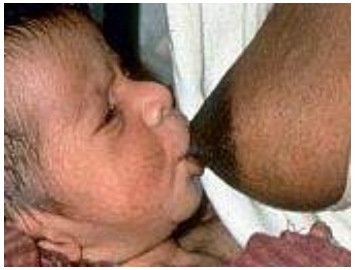
Why is it important to understand the oxytocin reflex in the way we care for mothers after delivery?

- A mother needs to have her baby near her all the time, so that she can see, touch and respond to him. If a mother is separated from her baby between feeds, her oxytocin reflex may not work so easily.
- You need to remember a mother's feelings whenever you talk to her. Try to make her feel good and build her confidence. Try not to say anything which may make her doubt her breast milk supply.



How to assess good breastfeeding

The most important criterion for assessing the milk transfer during a feeding at the breast is **audible swallow!**



	Good	Problem
Baby's body position	On side – chest to chest	On back – angled away from mother
Mouth	Open wide	Lips close together
Chin	Touching or pressing into the breast	Space between chin and breast
Lips	Flanged out	Tucked in, inverted
Cheeks	Well rounded	Dimpled or sucked in
Nose	Free of or just touching the breast	Buried in breast, baby pulls back
Breast in mouth	Good mouthful, more of bottom part of breast in mouth	Central, little breast tissue in mouth or only nipple in mouth
Jaw movement	Rhythmic deep jaw movement	Jerky or irregular shallow movement
Sounds	Muffled sound of swallowing milk	No swallowing, clicking sounds
Body language of the baby	Peaceful, concentrated	Restless, anxious
Body language of the mother	Comfortable, relaxed	Tense, hunched, awkward
Awareness of feelings during feed	Pain free, may feel a drawing feeling deep in breast or 'let down'	Nipple or breast pain
Nipple, post-feed	Nipple elongated, well-shaped	Not elongated, compressed 'stripe' or blanched

Source: Murray S. *Breast Feeding Information and Guidelines for Paediatric Units*, Royal Children's Hospital, Melbourne, Australia, 1992.

➢ Normal variations in breastfeeding

Frequency of feeds

Breastfed infants usually feed every 2–5 hour from both breasts each feed. Young babies feed frequently, but demand feeding (i.e. feeding when hungry) will usually have the baby settle into a fairly predictable pattern of feeds. The frequency of feeds is determined by the baby's appetite and gastric capacity, as well as the amount of mother's milk available.

Length of feeds

The duration of the feed is determined by the rate of transfer of milk from the breast to the baby, which, in turn, depends on the strength of the baby's suck and the force of the mother's 'let down' or flow of milk. This may vary from 10–30 minutes. Young infants tend to feed for longer. It is the cessation of strong drawing sucks and the appearance of shorter-duration bursts of sucking that indicate the 'end' of the feed – not the time.

Appetite spurts

Babies seem to experience appetite spurts at 2 weeks, 6 weeks and 3 months. During a growth spurt, a baby will suddenly begin to feed more frequently. It is crucial that parents are aware of this or the baby's natural increase in feed frequency may be mistaken for diminution of milk supply. This is especially true at 6 weeks when breasts are no longer carrying extra fluid and the supply is settling to the demands of the baby. Unfortunately, many women wean at this time through poor advice. During appetite spurts, let the baby feed on demand, even 2 hourly, and this pattern should settle in 48 hours.

➢ Contraindications to breastfeeding

Infant Conditions	Maternal Conditions
Inborn errors of metabolism: ▪ **Classic galactosemia:** a special galactose-free formula is needed ▪ **Maple syrup urine disease:** a special formula free of leucine, isoleucine and valine is needed ▪ **Phenylketonuria:** a special phenylalanine-free formula is needed (some breastfeeding is possible, under careful monitoring)	• **Infections:** Mothers with *human T-cell lymphotropic virus (HTLV) types I and II* should not breast-feed. For mothers with *active tuberculosis (before treatment), peripartum development of varicella, and herpes simplex (when lesions are present on the breast)*, expressed breast milk can be used, but infants should not feed directly from the breast. In the industrialized world, it is not recommended that *HIV-positive mothers* breast-feed. However, in the developing world, the risks of malnutrition and infectious diseases may outweigh the risk of acquiring HIV from breastfeeding. A 2009 Cochrane review demonstrated that in areas endemic for HIV, infants who were exclusively breast-fed for 3 months had a lower risk of HIV acquisition than infants fed a combination diet of human milk and other foods. • **Substance abuse or use:** Cocaine, stimulants, and marijuana. • **Medications:** Sulfonamides (for infants with hyperbilirubinemia or glucose-6-phosphate dehydrogenase deficiency), radioactive medicines, chemotherapeutic agents (alkylating agents), bromocriptine (suppresses lactation), and lithium (in general, psychotropic drugs should be used with caution).

➢ Feeding terms and definitions

- **EXCLUSIVE BREASTFEEDING:** the infant takes only breast milk and no additional food, water, or other fluids with the exception of medicines and vitamin or mineral drops.
- **PARTIAL BREASTFEEDING or MIXED FEEDING**: the infant is given some breast feeds and some artificial feeds, either milk or cereal, or other food or water.
- **BOTTLE-FEEDING**: the infant is feeding from a bottle, regardless of its contents, including expressed breast milk.
- **ARTIFICIAL FEEDING:** the infant is given breast-milk substitutes and not breastfeeding at all.
- **REPLACEMENT FEEDING:** the process of feeding a child of an HIV-positive mother who is not receiving any breast milk with a diet that provides all the nutrients the child needs.
- **COMPLEMENTARY FEEDING:** the process of giving an infant food in addition to breast milk or infant formula, when either becomes insufficient to satisfy the infant's nutritional requirements.

➢ Artificial feeding (infant furmula)

Infant formula is usually made from cows' milk that has been treated to make it suitable for babies. The concentration of protein and electrolytes such as sodium, potassium and chloride are lower than in cow's milk, while the levels of certain minerals, primarily iron and to a lesser extent zinc are higher.

Infant formula is available in two forms:

- ready-to-feed liquid infant formula, sold in cartons, which is sterile;
- powdered infant formula, which is not sterile.

First infant formula	This is often described as suitable for newborns. It is based on the whey of cows' milk and is thought to be easier to digest than other types of infant formula. The baby can stay on this formula when you start to introduce solid foods at around six months and continue on it throughout the first year. When the baby is one year old, they can start to drink whole cows' milk. There is no evidence to suggest that changing the brand of infant formula the baby drinks does any good or harm.
Casein-based infant formula	Infant formula that is mostly based on casein is thought to take the baby longer to digest than whey-based formula. It is not recommended for young babies. There is little nutritional difference between this formula and first infant formula. Although it is often described as suitable for "hungrier babies", there is no evidence that babies settle better or sleep longer when fed this type of formula.
Follow-on formula	This is also casein-based and should never be fed to babies under six months old. Research has found no clear benefit from its use. However, the labels on this formula can look very similar to those on first infant formula, so read them carefully to avoid making a mistake.
Specialized formula	**Specialised formulas** are available to use in conditions such as reflux, high-energy need, lactose intolerance, allergic conditions and metabolic diseases like phenylketonuria. These formulas are altered in one or more nutrients and should only be used for infants with the specific conditions under medical supervision.

➢ Complementary feeding

- **Complementary feeding means giving other food in addition to breast milk.**
- **After 6 months of age to meet their evolving nutritional requirements, all infants should receive nutritionally adequate and safe complementary food while breastfeeding continues until up to 2 years of age or beyond.**
- ***HONEY SHOULD NOT BE FED TO INFANTS YOUNGER THAN 1 YEAR OLD !***

Table: Introducing complementary food

Baby's Age	Number of meals per day	Average meal size	Consistency	Suitable foods
Around 6 months (Stage 1)	*2-3 meals/ day*	*5-10 teaspoons*	*Smooth thin purée without any lumps*	*Cereals e.g. baby rice, porridge, baby cereal. Puréed vegetables e.g. carrots, squash, potato. Peeled and puréed fruit e.g. banana and pear. Well cooked chicken, fish, meat and eggs.*
6-9 months (Stage 2)	*3 meals/ day*	*2-4 tablespoons*	*Thick with soft lumps*	*Well-cooked eggs, chicken or mince. White and oily fish (boned and skinless). Yoghurt, pasteurised cheese, bread, pasta, noodles, rice.*
9-12 months (Stage 3)	*3 plus 2-3 snacks*	*4-6 tablespoons*	*Chunky, mashed texture, moving to chopped, bite size pieces*	*Most family foods are now suitable but do not add sugar or salt. Finger Foods: mango, melon, banana, toast fingers, cheese, pasta shapes.*





Risks of starting complementary foods too early

- Take the place of breast milk, making it difficult to meet the child's nutritional needs and result in a low nutrient diet;
- Increase risk of illness because less of the protective factors in breast milk are consumed;
- Increase the risk of diarrhea because the complementary foods may not be as clean or as easy to digest as breast milk;
- Increase the risk of wheezing and other allergic conditions because the baby cannot yet digest and absorb other foods well;
- Increase the mother's risk of another pregnancy if breastfeeding is less frequent.

Risks of starting complementary foods too late

Delaying the introduction of complementary foods for too long is also not advisable because:

- Breast milk alone may not provide enough energy and nutrients and may lead to growth faltering and malnutrition;
- Breast milk alone may not meet the infant's growing requirements of some micronutrients, especially iron and zinc;
- The optimal development of oral motor skills, such as the ability to chew, and the infant's ready acceptance of new tastes and textures may be adversely affected.

Infants should, therefore, be started on complementary foods at around six months of age.

➢ Dental health and nutrition

Breastfeeding	Bottle-feeding
• Although breast milk alone is not cariogenic, it may become cariogenic when combined with other carbohydrate sources. • When a child is breastfed on demand, with high frequency and duration at night, it is important to implement oral hygiene following feedings. • Stop night feedings once teeth erupt. The majority of infants are physiologically able to tolerate a prolonged fast around 6 months of age, which is when teeth typically begin to erupt.	• Bottles should only be used with formula, breast milk, or water. Fruit juices, soft drinks, sweet teas, formula, or milk should not be put in a baby's bottle during bedtime or nap time. At these times, bottles should only contain water. • Infants should be held when bottle-fed. If a bottle is given with anything other than water at nap timeor bedtime, parents should use a cloth to wipe the baby's mouth prior to laying the baby down. • Bottles should not be propped with infants in cribs or car seats. Prolonged and frequent exposure to sugary liquids contributes to the caries process, and children who drink bottles while lying down may be more prone to ear infections.

➢ Feeding infants with craniofacial anomalies

Babies with isolated clefts of the lip and/or palate can usually feed by mouth with some adjustments to bottle-feeding techniques. Tube feeding is rarely required.

Fig. Upright positioning during breastfeeding of a baby with cleft lip/palate

Fig. Proper bottle-feeding technique of a baby with cleft lip/palate

- The strategies that have been developed to feed infants with clefts of the palate are designed to overcome the lack of negative pressure developed during sucking. These include:
  a. Cross-cutting fissured nipples
  b. Squeezing a soft bottle to help with the flow of milk
  c. Pumping the breasts to deliver breast milk via bottle
  d. Developing patience in feeding
  e. Feeding instruction and follow-up with a feeding specialist on the cleft palate team
- It is important to ensure that the energy that a child expends during feeding does not exceed the nutritional and caloric intake from the feeding. This problem may occur if feeding takes more than 30 minutes.
- Steady weight gain is the most important indicator of adequate food intake. Close follow-up with a pediatrician or other health care provider is necessary to ensure that consistent weight gain is achieved.
- Often a cleft palate is temporarily covered by a palatal obturator (a prosthetic device made to fit the roof of the mouth covering the gap).

Calculation of breast-milk substitutes daily requirements

- **Volumetric method**
  - The daily volume of breastmilk sunstitute for infants from 10 days to 2 months of age makes 1/5 of body weight, 2-4 months -1/6, 4-6 months - 1/7
  - 2-6 old child should get 150 ml of breastmilk suntitute per kg of body weight
- **Calorimetric method (energy density in a formula is 65 kcal/100 ml)**
  - Premature infants up to 3-4 months demand about 120-140 kcal per kg of weight per day
  - Term infants up to 3-4 months demand 110-120 kcal per kg per day
  - As the infant grows the demand per body weight decreases and for the one years old infant is about 100 kcal per kg per day
  - The daily volume of the milk (ml) = weight (kg) x caloric requirment (kcal/kg/day) / 0. 7
  - The calculated amount should not be more than one litre and has only orientational meaning.

Home-prepared formula

The milk used as the base for home-prepared formula may be:

- Fresh milk that is heat-treated at home,
- Commercially heat-treated whole milk (such as UHT or sterilized milk),
- Powdered full cream milk, or
- Non-sweetened evaporated milk.

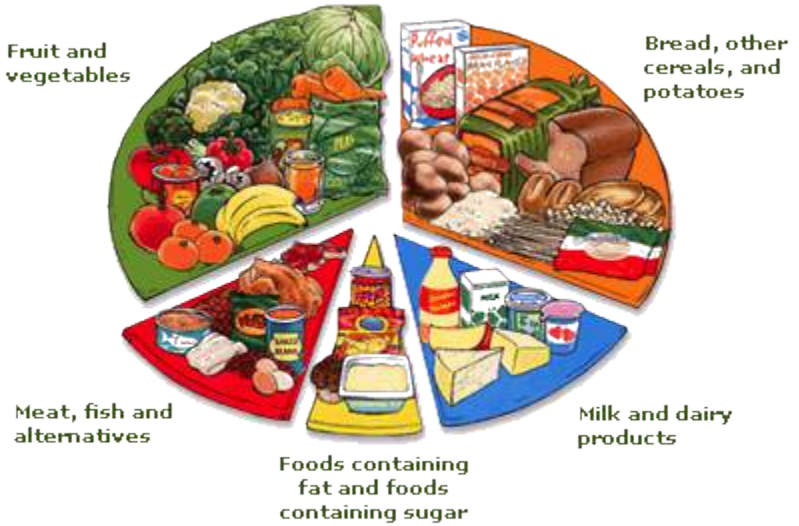
- The animal milks used may be from cows, buffalo, goat, ewe, camel or other animal.
- In full strength full cream milk, the level of protein and some minerals is too high, and it is difficult for an infant's immature kidneys to excrete the extra waste. These milks require some modification to make the proportions more appropriate.

- **WHO recommends the following recipe for home prepared formula:**
  - Boil 70 ml of water
  - Add 130 ml of boiled cow’s milk to make 200 ml of feed
  - Add 1 level teaspoonful (5g) of sugar
  - For sheep’s milk the milk and water amounts should be 100 ml to100 ml

Principles of a Balanced Nutritious Diet for Children over 1 Year

Foods can be divided into five food groups based on the nutrients they contain, and an average daily combination of a number of servings from each food group provides nutritional adequacy.

- The food groups and number of servings children require are:
  - bread, rice, potatoes, pasta and other starchy foods – include at each meal and some snacks: 3–5 servings
  - fruit and vegetables – include at each meal and some snacks: about five servings
  - milk, cheese and yogurt – three servings per day
  - meat, fish, eggs, nuts and beans – two servings per day or three for vegetarians
  - foods high in fat and foods high in sugar – small amounts that do not replace the other food groups.



- Sweet foods should be limited to four times per day.
- Between six and eight drinks should be offered each day.
- The number of average daily servings of each food group is the same throughout childhood from 12 months of age but portion sizes of food and drinks increase as children grow and their energy and nutrient requirements increase.
- Assessing the average number of daily servings from each food group can be used to help parents and children make changes to improve the nutritional adequacy of their diets.

Nutrient-dense vs. Energy-dense Food

Nutrient-dense foods are characterized by a high amount of nutrients such as vitamins, calcium, fiber (e.g. mg/g, g/L):

- Fruits, vegetables, whole grains
- Fat-free or low-fat milk and milk products, yogurt
- Lean meats, poultry, fish, beans, eggs, and nuts

Foods with added sugar or fat are usually not nutrient-dense.

Energy-dense food items are characterized by a high amount of calories (e.g. kcal/g, kcal/L):

- Chocolate
- French fries, crackers
- Regular sodas and alcoholic drinks

Most nutrient-dense foods are not energy-dense, but nuts are an exception.

Table. Food groups and recommended daily servings

[*Adapted from* More J. *Infant, Child and Adolescent Nutrition: A Practical Handbook*. CRC Press, 2013.]

Food groups	Foods included	Main nutrients supplied included supplied	Recommendations		
			Infants 6–12 months	Preschoolers 1–4 years	School children and adolescents
Group 1: Bread, rice potatoes, pasta and other starchy foods	Bread, chapatti, breakfast cereals, rice, couscous, pasta, millet, potatoes, yam, and foods made with flour such as pizza bases, buns, pancakes	Carbohydrate B vitamins Fibre Some iron, zinc and calcium	3–4 servings a day	Serve at each meal and some snacks	Serve at each meal and some snacks
Group 2: Fruit and vegetables	Fresh, frozen, tinned and dried fruits and vegetables	Vitamin C Phytochemicals Fibre Carotenes	3–4 servings a day	Offer at each meal and some snacks – about 5 small servings a day	Serve at each meal and some snacks – aim for 5 servings a day
Group 3: Milk, cheese and yogurt	Breast milk, infant formulas, follow-on milks, cow's milk, goat's milk, yogurts, cheese, milk puddings, toddler milks, calcium-enriched soya milks, tofu	Calcium Protein Iodine Riboflavin	Demand feeds of breast milk or infant formula as main milk drink (decreases from about 1000 mls/day down to about 500 mls/day as food in take increases) Some yogurt and cheese	3 servings a day 1 serving is: – 120 mL milk drink – 1 pot yogurt (120 g) – a serving of cheese in a sandwich or on a pizza – a milk-based pudding – a serving of tofu	3 servings a day 1 serving is: – 150–250 mL milk drink – 1–2 pots yogurt (120 g) – a serving of cheese in a sandwich or on a pizza – a milk-based pudding – a serving of tofu
Group 4: Meat, fish, eggs, nuts and pulses	Meat, fish, eggs, nuts and pulses (lentils, dahl, chickpeas, hummus, kidney beans and other similar starchy beans)	Iron Protein Zinc Magnesium B vitamins Vitamin A Omega 3 longchain fatty acids: EPA and DHA* from oily fish	1–2 servings a day 2–3 for vegetarians	2 servings a day or 3 for vegetarians Fish should be offered twice per week and oily fish at least once per week	2 servings a day or 3 for vegetarians Fish should be offered twice per week and oily fish at least once per week
Group 5: Foods and drinks high in fat and/or sugar	Cream, butter, margarines, cooking and salad oils, mayonnaise, chocolate, confectionery, jam, honey, syrup, crisps and other high-fat savoury snacks, biscuits, cakes Fruit juices and sweetened drinks	Some foods provide: – vitamin E – omega 3 fatty acids: alphalinolenic acid		In addition to but not instead of the other food groups	In addition to but not instead of the other food groups
Fluids	Drinks	Water Fluoride in areas with fluoridated tap water	Milk feeds and drinks of water offered with meals	6–8 drinks per day – each of 100–120 mL. More in hot weather or after extra physical activity	6–8 drinks per day – each of 150–250 mL. More in hot weather or after extra physical activity
Vitamin supplements			Vitamins D for breastfed infants and formula-fed infants drinking less than 500 mL formula milk/day		Folic acid and vitamin D for adolescent girls who could become pregnant and during pregnancy

* DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid

Nutrition for Preschool Children 1–4 Years

- **1–4 year olds need a balanced diet based on a combination of foods from the five food groups.**
- **A daily meal and snack routine of 3 meals and 2–3 planned nutritious snacks will provide adequate calories and nutrients and prevent toddlers becoming over hungry or too tired to eat.**
- **Toddlers' appetites vary from day to day and they should be allowed to eat to their appetite and finish eating when they have had enough.**
- **Snacks given should always be nutritious snacks as toddlers are unlikely to eat an adequate amount of nutrients in just three meals.**
- **High-calorie low-nutrient foods should be limited to small quantities and offered as part of a meal.**
- **Teeth of under-fives are vulnerable to dental decay and sugary and acidic foods should be limited to four occasions per day (e.g. three meals and one snack).**

Nutrition for School Age Children 5-10 Years

- **Children prefer familiar foods and most need to be motivated to try new foods.**
- **Children innately prefer sweet, salty and energy-dense foods.**
- **Parents and carers are responsible for food offered to primary school age children and have the power and influence to change eating habits.**

In a new policy statement, the American Academy of Pediatrics (AAP) urges schools and families to take a broader approach to nutrition, considering children's whole diet pattern – rather than the amount of sugar, fat or specific nutrients in individual foods [Murray et al. 2015]. The AAP recommends a five-step approach parents and schools can take in selecting food for packed lunches and social events:

- ***Select a mix of foods from the five food groups: vegetables, fruits, grains, low-fat dairy, and quality protein sources, including lean meats, fish, nuts, seeds and eggs.***
- ***Offer a variety of food experiences.***
- ***Avoid highly processed foods.***
- ***Use small amounts of sugar, salt, fats and oils with highly nutritious foods to enhance enjoyment and consumption.***
- ***Offer appropriate portions.***

Nutrition for Adolescents

Adolescents' nutritional needs are influenced by a number of factors.

● **Biologic considerations** include enhanced needs related to an increased growth rate and change in body composition; males have a greater blood volume and leaner body mass than females, who need a minimum fat mass for menstruation and reproduction. In addition to increased energy needs, growth in lean body mass will require increased intake of calcium, iron, nitrogen, zinc, magnesium, fluoride, and vitamins A, C, and D. Acute and chronic illness, trauma, and stress will add to the needs imposed by growth and physical activity.

● **Behavioral considerations** during the adolescent years include changes in food habits related to levels of activity, changes in schedules, and a desire for independence, resulting in skipped meals, more frequent snacking, and more meals outside the home (including fast food).

Psychological changes and emotional difficulties at this age can lead to **eating disorders**. Last, **dissatisfaction with body image** may be associated with frequent dieting. Because boys usually eat more food than girls, their risk of deficiencies is reduced.

QUIZ

You are seeing a 16-year-old girl for her annual health supervision visit. The girl has become a vegan, and her mother is concerned about possible nutritional deficiencies. The girl has no symptoms and has not lost any weight in the last 6 months. Her menses are regular and her physical examination findings are unremarkable. Of the following, the girl's diet puts her at GREATEST risk of a deficiency of

A. calcium
B. iron
C. vitamin A
D. vitamin B12
E. vitamin D

Typically, **vegetarian diets** are broken into three major groups including **lacto-ovo vegetarians** (whose diets include eating dairy products and eggs), **lacto vegetarians** (who eat dairy, but avoid eggs), and **vegan vegetarians** (those who avoid animal products altogether).

As a vegan, the girl described in the vignette is most likely to develop a **deficiency in B12**, a vitamin almost exclusively found in animal products. Vegans require supplements or fortified food products to meet their need for this vitamin. Because the high intake of folic acid in vegan diets may mask the hematologic aspects of vitamin B12 deficiency, diagnosis may be delayed until neurologic symptoms occur. Other potential deficiencies associated with a vegan diet include calcium, iron, zinc, vitamin A and D, and perhaps other trace elements, but adequate intake can be ensured by following recommended vegan food group allowances and serving sizes.

PEARLS

• Adolescents' eating habits put them at risk for nutritional deficiencies.
• Vegan diets pose potentially more serious health risks (deficiency of vitamin B12 but to a lesser extent vitamins A and D and calcium, iron, and zinc) compared with vegetarian diets.
• Vegans/vegetarians may have an underlying eating disorder.

Table. Eating behaviors of adolescents

EATING BEHAVIORS		
Indicators of Nutrition Risk	**Relevance**	**Criteria for Further Screening and Assessment**
Exhibits poor appetite.	A poor appetite may indicate depression, emotional stress, chronic disease or eating disorder.	Assess if BMI is less than the 15th percentile or if weight loss has occurred. Assess if irregular menses or amenorrhea has occurred for 3 months or more. Assess for organic and psychiatric disease.
Consumes food from fast-food restaurants 3 or more times per week.	Excessive consumption of convenience foods and foods from fast-food restaurants is associated with high fat, calorie, and sodium intakes, as well as low intake of certain vitamins and minerals.	Assess the adolescent who is at-risk for overweight/obese or who has diabetes mellitus, hyperlipidemia, or other conditions requiring reduction in dietary fat.
Skips breakfast, lunch, or dinner/supper 3 or more times per week.	Meal skipping is associated with a low intake of energy and essential nutrients, and, if it is a regular practice, could compromise growth and sexual development. Repeatedly skipping meals decreases the nutritional adequacy of the diet.	Assess the adolescent to ensure that meal skipping is not due to inadequate food resources or unhealthy weight loss practices.
Adolescent consumes a vegetarian diet.	Vegetarian diets can provide adequate nutrients and energy to support growth and development if well planned. Vegan diets may lack calcium, iron, vitamins D and B-12. Adolescents who have eating disorders may adopt low fat vegetarian diets.	Assess the adolescent who consumes fewer than 2 servings of meat alternatives per day. Assess the adolescent who consumes fewer than 3 servings of dairy products per day. Assess the adolescent for eating disorder and adequacy of energy intake who follows a low fat vegetarian diet and experiences weight loss.

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5. Horvath T, Madi BC, Iuppa IM, et al: Interventions for preventing late postnatal mother-to-child transmission of HIV, Cochrane Database Syst Rev 1:CD006734, 2009.
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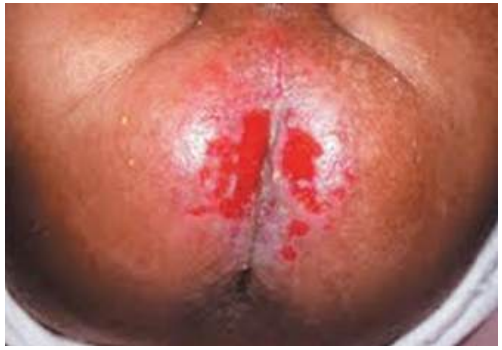
CASE: FOREMILK SYNDROME

CLINICAL PRESENTATION

A 20-day-old newborn was brought to outpatient department (OPD) for the 3rd time with many complaints. Baby passes motion frequently with every feed and few drops of motion with every cry, cough and otherwise. Baby regurgitates small amounts of milk often and is cranky most of the time.
Mother gives history that baby is sucking vigorously, but, only for few minutes, goes off to sleep and demands after an hour again. The baby's perianal area is red and ulcerated (fig).



TREATMENT AND FOLLOW-UP

Mother is educated that 1st milk (foremilk) is rich in 'sugars' and has short gastric emptying time, baby gets hungry frequently, but frequent feeding finds the baby with only little hunger. Baby sucks for a short while (<10 minutes) and gets only foremilk. Drinking only foremilk is the cause of frequent stool and regurgitation. Mother gradually spaces the feeds to 2.5–3 hours, feeds the baby for 15 minutes from one breast in one sitting. The baby's symptoms rapidly improve.

DIAGNOSIS

Foremilk syndrome.

INVESTIGATION

Good history.

DISCUSSION

Educating mothers on lactation by demand than by schedule, from one breast in one sitting and recognizing that every cry is not hunger is very important.

LEARNING POINT

Hindmilk is important for weight gain and is possibly a cure for 'colic'.

YEREVAN STATE MEDICAL UNIVERSITY AFTER MKHITAR HERATSI

DEPARTMENT OF PEDIATRICS №1

2017

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Musculoskeletal System

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THE SKELETAL SYSTEM

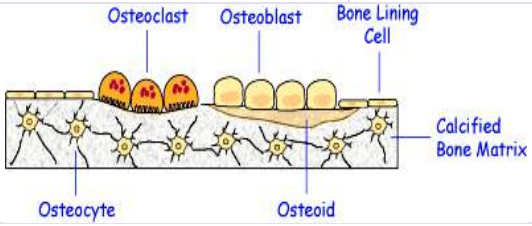
The skeletal system is comprised of different structures: bones, joints, cartilage , and ligaments.

Most bones form by replacing cartilage. The presence of cartilage is essential for bone growth and development. The cartilage ability to grow fast, while maintaining a sufficient degree of density makes it exceptionally favorable skeletal material for the fetus.

➢ *BONE TISSUE*

Bone tissue *is a unique connective tissue, 90-98% of which consists of intercellular substance – bone matrix. It contains large amounts of minerals, mainly calcium phosphate salts.*

Bone matrix		Bone cells (2-10%)		
Osteoid (organic matrix)	Minerals	Osteoblasts	Osteocytes	Osteoclasts
90-95% *Collagen type1* **5-10%** *Noncollagenous proteins: osteocalcin*, osteopontin, osteonectin etc.	**95%** Calcium phosphate salts	1. Plump cuboidal single nucleated cells that synthesize and deposit bone matrix. 2. Derived from mesenchymal stem cell lineage. Bone lining cells are inactive osteoblasts that cover all available bone surfaces.	1. A derivative of osteoblasts created when osteoblasts are encased in bone matrix 2. Connected to other osteocytes in a network via cell processes running through canaliculi	1. Giant multi-nucleated cells 2. Secrete acids and enzymes (collagenase) to break down bone matrix 3. Derived from macrophage lineage



Within the bone tissue phosphate salts of calcium are presented in two forms:

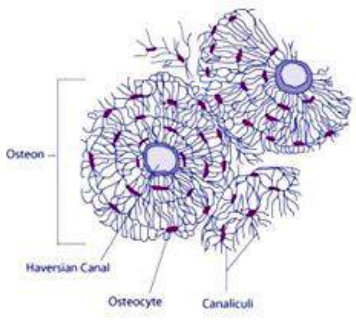
- ***amorphous calcium phosphate*** $Ca_3(PO_4)_2$***;***
- ***crystals of hydroxyapatite*** $Ca_{10}(PO_4)_6(OH)_2$***.***

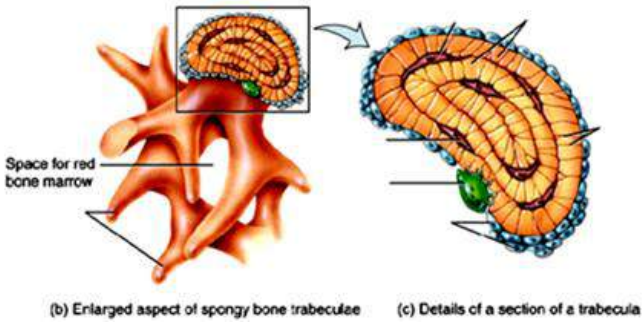
In early childhood amorphous masses of calcium phosphate are more predominant than crystals of hydroxyapatite. So their bones are demineralized easier than those in adults.

➢ *TYPES OF BONE TISSUE*

Bone tissues

- ***Cortical (compact) bone*** *- consists of concentrically arranged lamellae with central (Haversian) canals* — It's mineralized by 80-90% and predominates in the extremities
- ***Trabecular (spongy or cancellous) bone*** *- consists of irregularly arranged lamellae* — It's mineralized by 15-25% and predominates in the axial skeleton





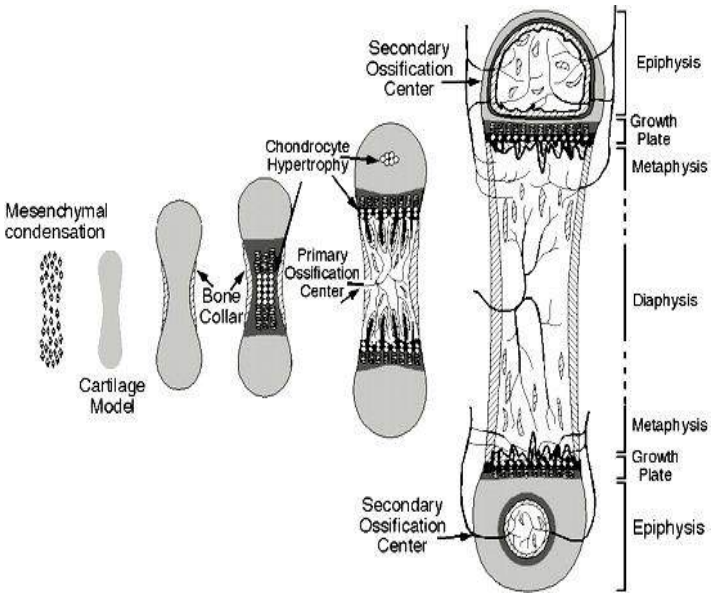
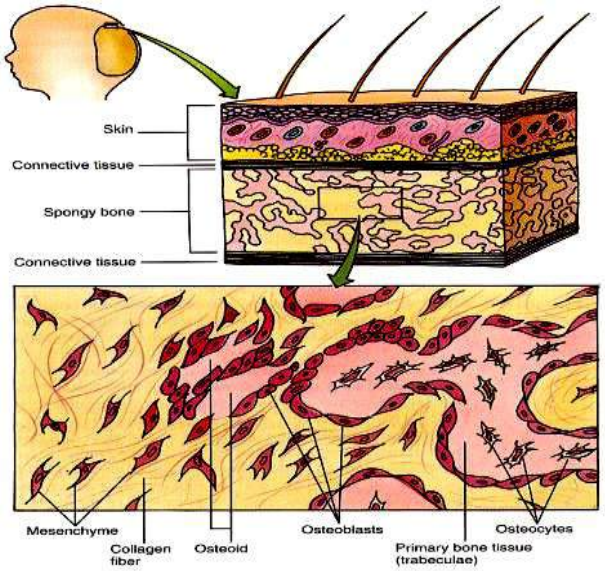
In comparison with adults, in the skeleton of children trabecular bone is more predominant than the cortical bone. A child's bones are more plastic and more porous than adult bone, with wider haversian canals.

➢ *BONE DEVELOPMENT*

During the development of bones three main processes occur: osteogenesis, modeling and remodeling.

OSTEOGENESIS	MODELING	REMODELING
Bone formed on soft tissue: Two major subclassifications: - Intramembranous: bone formed on soft fibrous tissue - Endochondral: bone formed on cartilage	Bone formed on existing bone tissue	Bone both resorbed and formed at the same site
Occurs during embryonic development, early stages of growth, and during healing	Occurs during growth, and during healing	Occurs from growth through death

In adults only remodeling occurs, while in children all processes mentioned above occur with high intensity.

Endochondral ossification, in which mesenchymal cells condense and undergo chondrogenesis to form cartilage that matures and hypertrophies, becomes calcified, and is then replaced by bone. Most bones in the axial and appendicular skeleton are formed in this way.	**Intramembranous ossification,** in which osteoblasts are formed by direct differentiation of mesenchymal cells with no cartilage precursor or model. Flat bones of the skull and clavicle are formed in this way.
	

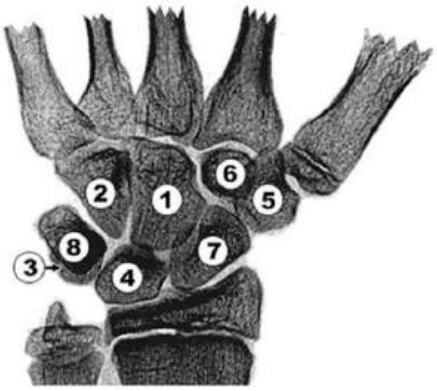
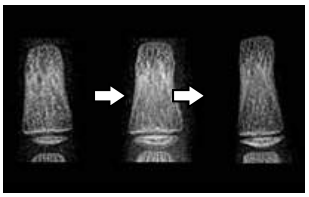
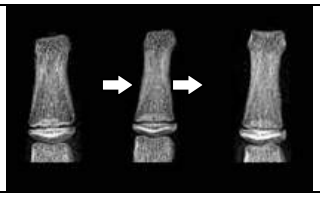
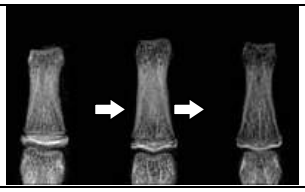
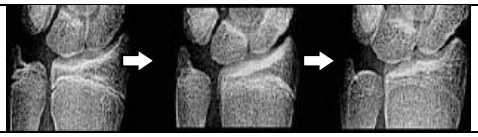
Centers of ossification:

Primary centers of ossification: At the beginning of the fetal period the chondrocytes in the midshaft of long bones from the primary centers, growth from which eventually lengthens the bone.

Secondary centers of ossification: These appear in the chondroepiphysis and mostly appear postnatally. They direct the formation of bone throughout growth.

The ossification centers that are typically present at term birth are the distal femur, proximal tibia, calcaneus, and talus.

The many ossification centers of the body—hand, foot, knee, elbow, and pelvis, for example—are not visible by radiography (x rays) until they begin to mineralize or ossify, even though they are actually present long before such mineralization begins. The age at appearance of individual ossification centers then becomes a useful measure of skeletal development and especially in the form of "**bone age**" assessments of the hand, foot, or knee. Such assessments, made by taking a series of radiographs and comparing them against appropriate standards, are both highly reliable and useful estimates of the stage of physical development. Bone age assessments are, therefore, used in pediatric evaluation, especially when malnutrition, malabsorption, food intolerance, or endocrinopathies (such as hypopituitarism or hypothyroidism) are suspected. Bone age assessments also have forensic application, such as estimating the chronological age of a cadaver. In addition, they can provide data for making age assessments for children whose birth date in unknown or for whom a birth certificate does not exist or is suspected of being inaccurate. Families adopting infants or children from countries in which there has been socioeconomic stress may find bone age **assessment** helpful in establishing the chronological age their adopted child has attained.

Depiction of the order of appearance of the individual carpal bones. The usual sequence is: capitate (1), hamate (2), triquetral (3), lunate (4), trapezium (5), trapezoid (6), navicular or scaphoid (7) and pisiform (8). The distal epiphysis of the radius ossifies before the triquetum and that of the ulna before the pisiform. **The Greulich-Pyle atlas** is commonly used for bone age assessment.	
Assessments of skeletal maturity in pre-pubertal children are primarily based on the epiphyseal size of the phalanges as they relate to the adjacent metaphyses. During this stage of development, the ossification centers for the epiphyses increase in width and thickness, and eventually assume a transverse diameter as wide as the metaphyses.	
As in pre-pubertal children, assessments of skeletal maturity in early and mid-puberty are also based on the size of the epiphyses in the distal phalanges (first) and the middle phalanges (second). The epiphyses at this stage continue to grow and their widths become greater than the metaphyses.	
Assessments of skeletal maturity in late puberty stage are primarily based on the degree of epiphyseal fusion of the distal phalanges.	
In post-pubertyall carpals, metacarpals and phalanges are completely developed, their physes are closed, and assessments of skeletal maturity are based on the degree of epiphyseal fusion of the ulna and radius.	

The normal variability of skeletal age is about 10 percent of attained chronological age. Thus, some chronological 12-year-olds may be assessed as 14 years of age in terms of skeletal development, while others may be assessed as ten. Bone age is useful in projecting final stature; research has shown that it is more meaningful in making such projections than chronological age alone.

Typical long bones are divided into:

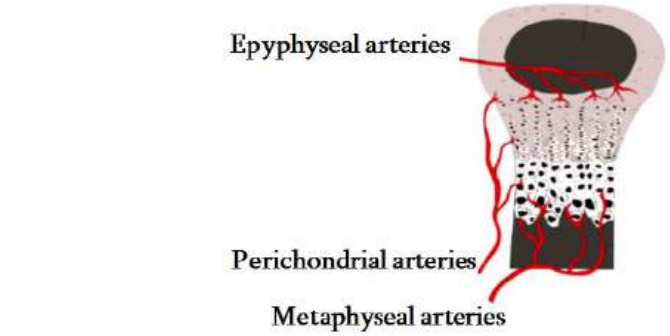
- **Physis**, which is the growth plate located at the end of bone
- **Epiphysis**, which is typically the secondary ossification center
- **Metaphysis**, which is the bone adjacent to the physis on the side away from the joint
- **Diaphysis**, which is the central part or shaft of long bones

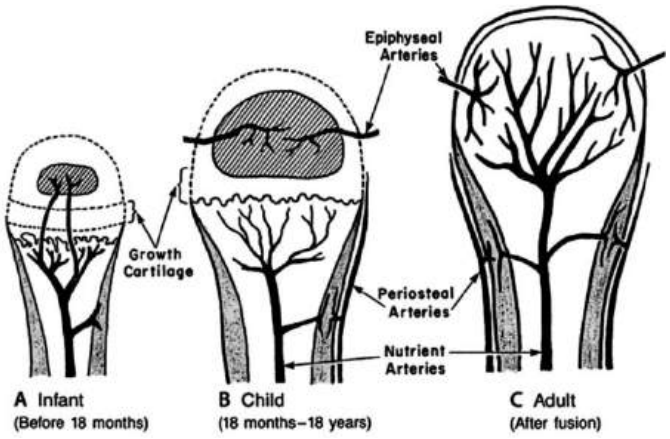
The long bones of the extremities (humerus, radius-ulna, femur, tibia-fibula) have **growth plates or physes at each end.** The ends of each long bone are composed of the epiphyses. These are covered by articular cartilage and form the associated joints. Epiphyses are almost entirely cartilaginous in the beginning and become progressively more ossified during growth.
The perichondrial ring, which surrounds the physes, as well as the perichondrium around the epiphyses and **periosteum**, which surrounds the metaphysis and diaphyseal regions of the bone, contributes to appositional or circumferential growth. Bones without physes (pelvis, scapulae, carpals, tarsals) grow by appositional bone growth from their surrounding perichondrium and periosteum. Other bones (metacarpals, metatarsals, phalanges, spine) grow by a combination of both appositional and endochondral ossification.
The periosteal sleeve is much thicker in children than in adults and acts as a restraint to displacement. Angular deformation of a child's bone may cause fracture of the cortices without displacement (**"greenstick" fracture**). This is due to high bone plasticity and thick fibrous structure of periosteal sleeve in children.

➢ *GROWTH PLATE (PHYSIS, EPIPHYSEAL PLATE)*

The most important difference between children and adults is the presence of growth plates. **Fusion of epiphyses is** a gradual process initiated by the secretion of oestrogen from the adrenals in boys and ovaries in girls. Epiphyseal fusion occurs at 18-19 years in boys and 16-17 years in girls. It limits final adult height.

Three separate vascular systems supply the metaphysis, perichondrium and epiphysis and their respective plate sections. The metaphyseal and epiphyseal vascular systems communicate with each other via the perichondrial system. But individual small vessels also pass directly through the epiphyseal plate, particularly during infancy, although such vessels also appear to be present during adolescence.
Vessels in the metaphysis have a tortuous course and slow, turbulemt flow. This is a common site of osteomyelitis in children, because bacteria or emboli easily gets trap in the hair-pin bends, causing infarction.
The perichondrial vascular system breaks down during puberty and is gradually replaced by vessels which, after closure of the epiphyseal plate, grow through the plate from the metaphyseal to the epiphyseal side. The vascular connection between the metaphysis and epiphysis is at its weakest, and the number of vessels penetrating the plate at its lowest, during the pubertal growth spurt. Any disruption of the perichondrial vascular system at this time can have disastrous consequences for the epiphysis, possibly resulting in **avascular necrosis**.





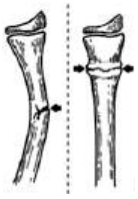
➢ *BIOMECHANICAL PECULIARITIES OF THE MUSCULOSKELETAL SYSTEM*

The musculoskeletal system consists of tissues with widely differing characteristics. Overloading causes failure to occur at the weakest point. The mechanical properties of the various structures change during growth.

! The critical structure in small children under 10 years of age is bone tissue, while this role is assumed by growth cartilage in adolescents. In young adults, the ligaments can ultimately be described as the weakest point in the tissue system of the musculoskeletal apparatus. In old age – because of osteoporosis – bone again becomes the organ with the lowest loading tolerance.

The bone in children is more plastic and less elastic than mature bone. In clinical terms, this plastic deformation is demonstrated by the greenstick and torus fractures typically seen in children (lat. torus - protuberance). This is owing in large part to the thick fiborous periosteum of immature bone. The bone of small children fractures at lower loads compared to bone in adults.

"Greenstick" fracture (a bend in the bone on one side and a visible break in the bone cortex on the other side)

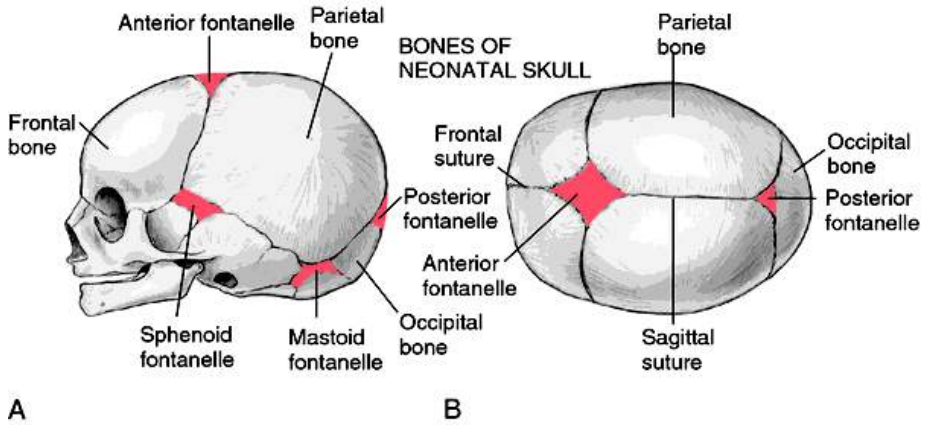


Torus fracture (a buckle injury without a visible break in the bone cortex)

➢ *POSTNATAL DEVELOPMENT OF THE SKELETON*

CRANIOFACIAL SKELETON

At birth, the ratio between cranial volume and facial volume is 8:1, where as in adults, this ratio is 2.5:1. Eighty percent of cranial growth occurs during the first years of life. Only after the first 2 years of life the rate of facial growth begins to exceed that of skull growth. The orbit and the brain are near growth completion by age 7; however, lower facial growth continues into the early 20s.

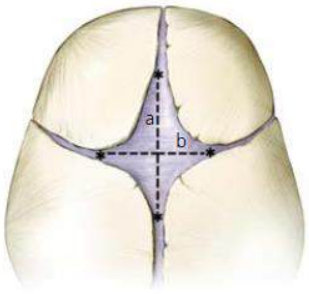


- *In newborns the **cranial sutures** are patent. They serve as the most important centers of growth in the skull.*
  *Some cranial bones of the newborn do not completely cover the brain but are connected by large fibrocartilaginous membranes, called **fontanelles (fonticuli crania**).*
  The fontanelles provide two important functions:
  - *they provide space between the bones and make the newborn skull flexible during the childbirth,*
  - *they support the fast growth of the brain by their expansion (the brain expands faster than the surrounding bone can grow):*
- *A newborn has **6 primary fontanelles:*** two along the midline of the top of the vault (the anterior or bregmatic and the posterior or lambdoid fontanelles) and two on each side of the lateral vault (right and left sphenoidal or anterolateral fontanelles and right and left mastoid or posterolateral fontanelles). The two midline fontanelles both participate in *anteroposterior and medioateral* brain growth. The fontanelles on the lateral vault permit *superoinferior brain growth*.
- Two additional fontanelles (metopic fontanelle and sagittal or third fontanelle) can also be present in humans.

- Posterior fontanelle generally closes 2-3 months after birth posterior fontanelle generally closes 2-3 months after birth.
- Anterior fontanelle is generally the last to close between 1-3 years of age (in one recent human sample, the anterior fontanelle was closed in most individuals by 31 months postnatally, in another sample most individuals older than 17 months exhibited closure of this fontanelle) *(The Center for Academic Research and Training in Anthropogeny).*
- With the exception of the metopic suture (fusion of which normally occurs in the first 12-24 months of life), the vault sutures remain patent until the third decade of life.

- **Delayed closure of the anterior fontanelle** is seen in rickets and in skeletal dysplasias.
- Premature fusion of one or more cranial sutures is called **craniosynostosis,** resulting in an abnormal head shape. Craniosynostosis and abnormal brain development are associated with a small fontanel or early fontanel closure.

Measurement of the anterior fontanel



a – anteroposterior diameter
b – transverse diameter

$$\frac{a+b}{2} = \text{anterior fontanel size}$$

On the first day of an infant's life, the normal fontanel ranges from 0.6 cm to 3.6 cm, with a mean of 2.1 cm.17 Black infants have larger fontanels (1.4 cm to 4.7 cm).
The fontanel can enlarge in the first few months of life.

TEETH AND JAWS

The first tooth eruption is usually between 4 and 15 months of age.

- If eruption of the first tooth has not occurred by 18 months, the child should be referred to a dentist for evaluation.
- Premature and low birth weight babies can have delayed primary tooth eruption and enamel defects, putting them at higher risk for decay.
- Eruption is usually symmetrical (lower teeth usually before upper) in the following pattern for primary teeth: central incisors, lateral incisors, first molars, canines, second molars. Exfoliation often follows a similar pattern.
- A helpful mnemonic to remember the timing of primary eruption is the 7+4 rule. At 7 months of age, children should have their first teeth; at 11 months (4 months later), they should have 4 teeth. At 15 months of age (4 months later), they should have 8 teeth; at 19 months, they should have 12 teeth; at 23 months, they should have 16 teeth; and at 27 months, they should have 20 teeth.

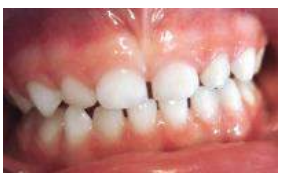
- **Some healthy babies may have tender and swollen gums when teething.**
- **Diarrhea, rashes, and a fever are not normal for a teething baby** *(A Pediatric Guide to Children's Oral Health. AAP; 2009).*

- Eruption is similar for the permanent teeth, beginning between 5 and 7 years and usually finishing by 13 to 14 years of age. The typical pattern is central incisors, lateral incisors, first molars, premolars, canines, second molars, and third molars (wisdom teeth), although not everyone develops or erupts third molars.
- It is common to see permanent teeth erupt behind the primary incisor teeth in the lower jaw. This typically resolves itself without intervention, although professional dental monitoring is indicated.
- The first permanent molars erupt around 6 years of age.
- Teeth will sometimes erupt entirely out of the "normal" anticipated sequence; this should not be a concern.
- Tooth loss (also known as shedding or exfoliation) usually starts with the lower primary central incisors.

- Teething begins as early as 3 months and continues until the child is approximately 3 years of age.
- The spacing between children's baby teeth is important because it allows enough room for the bigger, permanent teeth.
- Primary teeth have thinner enamel and appear whiter (translucent/almost bluish) than permanent teeth.
- Disease may progress more quickly in primary teeth.
- Permanent teeth have wavy edges (mamelons) when they erupt, which smooth out with normal wear and tear.

- ***Delayed teeth eruption*** *can be seen both in local dental problems and systemic or hereditary diseases (eg. rickets, hypothyroidism, osteogenesis imperfecta, skeletal dysplasias, Down syndrome etc.).*
- *Rarely* ***premature teeth eruption*** *occurs:*
  - natal teeth (observed at birth),
  - neonatal teeth (observed during the first month of life).

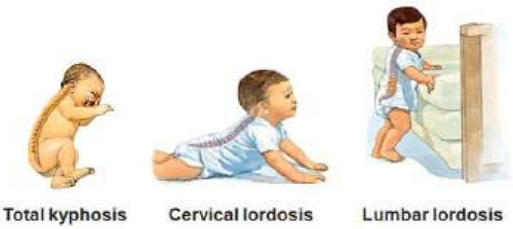
Most often they are the mandibular incisors of the normal dentition, rarely – supernumerary teeth that should be extracted. Radiographic examination is an essential tool for the differential diagnosis between supernumerary primary teeth and teeth of the normal dentition.


Normal primary teeth


Natal teeth

SPINAL COLUMN

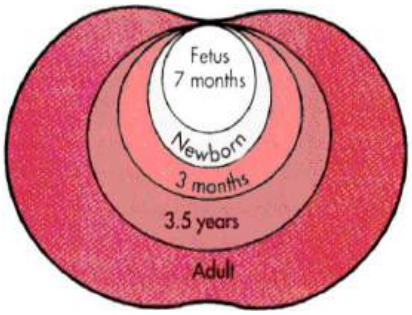
At birth the spinal column has only anterior curvature (total kyphosis).
Cervical and lumbar curvatures begin with holding head up and walking.
All curvatures are completely developed by age 10.
Various conditions may exaggerate the normal curves of the vertebral column (hyperkyphosis, hyperlordosis), or the column may acquire a lateral bend (scoliosis).

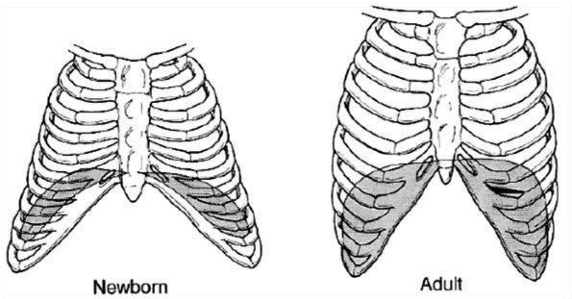


Q: *Leading scientists and car safety organizations (including the American Association of Pediatrics) all recommend keeping children* ***rear-facing*** *in their car seats for as long as possible. Why?*

CHEST

- In infants the anteroposterior diameter is approximately the same as the lateral diameter.
- In adults the anteroposterior diameter is less than the lateral diameter.



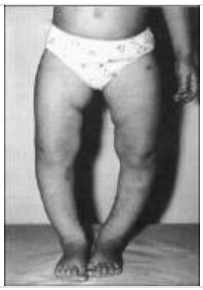


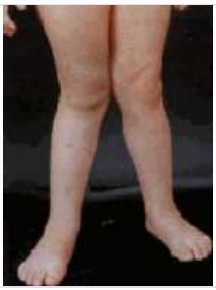
- The infant's rib cage is softer and thus more compliant compared to an adult's.
  Although a soft, highly compliant chest wall is beneficial to a baby in its passage through the birth canal and allows future lung growth, it places the young infant in a vulnerable situation under certain pathologic conditions.

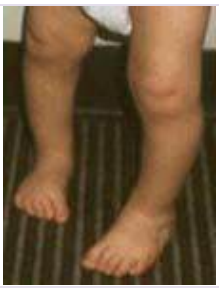
EXTREMITIES

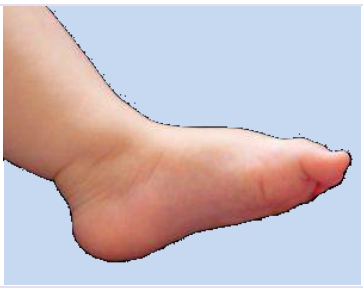
- *There are some normal variants of lower limb development (such as in-toeing, out-toeing, flat feet, bow-legs and knock knees) that are a common cause for parental concern.*

- **The alignment of the lower limbs** changes as the child progresses from crawling to the unsteady bipedal gait of the toddler and, finally, to the established bipedal gait of the child. The toddler demonstrates a **varus alignment (physiologic genu varum)** at the knee and a waddle in the gait; the foot arches are yet not developed. By about 2 years of age, knee alignment of the knee becomes neutral. Over the next few years, knee alignment progresses to a **physiologic genu valgum**, which spontaneously corrects itself to a normal tibiofemoral alignment by about 7 years of age. These variations are important to understand because parents often consult an orthopedist for these issues, which require nothing more than careful clinical examination and reassurance. The varus and valgus alignments are believed to be dictated by the relative growth rates of the articular cartilage and the adjacent physeal zone. The physis grows almost 5 times faster than the articular cartilage does. This difference may control varus and valgus alignment: varus develops if the medial sides grow more slowly than the lateral sides, and valgus develops if they grow more quickly.


Physiologic genu varum


Physiologic genu valgum


In-toeing


Flat feet

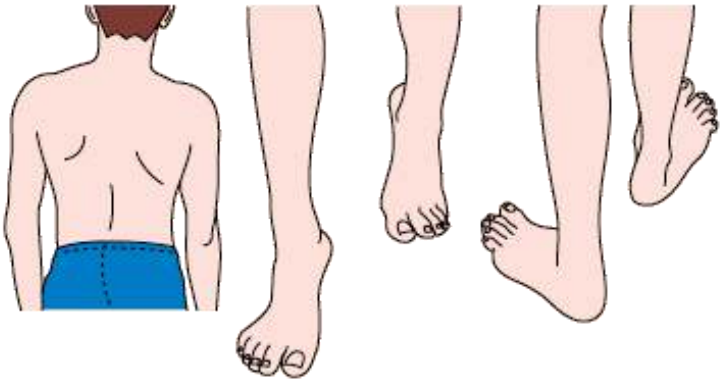
pGALS – MUSCULOSKELETAL SCREENING FOR SCHOOL-AGED CHILDREN

- **pGALS- pediatric Gait, Arms, Legs, Spine** (Differences from adult GALS highlighted in bold)

Screening questions

- *Do you (or your child) have any pain or stiffness in your joints, muscles or your back?*
- *Do you (or your child) have any difficulty getting yourself dressed without any help?*
- *Do you (or your child) have any difficulty going up and down stairs?*

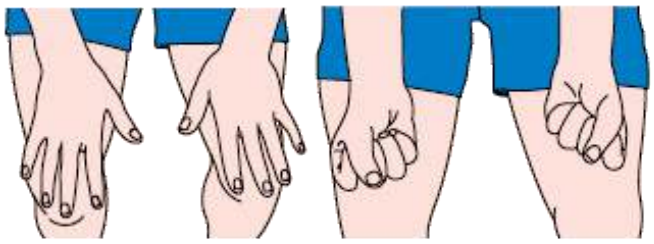
POSTURE AND GAIT



Observe standing (from front, back and sides)

Observe walking **'Walk on your tip-toes, walk on your heels'**

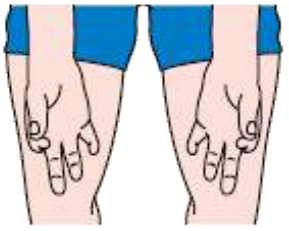
ARMS



'Put your hands out straight in front of you'

'Turn your hands over and make a fist'

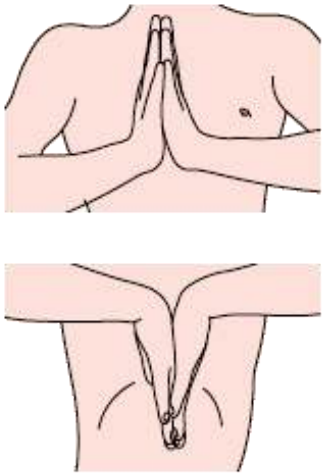
ARMS



'Pinch your index finger and thumb together'

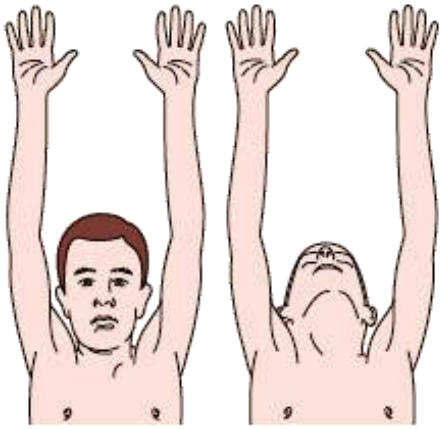
'Touch the tips of your fingers with your thumb'

Squeeze the metacarpo-phalangeal joints for tenderness



'Put your hands together palm to palm'

'Put your hands back to back'



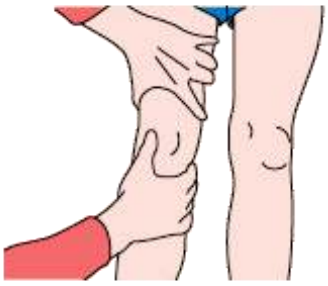
'Reach up and touch the sky'

'Look at the ceiling'

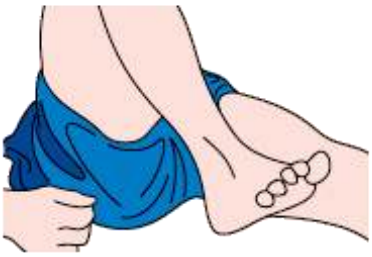
ARMS

'Put your hands behind your neck'

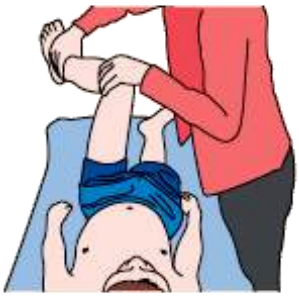
LEGS



Feel for effusion at the knee



'Bend and then straighten your knee' (Active movement of knees and feel for crepitus)

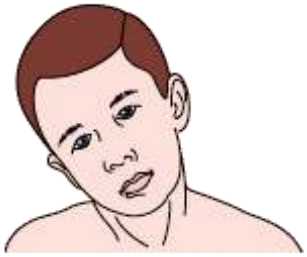


Passive movement of hip

TEMPOROMANDIBULAR JOINT

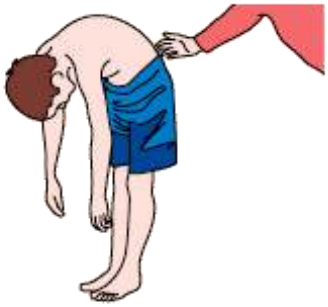
'Open your mouth and put three fingers in your mouth'

NECK AND SPINE



'Touch your shoulder with your ear'

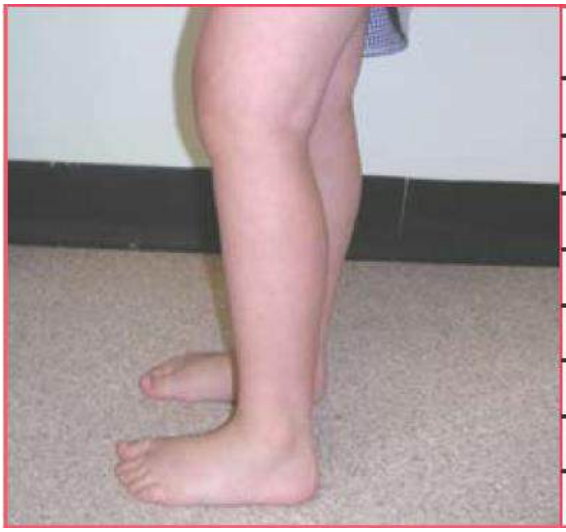
Observe lateral flexion of cervical spine



'Bend forward and touch your toes'

Observe curve of the spine

Ivestigate a child according to pGALS screening and record the results in the table below:



pGALS screening questions		
Any pain?	Left knee	
Problems with dressing?	No difficulty	
Problems with walking?	Some difficulty on walking	
	Appearance	Movement
Gait		✗
Arms	✓	✓
Legs	✗	✗
Spine	✓	✓

Following the screening examination, the observer is directed to a more detailed examination of the relevant area, based on the 'look, feel, move' principle as in the adult Regional Examination of the Musculoskeletal System (called REMS).

REGIONAL MUSCULOSKELETAL ASSESSMENT

Look:
- For signs of discomfort
- Skin abnormalities – rashes, scars, bruising, colour, nail abnormalities
- Limb alignment, leg length, muscle bulk and evidence of asymmetry
- Bony deformity, soft tissue, joint swelling or muscle changes

Feel:
Each joint, long bones and neighbouring soft tissues:

- Palpate along bones and joint line for tenderness
- Feel for warmth ***(infection or inflammation)***
- Delineate bony or soft tissue swellings
- Check for joint effusion, most readily at the knee

Move:
- For each joint, ask to move the joint first (active movement).

Observe for discomfort, symmetry and range of movement.
- Passively move the joint, noting range of any restriction of movement (compare sides but note bilateral changes)
- Lateral and rotational movements may be as important as flexion and extension.

Function:
- For lower limb joints – check gait
- For small joints such as hands - check grip

RED FLAGS

(Raise concern about infection, malignancy or nonaccidental injury)

- **Fever, malaise, systemic upset (reduced appetite, weight loss, sweats)**
- **Bone or joint pain with fever**
- **Refractory or unremitting pain, persistent night-waking**
- **Incongruence between history and presentation (such as the pattern of the physical findings and a previous history of neglect)**

MOTOR EXAMINATION

Muscle bulk	Muscle bulk represents the volume of muscle tissue. In many lower motor neuron conditions (neuropathies), muscle bulk is diminished or atrophic. Excessive muscle bulk is seen in rare conditions, such as myotonia congenita; boys with Duchenne muscular dystrophy have pseudohypertrophy of their calves.
Muscle tone	Tone represents the dynamic resistance of muscles to passive stretch. ▪ Lower motor and cerebellar lesions produce decreased tone (**hypotonia**). ▪ Upper motor lesions produce increased tone (**spasticity**). ▪ In extrapyramidal disease, an increase in resistance is present throughout passive movement of a joint (**rigidity**).
Muscle power	▪ In infants, power is assessed by observation of spontaneous movements and movements against gravity. Arm and leg movements should be symmetrical, seen best when the infant is held supine with one hand supporting the buttocks and one supporting the shoulders. The limbs should easily lift up. ▪ Strength in toddlers is assessed by observing functional abilities, such as walking, stooping to pick up an object, and standing up from the floor. An older child should be able to easily reach high above his or her head, wheelbarrow walk, run, hop, go up and down stairs, and arise from the ground. ▪ **Gowers sign** is a sign of significant proximal weakness: child arises from lying on the floor by using his arms to climb up his legs and body. ▪ Subtle asymmetry can be detected when the child extends arms out in front with the palms upward and eyes closed. The hand on the weaker side cups and begins to pronate slowly (**pronator drift**). ▪ Cooperative children can undergo individual muscle strength testing.

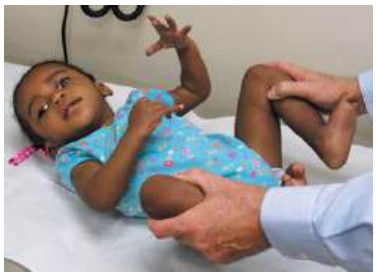


Fig. Assessing the tone and range of motion of a young child by alternately abducting and adducting the hips

Fig. Watching for pronator drift, an upper motor neuron sign, by having the patient stand with their eyes closed and arms extended

Fig. Gowers sign in a boy with hip girdle weakness because of Duchenne muscular dystrophy.
When asked to rise from a prone position, the patient uses his hands to walk up his legs to compensate for proximal lower-extremity weakness.

Gait

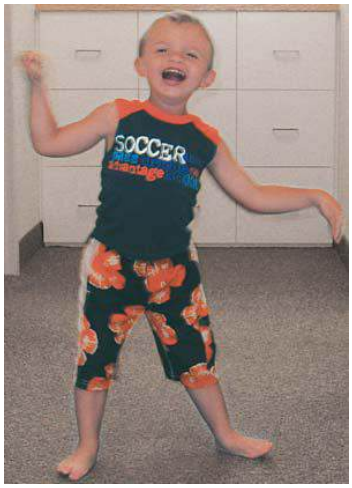
Watching a child creep, crawl, cruise, or walk is the best *global assessment for the motor and coordination systems*. Subtle deficits and asymmetries in power, tone, or balance may be observed.

The toddler gait is normally widebased and unsteady. The base of the gait narrows with age. By 6 years, a child is able to walk on toes, walk on heels, and tandem walk (heel to toe).

- Cerebellar dysfunction results in a **broad-based, unsteady gait accompanied by difficulty in executing turns**.
- Corticospinal tract dysfunction produces a **stiff, scissoring gait and toe walking**. Arm swing is decreased, and the affected arm is flexed across the body.
- Extrapyramidal dysfunction produces a slow, **stiff, shuffling gait with dystonic postures**.
- A **waddling gait** occurs with hip weakness due to lower motor neuron or neuromuscular disorders.
- A **steppage gait** results from weakness of ankle dorsiflexors (common peroneal palsy).

A normal toddler's gait

Performing the tandem gait by having the adolescent walk heel-to-toe



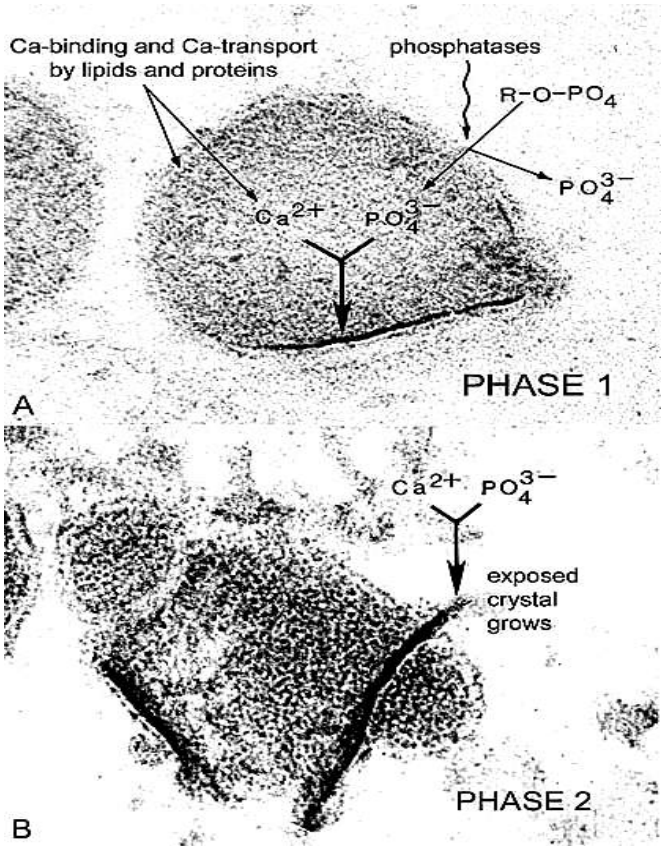
A wide-based gait in a young child with Angelman syndrome

DISORDERS OF BONE MINERALIZATION: RICKETS/ OSTEOMALACIA

➢ *BONE MINERALIZATION*

Biomineralization occurs in two phases:
1. During Phase I, intravesicular calcium concentration is increased by its affinity for lipids and Ca-binding proteins of the vesicle membrane interior. Phosphatase, for example **alkaline phosphatase**, pyrophosphatase, or adenosine triphosphatase at the vesicle membrane, acts on ester phosphate of matrix or vesicle fluid to produce a local increase in PO_4 in the vicinity of the vesicle membrane. The intravesicular ionic product (Ca^{2+}) x (PO_4^{3-}) is thereby raised, resulting in initial deposition of $CaPO_4$ near the membrane.
Alkaline phosphatase is inhibited by phosphate. Thus, in phosphate deficiency there is increased activity of alkaline phosphatase.

2. With mineral crystal accumulation and growth, intravesicular crystals are exposed to the extravesicular environment.

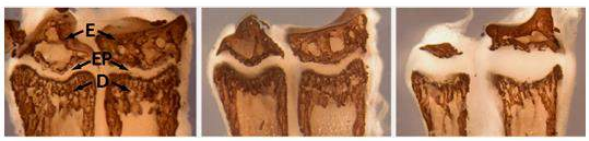


➢ RICKETS

Rickets is a disease of growing bone that is unique to children and adolescents and is due to defective mineralization of growing bone.
Normal bone growth and mineralization require adequate calcium and phosphate, the two major constituents of the crystalline component of bone. Deficient mineralization can result in rickets and osteomalacia.

Rickets refers to deficient mineralization at the growth plate, whereas osteomalacia refers to impaired mineralization of the bone matrix. Rickets and osteomalacia usually occur together as long as the growth plates are open; only osteomalacia occurs after the growth plates have fused.

Growth Plate Thickening in Rickets



Normal bone **Rickets induction** **Florid Rickets**

E *– epyphysis*

EP *– epyphyseal or growth plate*

D *– dyaphysis*

Growth plate thickness is determined by two opposing processes: **chondrocyte proliferation and hypertrophy** on the one hand and **vascular invasion** of the growth plate on the other. Vascular invasion requires mineralization of the growth plate cartilage and is delayed or prevented by deficiency of calcium or phosphorus. In these circumstances, growth plate cartilage accumulates and the growth plate thickens. In the bone tissue below the growth plate (metaphysis), the mineralization defect leads to the **accumulation of osteoid**.
These abnormalities decrease the biomechanical resistance of the involved skeletal sites, leading to a **secondary increase in the diameters of the growth plate and metaphysis.**

Rickets can be classified according to the underlying pathology into three main groups: vitamin D deficiency, calcium deficiency, or phosphate deficiency.

Many cases are due to poor vitamin D intake or calcium deficient diets and can be corrected by administration of calcium and vitamin D. However, some cases are refractory to vitamin D therapy and are related to renal defects. These include rickets of renal tubular acidosis (RTA), hypophosphatemic rickets, and vitamin D dependent rickets (VDDR).

Vitamin D deficiency is the most common cause of rickets.

Vitamin D is mostly obtained through skin synthesis initiated by ultraviolet B (UVB) radiation exposure, and typically only smaller amounts are obtained through diet. UVB radiation from the sun induces vitamin D synthesis by converting 7-dehydrocholesterol (7-DHC, present in the skin) to vitamin D3.

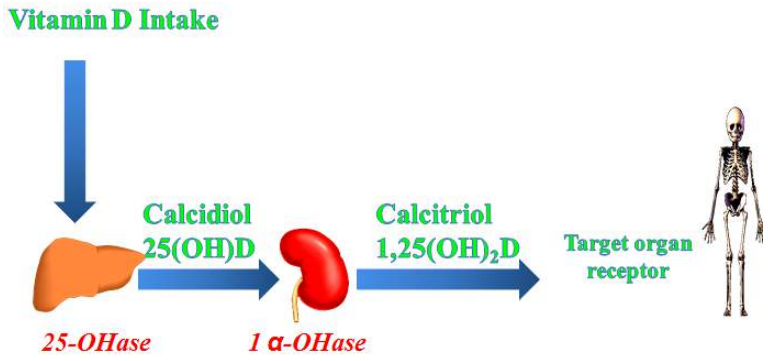
However, there are limitations of cutaneous synthesis of vitamin D:

- *Ineffectiveness of winter sun*
- *Avoidance of sunlight in muslim women*
- *Decreased cutaneous synthesis due to increased skin pigmentation*

! BESIDES, direct exposure to sunlight is not recommended for infants and young children because of the risk of skin cancer. Infant skin is very sensitive and burns easily and should not be directly exposed to the sun.
Therefore infants do not have the capacity to safely get vitamin D from the sun.

Major Food Sources of Vitamin D		
- *Cod liver oil* - *Fish* - *Caviar*	- *Oyster / crustaceans* - *Eggs* - *Milk*	- *Mushrooms* - *Dairy products, cereals, beans fortified with vitamin D*
 *Some fish oils also contain large amounts of vitamin A, which further can harm the liver, cause osteopenia/ osteoporosis and bone fractures.*		

THE METABOLIC PATHWAY OF VITAMIN D

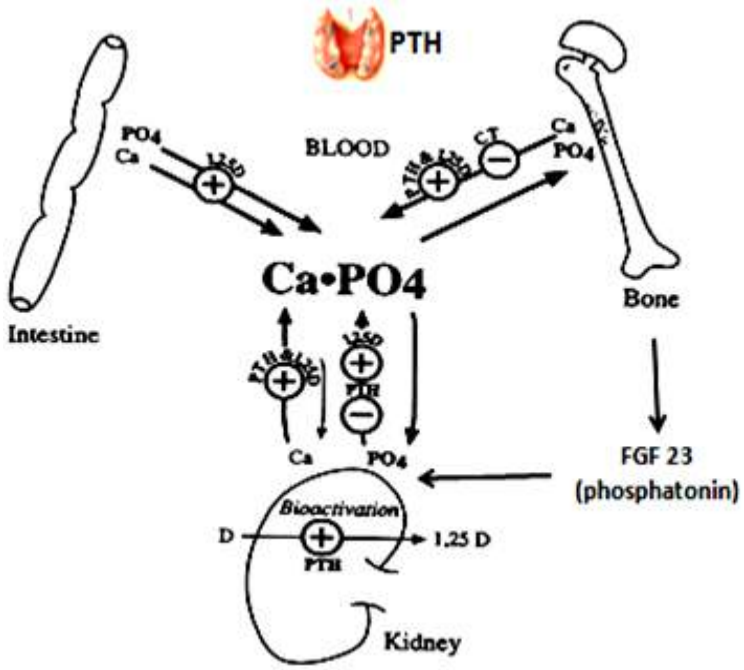


Vit D is a physiologically inactive prohormone.
*In the liver, D_3 is hydroxylated by **25 hydroxylase** to 25 hydroxy-D_3 (**calcidiol**).*
*Further hydroxylation of calcidiol by **1-hydroxylase** in the kidneys results in the formation of 1,25 dihydroxy-D_3 (**calcitriol**), which is the physiologically active hormone and acts via target organ receptors.*
NOTE *Hydroxylation of vitamin D to 25(OH)D in the liver has little regulation and circulating concentrations of 25(OH)D increase in proportion with vitamin D intake.* ***Therefore, it is used for assessment of Vit D status.***

Calcitriol regulates calcium and phosphate metabolisms by :
- releasing Ca and P from the bones into blood
- increasing Ca and P reabsorption in the kidney
- icreasing Ca and P absorption in the gut
- increasing calcification of growth plates (main antirachitic effect)

Vit D also has many **noncalcemic functions,** such as stimulation of innate immune system. Vit D deficiency leads to abnormal immune function with greater susceptibility to infections.

CONTROL OF BLOOD CALCIUM AND PHOSPHATE



The main determinants of serum levels of **Ca** and **P** are:

- **Calcitriol** _ increases Ca & P concentrations
- **Parathyroid hormone (PTH)** _ increases Ca concentration by mobilizing Ca from the bones, increases Ca reabsorption and synthesis of calcitriol in the kidney
- **PTH and Fibroblas Growth Factor (FGF) 23** _ decrease P concentration by inhibition of tubular reabsorption of P

Vitamin D disorders can be classified into four main groups:

I. ***Vitamin D Deficiency Rickets***
   a. Nutritional Vitamin D Deficiency
   b. Fat malabsorption (eg. in cystic fibrosis)
   c. Inadequate Sunlight Exposure

II. ***25-hydroxylase deficiency*** (due to gene mutation or severe liver disease) → calcidiol synthesis↓

III. ***1α-hydroxylase deficiency*** → calcitriol synthesis↓
This is due to:
   a. gene mutation with autosomal recessive inheritance (vitamin D dependant rickets type1)
   b. chronic kidney disease

IV. *Finally, calcitriol actions can be disturbed by the* ***defect of the target organ receptors.***
It is known as ***receptor-defect rickets (formerly Vit D dependant rickets type 2).*** *It has AR inheritance.*

In the vitamin D deficiency state, **hypocalcemia** develops, which stimulates excess secretion of parathyroid hormone (**secondary hyperparathyroidism**). *It lowers extracellular P and usually normalizes serum Ca.* All these lead to defective mineralization of the newly formed bone and demineralization of existing bone. In these circumstances osteoblastic activity and ALP production is increased. In severe vitamin D deficiency calcium reserves are depleted and stable hypocalcemia develops (especially in the periods of rapid growth).

The main causes of Ca deficiency:
- Vitamin D deficiency
- Nutritional Ca deficiency/ Malabsorption
- Reduced PTH production
- Impaired PTH action due to end organ resistance

Hypocalcemic signs include: carpopedal spasm (tetany), seizures, laryngeal spasm, muscular hypotonia and weakness.

Other signs of hypocalcemia:

- **Chvostek sign** - tapping of the facial nerve → twitch of upper lip of mouth
- **Trousseau sign** -blood pressure cuff is inflated slightly above Systolic BP for more than 3 min → carpopedal spasm (ischemia of motor nerve)

PHOSPHATE DEFICIENCY

Phosphate depletion may occur from inadequate intake or absorption or increased losses from either the kidney or the gut.

Phosphorus is abundant in many foods; thus, nutritional phosphate deficiency is very rare. It occurs mainly in preterm infants, in long-term ingestion of P-binding Al- or Mg-containing antacids. In addition, soy-based formulas, which contain phytates, may impair absorption of minerals, including Ca, P, Fe.

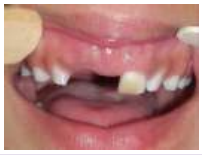
The main cause of P deficiency is **excess renal excretion of phosphate**. It occurs in:
- **Hyperparathyroidism**
- **Fanconi renal syndrome**, in which there is proximal tubular dysfunction with excess loss of P, bicarbonate, amino acids etc
- **X-linked hypophosphatemic rickets**, in which there is increased FGF 23 (due to mutation in the PHEX gene)
- Autosomal dominant hypophosphatemic rickets (ADHPR)
- Autosomal recessive hypophosphatemic rickets (ARHPR)

Assesment of mineral metabolism in rickets

PARAMETERS		VITAMIN D DEFICIENCY RICKETS	HYPOPHOSPHATEMIC RICKETS
Serum	*Ca*	↓ or N	N
	P	↓	↓↓
	Alkaline phosphatase (ALP)	↑	↑
	Parathyroid hormone (PTH)	↑	N
	25(OH)D	↓	N
	1,25(OH)$_2$D	N or ↑	N
Urine	*Ca*	↓	N or ↑
	P	↑	↑↑

Skeletal abnormalities in rickets

Rickets/osteomalacia softens the bones and cause skeletal deformities from top to toe.

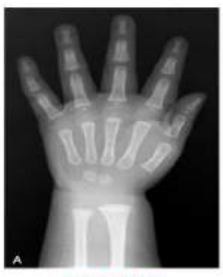
Bone pain	Demineralized collagen matrix is prone to hydration and swelling, which causes the periosteal covering to expand outward, and bone pain occurs, mediated by periosteal sensory pain fibers.
Craniotabes	Softening of the skull bones: when pressure is applied they will collapse underneath it; when the pressure is relieved, the bones will usually snap back into place. It is the first sign in infants with rickets.
Frontal bossing	- gives squared appearance of the head. It is due to excess osteoid in frontal bones.
Delayed closure of fontanelles	NB ● *Rickets may also be associated with both premature closure of fontanelles and craniosynostosis*
Dental problems	• Delayed teeth eruption • Enamel hypoplasia → decay (caries) • Dental abscesses – *seen in hypophosphatemic rickets* 
Rachitic rosary	Overgrowth of carlilage osteoid tissue at costochondral junctions
Harrison groove/sulcus	In rickets the diaphragm, which is always in tension, pulls the softened bone inward causing a horizontal groove along the lower border of the thorax.
Rachitic bracelets	Wrist and ankle enlargement (enlargement of distal epiphyses)
Spinal deformities	• kyphosis • scoliosis — *- due to vertebral softening and muscle hypotonia*
Deformities of lower extremities	Genu varum (bow-legs), genu valgum (knock knees) and windswept deformity
Pelvic deformities	This can predispose the girls to later difficulty during childbirth.

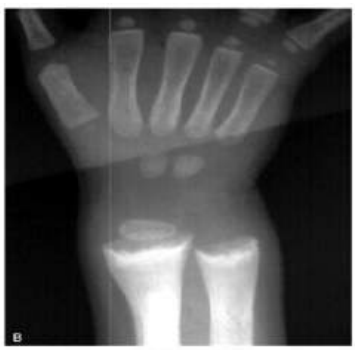
The diagnosis of rickets is made on the basis of history, physical examination, and biochemical testing and is confirmed by radiographs.

CHARACTERISTIC RADIOGRAPHIC SIGNS OF RICKETS:

FRAYING - Edge of metaphysis loses its sharp border.
CUPPING - Edge of metaphysis changes from convex or flat surface to a more concave surface.
SPLAYING - Widening of Metaphyseal end of bone
CORTICAL SPURS - Metaphyseal lines spread laterally.

Infants with rickets often suffer bone fractures. This sometimes leads to **child abuse allegations.**


NORMAL


RICKETS

Vitamin D deficiency should be considered a major global public health priority. It can have severe consequences, including death from cardiomyopathy or obstructed labor, myopathy, seizures, pneumonia, lifelong deformity and disability, impaired growth, and pain.

TREATMENT OF VITAMIN D DEFICIENCY

1. Vitamin D replacement

[Munns et al. J Clin Endocrinol Metab. 2016 Feb;101(2):394-415]

Age	Daily dose for 90 days, IU	Single dose*, IU	Maintenance daily dose, IU
<3 months	2000	-	400
3-12 months	2000	50 000	400
>12 months to 12years	3000-6000	150 000	600
>12 years	6000	300 000	600

***** *After the first month of age, high doses can be used in patients in whom compliance is an issue.*

- The minimal recommended dose of vitamin D is 2,000 IU/day (50 μg) for a minimum of 3 months.
- For daily treatment, both D2 and D 3 are equally effective. When single large doses are used, D3 appears to be preferable compared to D2 because the former has a longer half-life.
- There should be **radiologic evidence of bone healing** after 2 to 4 weeks of adequate therapy.

2. Calcium

- Oral calcium, 500 mg/day, either as dietary intake or supplement, should be routinely used in conjunction with vitamin D in the treatment regardless of age or weight to prevent the development of "**hungry bone" syndrome**.

- **In cases of convulsions or tetany**, parental boluses of calcium (10–20 mg of elemental calcium/ kilogram of 10% calcium gluconate over 5–10 minutes) are recommended until calcium levels are normalized. Oral calcium maintenance therapy is required until the PTH level has normalized, 25(OH)D stores have been replenished, and vitamin D has been transitioned to maintenance therapy. Patients also may require 20 to 100 ng/kg of calcitriol in two to three divided doses until calcium levels normalize.

3. Monitoring Therapy

[M Misra et al. Pediatrics 2008;122;398-417]

Timeframe	Investigations
1 month after initiatl therapy	*Serum Ca, P, ALP*
3 months	*Serum Ca, P, Mg, ALP, PTH, 25(OH)D* *Urine Ca/Cr* *X-ray*
Yearly	*25(OH)D*

If radiographic evidence of some healing is not observed with vitamin D and calcium replacement in 3 months, considerations should include malabsorption, liver disease, or a lack of compliance with replacement therapy.

Treatments of Other Types of Rickets

Vitamin D-dependent rickets Type I	- Calcitriol (Rocaltrol) - *Ca*
Vitamin D-dependent rickets Type II or receptor- defect rickets	- Massive doses of calcitriol and calcium
Hypophosphatemic rickets	- calcitriol - oral phosphate

PREVENTION OF VITAMIN D DEFICIENCY

1. Vitamin D Supplementation for the Prevention of Rickets and Osteomalacia

- 400 IU/day (10 μg) is adequate to prevent rickets and is recommended for all infants **from birth to 12 months of age**, independently of their mode of feeding.
- Beyond 12 months of age, all children and adults need to meet their nutritional requirement for vitamin D through diet and/or supplementation, which is at least 600 IU/day (15 μg), as recommended by the Institute of Medicine (IOM).

  Candidates for Preventative Vitamin D Supplementation **beyond 12 Months of Age**
  In the absence of food fortification, vitamin D supplementation should be given to:
  • Children with a history of symptomatic vitamin D deficiency requiring treatment
  • Children and adults at high risk of vitamin D deficiency, with factors or conditions that reduce synthesis or intake of vitamin D
  • Pregnant women
    - *• Maternal vitamin D deficiency should be avoided by ensuring that women of childbearing age meet intakes of 600 IU/day recommended by the IOM.*
    - *• Pregnant women should receive 600 IU/day of vitamin D, preferably as a combined preparation with other recommended micronutrients such as iron and folic acid.*

- Lactating women should ensure they meet the dietary recommendations for vitamin D (600 IU/day) for their own needs, but not for the needs of their infant. Lactating women should not take high amounts of vitamin D as a means of supplementing their infant.

2. Dietary Calcium Intake to Prevent Rickets

- In addition to an intake of 400 IU/day of vitamin D, complementary foods introduced no later than 26 weeks should include sources rich in calcium.
- For infants 0–6 and 6–12 months of age, the adequate calcium intake is 200 and 260 mg/day, respectively.
  - *• For children over 12 months of age, dietary calcium intake of <300 mg/day increases the risk of rickets independently of serum 25(OH)D levels.*
  - *• For children over 12 months of age, the panel recommends e following classification of dietary calcium intake:*
  - *– Sufficiency, >500 mg/day*
  - *– Insufficiency, 300–500 mg/day*
  - *– Deficiency, <300 mg/day*
- An intake of at least 500 mg/day of elemental calcium must be ensured during childhood and adolescence.
- Pregnant women do not need calcium intakes above recommended nonpregnant intakes to improve neonatal bone.
- Maternal calcium intake during pregnancy or lactation is not associated with breast milk calcium concentrations.

Vitamin D Toxicity

Toxicity is defined as hypercalcemia and serum 25OHD >250 nmol/l, with hypercalciuria and suppressed parathyroid hormone (PTH). It leads to malignant calcification of soft tissues: heart, blood vessels, renal tubules, stomach etc.
Patients with chronic granulomatous disorders (eg, sarcoidosis, tuberculosis) are more sensitive to serum 25(OH)D levels above 30 ng per milliliter because of macrophage production of calcitriol, which causes hypercalciuria and hypercalcemia.

Manifestations of Hypervitaminosis D/Hypercalcemia

Acute toxicity

- Muscle weakness
- Apathy
- Headache
- Anorexia
- Irritability
- Nausea, vomiting
- Bone pain

Chronic toxicity + Calcinosis

- aortic valvular stenosis
- retinopathy
- clouding of the cornea and conjunctiva
- nephrocalcinosis
- metastatic calcification

Therapy **consists of discontinuing of Vit D, decreasing Ca intake, rare - aluminum hydrochloride**

CONDITIONS MIMICKING RICKETS

Hypophosphatasia

- An autosomal recessive disorder that radiographically resembles rickets and is defined by **low serum alkaline phosphatase activity**.
- It is an inborn error of metabolism in which activity of the tissue-nonspecific (liver/bone/kidney) alkaline phosphatase isoenzyme (TNSALP) is deficient (although activity of the intestinal and placental isoenzymes is normal).
- The disease may appear in a lethal neonatal or perinatal form (congenital lethal hypophosphatasia), a severe infantile form, or a milder form occurring in childhood or late adolescence (hypophosphatasia tarda).

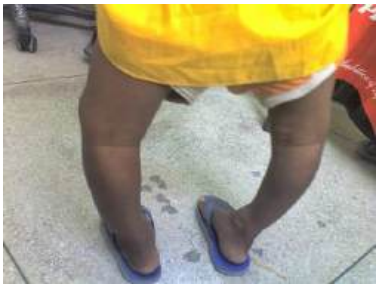
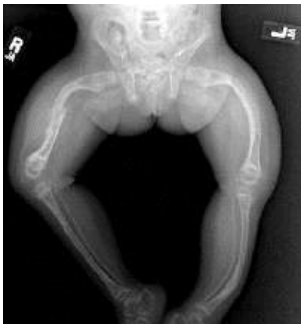


Fig. This 2 yo boy was brought to the clinic with an abnormal gait. His labs revealed mildly elevated calcium levels and low alkaline phosphatase activity.

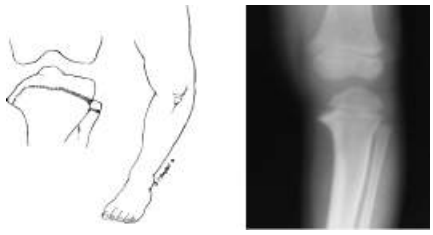
Osteogenesis Imperfecta

- A genetic disorder of type I collagen. It has the triad of fragile bones, blue sclerae, and early deafness. Serum calcium and phosphate concentrations are normal.



Blount Disease (Idiopathic Tibia Vara)

- Abnormal growth of the medial part of the proximal tibial epiphysis resulting in progressive varus angulation below the knee (bilateral or unilateral bowleg deformity).
- Tibia vara can occur in any age group in a growing child.
- Serum values of calcium, phosphorus, and alkaline phosphatase are normal.

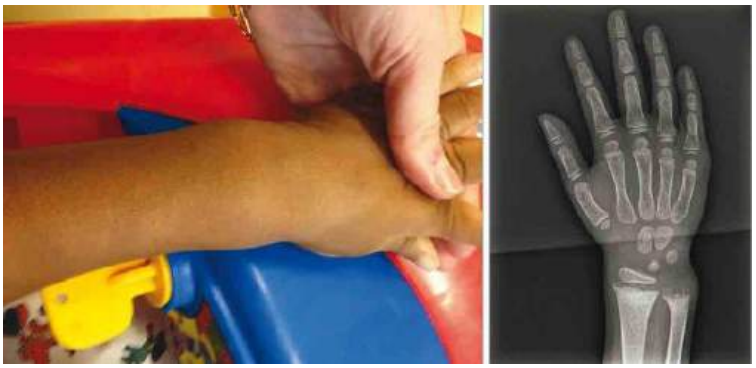


Skeletal Dysplasias

Some of these conditions may be confused with rickets because of bone deformity and occasionally because of metaphyseal changes on radiography (**metaphyseal chondrodysplasia**). However, serum Ca, P, ALP, PTH, and vitamin D metabolites are normal.

CASE STUDY

A 5-year-old boy presented with the signs of rickets and hypocalcemia (calcium 5.5mg/dL, PTH 798 pg/mL, vitamin D 7pg/mL), and a normal phosphorous level of 4.5mg/dL. Radiographs were abnormal (Fig). Oral and intravenous supplementations of calcium were started, but the patient's calcium levels remained refractory, even after correction of other electrolytes, including potassium and magnesium. He was placed on a continuous intravenous calcium infusion for 3 days with eventual normalization of his calcium level.
WHAT IS YOUR DIAGNOSIS?



For a patient who is chronically deprived of enteral calcium and vitamin D, as in the case of this patient, increasing the supplementation of calcium can cause a paradoxical drop in serum calcium levels. This occurs as the bones begin to reabsorb the calcium and vitamin D that were lost from the bones in an attempt to maintain adequate serum concentrations during the period of poor enteral intake. An increase in serum calcium leads to a decrease in serum PTH, which in turn allows serum calcium to be taken up into bone. This phenomenon is known as hungry bone syndrome and is usually seen in adults following a parathyroidectomy for primary hyperparathyroidism, with the surgical procedure leading to a sudden decrease in parathyroid hormone levels and an uptake of calcium. However, this disorder may be seen in children with food aversion, particularly those with autism spectrum disorder or other developmental delays. These children are at high risk for electrolyte abnormalities including those listed for our case, as well as others such as vitamin C deficiency, which may result in a presentation of scurvy.

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The Hematologic System

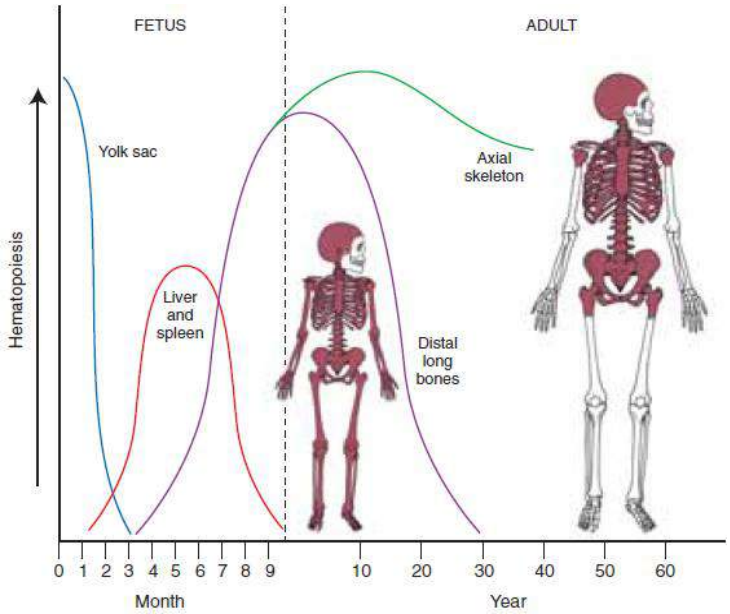
EMBRYONAL AND FETAL HEMATOPOIESIS (HAEMOPOIESIS)

Haemopoiesis is the process which maintains lifelong production of haemopoietic (blood) cells. All haemopoietic cells are derived from *pluripotent haemopoietic stem cells*, which are crucial for normal blood production.

- Hematopoiesis begins by 3 weeks of gestation with erythropoiesis in the yolk sac. This period of development, the **mesoblastic period**, produces primitive erythroblasts and **embryonic hemoglobins** such as *Hb Gower I and Gower II* and *Hb Portland (HbP)*. These Hgbs are constructed as tetramers with two alpha chains combined with either epsilon or zeta chains.
- By 2 months' gestation, the primary site of hematopoiesis migrates to the liver (**hepatic period)**. The main site of haemopoiesis in fetal life is the liver. White cells and megakaryocytes begin to appear in small numbers. The liver serves as an erythroid-producing organ primarily but also gives rise to **fetal Hb (HbF)**, which consists of alpha and gamma chains. The spleen, thymus, and lymph nodes also become hematopoietically active during this stage, producing red cells and lymphocytes.
- From 7 months until birth, the bone marrow assumes the primary role in hematopoiesis, a role that continues into adult life. Additionally, HbA, the majority adult Hb (alpha 2, beta 2), begins to form.

  At birth, the types of Hb are: **HbF, HbA and HbA2** (HbF is the predominant form of Hb in a fetus and a newborn). HbF is gradually replaced by HbA and HbA2 during the first year of life. By 1 year of age, the percentage of HbF is very low in healthy children and increased proportions of HbF are a sensitive indicator of some inherited disorders of hemoglobin production (hemoglobinopathies).

  Several cytokines play an important role in hematopoiesis. They are granulocyte colony-stimulating factor, interleukin (IL)-6, IL-1, IL-4, IL-9, insulin growth factor-1, and erythropoietin (EPO). EPO regulates RBC production in the bone marrow. Prior to birth, EPO is produced in the liver, and after birth, it is produced in the kidney. Tissue hypoxia induces formation of EPO via production of the transcriptional factor, hypoxia-inducible factor-1 (HIF-1).

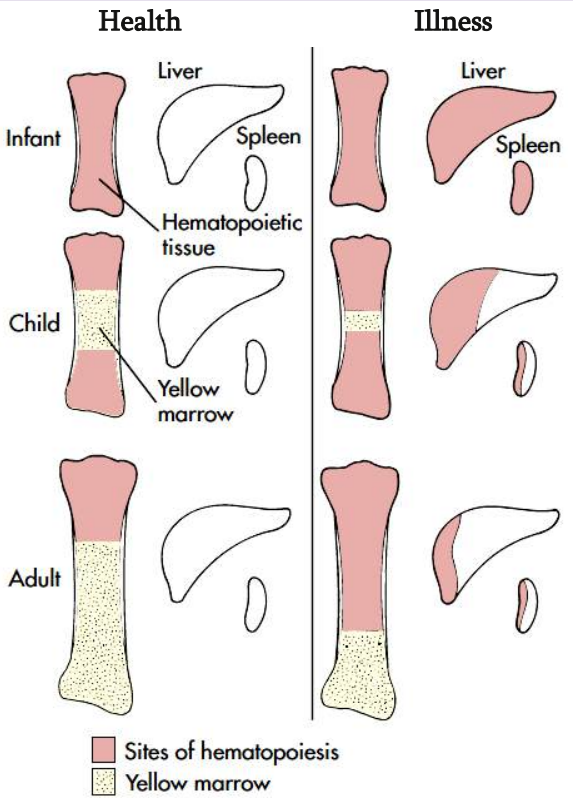


Hematopoiesis within the bone marrow is termed *intramedullary hematopoiesis*. The term *extramedullary hematopoiesis* describes hematopoiesis outside the bone marrow environment, primarily the liver and spleen. Because these organs play major roles in early fetal hematopoiesis, they retain their hematopoietic memory and capability.

An extremely premature infant may have significant extramedullary hematopoiesis due to limited bone marrow hematopoiesis.

During infancy, virtually all marrow cavities are actively hematopoietic and the proportion of hematopoietic to stromal elements is quite high. As the child grows, hematopoiesis moves to the central bones of the body (vertebrae, sternm, ribs, and pelvis), and the marrow is gradually replaced with fat.

In diseases characterized by hemolysis, erythrocyte production can increase as much as eight times the normal because erythropoietin causes hematopoietic marrow to increase in volume. Initially, hematopoietic marrow expands from the ends of the long bones toward the middle of the shafts, replacing fatty marrow. Next, blood cell production begins to occur outside the marrow cavities, especially in the liver and spleen. Extramedullary hematopoiesis is more likely to occur in children than in adults because the bony cavities of children already are filled with red marrow. This is why hemolytic disease causes especially pronounced ***enlargement of the spleen and liver*** *in children.*



DEVELOPMENTAL CHANGES IN BLOOD VOLUME

In term newborn infants, the average blood volume is 85 mL/kg. Premature newborns have an average blood volume of 90 mL/kg body weight. The blood volume increases to a mean of 105 mL/kg during the first few days of life and then decreases during the first few months. After these initial postnatal adjustments, blood volume maintains a relatively constant relationship to body weight throughout the remainder of life. The average blood volume of infants after 6 months of age is 75 to 77 mL/kg, similar to older children and adults.

Table. Calculation of circulating blood volumes in children
[Hazinski 2013]

Age of the child	*Blood volume (ml/kg)*
Neonates	85-90
Infants	75-80
Children	70-75
Adults	65-70

- *Riley AA et al (2010). Circulating blood volumes: a review of measurement techniques and a meta-analysis in children. ASAIO Journal 1;56(3):260-4.*

DEVELOPMENTAL CHANGES IN OXYGEN TRANSPORT

Hb is an oxygen-transport protein. It must have a high enough affinity to oxygen to bind it in the lungs, but also a low enough affinity to oxygen to release it to the tissues. This reversible binding of oxygen is described by the **oxy-Hb dissociation curve**. This curve describes the relationship between the percent oxygen saturation of Hb within a suspension of RBCs and the oxygen tension (pO2) of the solution.

To determine whether a Hb has altered oxygen affinity, one must measure its **p50** from the oxy-Hb dissociation curve. *The p50 is the partial pressure of oxygen at which Hb is 50% saturated with oxygen.* HbA is 50% saturated at an oxygen tension of about 26 mm Hg, which is the normal value of p50.

The affinity of Hb to oxygen is a function of the particular Hb (eg, HbA or HbF), but it is also regulated physiologically by pH, temperature, and concentration of 2,3–disphosphoglycerate (2,3-DPG, or BPG, biphosphoglycerate).

An increased p50 indicates a lower oxygen affinity, which shifts the oxygen-Hb dissociation curve to the right. A reduced p50 indicates higher oxygen affinity, which shifts the curve to the left.

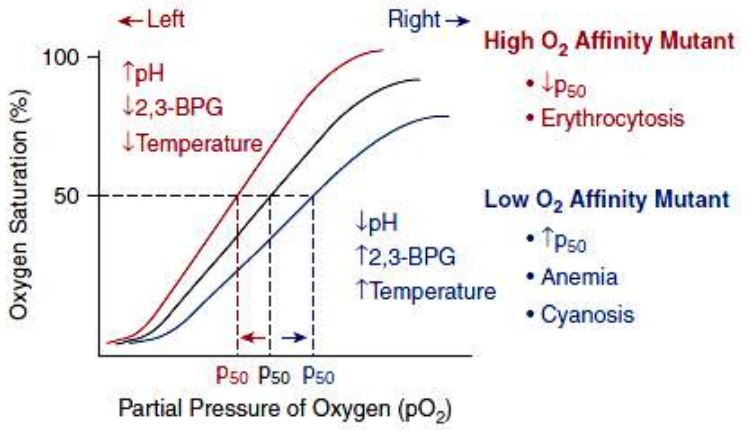


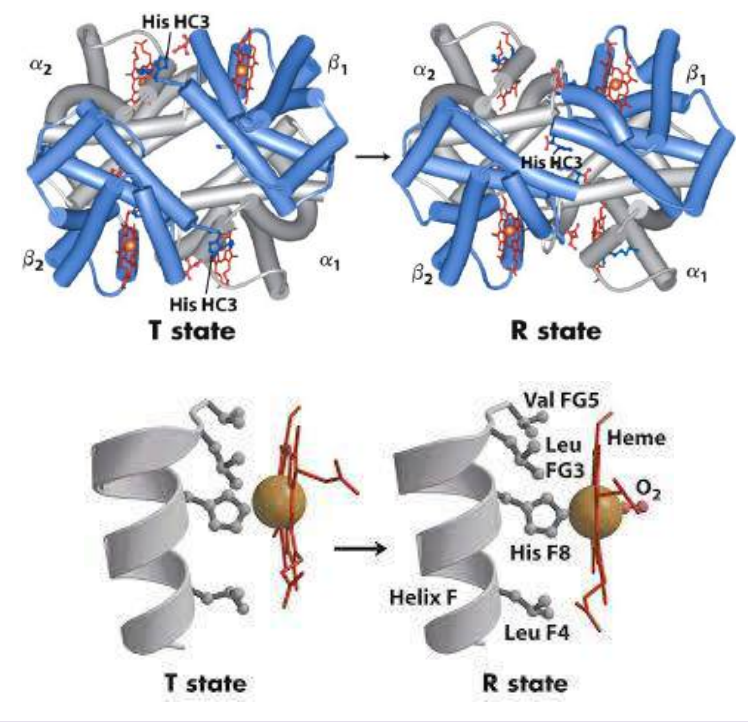
Fig. Oxyhemoglobin dissociation curve and its physiologic modulation and pathophysiologic perturbations. BPG, biphosphoglycerate

Hb can adopt two distinct quaternary structures, termed the tense (T) and relaxed (R) states or conformations. Quaternary structural changes in Hb regulate the O_2-binding affinity of the subunit chains.

***Tense (T) state**: Deoxygenated, under conditions where the oxygen concentration is low enough that none of the 4 binding sites are occupied, the binding affinity to oxygen is relatively low, T-conformation is present due to inter-and intra-salt bonds, hydrogen bonding, and hydrophobic interactions within the molecule.*

***Relaxed (R)**: Oxygenated, as oxygen becomes more available, 1 oxygen binds, the conformation changes and the other sites have higher binding affinity for oxygen. The sequential breaking of salt bonds leads to the R-conformation.*

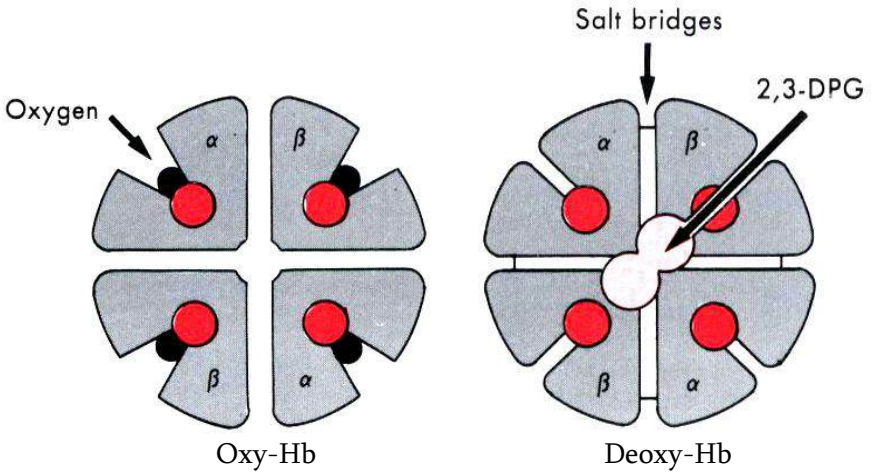
Mutations that alter the oxygen affinity of Hb typically alter amino acids at either the contact points between the α- and β-globin chains or at the C-terminal end of the β–globin chain. These sites are critical for stabilization of Hb in either the oxygenated or deoxygenated state and for interaction with 2,3-DPG.



• 2,3-DPG, a by-product of glycolysis, binds Hb to reduce its O_2 affinity. Hypoxia stimulates 2,3-DPG production to enhance O_2 delivery to tissues.

• The p50 of fetal blood is about 20 mm Hg. This high oxygen affinity, relative to blood of older children and adults, allows the extraction of oxygen from the maternal circulation. The high affinity is largely a function of HbF, which binds less avidly to 2,3-DPG than HbA. The relatively high total Hb concentration of the fetus, which increases total oxygen-carrying capacity, helps maintains oxygen delivery to the tissues despite the high oxygen affinity of the Hb.

• The extrauterine environment is relatively oxygen rich, so it is not necessary to maintain the high oxygen affinity needed for the intrauterine environment. Relative to HbF, HbA is more sensitive to the effects of 2,3-DPG, so p50 increases as HbA production increases. The postnatal change in the p50 of infants to normal adult values takes 2 to 3 months.



An abnormal Hb with altered oxygen affinity should be included in the differential diagnosis of **erythrocytosis** (high affinity) or anemia with or without cyanosis (low affinity).

High–oxygen affinity hemoglobin variants	Low–oxygen affinity hemoglobin variants	Erythrocytosis with normal hemoglobin
Almost 200 qualitatively abnormal Hbs with high oxygen affinity have been discovered	More than 50 qualitatively abnormal Hbs with low oxygen affinity have been discovered	Erythrocytosis of high altitudes Cyanotic cardiac disease Polycythemia vera (due to JAK2 mutations)

- **If oxygen affinity of Hb is increased**, then its oxygen delivery to tissues is decreased. The body compensates physiologically by increasing erythropoietin production, stimulating the bone marrow to increase erythropoiesis, thereby increasing the total Hb concentration and the oxygen-carrying capacity of the blood. Hence, patients with high oxygen affinity Hbs have **erythrocytosis**, but this is functionally appropriate because they maintain appropriate oxygen delivery to their tissues. Note that although the terms *erythrocytosis* and *polycythemia* are often used interchangeably, they are not equivalent.

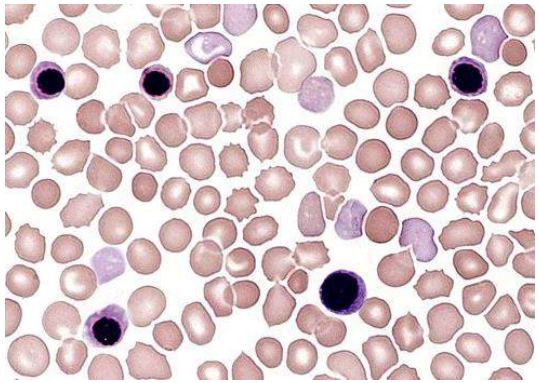
- In contrast, **if the oxygen affinity of Hb is decreased** (e.g., M-type Hbs), its oxygen delivery to tissues is increased. The body compensates physiologically by decreasing erythropoietin production, thereby decreasing the total Hb concentration and the oxygen-carrying capacity of the blood. Hence, individuals with low oxygen affinity Hbs may have a total Hb concentration that is lower than normal. Despite a low Hb concentration, affected individuals are not functionally anemic because they maintain appropriate oxygen delivery to their tissues. The anemia is usually mild, but some may have total Hb concentrations as low as 90 to 100 g/L. Individuals who have Hbs with greatly decreased oxygen affinity may also have cyanosis because a substantial fraction of Hb is deoxygenated.

In patients with hemoglobinopathies, aplastic anemia or thalassemias, fetal hemoglobin declines much slower and may persist throughout life.
Hereditary persistence of fetal haemoglobin (HPFH) – A condition in which fetal haemoglobin continues into adult life caused by a genetic mutation on β–globin gene cluster. The proportion of HbF can range from 10% to 100% depending on severity or the condition. It is mostly harmless and symptomless, usually only discovered when searching for other haemoglobin pathologies. HPFH can reduce severity of β-globin hemoglobinopathies (sickle cell disease; β thalassemias) and is therefore more prevalent in populations where incidence of these conditions is high, such as African populations with high incidence of β-thalassemia. However, high HbF may increase the risk of sudden infant death syndrome (SIDS) [Perry, 1997].

DEVELOPMENTAL CHANGES IN RED BLOOD CELLS (RBCs)

CASE STUDY. *A 4-week-old newborn comes into your office for a regularly scheduled newborn visit. The infant is growing and feeding well, but you decide to check a CBC anyway. Compared to his CBC at birth, his hemoglobin has decreased from 170 g/L to 120 g/L. What is wrong with this infant?*

RBC MORPHOLOGY

Erythrocyte size	Early in embryogenesis, the size and volume of erythrocytes are significantly greater than that of neonatal and adult erythrocytes, with the mean cell volume (MCV) ranging from 150 to 180 fl and cellular diameter ranging from 20 to 25 μ. Erythrocyte size and volume decrease throughout gestation to values of MCV between 108 to 118 fl and diameter between 8 to 10 μ at term. After birth, erythrocytes continue to decrease in size and volume, with values similar to those of adults by 1 year of age.
Erythrocyte shape, color and deformability	▪ Marked variability exists in the shape of fetal and neonatal erythrocytes. Irregularly shaped erythrocytes, acanthocytes, target cells, and immature erythroid cells with various membrane projections are frequently seen. These variations have been attributed to *poor or absent splenic function in neonates*. ▪ RBCs of the normal neonate show color variability as a population (**polychromasia**): some (usually the majority) are the usual red color, while others are bluish. ▪ As erythrocytes age, neonatal cells lose more volume, have a higher mean cell hemoglobin concentration (MCHC), and become less deformable than adult RBCs, with decreased deformability leading to increased splenic sequestration. Together these properties lead to accelerated membrane loss and **decreased erythrocyte life span**. *The life span of the erythrocyte in a term neonate is between 60 and 90 days, with preterm infants demonstrating even shorter life spans, from 35 to 50 days [Pearson, 1967].* 
Membrane differences	▪ Fetal and neonatal erythrocytes contain more phospholipid and cholesterol per cell, resulting in a larger surface to volume ratio and rendering them slightly more osmotically resistant. ▪ The surface charge of neonatal erythrocytes is more negative than that of adult cells because of a higher sialic acid content. This increased negative charge contributes to the decreased erythrocyte sedimentation rate (ESR) observed in newborns.

RED BLOOD CELL PARAMETERS

RBC count

Red blood cell count shows a great variability at the time of birth and ranges from 4.6 to 5.2 million/mm^3. The RBC count increases during the first 24 hours of life, remains at this plateau for about 2 weeks, and then slowly declines. This "polycythemia of the newborn" may be explained by in utero hypoxia, which becomes more pronounced as the fetus grows.

Hemoglobin (Hb)

- Hemoglobin concentration rises gradually throughout gestation and peaks shortly after birth. The mean hemoglobin at 10 weeks' gestation is 90 g/L, increasing to 110 to 120 g/L by approximately 23 weeks and to 130 to 140 g/L by 30 weeks' gestation. Hemoglobin concentration is relatively stable the last 6 to 8 weeks of gestation, with a mean concentration 160 to 170 g/L at term. Hemoglobin may increase by 10 to 20 g/L at birth as a result of placental transfusion. Decreased plasma volume leads to a peak in hemoglobin between 2 to 6 hours of life, with levels stabilizing by 8 to 12 hours of age.
  - *Failure of hemoglobin to rise during this period is a marker of blood loss.*
  - *Hemoglobin levels return to cord blood values by the end of the first week.*

  During the first few days after birth, there are significant differences in the Hb concentrations between venous and capillary blood. Capillary Hb is about 20 g/L higher than venous Hb because of loss of plasma from the capillaries and relative hemoconcentration. ***During the first 2 weeks of life, a venous hemoglobin value below 130 g/L or a capillary hemoglobin value below 145 g/L should be regarded as anemic.***

- Erythropoiesis decreases at birth, leading to a gradual decrease in hemoglobin concentration during the next several weeks of life. The lowest level of hemoglobin is reached at 8 weeks of life, with levels of approximately 110—95 g/L in healthy term infants. This fall, which reflects the physiologic transition from the relatively hypoxic intrauterine environment to the oxygen-replete extrauterine state, is appropriately called the **physiological anemia of infancy**.

- After 6–8 weeks, red cell production resumes as indicated by a rise in reticulocyte count, resulting in stabilization of the hemoglobin level, and then an increase in hemoglobin level. The mean Hb concentration increases slowly with age in prepubertal boys and girls from about 125 g/L at 1 year of age to about 135 g/L by 10 years of age. With the onset of puberty, the Hb concentration of boys and girls begins to diverge, becoming higher in boys because of the erythroid-stimulating effects of androgenic hormones.

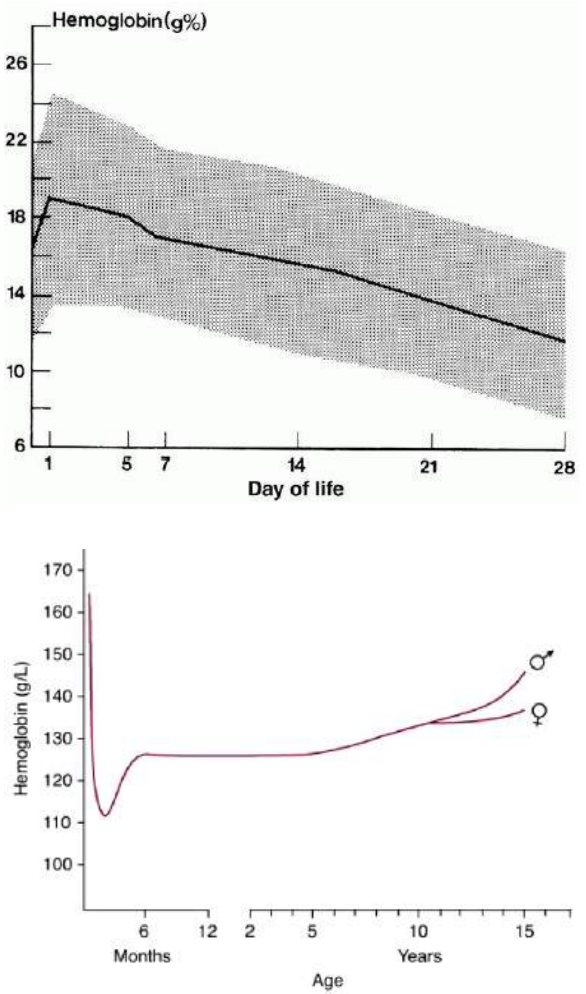


Fig. Mean Hb concentration in children as a function of age and sex.

Cord Clamping and Placental Transfusion

The timing of cord clamping significantly influences hemoglobin values in the newborn. Around the time of birth, placental blood is rapidly transferred to the infant. Approximately a quarter of this transfusion occurs within 15 seconds of birth and half occurs by the end of the first minute after birth. Delayed cord clamping (DCC) typically increases the infant's blood volume by 30%, because the placental vessels contain between 75 to 125 mL of blood at birth. Holding the infant above the level of the placenta prevents placental transfusion and may even lead to neonatal transfusion into the placenta, resulting in neonatal anemia.

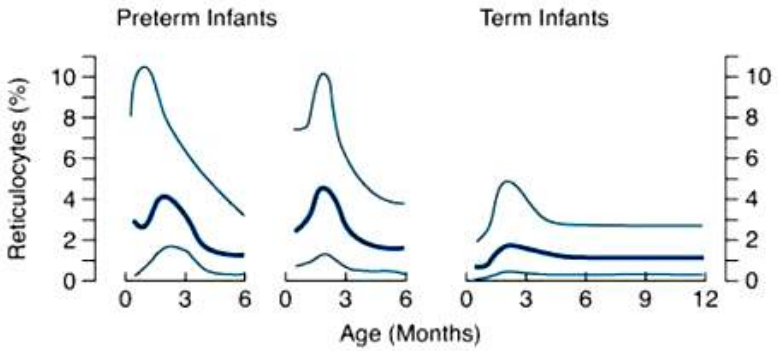
Hematocrit (Hct)

Normal values of hematocrit at birth ranges from mean of 51.3% to 56%. Just as Hb value, hematocrit value also shows increase during first few hours of life and reaches original value of cord blood by one week and mean capillary hemotocrit value is two percentage point higher than the mean venous hematocrit value at one week age.

Reticulocyte count

Many nucleated red blood cells (NRBCs) and reticulocytes are normally present in the peripheral blood of embryos and fetuses. NRBCs disappear from the peripheral circulation after 3 days of age, and their presence beyond then should be considered abnormal.

Reticulocyte counts and the absolute reticulocyte count range from **4% to 7%** and 200,000 to 400,000/μL in term infants and **6% to 12%** and 400,000 to 550,000/mL in preterm infants, respectively. In healthy infants, the reticulocyte count falls over the first few days of life to levels of 0 to 1% by day 4 of life.



This increased reticulocyte count in first 2 to 3 days of life reflects very active erythropoiesis during antenatal period.

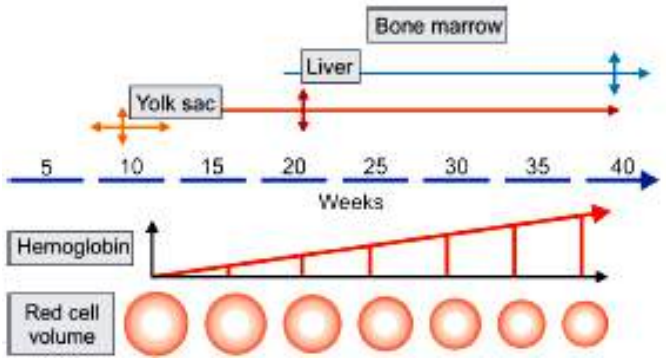
Persistent reticulocytosis in the neonate suggests:

- *Hemolytic process*
- *Hypoxia*
- *Blood loss*

At 2 months, the number of reticulocytes increases slightly, followed by a slight decline from 3 months to 2 years, when adult levels of 0.5% to 1.5% are attained.

RBC indices

Parameter	Definition	Units	Formula
Mean cell volume (MCV)	Average volume of the red blood cell	Femtoliters (fL) or 10^{-15} Liter	**MCV = Hct (%) x 10/ RBC ($x10^{12}$)** *e.g., 42x10/4.2 = 100 fL*
Mean cell hemoglobin (MCH)	Amount of hemoglobin in a single red blood cell	Picograms (pg) or 10^{-12} grams	**MCH = Hb (g/L)/ RBC ($x10^{12}$)** *e.g., 125/4.1 = 30.5 pg*
Mean cell hemoglobin concentration (MCHC)	Average concentration of Hb in the RBC volume	g/L	**MCHC = Hb (g/L) x 100/ Hct (%)** *e.g., 125x100/37 = 340 g/L = 34 g/dL*



- ***MCV*** *at birth ranges from 104 to 118 fL compared to normal adult value of 82 to 92 fL. When an MCV less than 95 fL is observed in a term neonate, α–thalassemia trait or iron deficiency should be considered.*
  Mean corpuscular volume rapidly decreases in the first week of life and at the age of 2 months, cell size is comparable to those in adult cells.
- *Similar to the MCV, the* ***MCH*** *is higher in preterm and term neonates, ranging from 33 to 41 pg/cell compared with 27 to 31 pg/cell in adults.*
- ***MCHC*** *does not vary between neonates and adults. Although neonatal erythrocytes are larger and contain more hemoglobin, the hemoglobin in the erythrocyte is not more concentrated.*

Table. Normal RBS parameters during the first-two weeks of life in the term infants
[From Oski FA, Naiman JL: Hematologic problems in the newborn, *ed 2, Philadelphia, 1972, WB Saunders, p. 13]*

Value	*Cord blood*	*Day 1*	*Day 3*	*Day 7*	*Day 14*
Hb g/dL	16.8	18.4	17.8	17.0	16.8
Hematocrit (%)	53.0	58.0	55.0	54.0	52.0
Red cells (mm3)	5.25	5.8	5.6	5.2	5.1
MCV (fL)	107	108	99.0	98.0	96.0
MCH (Pg)	34	35	33	32.5	31.5
MCHC (g/dL)	31.7	32.5	33	33	33
Reticulocytes	3–7	3–7	1–3	0–1	0–1
Nucleated RBCs	500	200	0–5	0	0

Table. Sex- and age-stratified pediatric reference ranges for hematocrit, hemoglobin, and mean corpuscular volume

[From Cembrowski GS,Chan J, Cheng C, et al: NHANES 1999-2000 data used to create comprehensive health-associated race-, sex- and age-stratified pediatric reference intervals for the Coulter MAXM. Laboratory Hematol 10:245–6, 2004. Presented at the annual meeting of the International Society for Laboratory Hematology, Barcelona, Spain, May 2004. Numerical summary provided by GS Cembrowski, MS Cembrowski, KA Versluys, 2013.]

Hematocrit (%)

	Black								Mexican American & White							
	2.5 Percentile		50.0 Percentile		95.0 Percentile		97.5 Percentile		2.5 Percentile		50.0 Percentile		95.0 Percentile		97.5 Percentile	
Age Range	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
1	31.0		36.0		39.0		39.5		32.0		37.0		40.0		41.0	
2-3	32.0		36.0		39.0		39.5		33.0		37.0		40.5		41.0	
4-6	33.0		37.0		41.0		42.0		34.0		38.0		42.0		42.5	
7-10	34.0		38.0		42.0		42.5		35.0		39.5		43.5		45.0	
11-14	35.0	33.0	40.0	38.0	45.0	43.0	46.0	43.5	36.5		42.0	40.0	47.5	44.0	48.0	45.0
15-18	38.0	32.0	44.0	38.0	49.0	42.0	51.0	43.5	40.0	34.0	46.0	40.0	50.0	43.5	51.5	44.5

Hemoglobin (g/dL)

	Black								Mexican American & White							
	2.5 Percentile		50.0 Percentile		95.0 Percentile		97.5 Percentile		2.5 Percentile		50.0 Percentile		95.0 Percentile		97.5 Percentile	
Age Range	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
1	10.4		12.0		13.1		13.2		10.5		12.5		13.7		13.9	
2-3	10.8		12.0		13.4		13.5		11.0		12.6		13.9		13.9	
4-6	11.0		12.5		14.0		14.1		11.7		12.9		14.2		14.2	
7-10	11.2		12.7		14.1		14.4		12.0		13.5		14.7		15.0	
11-14	11.8	10.6	13.6	12.9	15.2	14.4	15.4	14.7	12.6	12.3	14.3	13.7	16.0	14.9	16.1	15.0
15-18	12.9	10.7	14.9	12.8	16.5	14.2	16.7	14.6	13.7	11.5	15.4	13.7	17.0	14.9	17.2	15.0

Mean Cell Volume (fL)

	Black								Mexican American & White							
	2.5 Percentile		50.0 Percentile		95.0 Percentile		97.5 Percentile		2.5 Percentile		50.0 Percentile		95.0 Percentile		97.5 Percentile	
Age Range	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
1	63.0		77.0		87.0		88.0		71.0		79.5		84.0		85.5	
2-3	64.0		80.0		88.0		88.5		74.0		81.5		88.5		89.0	
4-6	67.0		82.5		89.0		90.5		77.0		84.0		90.0		90.5	
7-10	72.0		84.0		91.5		92.5		78.0		85.0		90.0		90.5	
11-14	73.0	71.0	85.5		93.5		95.0		80.0		87.0		92.5		93.5	
15-18	75.0	71.0	87.0		94.5		95.5		81.0		89.0		95.0		95.5	

ANAEMIA (ANEMIA). IRON DEFICIENCY IN CHILDREN

Anemia is defined as an Hb level below the normal range. The normal range varies with age.

Table. Hemoglobin levels to diagnose anemia at sea level [WHO, 2001]

Age	Hemoglobin (g/L)			
	Non-Anemia	Mild Anemia*	Moderate Anemia	Severe Anemia
6 months to 5 years	≥ 110	100-109	70-99	< 70
5 to 11 years	≥ 115	110-114	80-109	< 80
12 to 14 years	≥ 120	110-119	80-109	< 80
Nonpregnant females ≥ 15 years	≥ 120	110-119	80-109	< 80
Pregnant females	≥ 110	100-109	70-99	< 70
Men ≥ 15 years	≥ 130	110-129	80-109	< 80

*** "Mild" is a misnomer: iron deficiency is already advanced by the time anemia is detected. The deficiency has consequences even when no anemia is clinically apparent.**

Table. Hemoglobin adjustments

[From Nestel P. Adjusting hemoglobin values in program surveys. Washington, DC: International Nutritional Anaemia Consultative Group, ILSI Human Nutrition Institute. 2002 Jun 23:2-4.]

For altitude	
Altitude (m)	Hb g/L
m < 1000	No adjustment
1000≤ m <1250	+2
1250≤ m <1750	+5
1750≤ m <2250	+8
2250≤ m <2750	+13
2750≤ m <3250	+19
3250≤ m <3750	+27
3750≤ m <4250	+35
4250≤ m <4750	+45
4750≤ m <5250	+55
5250≤ m	+67

For pregnancy in women living at sea level	
Stage of pregnancy (trimester)	Hb g/L
First	-10
Second	-15
Third	-10
Trimester unknown	-10

For smokers	
Amount smoked	Hb g/L
1/2–1 pack/day	+3
1–2 packs/day	+5
>2 packs/day	+7
Smoker, amount unknown	+3

For healthy people of african extraction living at sea level	
	Hb g/L
Everyone	–10

Lake Sevan - at the altitude of 1900m above sea level
Yerevan - at the altitude of 900-1300m above sea level

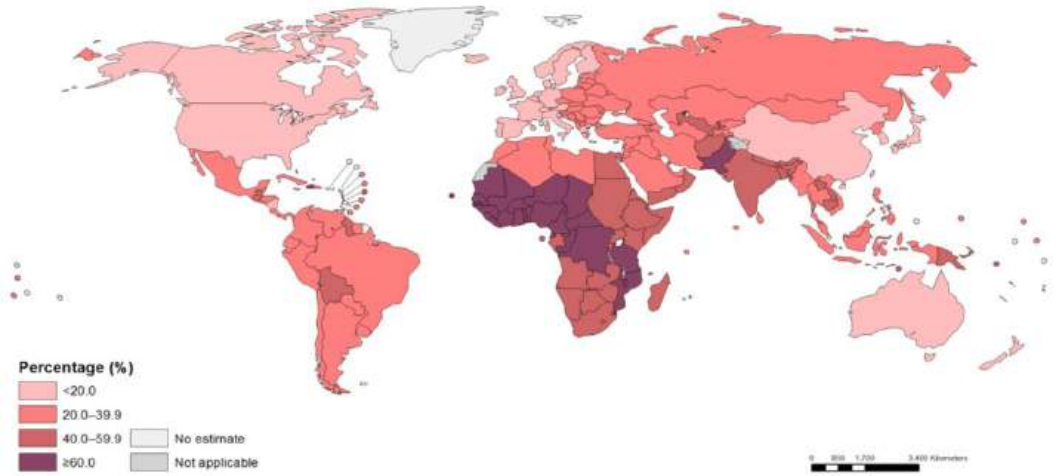
A global health problem

Anemia is common throughout the world.

For the year 2011, it is estimated that roughly 43% of children, 38% of pregnant women, and 29% of nonpregnant women and 29% of all women of reproductive age have anaemia globally, corresponding to 273 million children, 496 million non-pregnant women and 32 million pregnant women.

Fig. **Global estimates of the prevalence of anemia in infants and children aged 6–59 months, 2011**

[Source: WHO. The global anemia prevalence in 2011. Geneva: World Health Organization; 2015.]



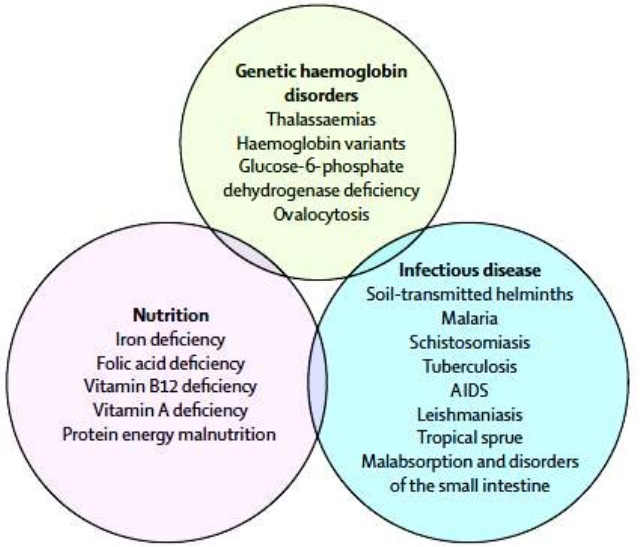
Causes of anemia

Anemia may result from a number of causes, with the most significant contributor being iron deficiency. Approximately 50% of cases of anaemia are considered to be due to iron deficiency. The most susceptible groups are pregnant women and young children. Women of childbearing age need to absorb 2-3 times the amount of iron required by men or older women.

Other causes of anemia include other micronutrient deficiencies (e.g. folate, riboflavin, vitamins A and B12), acute and chronic infections (e.g. malaria, tuberculosis and HIV), cancer, and inherited or acquired disorders that affect Hb synthesis, RBC production or survival (e.g. hemoglobinopathies).

Fig. **Causes of anemia in countries with low or middle incomes**

[From Balarajan Y et al: Anemia in low-income and middle-income countries. Lancet 378:2123–2134, 2011, Fig. 3.]



CASE STUDY *A 12-month-old infant is found to have Hb 80 g/L and mean corpuscular volume (MCV) 65 fL on routine complete blood (cell) count (CBC) screen. What is the likely cause of these abnormal laboratory values?*

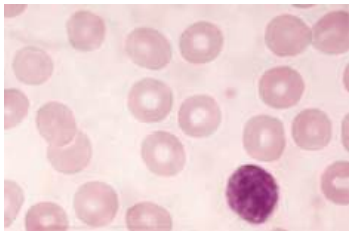
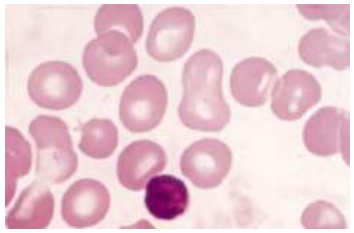
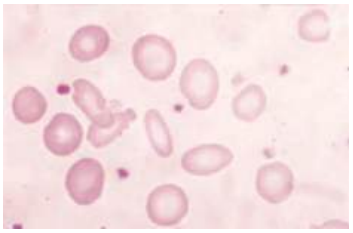
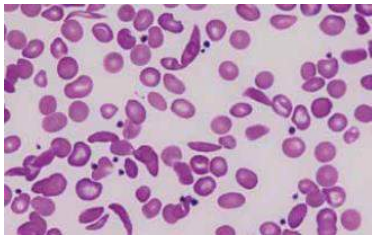
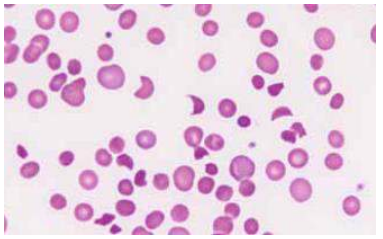
Although the most reliable indicator of anemia at the population level is blood hemoglobin concentration, measurements of this concentration alone do not determine the cause of anaemia. The first step in diagnosis of anemia is to establish whether the abnormality is isolated to a single cell line (red blood cells only) or whether it is part of a multiple cell line abnormality (red cells, white cells and platelets). Abnormalities of two or three cell lines usually indicate one of the following:

- *bone marrow involvement, (e.g., aplastic anemia, leukemia)*
- *an immunologic disorder (e.g., SLE, immune hemolytic anemia singly or in combination)*
- *sequestration of cells (e.g., hypersplenism)*

To narrow the diagnostic possibilities, anemias may be classified on the basis of their morphology and physiology.

- Anemias may be **morphologically** categorized on the basis of RBC size (mean corpuscular volume [MCV]), and microscopic appearance. They can be classified as microcytic, normocytic, or macrocytic based on whether the MCV is low, normal, or high, respectively.

Fig. **Examples of variations in RBC morphology**

				
Normal RBCs	**Macrocytes**	**Hypochromic microcytes**	**Sickle cells**	**Fragmented RBCs (Schistocytes)**
Normal mean cell volume (MCV)	Macrocytes are large red cells with a high MCV. Their hemoglobin concentration (MCHC) is normal.	The central pallor zone of the erythrocyte must be greater than one-third of the diameter of the cell before it is classified as hypochromic. Not all hypochromic cells are microcytic, but all microcytic cells are hypochromic.	Sickle cells are red cells with two pointed ends which are in the shape of a crescent or sickle. This is due to the polymerization of deoxygenated HbS causing changes to the red blood cell making it less deformable and much more rigid.	Fragmented red cells are red cells that are injured and torn due to a microangiopathic process in which fibrin strands are generated and are responsible for injury to the red cells.
⇩	⇩	⇩	⇩	⇩
• Normal blood • Normocytic anemia	• Normal newborn • Folic acid or vitamin B12 deficiency	• Iron deficiency anemia • Lead poisoning • Thalassemias • Sideroblastic anemia	• Homozygous hemoglobin S disease	• Microangiopathic hemolytic anemia (in HUS, TTP, DIC)

- Anemias may also be further divided on the basis of underlying physiology. The 2 major categories are decreased production and increased destruction or loss.

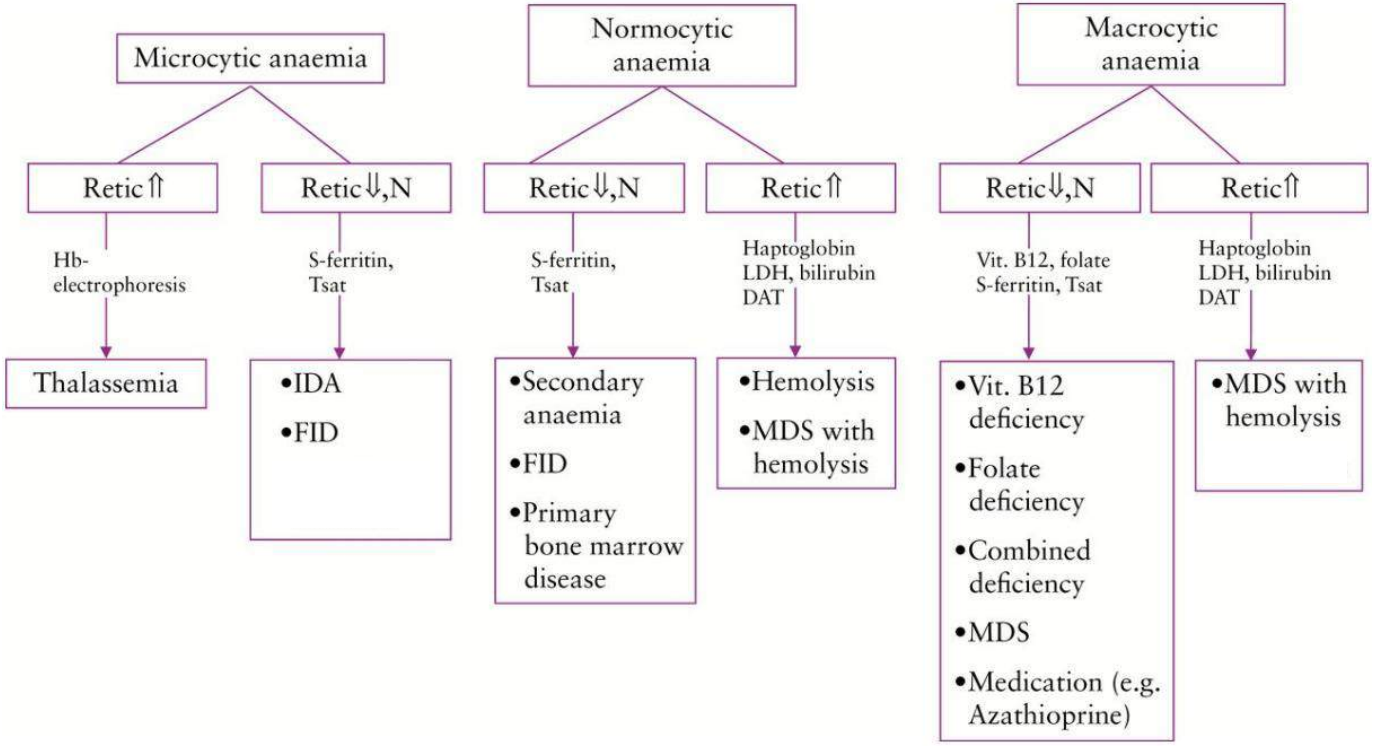
Decreased RBC production (hypoproliferative anemia)	Increased RBC destruction or loss
• Nutrient deficiency (iron, folate, vitamin B12), • Bone marrow failure (acquired or inherited) • Bone marrow infiltration (eg, malignancy)	• Hemolysis • Sequestration • Bleeding

The peripheral blood reticulocyte percentage or absolute number will help to make a distinction between the 2 physiologic categories. The normal reticulocyte percentage of total RBCs during most of childhood is approximately 1%, with an absolute reticulocyte count of 25,000-75,000/mm3. In the presence of anemia, EPO production and the absolute number of reticulocytes should rise.

- *Low or normal numbers of reticulocytes generally represent an inadequate response to anemia that is associated with relative bone marrow failure or ineffective erythropoiesis.*
- *Increased numbers of reticulocytes represent a normal bone marrow response to ongoing RBC destruction (hemolysis), sequestration, or loss (bleeding).*

Fig. Anaemia classification based on MCV and reticulocyte count

[From Dignass AU et al. European consensus on the diagnosis and management of iron deficiency and anaemia in inflammatory bowel diseases. Journal of Crohn's and Colitis. 2015 Mar 1;9(3):211-22.]



The reticulocyte count tells whether the bone marrow can respond by increasing erythropoiesis, which gives early and important information on the direction of the investigation. All deficiency states are excluded by increased reticulocytes.

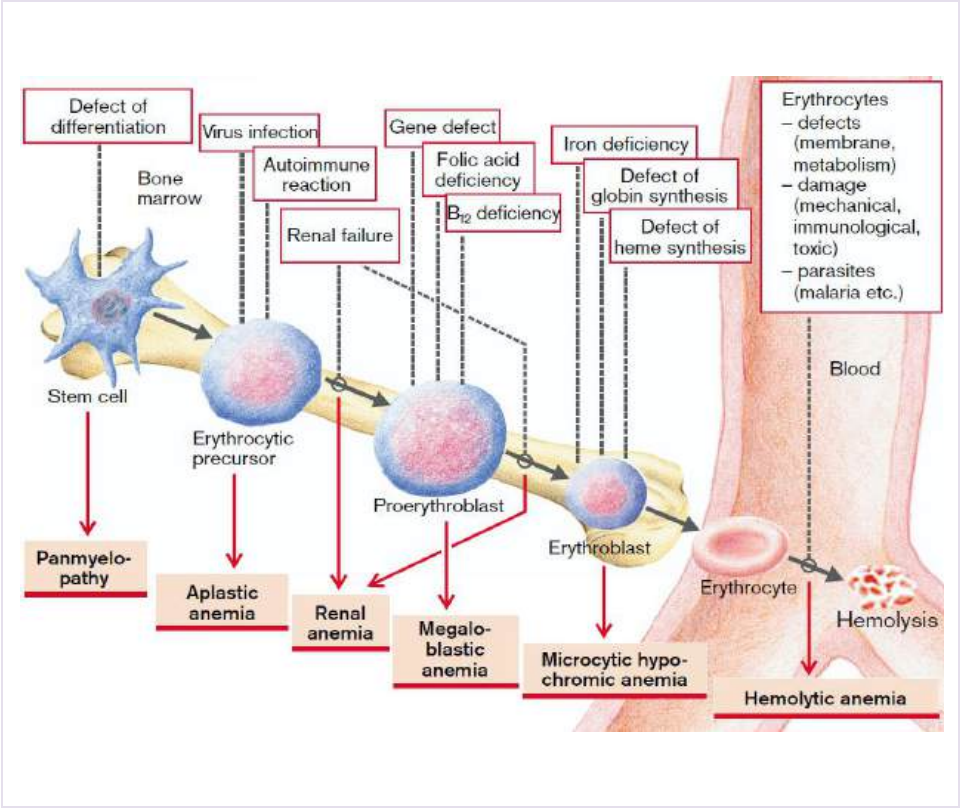
Retic, reticulocyte count; N, normal; Tsat, transferrin saturation; S–ferritin, serum ferritin; LDH, lactate dehydrogenase; MCV, mean corpuscular volume; DAT, direct antibody test; Hb, hemoglobin; IDA, iron deficiency anaemia; FID, functional iron deficiency; MDS, myelodysplastic syndrome;

** anemia secondary to malignancy, infection, kidney disease etc.*

Major forms of anemia in childhood

Acquired hypoproliferative anemia

- Nutritional deficiency *(see p. 15)*
- Lead poisoning *(see p. 25)*
- Acquired aplastic anemia: associated with bicytopenia or pancytopenia (as opposed to pure RBC aplasia)
- Transient erythroblastopenia of childhood: generally occurs during the first 3 years of life in otherwise healthy children, although it can be seen in children from 6 months to 10 years old. It is thought to have a viral or immunologic cause and resolves without specific intervention.
- Anemia of acute inflammation: may be encountered in children who are hospitalized and is generally transient, resolving when the underlying condition has improved. Acute infection may cause anemia through a variety of mechanisms, including bone marrow suppression, shortened RBC lifespan, red-cell fragmentation, and immune-mediated RBC destruction.
- Anemia of chronic inflammation: multifactorial anemia associated with increased cytokine production, up-regulation of hepcidin, and abnormal iron homeostasis.
- Marrow replacement caused by malignancy (leukemia) — is usually associated with abnormalities in other cell lineages in addition to RBCs.



Congenital hypoproliferative anemia

- Diamond-Blackfan anemia — is congenital pure RBC aplasia, which usually presents in the first 3 months of life; although often macrocytic, it may be normocytic.
- Refractory sideroblastic anemia
- Congenital dyserythropoietic anemias

Hemolytic anemia

- Inherited disorders of hemoglobin or the RBC membrane
- Acquired causes: autoimmune hemolytic anemia; microangiopathic hemolytic anemia, particularly Shiga toxin–associated hemolytic uremic syndrome (HUS).

IRON-DEFICIENCY

Iron deficiency affects more than 2 billion people worldwide, and iron-deficiency anemia remains the top cause of anemia.

In childhood **iron deficiency** occurs most frequently during late infancy through the first few years of life and again during adolescence. This prevalence pattern corresponds to periods of rapid growth, and when combined with poor dietary intake can predispose to iron deficiency. Other contributing factors to iron deficiency include prematurity (low iron reserves), blood loss (most commonly menstrual or gastrointestinal), and GI conditions associated with decreased iron absorption.

Definitions of iron deficiency state

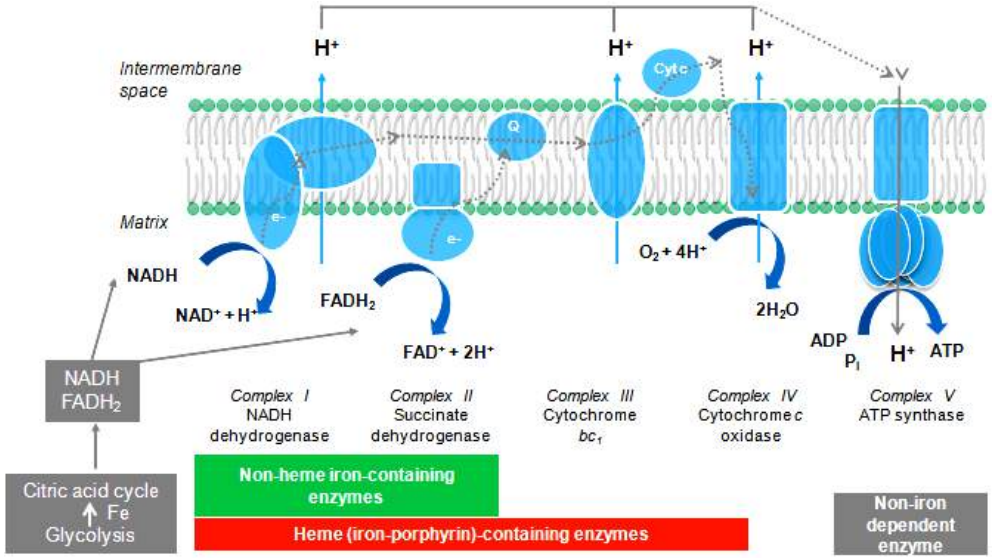
[Camaschella C. (2015). Iron-deficiency anemia. N Engl J Med, 2015(372), 1832-1843.]

Iron deficiency (ID)	- Depressed levels of total body iron, especially iron stores, with preservation of levels of erythroid iron.
Iron deficiency anemia (IDA)	- Depressed levels of total body iron in the presence of anemia.
Functional iron deficiency (FID)	- Insufficient mobilization of erythroid iron in the presence of increased requests, as occurs after treatment with erythropoiesis-stimulating agents. Iron is sequestered in the RES as a consequence of immune activation due to infection, autoimmune disorders, cancer etc.
Iron-restricted erythropoiesis (IRE)	- A reduced supply of iron for the purpose of erythropoiesis, regardless of the level of iron stores. Stores may be normal or even increased because of iron sequestration in cases of anemia of chronic inflammation, which is observed in patients with autoimmune disorders, cancer, infections, and chronic kidney disease. *Thus, both absolute ID and FID cause IRE.*
Iron-refractory iron-deficiency anemia (IRIDA)	- Iron-deficiency anemia that is unresponsive to oral iron treatment, in most cases referring to the genetic disease caused by a mutation in TMPRSS6, the gene encoding transmembrane protease, serine 6, also known as matriptase-2. *This protein is a transmembrane serine protease that plays an essential role in down-regulating hepcidin, the key regulator of iron homeostasis. Hallmarks of this disease are microcytic hypochromic anemia, low transferrin saturation and normal/high serum hepcidin values. The anemia appears in the post-natal period, although in some cases it is only diagnosed in adulthood. The disease is refractory to oral iron treatment but shows a slow response to intravenous iron injections and partial correction of the anemia.*

Physiological role of iron

Iron is an essential micronutrient, as it is crucial to biologic functions, including respiration, energy production, DNA synthesis, and cell proliferation.

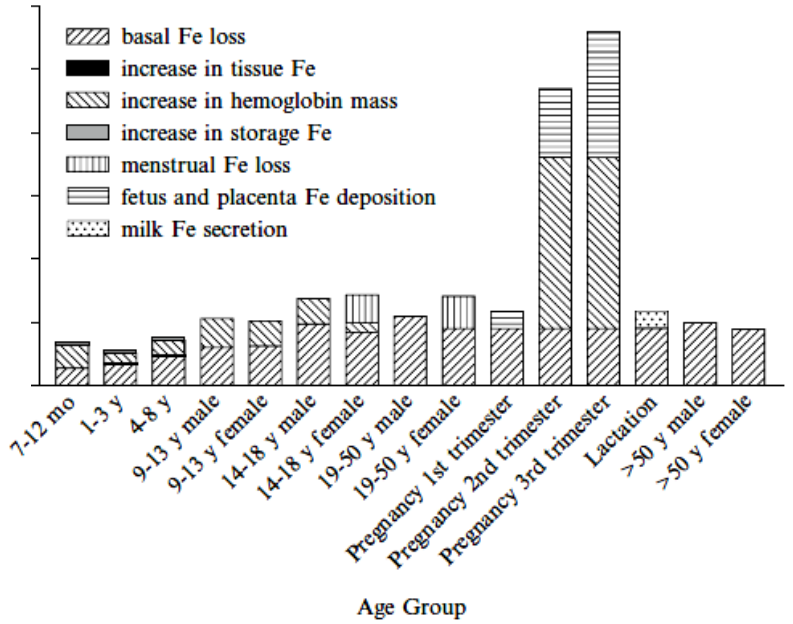
- Required for oxygen binding to hemoglobin (oxygen transport)
- Essential component of myoglobin (oxygen storage)
- Component of oxidative enzymes and respiratory chain proteins (transfer of electrons/redox cycling):
  Fe^{2+} (ferrous, reduced state) ↔ Fe^{3+} (ferric, oxidised state)
  - Energy metabolism
  - Enzyme activity and cellular metabolism
  - Neurodevelopmental and cognitive function
  - Growth
- Required for enzymes and proteins involved in DNA synthesis and DNA repair mechanisms
- Essential component of cytochrome P450 enzymes (drug metabolism, steroid hormone production)



Dietary Recommended Intake of Iron

[Institute of Medicine. Dietary reference intakes. 2003]

Age	Gender	Level of iron intake
0-6 mo	Male and female	0.27 mg/day
7-12 mo	Male and female	11 mg/day
1-3y	Male and female	7 mg/day
4-8y	Male and female	10 mg/day
9-13y	Male and female	8 mg/day
14-18y	Male	11 mg/day
14-18y	Female	15 mg/day



Main pathways of iron homoeostasis

The human body has evolved to conserve iron in several ways, including the recycling of iron after the breakdown of red cells and the retention of iron in the absence of an excretion mechanism. However, since excess levels of iron can be toxic, its absorption is limited to 1 to 2 mg daily, and most of the iron needed daily is provided through recycling by macrophages that phagocytose senescent erythrocytes. The latter two mechanisms are controlled by the hormone hepcidin, which maintains total-body iron within normal ranges, avoiding both iron deficiency and excess.

➢ Iron absorption

Dietary iron is found in heme (10%) and non-heme (ionic, 90%) forms and their absorption occurs at the apical surface of duodenal enterocytes via different mechanisms.

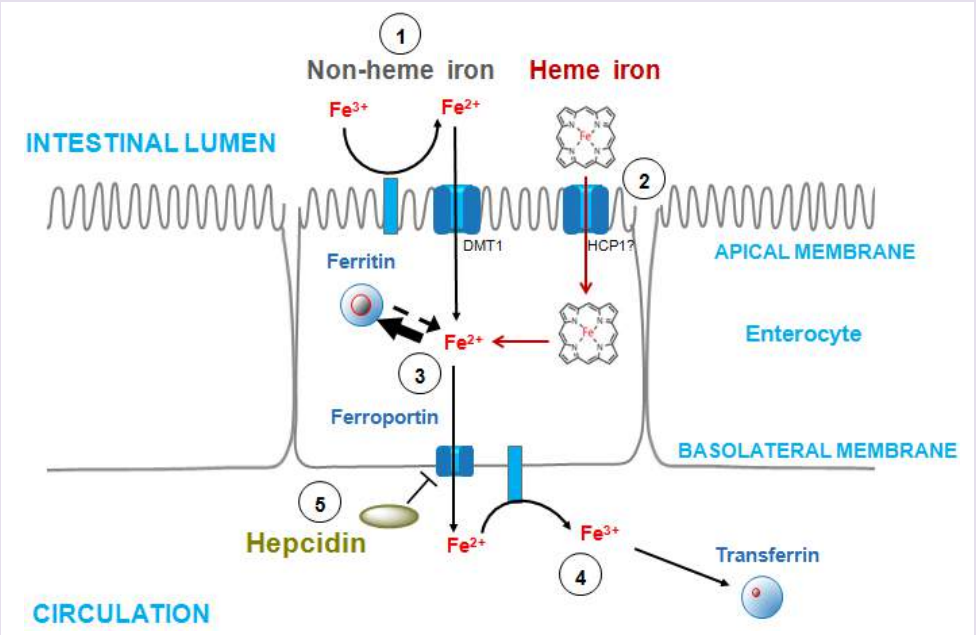
(1) Dietary **non-heme iron** primarily exists in an oxidised (Fe^{3+}) form that is not bioavailable and must first be reduced to the Fe^{2+} form by a *ferrireductase enzyme*, which uses vitamin C as coenzyme, before being transported across the intestinal epithelium. This is accomplished by a carrier protein called *divalent metal transporter 1 (DMT1)*, which also traffics other metal ions such as zinc, copper and cobalt by a proton-coupled mechanism.

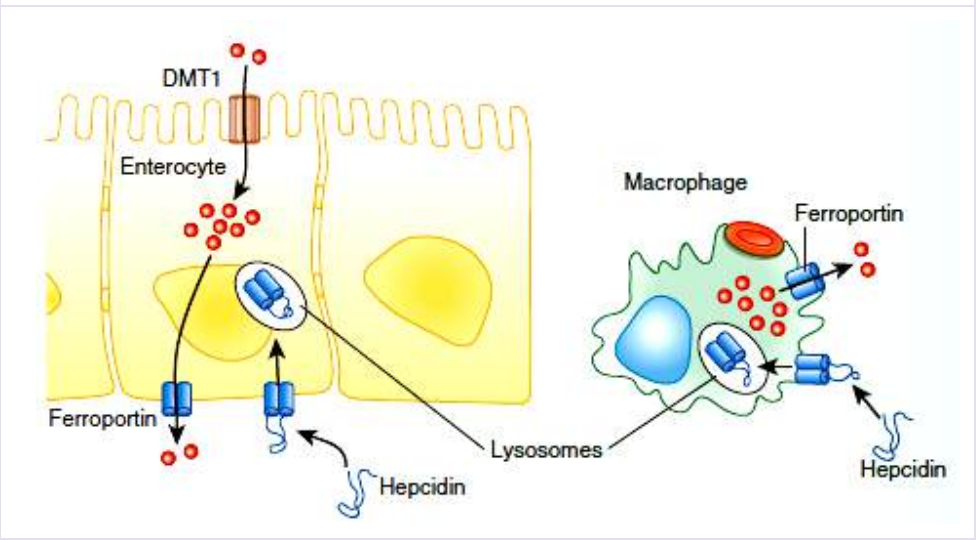
(2) **Heme iron** is absorbed independently by mechanisms that remain uncertain (proposed transporter — heme carrier protein 1, HCP1).

(3) Once inside the intestinal epithelial cell, most Fe^{2+} is exported by **ferroportin** across the basolateral membrane of the enterocyte (absorbed iron), and re-oxidised to Fe^{3+} (4) by *hephaestin* before being bound by plasma transferrin for delivery to cells.

Ferroportin is also expressed in hepatocytes, reticuloendothelial macrophages and placental syncytiotrophoblasts (where it regulates iron entry into fetal circulation).

(5) Levels of iron absorption are controlled by the iron-regulatory peptide hormone, hepcidin, which is synthesised in the liver. **Hepcidin** binds to a specific extracellular domain of ferroportin and induces its degradation in the lysosome.





Heme iron is mainly derived from hemoglobin and myoglobin and is found in animal foods, such as red meat, fish and poultry. Non-heme iron is obtained from plant foods, such as lentils and beans.

The relative absorption of iron in the gut differs between these dietary forms of iron; heme iron is absorbed better than non-heme iron. This is because non-heme iron is predominantly found as Fe^{3+} and therefore must be reduced to Fe^{2+} before it can be absorbed.

The absorption of heme iron is largely unaffected by diet, whereas non-heme iron absorption can be influenced by several dietary factors. Ascorbic acid (vitamin C) is an enhancer of iron absorption, as it reduces Fe3+ to Fe2+. In contrast, the intake of bran, phytates (high-fibre diets), phenolic compounds (coffee, tea), calcium and phosphates can result in the inhibition of non-heme iron absorption owing to their ability to chelate metals such as iron.

Non-heme iron absorption can also be reduced by drugs, such as antacids and proton pump inhibitors which decrease stomach acid levels, as gastric acid enhances the dissociation and solubilisation of iron salts in non-haem iron, allowing them to be reduced to the Fe2+ oxidation state. In addition, Helicobater pylori infection produces gastric atrophy, which can lead to profound IDA.

The acquisition of iron absorption capacity (mediated by DMT1) increases linearly after birth, reaching adult levels by early childhood.

Fig. Iron absorption from different food sources

[From Scrimshaw NS. Iron deficiency. Scientific American 1991;265:46–52.]

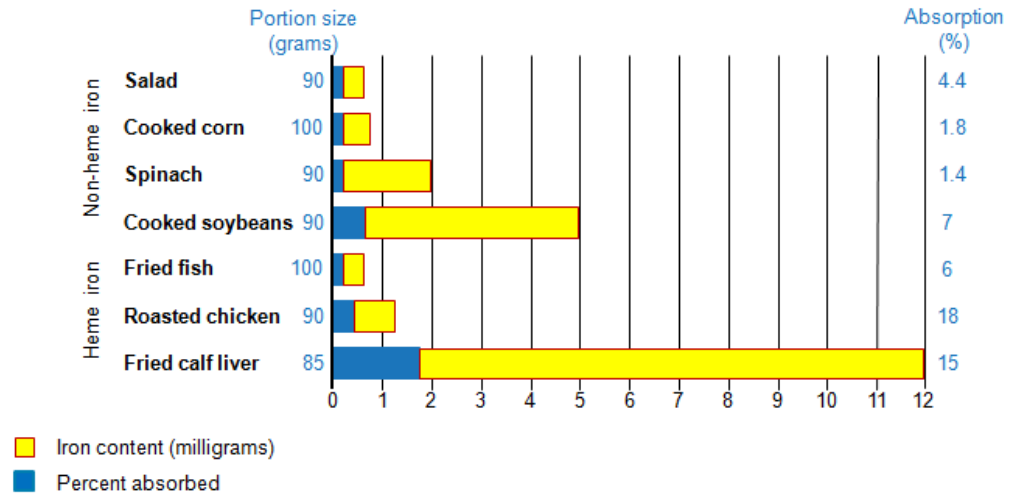
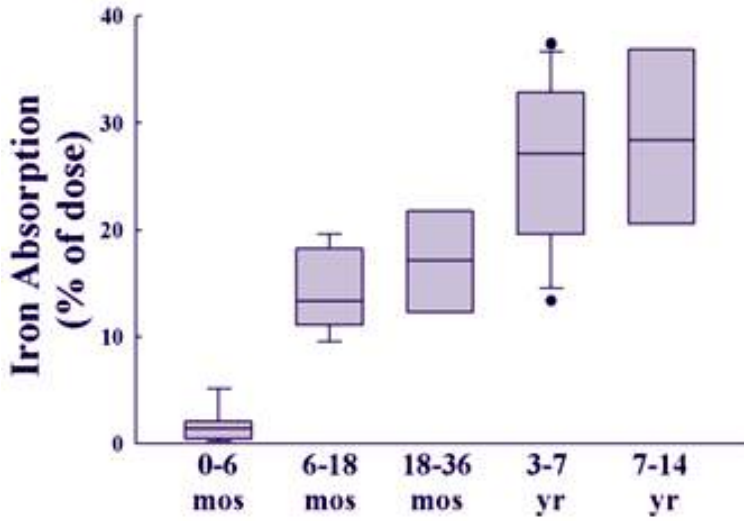
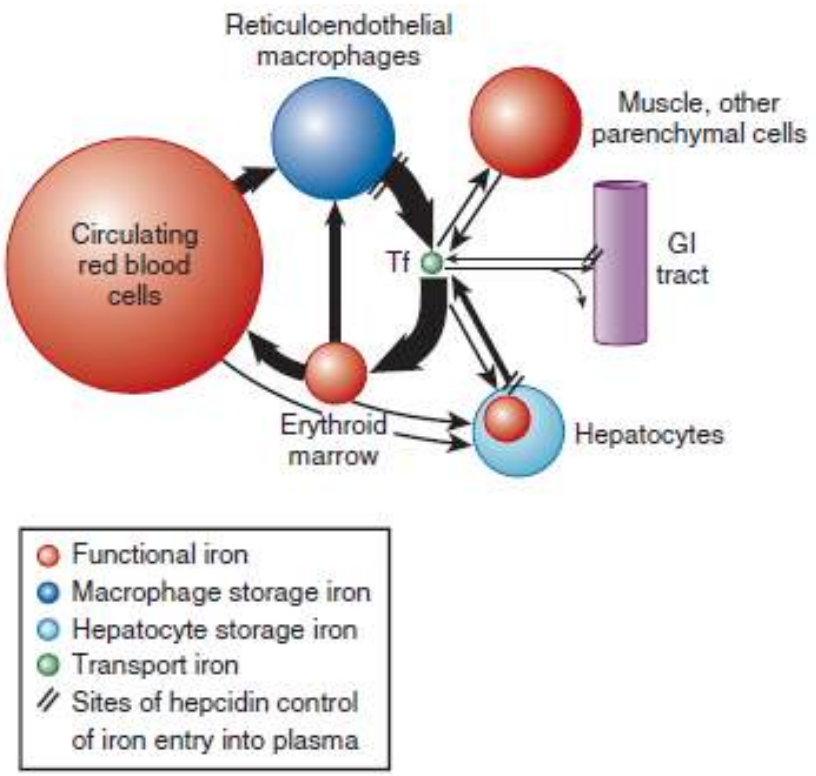


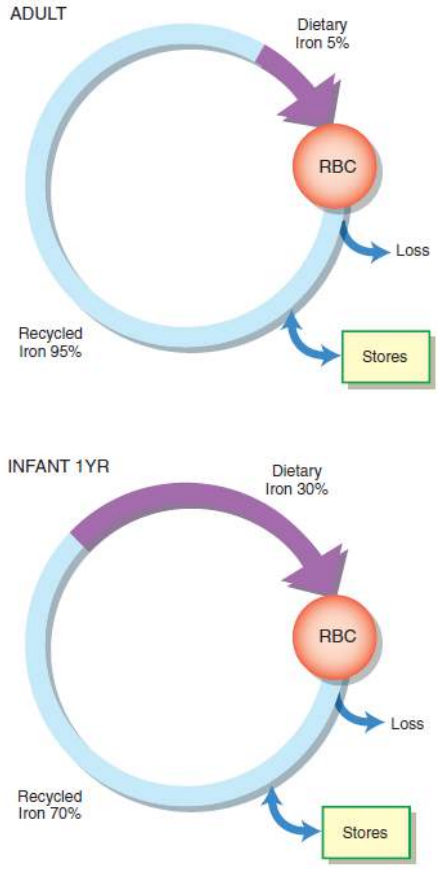
Fig. Age-dependent enteral absorption of iron expressed as a percentage of the dose dministered [Funk et al. 2012]



➢ Body iron distribution and recycling



- Once in circulation, iron is transported bound to transferrin to the site of use or storage. Erythrocyte precursors express high levels of transferrin receptor 1 (TfRl) and, thus, have preferred access to circulating iron.
- The major portion of iron is found in the erythron as hemoglobin iron dedicated to oxygen transport and delivery. Small amounts of erythron iron are also present in heme and nonheme enzymes in developing RBCs.
- The remainder of functional iron is found as myoglobin iron in muscle and as iron-containing and iron-dependent enzymes throughout the cells of the body.
- Most storage iron is held in reserve by hepatocytes and macrophages (ferritin and hemosiderin).
- The small fraction of transport iron in the plasma and extracellular fluid is bound to the protein transferrin (Tf).



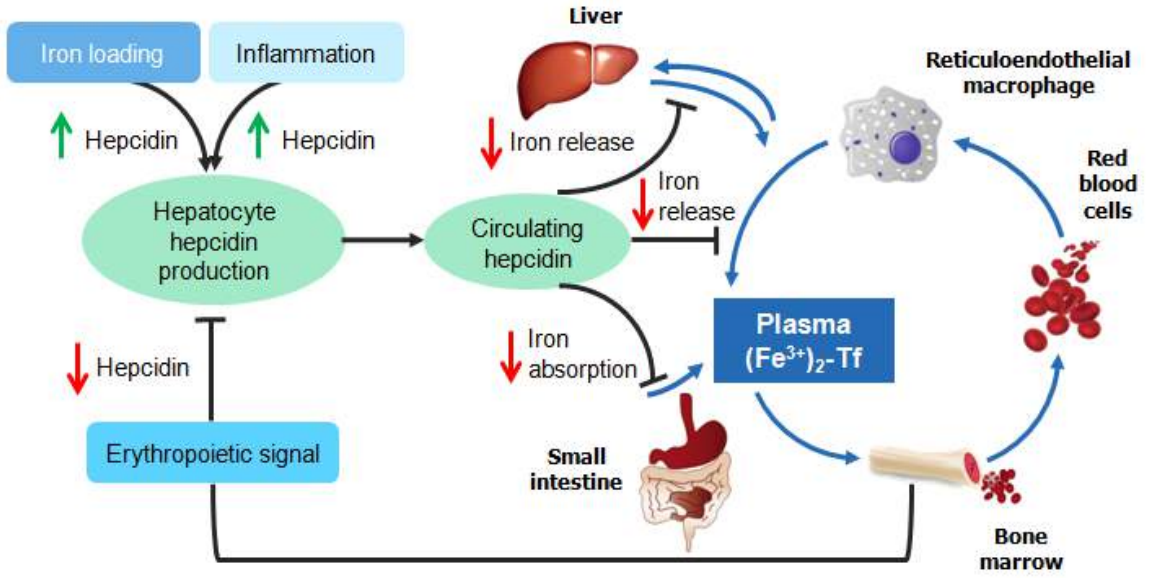
- The recycling of iron from heme and amino acids from globin following the lysis of aged red cells is a very efficient process. Heme is returned to the bone marrow, and the amino acids of the globin chain are returned to the amino acid pool. Each of these products will later be recruited for hemoglobin formation and red cell production.
- In the adult, approximately 95% of recycled iron is used for red cell production, whereas in the infant, only 70% is used for this purpose. Because of this relationship, it is easy to understand the significance of adequate iron sources in the early years of development.

Ferritin

- Ferritin is an intracellular protein and each ferritin complex can store about 4500 iron (Fe^{3+}) ions
- Ferritin is found in all cells of the body
  - Liver hepatocytes and RES macrophages of the liver and spleen are the most prominent sites of ferritin accumulation
- Ferritin can also be found in serum
  - Serum ferritin contains very little iron
  - Serum ferritin is increased in patients with inflammation
- In healthy individuals, serum ferritin levels correlate with body iron store levels
  - Serum ferritin levels decrease as iron stores become depleted
  - Therefore it is the most useful estimate of body iron stores in individuals without inflammation

Hepcidin is the principal regulator for systemic iron homeostasis

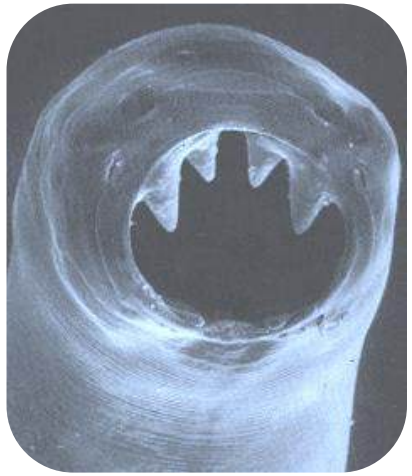
- Hepcidin synthesis is induced by iron loading and inflammation and suppressed by erythropoiesis.
- In the case of an iron load, increased hepcidin levels limit further enteral iron absorption and release of iron from the liver and the reticuloendothelial system to normalize plasma iron levels.
- With increased inflammation, elevated hepcidin levels cause the same sequence of events, leading to reticuloendothelial blockade and **anemia of inflammation**.
- Conversely, by suppressing hepcidin production, erythropoietic activity increases the availability of iron by enhancing enteral absorption and release of iron from the liver and the reticuloendothelial system.



CASE STUDY *A 4-year-old girl, recently immigrated from a developing country, is found on a routine screening CBC to have what appears to be iron deficiency anemia. What further test must be performed to understand the etiology?*

Causes of iron deficiency

Cause	Example
Physiologic (increased demand)	Rapid growth (infancy, adolescence), menstrual blood loss, pregnancy (second and third trimesters), blood donation
Environmental	Insufficient intake, resulting from poverty, diet (e.g., vegetarian, vegan, lack of meat consumption, **excessive consumption of cow's milk**, confectionery, which contain iron-binding substances)
Malabsorption in the gastrointestinal tract	*Helicobacter pylori* infection, atrophic gastritis, celiac disease, inflammatory bowel diseases (ulcerative colitis, Crohn disease)
Chronic blood loss	*Gastrointestinal tract:* **hookworm infestation (Ancylostoma duodenale)**, erosive gastritis, peptic ulcer, Meckel diverticulum, **cow's milk protein allergy**, benign tumors, intestinal cancer, inflammatory bowel diseases, angiodysplasia, hemorrhoids *Genitourinary system:* heavy menses, menorrhagia, intravascular hemolysis (e.g., paroxysmal nocturnal hemoglobinuria, autoimmune hemolytic anemia with cold antibodies, march hemoglobinuria, damaged heart valves, microangiopathic hemolysis) *Systemic bleeding:* bleeding disorders, hemorrhagic telangiectasia, chronic schistosomiasis, Munchausen syndrome (e.g, self-induced hemorrhages)
Drug-related	Glucocorticoids, salicylates, NSAIDs, proton-pump inhibitors
Genetic	Iron-refractory iron-deficiency anemia
Iron-restricted erythropoiesis	Treatment with erythropoiesis-stimulating agents, anemia of chronic disease, chronic kidney disease



Clinical presentation of iron deficiency

Patients with iron deficiency may present with

(1) no signs or symptoms, coming to medical attention only because of abnormalities noted on laboratory tests

(2) features of the underlying disorder responsible for the development of iron deficiency

(3) manifestations common to all anemias:

- Fatigue, weakness, dizziness and drowsiness, anorexia
- Loss of normal colour in the skin (in fair skinned people) and also in the lips, tongue, nail beds and the blood vessels in the white of the eye
- In severe cases growth impairment may occur and *resistance to infection may be decreased*

• Decreased oxygen transport leads to fatigue, dyspnea, angina pectoris, and syncope
• Decreased blood volume leads to pallor, postural hypotension, and shock
• Increased cardiac output leads to palpitation, strong pulse, and heart murmurs

Pallor of the skin and mucous membranes is an unreliable indicator and is usually seen only when the hemoglobin is less than 80 g/L.

- **Mucosal conditions**, such as glossitis, recurrent aphthae, candidal infections, and angular stomatitis may be more common in patients with anemia. The tongue appears reddened, and the papillae are atrophic, producing a smooth ("bald") appearance. Angular stomatitis is commonly caused by a candidal infection, and it has been linked to iron deficiency.

As cells of the tongue papillae have a high rate of turnover, deficiencies in micronutrients needed for cell proliferation or cell membrane stabilisation may lead to depapillation. Nutritional deficiency is also thought to change the pattern of microbial flora, thus contributing to glossitis.

(4) Features *unique* to the IDA: pagophagia, koilonychias (spooning of the nail bed), and blue sclerae.
Additionally, evidence suggests that **iron deficiency with or without anemia may result in developmental delays and behavioral disturbances.**

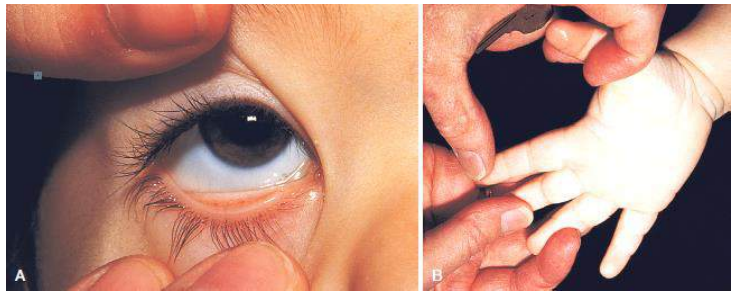


Fig. Severe anemia. **A,** Pale conjunctiva may be seen in the patient with severe anemia. **B,** Pale palmar creases are also visible in cases of severe anemia. The child in this photograph has a hemoglobin level of 40 g/L.

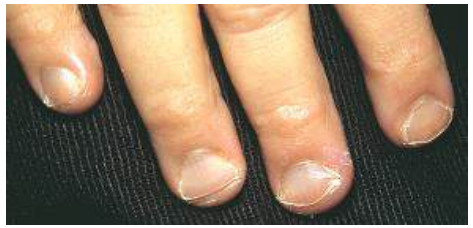


Fig. Spooning of the fingernails occurs in children with severe iron deficiency anemia (koilonychia)

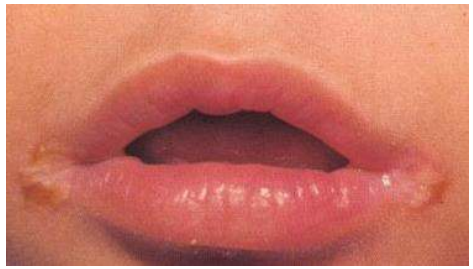


Fig. Angular stomatitis

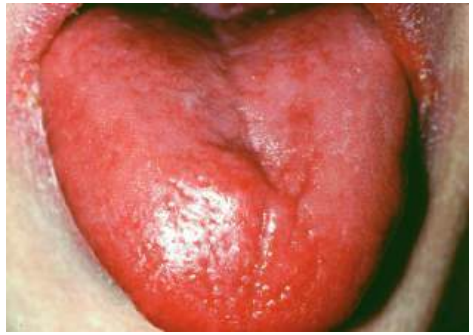


Fig. Atrophic glossitis

IRON DEFICIENCY WITHOUT ANEMIA ALSO HAS SIGNIFICANT EFFECTS

Iron is a necessary cofactor for many enzymes. It is particularly crucial to the **dopaminergic system** in the central nervous system. Among the nonhematologic neurologic conditions that have been associated with iron deficiency are *breath-holding spells, attention-deficit/hyperactivity disorder, febrile seizures, pagophagia*, and restless legs syndrome (RLS)** [Zehetner AA 2010; Lozoff B 2011].*

Some studies have indicated that even after iron stores are rebuilt the developmental consequences of early iron deficiency may not be reversible. In addition to the direct effects of inadequate iron stores, **iron deficiency promotes lead absorption** and its neurologic consequences.

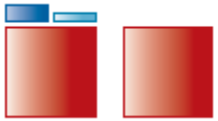
** **Pagophagia**, a variant of pica in which ice is the substance obsessively consumed, is a behavioral abnormality that is considered to be a highly specific symptom of iron deficiency, resolving within a few days to 2 weeks after beginning iron therapy.*

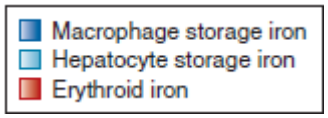
*** **Restless legs syndrome (RLS)** is a neurologic disorder characterized by a distressing need or urge to move the legs. The etiology of RLS is complex. One major potential pathophysiological pathway in the development of RLS is the iron deficiency-dopamine interaction [Earley CJ 2014].*

Common clinical laboratory tests to assess iron status

Test	What It Indicates	Result in Iron Deficiency
Serum iron	Iron recycling/usage, stores (indirect)	↓
Total iron-binding capacity (TIBC)	Serum/plasma transferrin	↑
Transferrin saturation: Tsat(%) = (100 × serum iron)/TIBC	% plasma iron-binding sites on transferrin that are occupied	↓ - ↓↓
Free or zinc protoporphyrin (ZnPP)	Functional mitochondrial iron status	↑
Soluble transferrin receptor (sTfR)	Adequacy of marrow activity for any level of anemia	↑
Serum ferritin	Iron stores (indirect)	↓ - ↓↓
Bone marrow iron	Macrophage iron stores/retention, RBC iron uptake	↓
Hepcidin	Hepatocyte iron	↓ - ↓↓
Red blood cell distribution width (RDW)	The degree of variation in RBC size	↑ (anisocytosis)

Phases of development of iron deficiency (without coexisting disorders)

Parameter	NORMAL	PRELATENT IRON DEFICIENCY	LATENT IRON DEFICIENCY	IRON DEFICIENCY ANEMIA
			Iron-deficient erythropoiesis 	
Iron stores	Present	Decreased	Absent	Absent
Ferritin	N	↓	↓	↓↓
Transferrin saturation	N	Normal	↓	↓
sTfR	N	↑	↑↑	↑↑↑
Zinc protoporphyrin	N	Normal	↑	↑
Ratio of ZnPP to heme	N	Normal	↑	↑
Hemoglobin	N	Normal	Normal	↓
MCV	N	Normal	Normal	↓



Iron deficiency progresses through three discernible phases:

1. *First, in the pre–latent phase, iron stores are depleted and ferritin levels are typically low. Importantly, ferritin levels can remain normal or elevated if there is concurrent inflammation.*
2. *This is followed by latent iron deficiency, which is evident in a decrease in transferrin saturation. The final step of heme formation is the incorporation of an iron molecule into the porphyrin ring. As the amount of iron being transported in the plasma decreases, there is less iron available to be incorporated into the porphyrin ring and a resulting rise in the ratio of zinc protoporphyrin to heme.*
3. *Finally, with overt iron-deficiency anemia, there is a diminution in red blood cell volume and quantity (anemia and microcytosis are late findings in iron deficiency).*

No single test value will completely characrerize iron status. A set of tests is required to establish the iron starus of an individual. The tests most easily obtained are:

- *Hb concentration to establish presence of anemia*
- *serum ferritin concentration to suggest iron as the cause of the anemia*
- *CRP to ensure that an elevated serum ferritin concentration is truly attributable to lack of iron and not secondary to an inflammatory state*

CASE STUDY *An 8-month-old infant is found to have low hemoglobin and low MCV on a routine CBC. He is treated with iron supplementation for 5 months, but on repeat CBC, he is still anemic. What is the likely cause of his anemia?*

Differential diagnosis of IDA

Iron deficiency is the only microcytic hypochromic disorder in which mobilizable iron stores are absent; in all other disorders, storage iron is normal or increased.

Diagnosis	MCV	Serum iron	Serum ferritin	TIBC	Tsat	sTfR
IDA	↓	↓	↓	↑	↓	↑
Anemia of inflammation	Normal (may be mildely low)	↓	Normal or elevated	Normal	↓	Normal
Microcytic hemoglobinopathies (eg, thalassemia)	Low or normal	Normal	Normal or elevated	Normal	Normal or elevated	Normal or elevated
IDA with coexistent inflammation	↓	↓	Low or normal	Normal or high	↓	↑

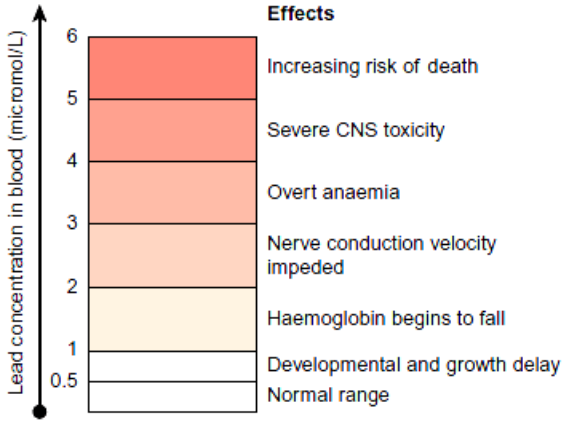
Lead poisoning (plumbism)

In the developing world, lead is a much more significant public health problem. Sources vary from country to country, but lead-glazed ceramics are a common cause, particularly as their production is often a home-based industry in which children are actively employed. Other sources include leaded petrol, groundwater contamination from mining, smelting and battery factories, as well as exposure to other occupational sources via parents.

The toxic effects of lead span several different systems:

- *Hematological* – Lead inhibits the enzymes 5-aminolaevulinic acid dehydratase (ALAD) and ferrochelatase, which are essential for the production of heme. This results in a microcytic, hypochromic anemia with elevated plasma concentrations of 5-aminolaevulinic acid (ALA) and zinc protoporphyrin.
- *Neurological* – Children may present with cognitive impairment as a result of chronic low-level lead exposure or an acute encephalopathy. The mechanism of neurotoxicity is not known.
- *Renal* – Acute severe lead exposure may give rise to proximal tubular dysfunction resulting in glycosuria and aminoaciduria. Chronic exposure leads to interstitial nephritis.

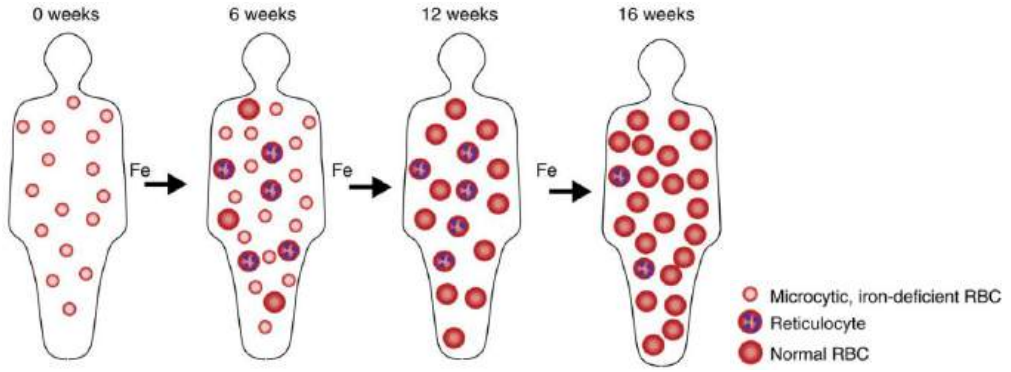
The toxic effects of lead are dose-related.



Therapeutic trial of iron and recovery from IDA

The diagnosis of iron deficiency often is confirmed by the outcome of a therapeutic trial of iron. A specific orderly response to, and only to, treatment with iron constitutes the final definitive proof that a lack of iron is the cause of anemia. The unequivocal diagnostic response consists of:
(1) a reticulocytosis, which begins approximately 3 to 5 days after adequate iron therapy is instituted, reaches a maximum on days 8 to 10, and then declines;
(2) a significant increase in hemoglobin concentration, which should begin shortly after the reticulocyte peak, is invariably present by 3 weeks after iron therapy is begun, and persists until the hemoglobin concentration is restored to normal.

Fig. Impact of iron supplementation on RBC population dynamics *[Clark MA et al, 2014]*



After iron supplementation for IDA, the reticulocyte count should double in 1 to 2 weeks, and hemoglobin should increase by 20 g/L after 3 weeks. Common reasons for persistence of iron deficiency anemia are: poor compliance with supplementation; malabsorption of therapeutic iron; continuing blood loss; and the effects of coexisting conditions, especially infectious, inflammatory, or malignant disorders.

Iron Supplements

Compound	Trade name	Formulation	Elemental Fe (mg)	Other ingredients
FERROUS SULFATE	Aktiferrin	Sirup	6.87 mg/ml	
		Drops	0.53 mg/drop	
		Capsule	34.5 mg/caps	
	Sorbifer durules	Tablets	100 mg/tab	Vitamin C
FERROUS GLUCONATE	To'thema	Solution	5 mg/ml	Manganese Copper
FERROUS FUMARATE	Heferol	Capsule	115 mg/caps	
POLYSACCHARIDE/ IRON COMPLEX	Ferrum Lek	Sirup	10 mg/ml	
		Chewable tablets	100 mg/tab	

Management of anemia

Non-severe anemia

- Give (home) treatment with oral iron supplementation. Oral iron therapy should begin with a ferrous iron salt taken separately from meals in three or four divided doses and supplying a daily total of **150 to 200 mg of elemental iron in adults or 2-6 mg of iron per kilogram of body weight in children**. Simple ferrous preparations are the best absorbed and least expensive. Ferrous sulfate is the most widely used, either as tablets for adults or as a liquid preparation for children. Administration between meals maximizes absorption.
  It takes 2–4 weeks to correct anemia. After the anemia has been fully corrected, oral iron should be continued to replace storage iron, either empirically for an additional 3-4 months or until the plasma ferritin concentration exceeds approximately 50 μg/L.

- If the child is ≥1 year and has not received mebendazole in the previous 6 months, give one dose of mebendazole (500 mg) for possible hookworm or whipworm infestation.

- Advise the mother about good feeding practice.

Severe anemia

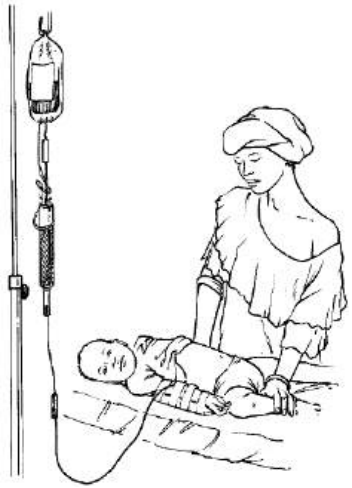
- Give a blood transfusion as soon as possible to:
  - all children with an Hct of ≤12% or Hb of ≤40 g/L
  - less severely anemic children (Hct, 13–18%; Hb, 40–60 g/L) with any of the following clinical features:
    clinically detectable dehydration; shock; impaired consciousness; heart failure; deep, laboured breathing; very high malaria parasitemia (> 10% of red cells with parasites).

• If packed cells are available, give 10 ml/kg over 3–4 h in preference to whole blood. If not available, give fresh whole blood (20 ml/kg) over 3–4 h.

• Check the respiratory rate and pulse rate every 15 min. If either rises or there is other evidence of heart failure, such as basal lung crepitations, enlarged liver or raised jugular venous pressure, transfuse more slowly. If there is any evidence of fluid overload due to the blood transfusion, give IV furosemide at 1–2 mg/kg, up to a maximum total of 20 mg.

• After the transfusion, if the Hb remains as low as before, repeat the transfusion.

• In children with severe acute malnutrition, fluid overload is a common and serious complication. Give packed cells when available or whole blood at 10 ml/kg (rather than 20 ml/kg), and do not repeat transfusion based on the Hb level, or within 4 days of transfusion.



Giving a blood transfusion.
Note: A burette is used to measure the blood volume, and the arm is splinted to prevent flexion of the elbow.

Parenteral iron therapy, with the risk of adverse reactions, should be reserved for the exceptional patient who (1) remains intolerant of oral iron despite repeated modifications in dosage regimen; (2) has iron needs that cannot be met by oral therapy because of either chronic uncontrollable bleeding or other sources of blood loss, such as hemodialysis, or a coexisting chronic inflammatory state; or (3) malabsorbs iron.

In addition to iron dextran, which can be administered intravenously or intramuscularly, there are newer intravenous formulations, including iron gluconate and iron sucrose, that are primarily used for iron replacement in the setting of hemodialysis.

- *Iron supplementation should never be taken with milk, food, or proton pump inhibitors as these all inhibit the absorption of iron.*
- *Taking iron supplementation with orange juice can improve absorption (ascorbic acid enhances iron absorption).*
- *Oral iron may cause staining of the teeth, but this is temporary and can be avoided by rinsing the mouth or brushing the teeth after the medication is given.*
- *Adequate dosage will turn the stools a tarry green color.*

Iron deficiency, with or without anemia, is associated with growth impairment, neurocognitive delays, and behavioral problems as well as other neurologic abnormalities.

An increase in the hemoglobin concentration of at least 20 g/L after 3 weeks of therapy generally is used as the criterion for an adequate therapeutic response.

Some iron deficiency-related conditions such as cognitive delay may not be reversible even when iron stores have been restored.

The most common worldwide cause of chronic gastrointestinal (GI) blood loss is hookworm infection, which is often associated with iron deficiency anemia.

Restless leg syndrome has been associated with low ferritin levels, and treatment with iron has been demonstrated in many cases to improve both the ferritin level and the symptoms of the condition.

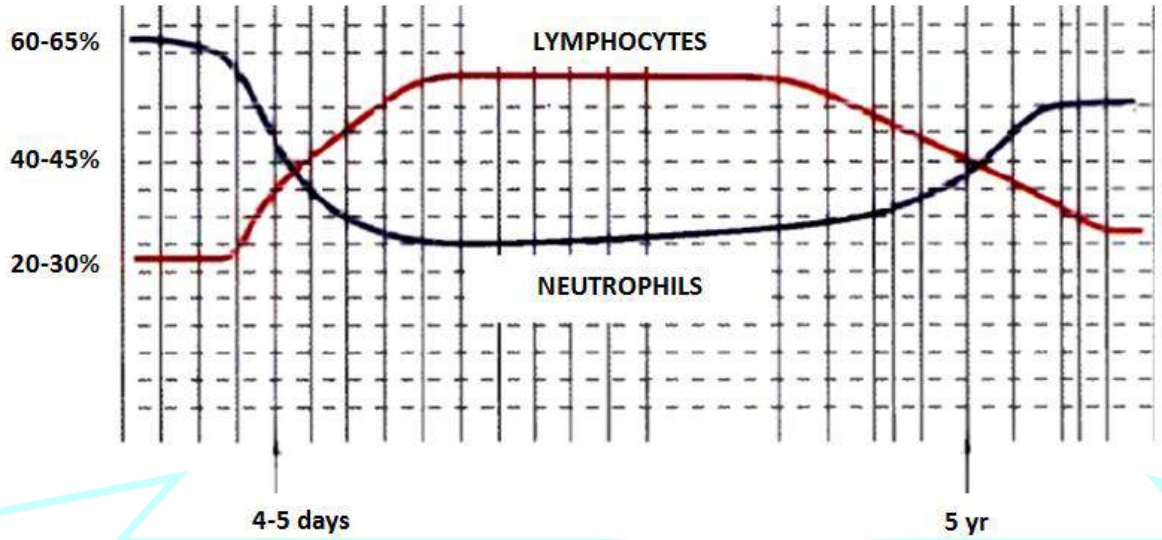
DEVELOPMENTAL CHANGES IN WHITE BLOOD CELLS (WBCs)

The normal leukocyte and neutrophil counts vary tremendously, even by the hour of life, in the first few days after birth. Therefore, it is necessary to consult appropriate nomograms in the immediate neonatal period to properly interpret leukocyte counts. Outside the neonatal period, the normal absolute neutrophil count has a lower limit of normal of approximately 1000/mm^3, except in African American infants, where it may normally be as low as 700 to 800/mm^3. This has been called “ethnic pseudoneutropenia,” an arcane name unnecessarily ascribed to a biologically normal state.

The absolute neutrophil count (ANC) *is the product of the total leukocyte count and the percentage of neutrophils (segmented neutrophils and band forms):*

$$\frac{(\%neutrophils + \%bands) \times (WBC)}{(100)}$$

Number of neutrophils and lymphocytes at different periods of childhood



The relative amount of neutrophils at birth ranges from 60 to 65%. During the first days of life it decreases. The number of lymphocytes at birth ranges from 20 to 30%. At the age of 5–6 days the curves of neutrophils and lymphocytes counts intersect — so-called **"the first cross".** Then, the number of lymphocytes continues to grow (by the end of the second week of life it reaches approximately 55%) and the number of neutrophils decreases.

At the age of 5–7 years, the amount of neutrophils and lymphocytes is the same (**"the second cross" of neutrophils and lymphocytes curves**). Then, the number of neutrophils continues to grow, and the number of lymphocytes decreases.

Fig. Reference ranges for blood neutrophil concentration during the first 72 hours of life

[From Christensen RD, Henry E, Jopling J, et al: The CBC: reference ranges for neonates. Semin Perinatol 33:3–11, 2009.]

< 28-week gestation preterm neonates	28 to 36 weeks' gestation preterm neonates	≥36 weeks' gestation neonates

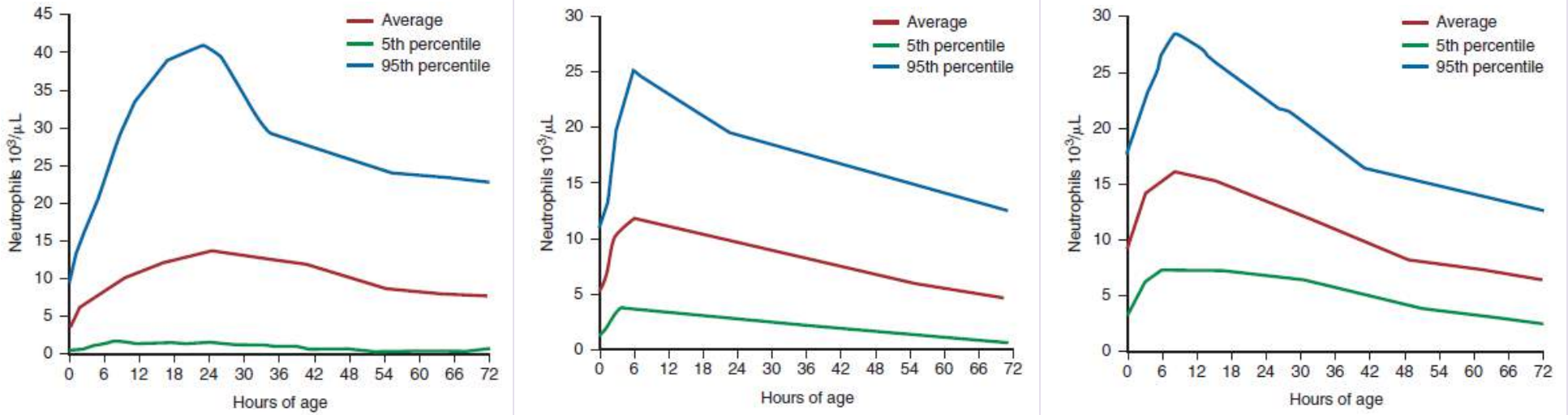


Table. WBC Manual Differential Counts in Normal Fetuses at Different Gestational Ages

[From Forestier F, Daffos F, Catherine N, et al: Developmental hematopoiesis in normal human fetal blood. Blood 77:2360, 1991. RBCs, Red blood cells; WBCs, white blood cells.]

Week of Gestation	Lymphocytes (%)	Neutrophils (%)	Eosinophils (%)	Basophils (%)	Monocytes (%)
18-21	88 ± 7	6 ± 4	2 ± 3	0.5 ± 1	3.5 ± 2
22-25	87 ± 6	6.5 ± 3.5	3 ± 3	0.5 ± 1	3.5 ± 2.5
26-29	85 ± 6	8.5 ± 4	4 ± 3	0.5 ± 1	3.5 ± 2.5
> 30	68.5 ± 15	23 ± 15	5 ± 3	0.5 ± 1	3.5 ± 2

Table. White blood cell count in children (x10⁹/L)

[From Cembrowski GS, Chan J, Cheng C, Bamforth FJ. NHANES 1999-2000 Data used to create comprehensive health-associated race-, sex-, and age-stratified pediatric reference intervals for the Coulter MAXM. Lab Hematol *10:245–246, 2004. Presented at the annual meeting of the International Society for Laboratory Hematology, Barcelona, Spain, May 2004. Numerical summary kindly provided by GS Cembrowski, MS Cembrowski, KA Versluys, 2013.]*

	African American									Mexican American and White								
	2.5 Percentile		50 Percentile		95 Percentile		97.5 Percentile			2.5 Percentile		50 Percentile		95 Percentile		97.5 Percentile		
Age	M	F	M	F	M	F	M	F	Age	M	F	M	F	M	F	M	F	
1y	5.0		8.0		11.5		13.2		1y	6.0		9.5		16.5		17.5		
2-3y	4.0		6.8		10.0		11.0		2-3y	5.5		8.0		12.0		13.0		
4-6y	4.0		6.5		9.2		10.0		4-6y	5.0		7.5		11.5		12.5		
7-10y	3.3		6.0		9.3		11.4		7-10y	4.5		7.3		11.0		11.5		
11-14y	3.3		6.0		9.0		10.0		11-14y	4.5		7.0		11.0		11.5		
15-18y	3.0	4.0	5.5	6.3	9.0		9.7		15-18y	5.1		7.0		11.0		12.0		

Neutrophil count in children (x10⁹/L)

	African American									Mexican American & White								
	2.5 Percentile		50 Percentile		95 Percentile		97.5 Percentile			2.5 Percentile		50 Percentile		95 Percentile		97.5 Percentile	
Age	M	F	M	F	M	F	M	F	Age	M	F	M	F	M	F	M	F
1y	1.0		2.6		4.6		4.6		1y	1.5		3.1		6.2		7.4	
2-3y	1.0		2.4		4.8		7.5		2-3y	1.5		3.3		6.3		7.5	
4-6y	1.0		2.8		5.2		5.8		4-6y	1.7		3.5		6.7		7.9	
7-10y	1.1		2.5		5.7		6.8		7-10y	1.8		3.6		6.7		7.2	
11-14y	1.2		2.8		5.7		5.6	7.0	11-14y	1.9	3.4	4.1	6.7	7.5	7.4	8.2	
15-18y	1.1	1.6	2.7	3.2	5.7		6.8	5.9	15-18y	2.3	3.5	4.6	7.0	7.9	7.9	8.3	

Lymphocyte count in children (x10⁹/L)

	African American									Mexican American & White								
	2.5 Percentile		50 Percentile		95 Percentile		97.5 Percentile			2.5 Percentile		50 Percentile		95 Percentile		97.5 Percentile	
Age	M	F	M	F	M	F	M	F	Age	M	F	M	F	M	F	M	F
1y	1.8		4.1		6.0		6.7		1y	2.5		5.0		8.5		9.5	
2-3y	1.1		3.4		5.0		5.4		2-3y	5.0		3.6		6.0		6.3	
4-6y	1.1		2.7		4.6		5.1		4-6y	1.5		3.0		4.8		4.7	
7-10y	1.3		2.3		3.7		4.0		7-10y	1.5		2.7		4.0		4.5	
11-14y	1.3		2.3		3.4		3.7		11-14y	1.3		2.4		3.6		3.8	
15-18y	1.4		2.1		3.2		3.3		15-18y	1.2		2.0		3.6		3.5	

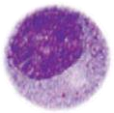
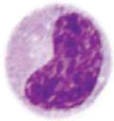
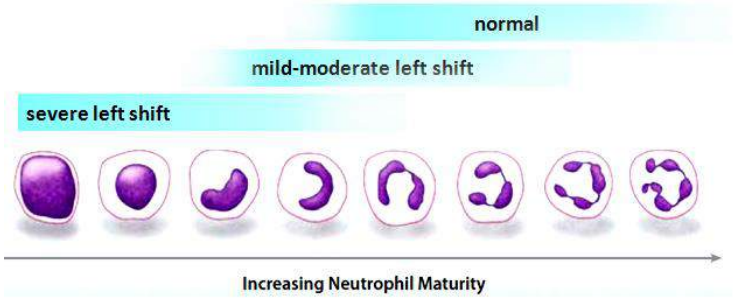
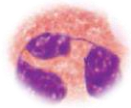
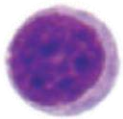
Monocyte count in children (x10⁹/L)

	African American									Mexican American & White								
	2.5 Percentile		50 Percentile		95 Percentile		97.5 Percentile			2.5 Percentile		50 Percentile		95 Percentile		97.5 Percentile	
Age	M	F	M	F	M	F	M	F	Age	M	F	M	F	M	F	M	F
1y	0.4		0.6		1.38		1.66		1y	0.45		0.8		1.4		1.5	
2-3y	0.3		0.6		0.92		1.03		2-3y	0.35		0.6		0.95		0.95	
4-6y	0.3		0.5		0.9		0.9		4-6y	0.35		0.6		0.95		1.1	
7-10y	0.2		0.5		0.9		1.0		7-10y	0.3		0.6		0.9		0.9	
11-14y	0.25		0.5		0.8		0.85		11-14y	0.3		0.55		0.9		0.97	
15-18y	0.3		0.5		0.88		0.95		15-18y	0.35		0.55		0.87		0.9	

Eosinophil count in children (x10⁹/L)

	African American									Mexican American & White								
	2.5 Percentile		50 Percentile		95 Percentile		97.5 Percentile			2.5 Percentile		50 Percentile		95 Percentile		97.5 Percentile	
Age	M	F	M	F	M	F	M	F	Age	M	F	M	F	M	F	M	F
1y	0.1		0.3		1.0		1.1		1y	0.1		0.2		0.7		0.8	
2-3y	0.0		0.2		0.7		0.9		2-3y	0.1		0.2		0.75		0.9	
4-6y	0.05		0.3		0.8		0.95		4-6y	0.05		0.25		0.75		0.8	
7-10y	0.1		0.2		0.9		1.0		7-10y	0.1		0.2		0.75		1.0	
11-14y	0.0		0.2		0.55		0.6		11-14y	0.05		0.15		0.7		0.8	0.7
15-18y	0.0		0.15		0.45		0.55		15-18y	0.05		0.15		0.55	0.4	0.5	

Table. Quantitative alterations of WBCs

White Blood Cells (Leukocytes)			Brief characteristics	High WBC count (leukocytosis)	Low WBC count (leukopenia)
Myeloid cells	**Segmented neutrophils (segs)**		• *The predominant WBCs in the peripheral blood* • *The nucleus is lobulated (between 2 and 5 lobes) and the lobes are connected by a thin filament*	**Neutrophilia** ▪ *Infection/inflammation, necrosis* ▪ *Any stressor/ heavy exercise* ▪ *Drugs (steroids, heparin, epinephrine)* ▪ *Chronic myeloid leukaemia (CML)*	**Neutropenia** *(see p. 33)* ▪ *Viral (overt or occult)* ▪ *Autoimmune/idiopathic* ▪ *Chemotherapeutic agents* ▪ *Bone marrow defects (pancytopenia)*
	Band neutrophils (bands)		• *Constitute 0—5% of the nucleated cells under normal conditions in the peripheral blood*	**Bandemia** (>500/mm^3) ▪ *Severe infections* ▪ *Inflammation*	—
	Immature neutrophil forms	 	• *These include myelocytes and metamyelocytes, that do not belong in circulation even with severe infection* • *The presence of these cells in the circulation is an ominous marker for life-threatening bacterial infection (severe left shift)*	*The neutrophils tend to be more immature, as they are being released earlier. This is called a* ***left shift****.* 	
	Basophils		• *Lobate nuclear granulocyte with granules stainable by basic dyes*	**Basophilia** ▪ *Myeloproliferative disorders*	**Basopenia** ▪ *Difficult to demonstrate as the normal basophil count is so low*
	Eosinophils		• *Segmented polymorphonuclear granulocyte with granules stainable by eosin dyes*	**Eosinophilia** ▪ *Allergy/atopy, asthma/hayfever* ▪ *Parasites (less common in developed countries)*	**Eosinopenia** ▪ *Stress* ▪ *Drugs (Steroids)*
	Monocytes		• *Mononuclear phagocytes*	**Monocytosis** ▪ *Usually not significant* ▪ *Watch levels >1.5×10⁹/L more closely, consider chronic infection or inflammation*	**Monocytopenia** ▪ *Not clinically significant if other cell counts are normal*
Lymphocytes			• *There are two broad morphologic categories of lymphocytes which can be distinguished under the light microscope, large granular lymphocytes and small lymphocytes.*	**Lymphocytosis** ▪ *Acute infections (EBV, viral hepatitis, pertussis)* ▪ *Chronic intracellular bacterial infections (tuberculosis, brucellosis)* ▪ *Chronic lymphocytic leukaemia (in the Elderly)*	**Lymphocytopenia** ▪ *Immunodeficiency syndrome AIDS, agammaglobulinemia* ▪ *Some types of chemotherapy or malignancies*

In a severe infection the neutrophils may show and other **toxic changes** such as:
(1) toxic granulation
(2) toxic vacuolation
(3) the presence of Döhle bodies

Major forms of neutropenia in children and adolescents

● **Acute forms** — usually fatal.

● The most common form of neutropenia in infants and young children is **transient neutropenia** with or following a viral illness. It resolves itself within 2 weeks.

● **Chronic forms** last over 6 months and have indolent progression.
The most common type of chronic neutropenia in pediatric patients is **chronic benign neutropenia of childhood** (also known as primary autoimmune neutropenia). Infections associated with the primary form are usually limited and mild. The mean age at diagnosis of autoimmune neutropenia is 6-12 months, with a range of 3-30 months. Spontaneous recovery occurs by age 5 years, and the mean duration of neutropenia is approximately 20 months.

● **Cyclic neutropenia** is characterized by an episodic decrease in the number of neutrophils every 3–4 weeks and lasts for **5 to10 days**. Peripheral neutrophil counts usually drop to zero and during this time the child is extremely susceptible to infection. **Painful oral ulcerations** covered by a whitish membrane and surrounded by slight erythema are the most constant findings. The lips, tongue, buccal mucosa, and gingiva are the areas most commonly affected.

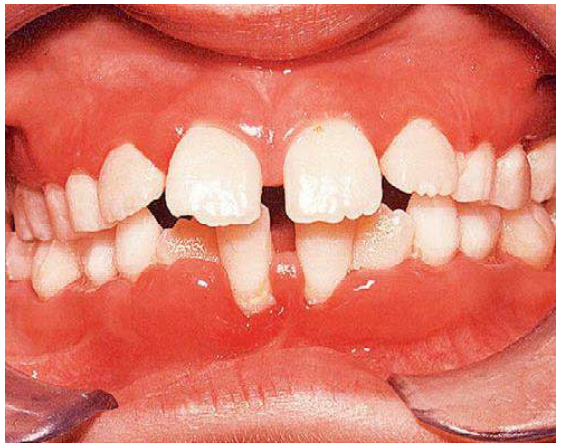


Fig. Gross gingival inflammation in an adolescent with cyclic neutropenia. This girl lost most of her primary teeth by the age of 7 years.

● **Intermittent forms** — as part of Shwachman-Diamond syndrome (a rare autosomal recessive disorder characterized by exocrine pancreatic insufficiency, bone marrow dysfunction, and skeletal abnormalities).

KEY RECOMMENDATIONS FOR PRACTICE

[From Sills RH, editor. Practical algorithms in pediatric hematology and oncology. Karger Medical and Scientific Publishers; 2003. Riley LK, Rupert J. Evaluation of Patients with Leukocytosis. American family physician. 2015 1;92(11).]

- **Each blood count should be evaluated on the basis of the absolute number of cells/μl and NOT on the basis of the differential count percentage** (e.g., a relatively high percentage of neutrophils may not be abnormal if the total WBC is not high). Consideration must be made of the age of the patient because the leukocyte values change during childhood (see tables of normal values).
- Leukocytosis greater than100.0 × 10^9/L (**hyperleukocytosis**) is almost always caused by leukemias or myeloproliferative disorders.
- Patients with leukocytosis and no other signs of systemic inflammatory response syndrome do not require blood cultures.

Qualitative leukocyte disorders

Qualitative leukocyte disorders consist of disruptions of leukocyte function (**primary and secondary immune deficiencies**).

- Phagocytic cells (granulocytes, monocytes, macrophages) may lose their phagocytic capacity to function, e.g., *leukocyte adhesion defect* — a rare autosomal recessive condition associated with a reduced level of adhesion molecules on peripheral leukocytes resulting in severely reduced resistance to infection. Children present with delayed wound healing, persistent severe oral ulceration, cellulitis without pus formation, severe gingival inflammation, periodontitis and premature loss of primary teeth. Also present is a persistently high leukocytosis and reactive marrow, without evidence of leukaemia. One important indicator of this condition is late separation of the umbilical cord after birth.
- Lymphocytes may lose their capacity to respond to antigens (T-cell defects, B-cell defects, combined T- and B-cell defects).

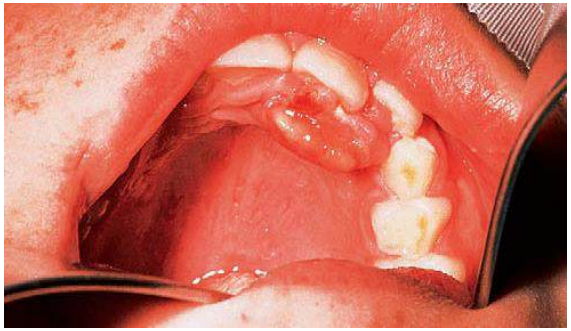


Fig. Severe unexplained palatal ulceration in a child with a leukocyte adhesion defect. The maxillary left incisor exfoliated a short time later

Other leukocyte alterations include infectious mononucleosis and cancers of the blood — leukemia and multiple myeloma (the latter is seen only in adults).

Infectious mononucleosis (IM) is an acute, self-limiting, neoplastic lymphoproliferative clinical syndrome characterized by acute viral infection of B lymphocytes (B cells). Common etiologic agents are Epstein-Barr virus (EBV) that (85% of all IM cases), cytomegalovirus (CMV), adenovirus, HIV, hepatitis A, influenza A and B, and rubella, as well as *Toxoplasma gondii, Corynebacterium diphtheriae,* and *Coxiella burnetii.* The major manifestations of EBV-induced IM are the classic triad of symptoms of pharyngitis, lymphadenopathy, and fever. Approximately 50% to 85% of children are infected with EBV by age 4.

The blood of affected individuals contains an increased number of atypical lymphocytes (Fig). Diagnosis of IM is commonly based on **Hoagland's criteria** of at least 50% lymphocytes and at least 10% atypical lymphocytes in the blood in the presence of fever, pharyngitis, and adenopathy confirmed by a positive serologic test.

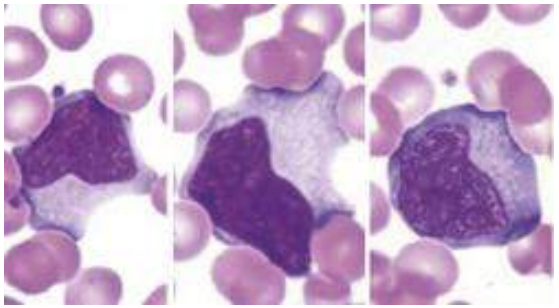


Fig. Atypical lymphocytes (also referred to as "reactive" lymphs) in IM

Leukemia and Lymphoma in Children

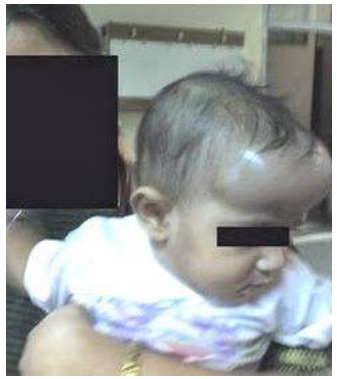
- The types of childhood leukemia include, in order of their rate of incidence, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), and chronic myeloid leukemia (CML). *Acute lymphoblastic leukemia is a potentially curable disease, with more than 80% of cases cured.*

- The lymphomas of childhood are non-Hodgkin lymphoma and Hodgkin lymphoma. *Non-Hodgkin lymphoma has a favorable prognosis, with a 70% to 80% cure rate. The risk of Hodgkin lymphoma is associated in part with infectious diseases, immune deficits, and genetic susceptibility. Hodgkin lymphoma is a readily curable disease with longterm cure rates of 90% to 95%.*

DEVELOPMENTAL CHANGES IN PLATELETS AND HEMOSTASIS

Platelets (PLT)	▪ Platelet counts at birth and throughout the childhood are within the normal adult range (150–450×10⁹/L). Thrombocytosis (platelet counts >450×10⁹/L) may occur in thriving preterm infants without adverse consequences.
Blood coagulation system	▪ Low activity of clotting factors (the blood clotting factors of newborn babies are 25—75% of adult values) - protects infants from thrombosis that can occur when tissues are damaged during delivery. ▪ Levels of the coagulation factors gradually increase over the first year of life approaching the normal adult range.

CASE STUDY



This 3 month old boy was brought to the hospital with history of increase in the head size over last 1 week. He does not have altered mental status, seizures, weakness or vomiting. He was born at home to a 30 year old G3P2 mother vaginally at term. He is exclusively breastfed and immunized till date.
What is the diagnosis ?

Table. Pro- and anti-coagulant levels in the neonate compared to adult values

[Adapted from Resontoc LP, Yap HK. Renal vascular thrombosis in the newborn. Pediatric Nephrology. 2016, 1;31(6):907-15.]

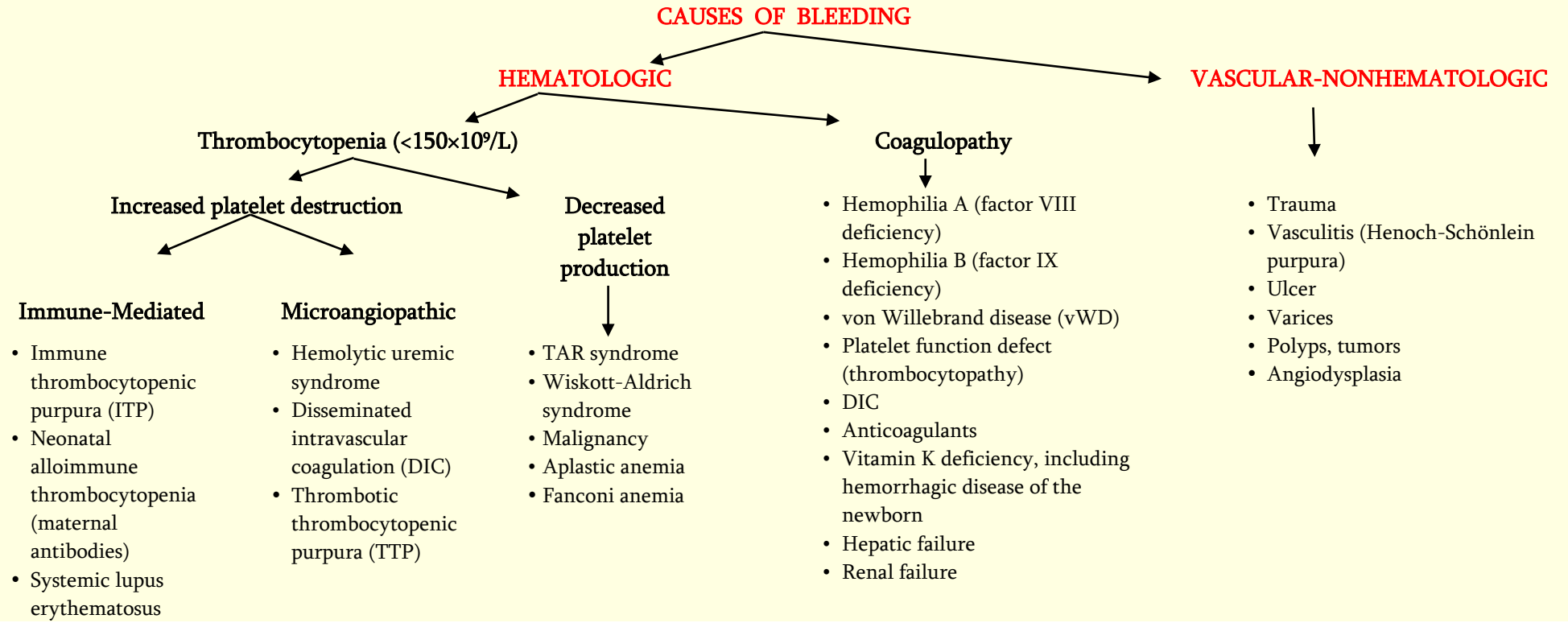
Procoagulant factors		**Anticoagulant factors**	
Increased (compared to adult values)	Decreased (25–70 % of adult values)	Increased (compared to adult values)	Decreased (≈50 % of adult values)
• Factors V, VIII and XIII • vonWillebrand factor (vWF)	• Vitamin K-dependent clotting factors (II,VII, IX, X) • Contact factors (XI, XII, prekallikrein, high-molecular-weight kininogen)	• α-2 macroglobulin • Tissue plasminogen activator • Plasminogen activator inhibitor-1	• Vitamin K-dependent anticoagulant factors (protein C, protein S, and protein Z) • Antithrombin • Heparin cofactor II • α-1-antiplasmin

QUIZ

Which of the following clinical features is most likely to be associated with a benign condition?

A. Bleeding 7 days after a tonsillectomy.
B. Bruises over the bony prominences of the extremities, both proximal and distal.
C. Epistaxis (worse in winter).
D. Hemarthrosis.
E. Menstrual bleeding that lasts 8 days.

Bleeding disorders in children



Vitamin K deficiency bleeding (aka "hemorrhagic disease of the newborn")

DEFINITIONS	RISK FACTORS
Early onset disease – onset within first 24 hours of life	▪ Maternal anti-convulsants that interfere with vitamin K metabolism (phenytoin, phenobarbital, carbamezepine, or primidone) ▪ Maternal anti-coagulants (warfarin, aspirin) ▪ Maternal antibiotics, especially cephalosporins
Classic disease – onset between day 2 – 7	▪ Breastfeeding exclusively
Late onset disease – onset between 2 weeks and 6 months	▪ Marginal levels of vitamin K in breast milk ▪ Fat malabsorption (eg, in cystic fibrosis, cholestasis)

Vitamin K prophylaxis *(1mg vitamin K IM at birth)*

Newborn infants are at risk of developing vitamin K deficiency, and this coagulation abnormality leads to serious bleeding (eg, intracranial hemorrhage).

- *Transplacental transfer of vitamin K is very limited during pregnancy, and the storage of vitamin K in neonatal liver is also limited.*
- *Breastmilk contains only small amounts of vitamin K (1 – 9 mcg/L).*

This makes the newborn infant uniquely vulnerable to hemorrhagic disorders unless exogenous vitamin K is given for prevention of bleeding immediately after birth. Once the infantile gut is colonized with bacterial flora, the microbial production of vitamin K results in a lower risk of infantile vitamin K deficiency bleeding.

Many antibiotics have been reported to have caused vitamin K deficiency and hypoprothrombinemia by eliminating the gut flora if used for long enough times (eg, in recurrent attacks of tonsillitis or other infections with frequent or long-term antibiotic therapy).

Pattern of bleeding

- ***Mucous membrane bleeding (epistaxis; menorrhagia; oral, genitourinary, or rectal bleeding) and skin haemorrhage*** – characteristic of platelet disorders, von Willebrand disease, or vessel wall defect.

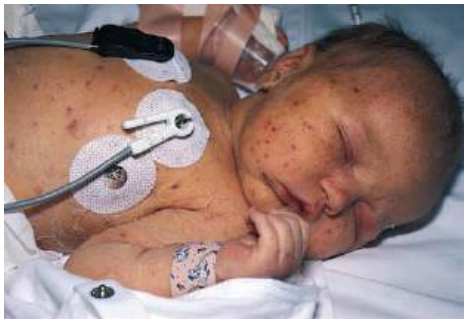


Fig. Petechiae. This infant with severe immune thrombocytopenia has visible petechiae, as well as large ecchymoses

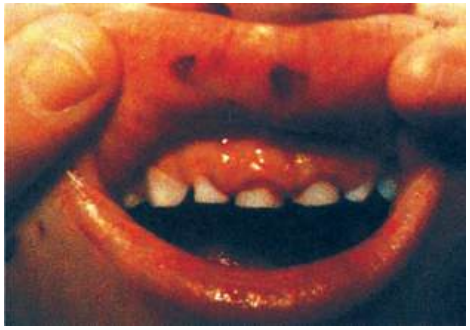
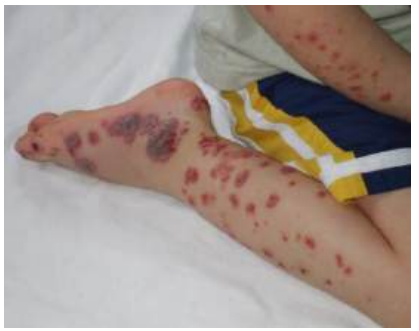


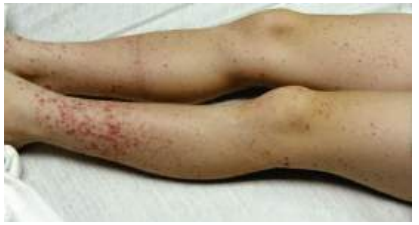
Fig. Purpuric lesions on the oral mucosa or retina are called "**wet purpura**" and may suggest an increased tendency for major bleeding in the thrombocytopenic patient.

Henoch-Schönlein purpura (HSP) — is a form of vasculitis (IgA vasculitis) characterized by:



(1) ***Palpable purpura*** *(100%) — the hallmark of HSP, caused by small vessel inflammation in the skin leading to extravasation of blood into the surrounding tissues.*

(2) ***Arthritis*** *(≈80%).*



(3) ***Gastrointestinal vasculitis*** *(≈50%) — may presents as abdominal pain, bloody diarrhea, intussusception (rare).*

(4) ***Renal vasculitis*** *(≈35%) — is mild in most cases, can manifest by hematuria, proteinuria, hypertension, or acute renal failure (rare).*

- ***Deep-tissue bleeding (hematomas, joint and muscle hemorrhages) and "delayed" surgical bleeding*** are more suggestive of a coagulation factor abnormality such as hemophilia.

Surgical bleeding in children is associated most often with circumcision, tonsillectomy, and dental extractions. In addition to uncontrolled bleeding in the surgical field, bleeding in an affected individual may extend beyond the surgical site (ie, drains, vascular access), with associated poor wound healing and infection.

The need for transfusion during or after surgery that normally does not cause significant blood loss can suggest an underlying bleeding disorder. Bleeding after tonsillectomy or adenoidectomy often is delayed until 7 to 10 days postoperatively when there is an underlying bleeding disorder.

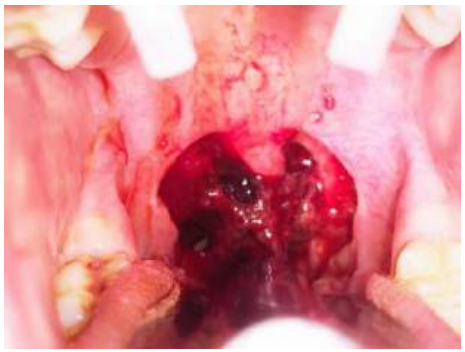


Fig. Bleeding after tonsillectomy in a 5-year-old patient

Epistaxis is a common childhood complaint and most likely is due to local factors such as drying of the nasal mucosa, trauma, or allergic rhinitis. However, among patients referred to a pediatric hematology clinic for recurrent epistaxis, 25% to 33% are diagnosed as having a bleeding disorder. Epistaxis requiring an emergency department visit, occurring in both nostrils, and occurring in association with other bleeding signs and a family history of similar bleeding increases the likelihood of an underlying bleeding disorder.

Menorrhagia may be the presenting sign in an adolescent girl who has a bleeding disorder and often can occur with the first cycle at menarche. Menorrhagia frequently is associated with anemia and a suboptimal quality of life. A pictorial blood flow assessment chart can be used in the office to provide a semiquantitative assessment of menstrual blood loss. Frequent pad changes (2 h frequency), menses lasting more than 7 days, or more than one menstrual period per month all are consistent with menorrhagia. The American College of Obstetrics and Gynecology recommended that women who have menorrhagia be evaluated for vWD. Platelet function disorders and other coagulopathies also are frequent causes of menorrhagia.

Intramuscular hematomas may be more difficult to see, but they cause swelling of the muscle group and pain with use of the muscle.

Hemarthrosis (bleeding into a joint) causes joint effusion, warmth, and pain with passive movement of the joint and is a common feature of hemophilia. For young children, refusal to walk or use the affected limb may be the only apparent sign.

Repeated hemarthroses lead to chronic arthropathy, joint deformity, muscle atrophy, and soft tissue contractures.

Fig. Scrotal hematoma in a severe hemophilia patient

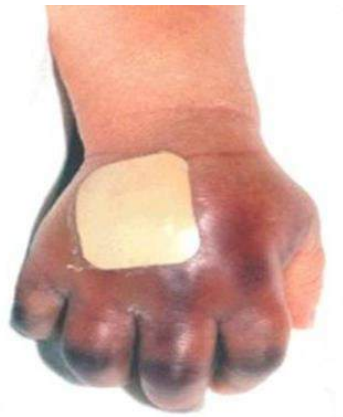


Fig. Hematoma in a child with hemophilia after injection

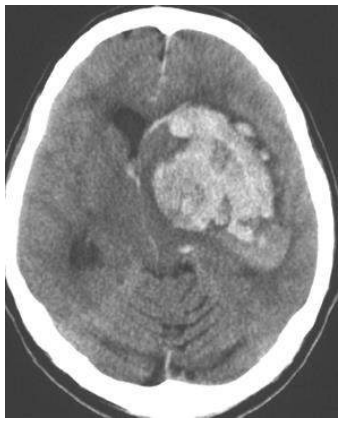


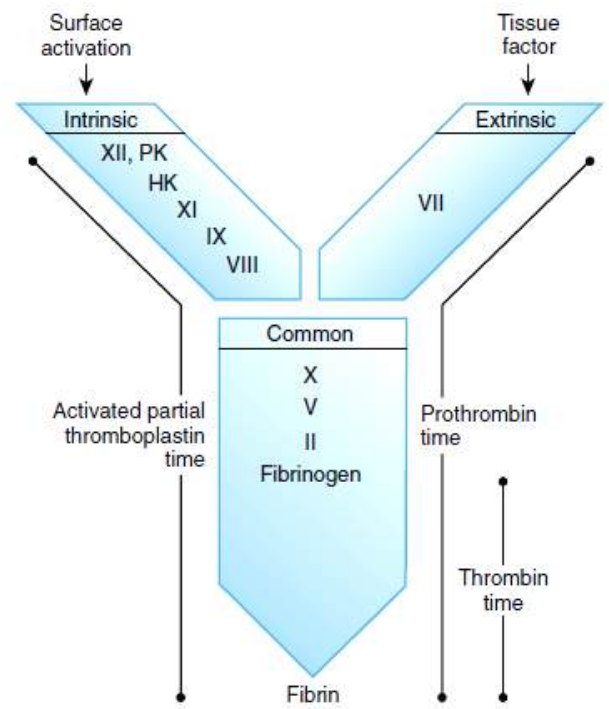
Fig. Intracranial bleeding in hemophilia

Basic coagulation tests (screening tests)

The original model of blood coagulation, entailing a separation between extrinsic, intrinsic, and common pathways, has long represented the most common basis for first-line tests, as these were mostly developed for screening of patients with suspected hemorrhagic disorders. These essentially include the *prothrombin time (PT), international normalized ratio (INR), the activated partial thromboplastin time (APTT), the thrombin time (TT), fibrinogen (Fbg), and the bleeding time (BT).*

Test	Principle	Required factors
PT	Measures the activity of the extrinsic and common pathways of coagulation (the time it takes plasma to clot after addition of tissue factor)	VII, X, V, II, and fibrinogen
INR	Measures the ratio of a patient's prothrombin time to a normal (control) sample: $$\mathrm{INR} = \left(\frac{\mathrm{PT_{test}}}{\mathrm{PT_{normal}}}\right)^{\mathrm{ISI}}$$ The INR was devised to standardize the results.	—//—//—//—//—
APTT	Measures the activity of the intrinsic and common pathways of coagulation (performed by adding a "partial thromboplastin" reagent and recording the clotting time)	Presence of every protein except tissue factor and factor VII
TT	Measures the thrombin-induced conversion of fibrinogen to fibrin (performed by adding bovine thrombin to the patient's citrated plasma and recording the clotting time)	Fibrinogen
BT	• A measurement of length of time that bleeding continues after a standardized wound is made on the forearm or ear lobe. Normal range is between 2 to 9.0 minutes. • No longer in clinical use in developed countries, as it is unreliable. It has been replaced by in vitro tests of platelet function on a platelet function analyser, which can be performed on a peripheral blood sample.	PLT

Fig. Organization of the coagulation system based on current screening assays



- **The intrinsic coagulation system** consists of the protein factors XII, XI, IX, and VIII and prekallikrein (PK) and high-molecular-weight kininogen (HK).
- **The extrinsic coagulation system** consists of tissue factor and factor VII.
- **The common pathway** of the coagulation system consists of factors X, V, and II and fibrinogen (I).

Table. Interpretation of the clotting screen

Bleeding disorders are characterized by prolongation of clotting times.

Condition	Coagulation defect	PT	INR	APTT	TT	PLT count	BT
Vitamin K Deficiency	Deficiency of factors II, VII, IX, X	Prolonged	Elevated	Prolonged	Normal	Normal	Normal
Hemophilia A	Deficiency of factor VIII	Normal	Normal	Prolonged	Normal	Normal	Normal
Hemophilia B	Deficiency of factor IX	Normal	Normal	Prolonged	Normal	Normal	Normal
von Willebrand disease (vWD)	Deficiency of vWF	Normal	Normal	Prolonged	Normal	Normal	Prolonged
Disseminated intravascular coagulation (DIC)	Consumption of clotting factors and platelets	Prolonged	Elevated	Prolonged	Prolonged	Decreased	Prolonged
Immune thrombocytopenic purpura (ITP)	Thrombocytopenia	Normal	Normal	Normal	Normal	Decreased	Prolonged
Thrombocytopathy	Platelet function defect	Normal	Normal	Normal	Normal	Normal	Prolonged

Specific coagulation tests

Interpretation of the screening tests will provide a differential diagnosis and inform further testing for:

- specific clotting factors
- platelet function tests (eg, platelet aggregometry)

1. A newborn boy continues to bleed after routine circumcision. What is the most likely diagnosis?

2. Shilpa has recently been on broad-spectrum antibiotics for a recurrent urinary bladder infection. While slicing vegetables, she cut herself and had difficulty stopping the bleeding. How could the antibiotics have played a role in her bleeding?

Thrombocytosis in children

Primary thrombocytosis	Secondary (reactive) thrombocytosis
Exceedingly rare	Common (particularly in infants)
Occurs in myeloproliferative disorder (eg, essential thrombocythemia, myelofibrosis with myeloid metaplasia, polycythemia vera, chronic myelocytic leukemia [rare]) or, in rare cases, of acute myelocytic leukemia	Occurs in infection, chronic inflammation, vasculitis, iron deficiency, tissue damage, cancer, drugs and surgical or functional splenectomy
Thrombosis and bleeding are common complications of primary thrombocytosis	▪ Usually transient and subsides when the primary stimulus ceases ▪ Despite the strikingly high platelet count (on occasions exceeding 1000 X 10^9/L, or 1 million/mcL), thrombotic and/or hemorrhagic complications are highly exceptional

Common thrombotic disorders (thrombophilia) in children

Thrombotic events are less common in children than adults.

Congenital thrombophilic disorders	Acquired thrombophilic disorders
• Activated protein C resistance (APC-R) — is the most common congenital thrombophilic disorder; occurs in 3% to 8% of Caucasians and is less common in other ethnic groups. • Prothrombin G20210A mutation — present in approximately 1% to 2% of Caucasians.	• Iatrogenic (such as the use of central venous access devices) • A combination of factors that can include an underlying disease (eg, malignancy, infection, congenital heart defects, nephrotic syndrome) and immobility, dehydration, obesity, or use of estrogen-containing medications • Elevation of procoagulant proteins such as FVIII and vWF as an acute-phase reactant phenomenon • Acquired deficiency of antithrombin secondary to medications (eg, asparaginase in leukemia therapy), or protein loss such as through nephrotic syndrome • Antiphospholipid syndrome — can arise spontaneously (primary) or secondary to another condition (secondary) such as autoimmune disorders (eg, SLE).

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The Digestive System

Quick Quiz

1. What diagnosis would you suspect in a newborn presenting with accumulation of frothy saliva in the mouth?

2. A 1-month-old newborn presents with projectile, nonbilious vomiting after feeds that has progressively worsened over the past week. He is found to have a hypochloremic, hypokalemic metabolic alkalosis, and dehydration. An olive-shaped mobile mass is palpable in the epigastric area. What diagnosis would you suspect?

3. An 8-month-old infant presents with episodes of bilious vomiting, abdominal pain, and currant jelly stool. He has a right upper quadrant mass on physical examination. What diagnosis do you suspect?

4. A 14-year-old adolescent girl presents with episodic abdominal pain and diarrhea interspersed with periods of constipation over the past year. She has undergone multiple workups in the past with no diagnosis. What is a probable cause of her symptoms?

COMPETENCIES

You must…

Know	Be able to	Appreciate
• The normal and abnormal development of the digestive system • Characteristic features of gastrointestinal disorders in children • How to manage a child who has a gastrointestinal disorder	• Carry out a good examination of the digestive system • Identify the signs and symptoms of gastrointestinal disorders in children • Interpret results of diagnostic tests and procedures • Advise a parent about oral rehydration and diet for a child with gastroenteritis • Differentiate non-organic from organic recurrent abdominal pain • Develop an approach to managing recurrent abdominal pain	• The difference between vomiting and posseting (regurgitation) • That constipation is not diagnosed on infrequent stools alone • That antiemetics and antidiarrhoeal agents are generally inappropriate for children • That encopresis is a sign of severe behavioural problems • That most recurrent abdominal pain is non - organic but children still benefit from medical attention

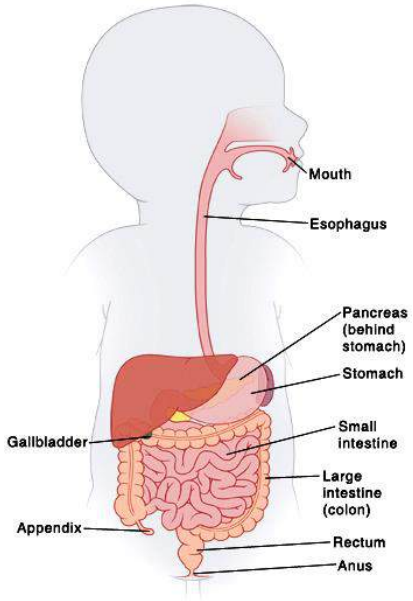
Introduction

- By the time a baby is born, the gastrointestinal tract must be ready to supply fully the baby's needs for fluid and electrolyte intake, to digest its food, initially completely milk, to provide sufficient energy and biochemical raw materials for extremely rapid growth and development, and to do so efficiently enough not to upset the immature homeostatic control mechanisms. At the same time, a sudden onslaught of pathogenic organisms and potential poisons has to be resisted.
- Within a few months of birth, the gastrointestinal tract has to be ready for weaning from its comforting milk diet to whatever the environment can be made to provide – one of the first crucial steps to independent existence.
- Thereafter, the demands made on the gastrointestinal tract do not alter so radically, and although there is a lot of growing to be done and full functional maturity will not be attained for some years, the processes remain more or less unchanged for the rest of the individual's life. This timescale means that the pace of development in utero is hectic, and after birth many of the remaining functional changes normally happen soon.

Organs of The Digestive System

Gastrointestinal tract (gut)

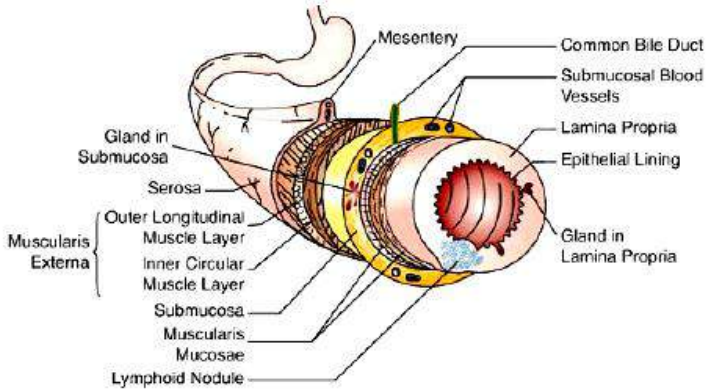
- **Mouth**
- **Pharynx**
- **Esophagus**
- **Stomach**
- **Small intestine**
- **Large intestine (colon)**



Accessory organs

- **Major salivary glands**
- **Liver & biliary system**
- **Pancreas**

The gastrointestinal tract is consists of the wall and the lumen that contains chyme, gas and microbiome.



Embriology

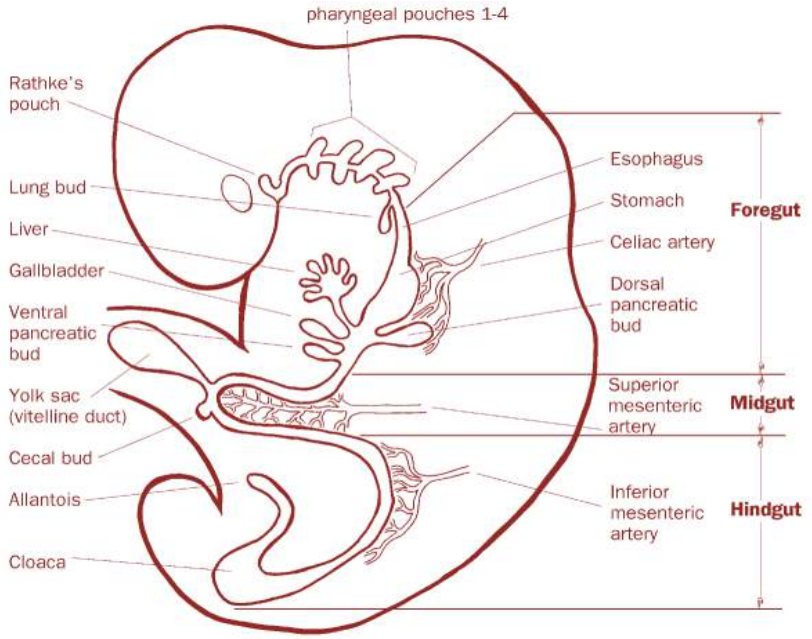
In the embryo, the primitive gut tube develops in weeks 3-4 by incorporating the yolk sac during the craniocaudal and lateral folding of the embryo. The tube is divided into 3 distinct sections:

- **the foregut** — gives rise to the pharynx, lower respiratory system, esophagus, stomach, liver, gallbladder, bile ducts, pancreas and proximal duodenum

- **the midgut** — develops into the distal duodenum, jejunum, ileum, cecum, appendix, ascending colon, and proximal 2/3 of transverse colon

The midgut remains temporally connected to the yolk sac by means of the vitelline duct

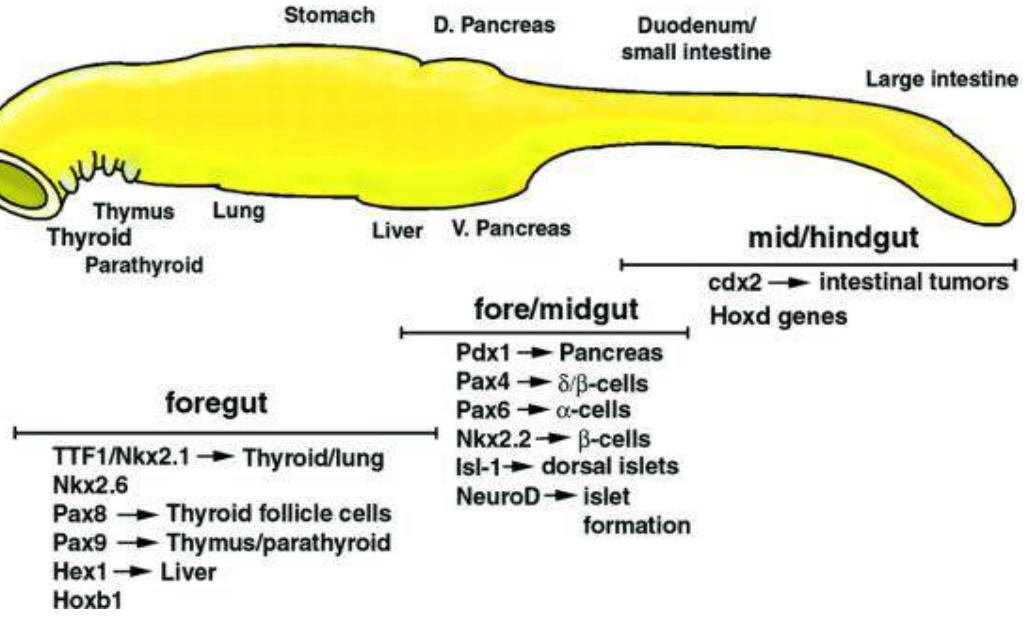
- **the hindgut** — becomes distal 1/3 of the transverse colon, descending colon, sigmoid colon and the upper anal canal



Gut tube = 2 layers (endoderm + mesoderm)

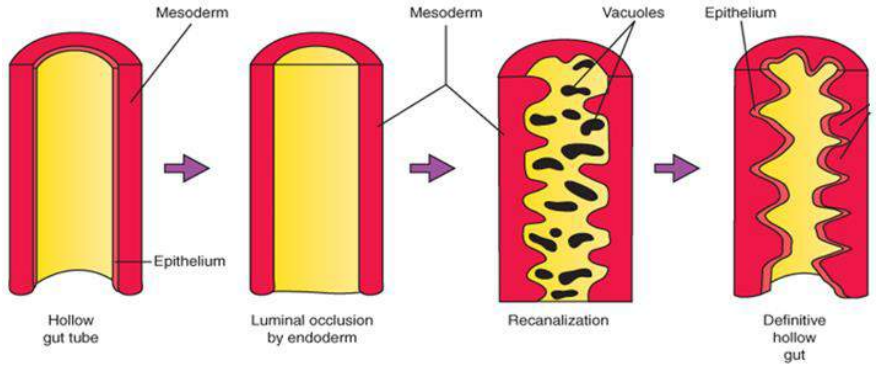
Regional gut tube patterning and organogenesis require bi-directional endoderm-mesoderm cross-talk and inductive signals from other nearby structures.

Development of the digestive system occurs by the following major processes:
- gut «budding» (e.g. formation of lung bud, liver bud, ventral and dorsal pancreatic buds)
- recanalization
- elongation
- herniation
- rotation



➢ *RECANALIZATION*

Proliferation of the epithelial lining of the gut tube results in obliteration of the lumen by week 6. The central cells then degenerate via apoptosis and the tube is recanalized by week 8.
Abnormalities in this process result in: stenosis, atresia, fistulas, and duplications.



Region of foregut just caudal to lung bud develops into esophagus. *Errors in forming the esophagotracheal septa and/or recanalization lead to tracheoesophageal fistulas (TEF) and/or esophageal atresia (EA), respectively.*

Fig. Formation of esophagotracheal septa and recanalization

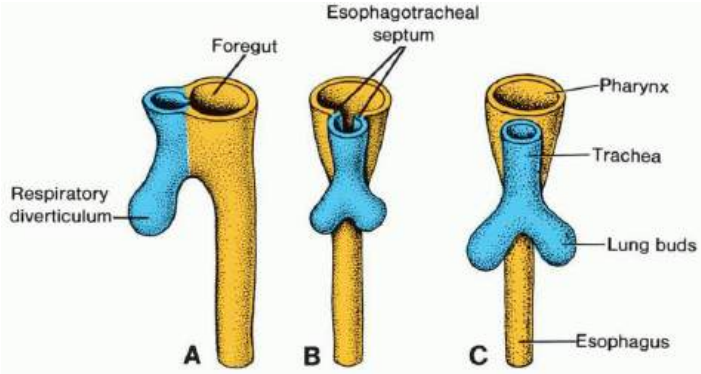
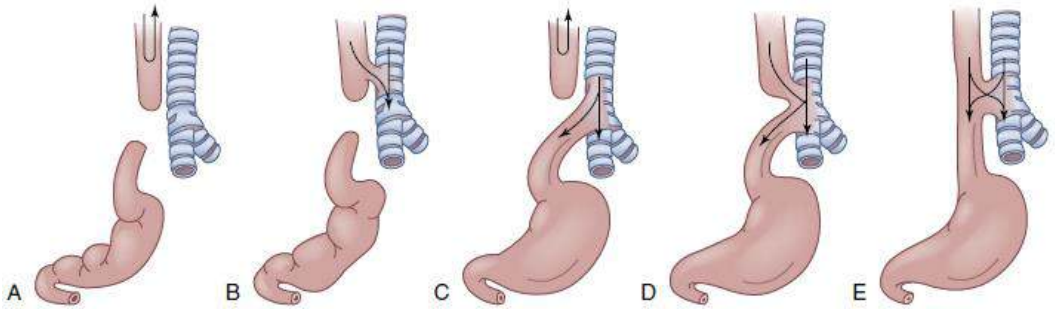


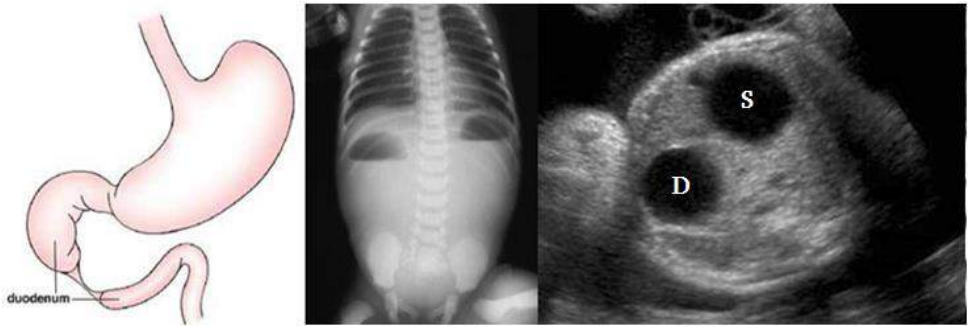
Fig. Types of esophageal atresia and esophagotracheal fistulae



NOTE: this process of recanalization occurs throughout the gut tube, so occlusion can occur anywhere along the GI tract (e.g. duodenal stenosis).

Obstruction of the upper gastrointestinal tract (e.g. esophageal, duodenal, or intestinal atresia) leads to ***polyhydramnios*** *(excessive volume of amniotic fluid) due to decreased swallowing and absorption of fluid. The diagnosis is made prenatally by ultrasound examination.*

Fig. "Double-bubble" sign, typical for duodenal atresia. Dilated stomach (S) and duodenum (D) with pylorus in between.



Classically, the neonate with esophageal atresia presents with copious, fine, white, frothy bubbles of mucus in the mouth and, sometimes, the nose. These secretions may clear with aggressive suctioning but eventually return. There are episodes of cough, choking and cyanosis, typically exaggerated with attempted feeding. Cyanosis is a result of laryngospasm (a protective mechanism that body has to prevent aspiration into trachea). Over the time respiratory distress develops. Abdomen is distended if there is associated TEF (as air builds up in the stomach) and scaphoid if there is isolated EA.

Duplications and cysts may occur anywhere along the length of the gut tube. They are most frequently found in the región of the ileum, where they may vary from a long segment to a small diverticulum. Manifestations usually occur early in life, and 33% are associated with other defects.

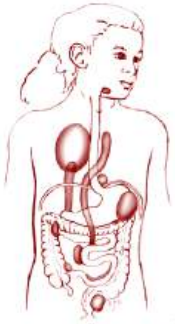


Fig. Illustration depicting the many locations where alimentary tract duplications may be found

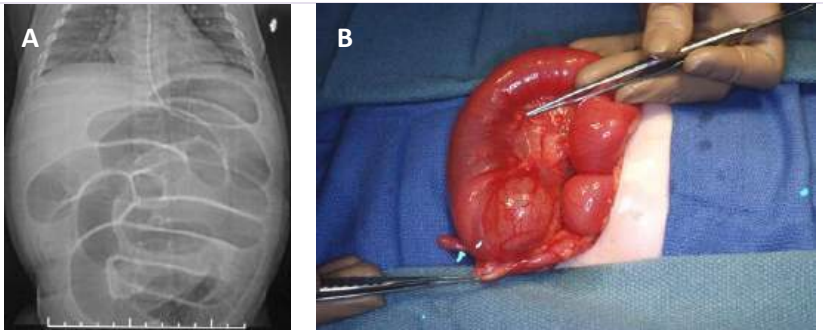
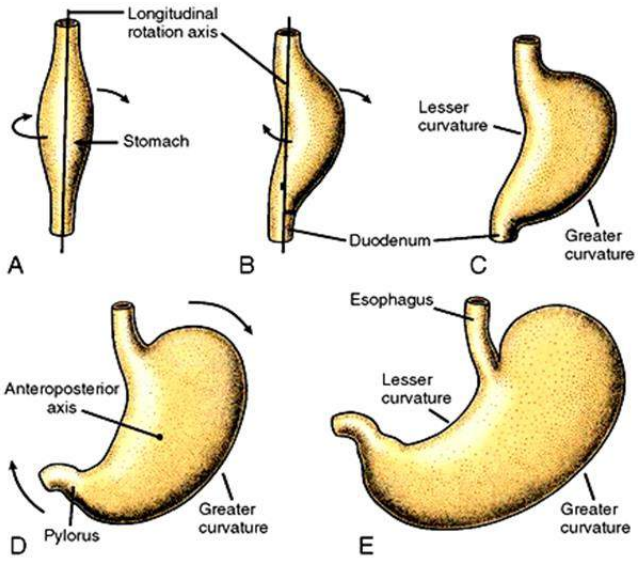
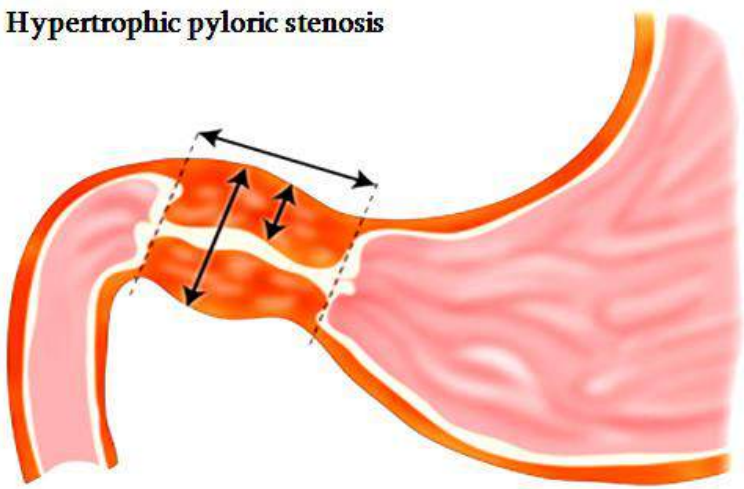


Fig. A - abdominal radiograph of an infant with acute onset of bilious vomiting and abdominal distention secondary to a duplication cyst at the terminal ileum. B - a small ileal duplication cyst causing complete obstruction of the small bowel (the same patient)

- Stomach appears first as a fusiform dilation of the foregut endoderm which undergoes a 90° rotation such that the left side moves ventrally and the right side moves dorsally (the vagus nerves follow this rotation which is how the left vagus becomes anterior and the right becomes posterior).
- Differential growth occurs to establish the greater and lesser curvatures.
- Unlike other parts of the gut tube, the dorsal and ventral mesenteries are retained to become the greater and lesser omenta, respectively.
- Caudal end of the stomach separated from the duodenum by formation of the pyloric sphincter (dependent on factors such as SOX-9, NKX-2.5, and BMP-4 signaling) – errors in this process lead to **hypertrophic pyloric stenosis**.





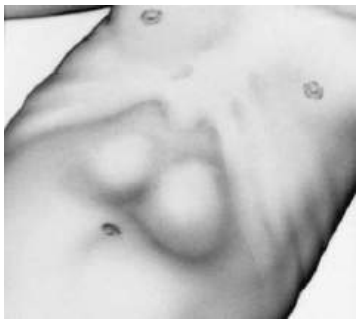


Fig. Gastric peristaltic wave in an infant with pyloric stenosis

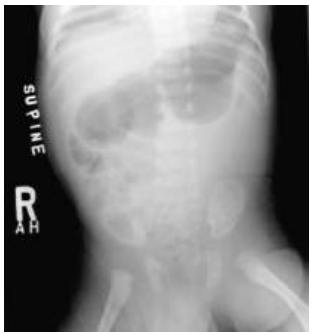


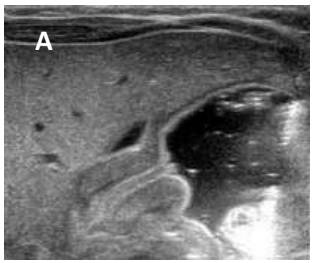
Fig. Pyloric stenosis. Note the huge, gas-filled stomach extending across the midline, with minimal air in the intestine downstream

- Rather common malformation: present in 0.5% - 0.1% of infants. More common in males than females. Stenosis is due to overproliferation / hypertrophy of pyloric sphincter… NOT an error in recanalization.
- Characterized by **non-bilious postprandial vomiting** between birth - 12 weeks (usually begins between 2-4 weeks). The emesis becomes increasingly frequent and forceful (aka "projectile") as time passes.

NOTE: the presence of bile would indicate POST-duodenal blockage of some sort.

- Affected infants are ravenously **hungry** early in the course of the illness, but become more lethargic with increasing malnutrition and dehydration.
- The stomach becomes massively enlarged with retained food and secretions, and gastric peristaltic waves are often visible in the epigastric area.
- A hypertrophied pylorus (the "olive" 5-15 mm in longest dimension) may be palpated in the right upper abdomen under the liver edge.
- Jaundice can occur in 5% of infants due to indirect hyperbilirubinemia.
- As the illness progresses, very little of each feeding is able to pass through the pylorus, and the child becomes progressively thinner and more dehydrated. The classic metabolic findings in *pyloric stenosis are hypochloremic alkalosis with potassium depletion.*

Two imaging studies are commonly used to establish the diagnosis. Ultrasound is the modality of choice in right clinical setting because of its advantages over a barium meal are that it directly visualises the pyloric muscle and does not use ionising radiation. The hypertrophied muscle is hypoechoic, and the central mucosa is hyperechoic. Normal measurements include: pyloric muscle thickness <3 mm (most accurate); length: <15 mm; width <7 mm.



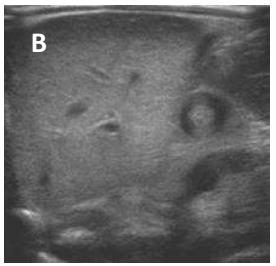


Fig. A - Horizontal sonogram demonstrating a pyloric channel length >14 mm in an infant with pyloric stenosis. B - Transverse sonogram demonstrating a pyloric muscle wall thickness of >4 mm and target sign.

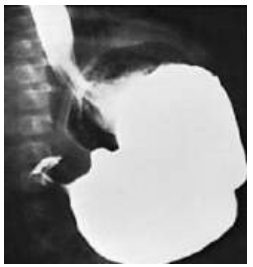
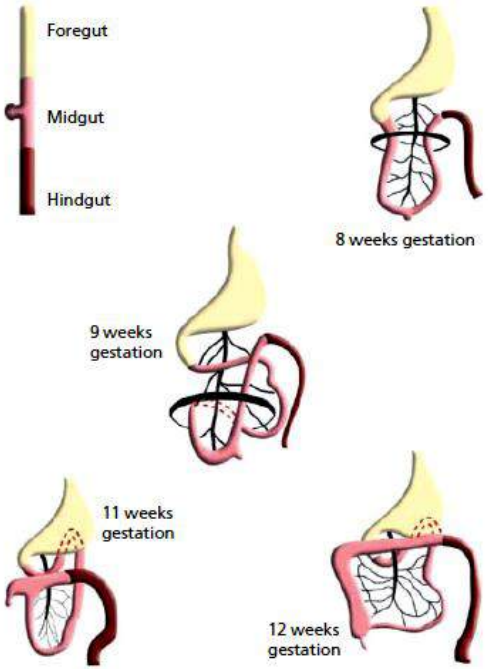


Fig. Barium in the stomach of an infant with the attenuated pyloric canal.

➢ *HERNIATION AND ROTATION*



The primitive gut undergoes rapid elongation and extension through the umbilical orifice between 5 and 10 weeks, and subsequently between 10 and 12 weeks the gut returns to the abdominal cavity. Failure of this process results in **omphalocele (or exomphalos).**

Omphalocele is covered by a membranous sac and is frequently associated with other structural and chromosomal anomalies. This differentiates it from ***gastroschisis*** *(a congenital anterior abdominal wall defect resulting in herniation of the abdominal contents into the amniotic sac). Gastroschisis has no covering sac and no associated syndromes.*

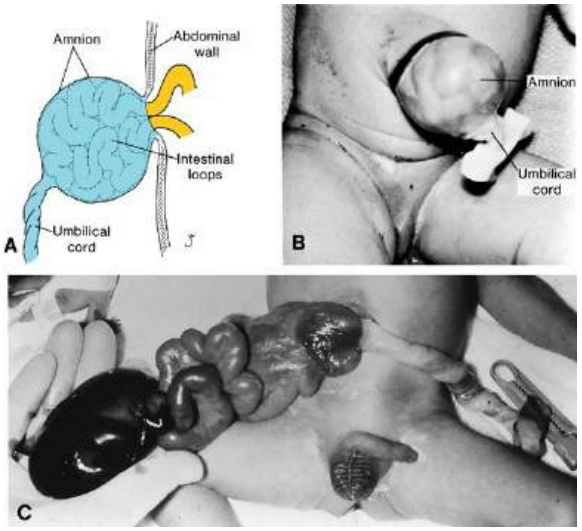
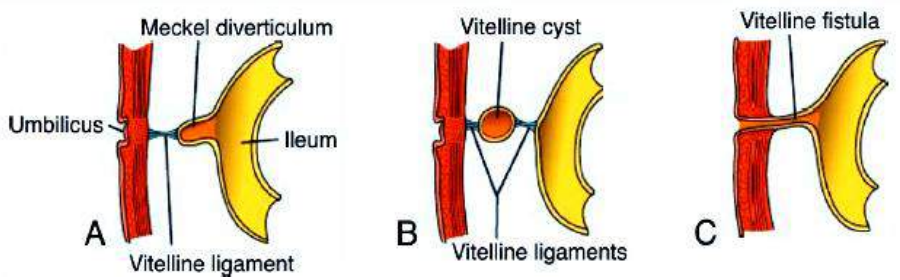


Fig. A,B – Omphalocele. C – Gastroschisis

The gut undergoes a **counter-clockwise rotation** through 270 degrees (around the superior mesenteric artery), which leaves the small intestine positioned centrally with the cecum in the right iliac fossa and the colon lying in a lateral position. The failure of this process, called **malrotation**, can lead to torsion or obstruction of the gut, and presents as a surgical emergency.

Vitelline Duct Anomalies are secondary to the persistence of the embryonic vitelline duct.

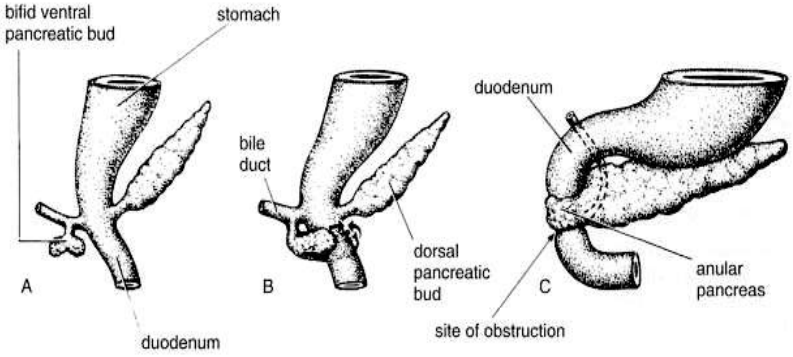
The most frequent malformation is Meckel diverticulum. Remember the rule of 2s: occurs in 2% of the population, is 2 inches in length, is 2 feet from the ileocecal valve, most commonly presents at age 2, and 2% are symptomatic. It most commonly presents with intermittent painless rectal bleeding, but may also present as intestinal obstruction, volvulus, or diverticulitis.

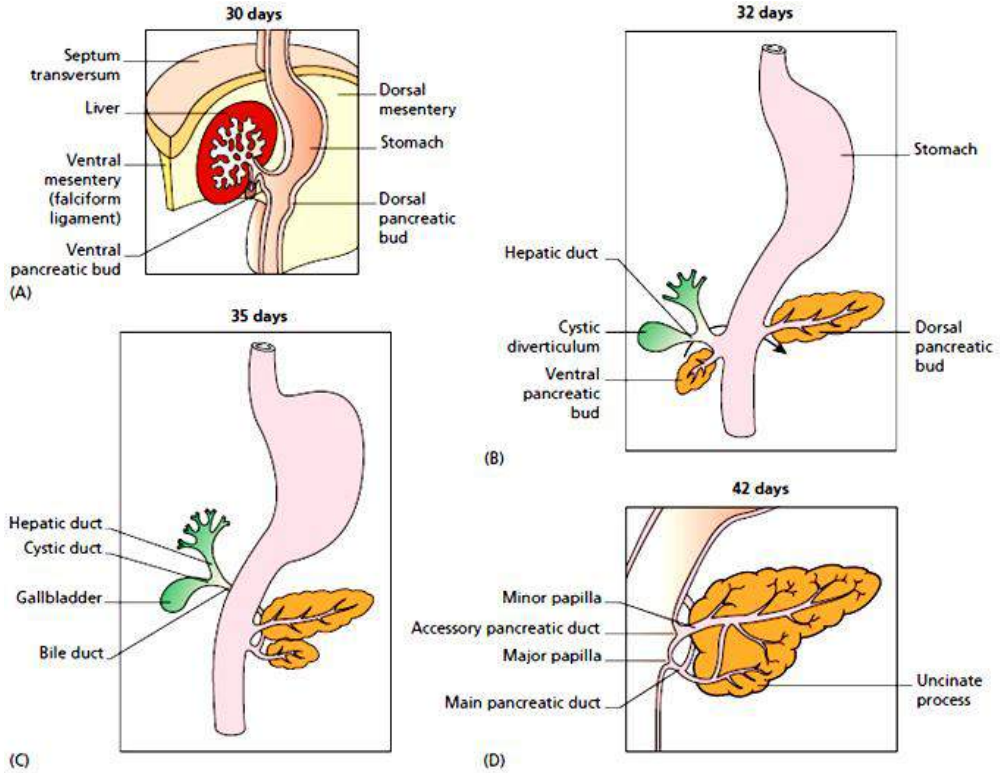


➢ *LIVER AND PANCREAS DEVELOPMENT*

Liver and pancreas arise from foregut endoderm in response to signals from nearby mesoderm.

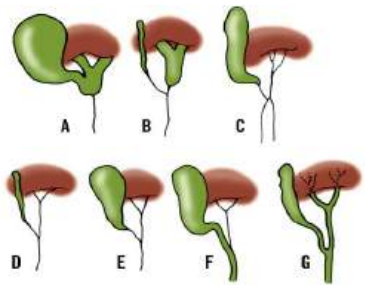
Pancreas actually has ventral and dorsal components, each specified in a different manner. Rotation of the duodenum brings the ventral and dorsal pancreas together. Aberrations in this process may result in an ***annular pancreas****, which can constrict the duodenum.*





Biliary tract anomalies

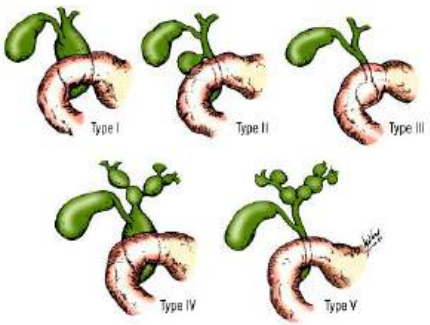
Atresias of biliary tract



A-F, Extrahepatic biliary atresias. G, Intrahepatic atresia with normal extrahepatic ducts. Defects A-C are "correctable"; at least one patent duct emerges from the liver. D-G are termed "noncorrectable."

[Modified from Skandalakis JE, Gray SW. Embryology for Surgeons. 2nd ed. Baltimore: Williams & Wilkins, 1994]

Choledochal cysts



I, Single cystic dilatation of the common bile duct

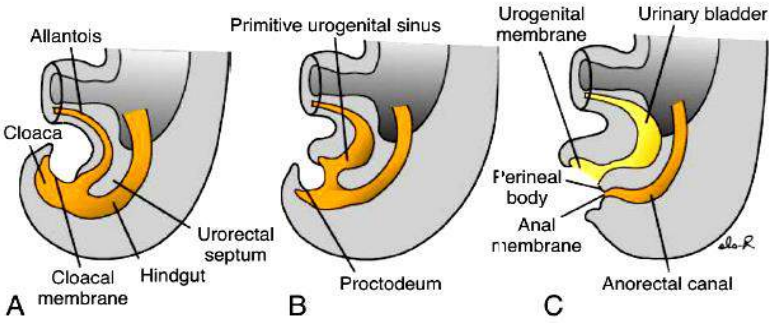
II, Isolated diverticulum protruding from the common bile duct

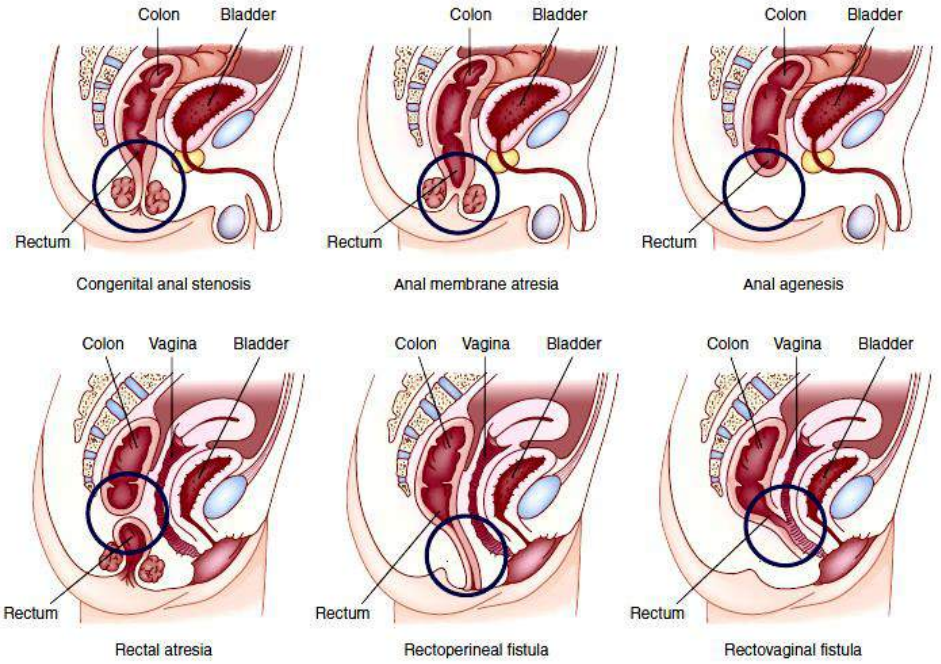
III, Cystic biliary dilatation within the duodenal wall (choledochocele)

IV, Any combination of multiple cysts

V, Caroli disease/multiple intrahepatic cysts

➢ *HINDGUT AND ANORECTUM DEVELOPMENT*

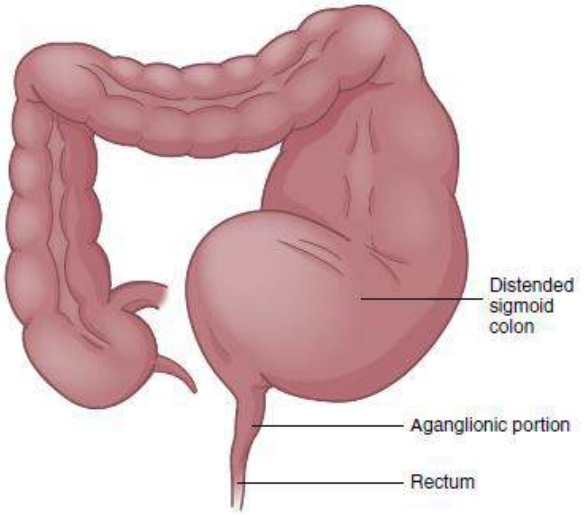




The terminal part of the hindgut enters into the cloaca. Between the 4th and 6th weeks the urorectal septum separates the cloaca into a primary urogenital sinus (ventrally) and the rectum (dorsally). Errors in this process can lead to **imperforate anus, atresia, and/or fistulas**.

As with the rest of the GI tract, enteric neurons arise from **vagal neural crest**. Distalmost portions of the hindgut are farthest away and therefore more sensitive to perturbations in migration (e.g. mutations in RET gene), resulting in **congenital megacolon (Hirschsprung disease)**.

Intestinal smooth muscle contraction and relaxation are under the control of enteric nervous system (ENS). Most enteric nervous activation causes muscle relaxation, mediated by nitric oxide and other enteric neurotransmitters. Extrinsic neural afferents to the ENS contain cholinergic and adrenergic fibers. The cholinergic fibers generally cause contraction, while the adrenergic fibers mainly cause inhibition. In patients with Hirschsprung disease, both myenteric and submucosal plexuses are absent. In the absence of ENS reflexes, control of the intestinal smooth muscle is overwhelmingly extrinsic. With the loss of the intrinsic enteric relaxing impulses, the increased muscle tone is unopposed. This phenomenon leads to an imbalance of smooth muscle contractility, uncoordinated peristalsis, and a functional obstruction.

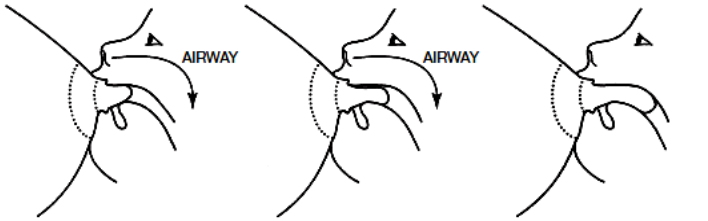


Postnatal development of the digestive system

The maturation of the gastrointestinal tract takes several months after birth in humans and includes maturation of feeding abilities and swallowing, changes in the composition of the intestinal microbiota, the function of epithelial barrier mechanisms, and the intestinal immune system.

➢ ORAL CAVITY

At birth the infant's lips are well adapted to closing round a nipple to feed. At rest, the back of the mouth is firmly closed with the tongue against the palate if not swallowing.
The buccal fat pad (BFP) (also known as the Bichat or masticatory fat pad) is an encapsulated mass of adipose tissue located between the masticatory muscles. Its perceived function in fetuses and infants is for sucking and enhancing the capabilities of the buccinators and other masticatory muscles [Ponrartana et al. 2014].
When feeding, the baby draws the nipple far back into the mouth, then squeezes milk by elevating the dorsum of the tongue from the front to the back against the hard palate. The gums then open, the tongue slides forward and the system refills with milk. This stripping and swallowing cycle then repeats. There is usually a rhythm of one breath to one or two swallows.
Infants appear to accept both breast and bottle nipple quite readily, but as the skill is perfected nipple preference becomes evident and breastfeeding may become more difficult if the baby is fed complementary or supplementary infant formula milk from a bottle.
The ability to suck semi-solid food, bite and chew, appears at five to six months and lumpy food can be tolerated at six to seven months, a 'sensitive period' for this motor ability. However, many children will gag or spit out lumps for some months over their first year.



Tongue moves forward to draw nipple in | **Nipple and areola move toward palate** | **Tongue moves along nipple pressing it against hard palate with peristaltic action**

Rubber nipple fills mouth to stop tongue action

Flow of formula occurs even if lips not tight around nipple hub

Digestion in the mouth

- Only small amounts of saliva are produced by the salivary glands in the neonate with little enzyme function; these develop full function by the age of two years.
- Some drooling in infants and toddlers is normal. It may occur with teething.
- Saliva contains enzymes:
  - **lingual lipase** (hydrolyzes the milk fat in the the stomach),
  - **alfa-amylase**.
- All babies have taste and smell present at birth, and all young babies can soon learn to like sweet tastes distinguished by the taste buds at the tongue tip, soft palate and inside of the cheek.

The parent of a newborn asks, "Will my baby spit out the formula if it is too hot or too cold?" What is your best response?

Reflexes of the mouth and throat

1. Rooting - touching cheek stimulates movement towards touch (goes at four to twelve months).
2. Sucking and swallowing (see below).
3. Retching (gag): Spasmodic respiratory movements against a closed glottis with contractions of the abdominal musculature without expulsion of any gastric contents (elicited by touching the soft palate or posterior pharynx).
4. Extrusion – if tongue is touched or depressed the response is to force it out of mouth (goes at 4–6 months).

SUCKING AND SWALLOWING

Eating requires active effort by infants who must have exquisite timing and **coordination for sucking, swallowing, and breathing** at the breast or bottle.

- ***Swallowing movements*** *are evident in the fetus at 16 or 17 weeks ' gestation, and there is a steady increase in the volume of amniotic fluid swallowed, from less than 20 mL daily at 20 weeks to around 450 mL daily at term. Amniotic fluid contains nutrition and growth factors, and the development of the gut is promoted by it. An interruption of fetal swallowing can lead to polyhydramnios.*
  Swallowing is an autonomic reflex for the first three months of life until the striated muscles in the throat establish cerebral connections but by six months the baby is capable of swallowing, holding food in the mouth or spitting it out.
  The mature swallow consists of a voluntary oral-preparatory phase, a voluntary oral phase, and involuntary pharyngeal and esophageal phases. The infant swallow does not have a voluntary oral-preparatory and oral phase but is otherwise similar.

- ***Sucking movements*** *can be seen from 28 to 30 weeks' gestation but effective coordination with swallowing and breathing is generally not achieved until 37 weeks or so. Babies more premature than this may still be able to suckle by stopping breathing for short periods and then resting.*

- Sucking helps babies feel secure and happy and helps them learn about their world. Babies may suck their thumbs, fingers, or hands, or a pacifier or other inanimate object such as a blanket or toy (**non-nutritive sucking**). Most children discontinue their nonnutritive sucking habit between the ages of 2 and4 years. Babies who suck their thumbs usually continue the habit longer than pacifier users. Prolonged thumb sucking may cause problems with proper growth of the mouth and the alignment of teeth. The most common dental effect of nonnutritive sucking is anterior, upward movement of the maxillary central incisors and palatal bone, which may result in an anterior open bite. Other possible effects include maxillary constriction and posterior crossbite.

- Pacifiers should never be used to replace or delay meals and should be offered only when the caregiver is certain the child is not hungry. Pacifiers should never be dipped in sugary substances such as honey and sugar. Pacifier use during sleep is associated with a decreased incidence of sudden infant death syndrome [A Pediatric Guide to Children's Oral Health. AAP; 2009]. Physiologic pacifiers are preferable to conventional pacifiers because they may have less dental effects.

A premature baby born at 32 wks of gestation with a birth weight of 1500 gm has stable vitals. Which is the initial feeding method of choice for this baby?

Infants less than 34 weeks gestation often do not suck effectively, lack co-ordination of sucking, swallowing and breathing and have delayed gastric emptying [Spence 2000]. Therefore, most infants in the NICU require naso/orogastric tube feeding. Infants are obligatory nose breathers and the presence of a nasogastric tube can increase airway resistance [Rogahn 1998]. Therefore, **nasogastric tubes** should be used in *infants who are ventilated; infants who are establishing breast/bottle feeding; bigger infants with no respiratory problems.* **Orogastric tubes** should be used in *infants on nasal CPAP; those with respiratory problems; those who are small and sick.*

The mode of initial feeding depends upon the gestational maturity and hemodynamic stability of the baby. Infants with severe birth asphyxia, respiratory distress, apneic attack, sezures, sepsis, NEC, shock babies should be maintained on intravenous infusion till their clinical condition stabilizes *[Ref: Meharban Singh 7th, Pg. 191]*.

Table. Mode of Initial Feeding Based on Gestational Maturity

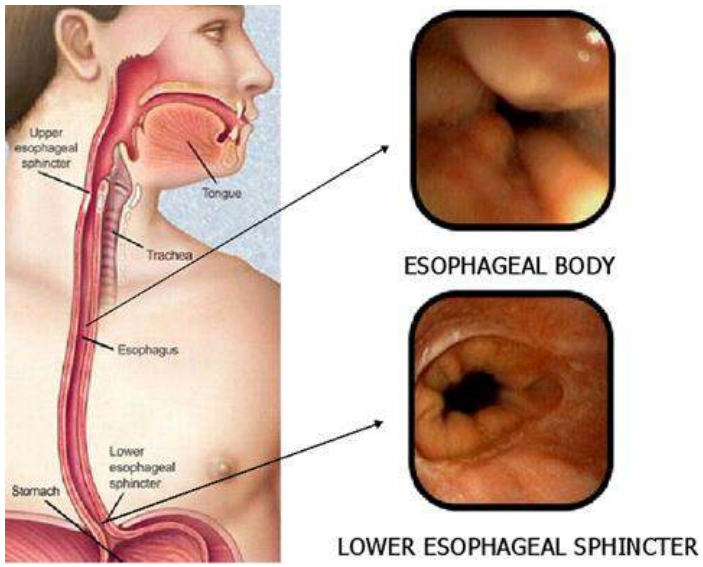
Gestational age (Birth weight)	Maturation of feeding skills	Initial feeding method
<30 wks (<1200 g)	No proper sucking efforts No propulsive gut motility	Intravenous fluids (parenteral nutrition)
30–32 wks (1200–1500 g)	Sucking bursts develop No coordination between suck/swallow and breathing	Oro-gastric Or Naso - gastric feeds  
33–34 wks (1500–1800 g)	Slightly mature sucking Coordination between breathing and swallowing begins	Spoon, syringe, paladai Or cup feeding  
>34 wks (1800 g)	More mature sucking More coordination between breathing and swallowing	Breast feeding

Feeding is hard work for babies! Feeding requires caloric expenditure because of the work of sucking: using and coordinating all these muscles requires extra oxygen. The demand for increased oxygen leads to changes in heart rate and breathing rate. This is why babies with heart failure so frequently have **feeding difficulties** (prolonged feeding times, fatigue, tachypnea or diaphoresis with feeding).

Types of medical trauma such as prolonged intravenous or nasogastric feeding, gastrointestinal and respiratory disorders that may be associated with discomfort with eating may contribute to the development of **oral aversion (oral-tactile hypersensitivity)**: reluctance, avoidance, or fear of eating, drinking, or accepting sensation in or around the mouth. An infant with oral aversion may not take anything into the mouth; not the breast, a pacifier, bottle nipple, spoon, or finger. Some infants also will not tolerate anything touching their lips, such as a cup [Lefton-Greif 2007].

➢ ESOPHAGUS

The bolus of food moves down the oesophagus into the stomach through the lower esophageal sphincter (LES). When food reaches the LES, it relaxes so that food enters the stomach. The muscle then squeezes shut to prevent food and acid from backing up into the esophagus. However, the muscle does not always stay completely closed, allowing the stomach juices and acid to back up into the esophagus occasionally (**gastro-esophageal reflux [GER]**). It is a common physiological event due to **transient relaxations in the lower esophageal sphincter.** It happens at all ages from infancy to old age, and is often asymptomatic. It occurs more frequently after feeds/meals. In many infants, GER is associated with a tendency to **intermittent vomiting and repeated, efortless regurgitation of feeds**. Most manifestations of uncomplicated GER in infancy resolve without treatment between 12, and 18 months of age.
Acid reflux becomes **gastro-esophageal reflux disease (GERD)** when the reflux causes irritation, injures the esophagus, or causes extraesophageal problems, such as chronic cough and asthma.



It is important to take a complete history to determine if the reflux falls into the spectrum of normal physiologic reflux or has characteristics of gastroesophageal reflux disease (GERD).
Historical points that would increase the concern for GERD requiring treatment would be posturing or back arching, excessive crying or fussing around feedings, and failure to gain weight. If one or more of these symptoms is present, then a diagnosis of GERD should be considered, and the infant may be a candidate for acid suppression therapy.

➢ STOMACH

- The position and shape of the infant stomach is high in the abdomen and is orientated transversely rather than vertically as in the older (seven to ten years) child.
- As the child feeds so gas is taken in. A 3.5kg baby will take in 100ml of milk in fifteen minutes and the same volume of air. The best position to 'burp' a baby is to hold it sitting supported at the back and neck so as to allow the gas to bubble up a straight esophagus.
- The capacity of the stomach changes with age. Infants should be fed often and in low portions as their gastric capacity is lower, than in older children. Stomach capacity of the neonate gradually increases to 200 to 350 ml by age 12 months and to 1,500 ml as an adolescent.

A newborn's stomach capacity

Day 1	Day 3	Week 1	Month 1
Size of a cherry	Size of a walnut	Size of an apricot	Size of a large egg
5-7 ml	22-27 ml	45-60 ml	80-150 ml

- Enzymes in gastric juice:
  - **proteolytic enzymes** (pepsinogen/pepsin, gastrixin, cathepsins);
  - **gastric lipase**, together with lingual lipase, comprise the two acidic lipases. These lipases, unlike alkaline lipases (such as pancreatic lipase and breastmilk lipase), do not require bile acid or colipase for optimal enzymatic activity.
- **Gastric acidity** is reduced at birth (gastric pH is greater than 4). Adult levels of acidity are not reached until 3 to 7 years of age. In addition, consumption of alkaline milk likely contributes to decreased gastric acidity in the child.
- **Gastric emptying** in the neonate is prolonged and varies according to meal type (slower in formula feeding) [Cavell 1981; Bonner 2015]. Adult rates of gastric emptying (10 to 20 minutes of rapid phase) are not approached until 6 to 8 months of age [Fernandez 2011].

Clinical correlations

- Reduced gastric acid decreases barrier function of gastric mucus and increases the risk of enteric infections.
- High gastric pH and slow emptying can facilitate rapid absorption of acid-labile compounds (such as penicillins).
- Acid secretion limitations in premature infants should be kept in mind when considering the use of histamine-2 (H2) blockers, which are widely prescribed in many neonatal intensive care units. *Studies suggest that critically ill premature infants treated with H2 blockers have a higher incidence of nosocomial sepsis and necrotizing enterocolitis. Although speculative, it is possible that with the already limited hydrogen ion production in the stomach of the premature infant, additional blockage further diminishes the acid barrier to microorganisms and allows for a higher load of bacteria in the more distal regions of the intestine [Beck-Sague 1994; Guillet R 2006].*

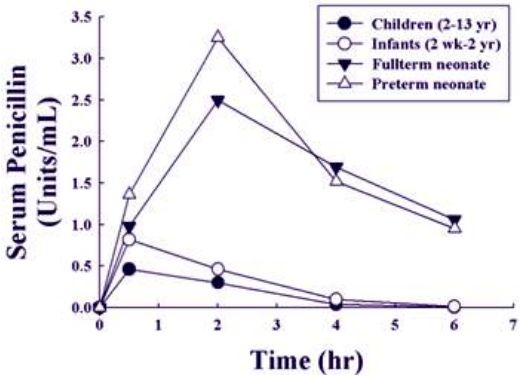
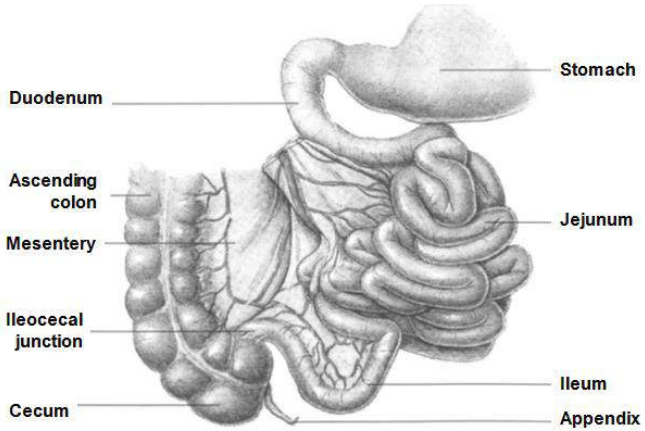


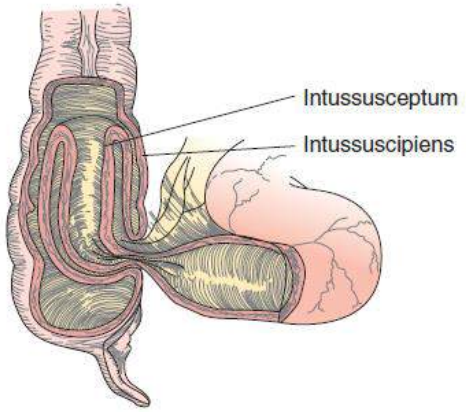
Fig. Penicillin plasma concentrations following the oral administration of a single 22,000 units/kg dose in neonates, infants, and children [Funk et al. 2012]

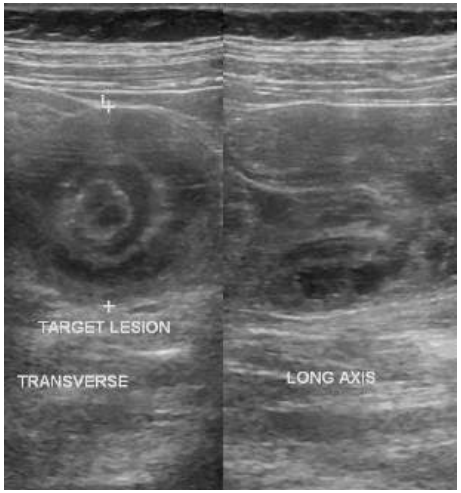
➢ INTESTINE & BOWELS



- The intestine is relatively longer with well developed circular muscles.
- Greater omentum is shorter (it predisposes to diffuse peritonitis in local inflammatory abdominal processes, e.g. in appendicitis).
- The sigmoid colon is relatively longer and forms additional loops (it predisposes to constipation, especially in fat-rich diet). The rectum in infants is also longer and poorly fixed that predisposes to **rectal prolapses** in tenesmus and constipation.
- Transverse mesentery is longer and predisposes to **volvulus** or **intussusception of bowels**.

- ***Intussusception*** *is telescoping of one segment of intestine into another, usually in children between ages 6 mo and 3 yr. It is the most common cause of intestinal obstruction in this age group.*
- *Most cases are idiopathic and no anatomic lead point can be identified. In about 25% of children who have intussusception, typically very young and older children, a lead point (i.e. a mass or other intestinal abnormality) triggers the telescoping. Examples include polyps, lymphoma, Meckel diverticulum, and IgA–associated vasculitis (Henoch-Schönlein purpura) when purpura involve the bowel wall. Cystic fibrosis is also a risk factor.*
- *Peak incidence coincides with the viral enteritis season. An older rotavirus vaccine was associated with a marked increase in risk of intussusception and was taken off the market in the US. The newer vaccines, when given in the recommended sequence and timing, are not associated with any clinically significant increased risk.*





- *Children typically present with colicky abdominal pain and vomiting, followed by passage of currant-jelly stool.*
- *Diagnosis is made by ultrasonography (**target sign**).*
- *Treatment is reduction by **air contrast enema (pneumoreduction)** and sometimes surgery. Therapeutic enema is of no value in patients with small bowel–to–small bowel intussusception, which usually occurs in older children who have other associated diseases (eg, HSP, hemophilia, Peutz-Jeghers syndrome, malignancies).*

Postnatal maturation of the intestinal mucosa

- After birth, enteral nutrition is critical in sustaining normal gut mucosal growth.
  Fasting, starvation and exclusive parenteral nutrition all deprive the gut of luminal nutrients resulting in a loss of gut tissue mass with blunted villi, net loss of protein, decreased cell proliferation, decreased brush border disaccharidase activity, increased intestinal permeability and increased catabolism [Sanderson IR, Walker WA, 2000].

- Intestinal enzyme activity increases with age, except **lactase** (an enzyme of the microvillous brush border that is involved in hydrolysis of milk lactose). Breastfed and formula-fed infants have comparable levels of lactase activity. This lactase enzyme activity is high in the small intestine at birth, but declines during infancy and is lost by adult life in many individuals. **Amylase**, a pancreatic enzyme secreted into the duodenum that breaks down carbohydrates, and **enterokinase**, which is secreted from the ileum mucosa to activate trypsin for the breakdown of protein to peptides, are also present in the neonate gut.

  All infants have efficient protein digestion and absorption; there is no difference between breastfed and formula-fed infants.

  Both breastfed and formula-fed newborn infants have relatively **lower pancreatic lipase and bile salt secretion**, which limits the baby's capacity to convert fat into fatty acids and glycerol.
  - *Breastfed infants absorb significantly more dietary lipid when compared with formula-fed infants because they ingest a unique **breast milk lipase** that assists in the majority (up to two thirds) of lipid hydrolysis.*
  - ***Specific long-chain polyunsaturated fatty acids (LCPs)** are present in breast milk to feed the large developing brain; thus nature has matched the milk supply to the young human's physiology.*
  - *Both breastfed and formula-fed infants are able to absorb **medium-chain fatty acids** directly into the portal system, whereas long-chain fatty acids require transport proteins for absorption.*

- In infants absorptive capacity of the intestine is higher than in adults: they have increased intestinal permeability to macromolecules, e.g. milk proteins, maternal antibodies, as well as toxins and antigens [de Zwart et al., 2004]. This permeability is mediated by a specific transport process (**receptor-mediated endocytosis**). The permeability of the gut decreases significantly during the first months of life (**gut closure**). An important factor that modulates the gut closure is breastfeeding by its direct effects on epithelium [Roberton et al. 1982].

Fig. Growth of the small intestine [Cummins, 2002].

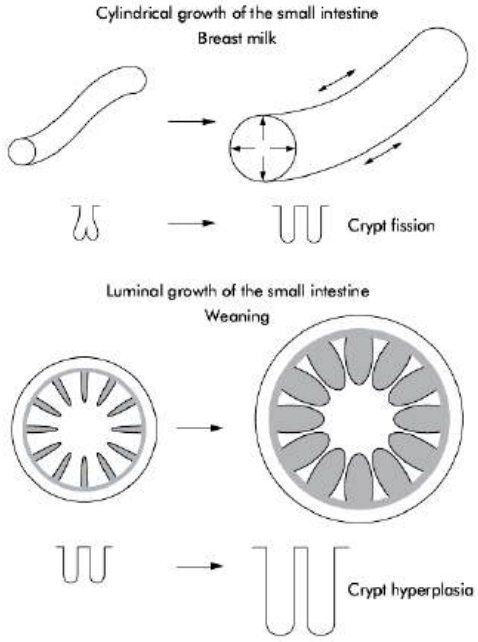
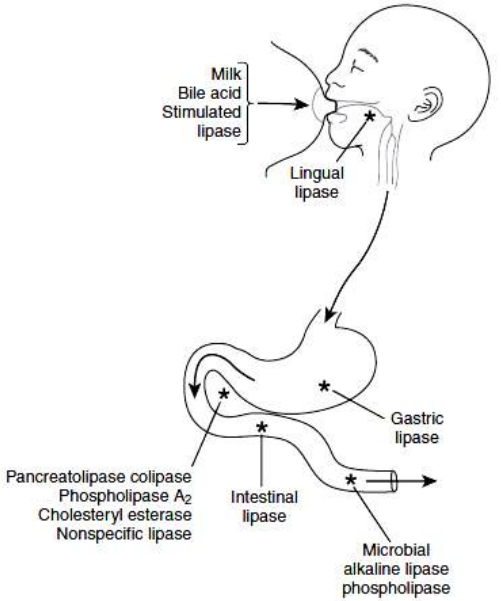


Fig. Lipases from different sources.



Bacterial colonization

The colonization of the intestinal tract starts after birth, and the intestinal tract of the newborn is first colonized by facultative anaerobes and then by bifidobacteria, clostridia, bacteroides, and other strict anaerobes. The source of nutrition plays a role in the type of bacteria that populate the intestine. For example, the small intestine of breast-fed infants is primarily populated by beneficial bacteria such as bifidobacteria and lactobacilli because human milk promotes growth of these types of bacteria. One of the many benefits of bifidobacteria and lactobacilli are that they can limit the growth of numerous pathogens by lowering the intestinal pH.

During the first year of life, the enteric microflora is highly dynamic, but the microbial diversity is low.

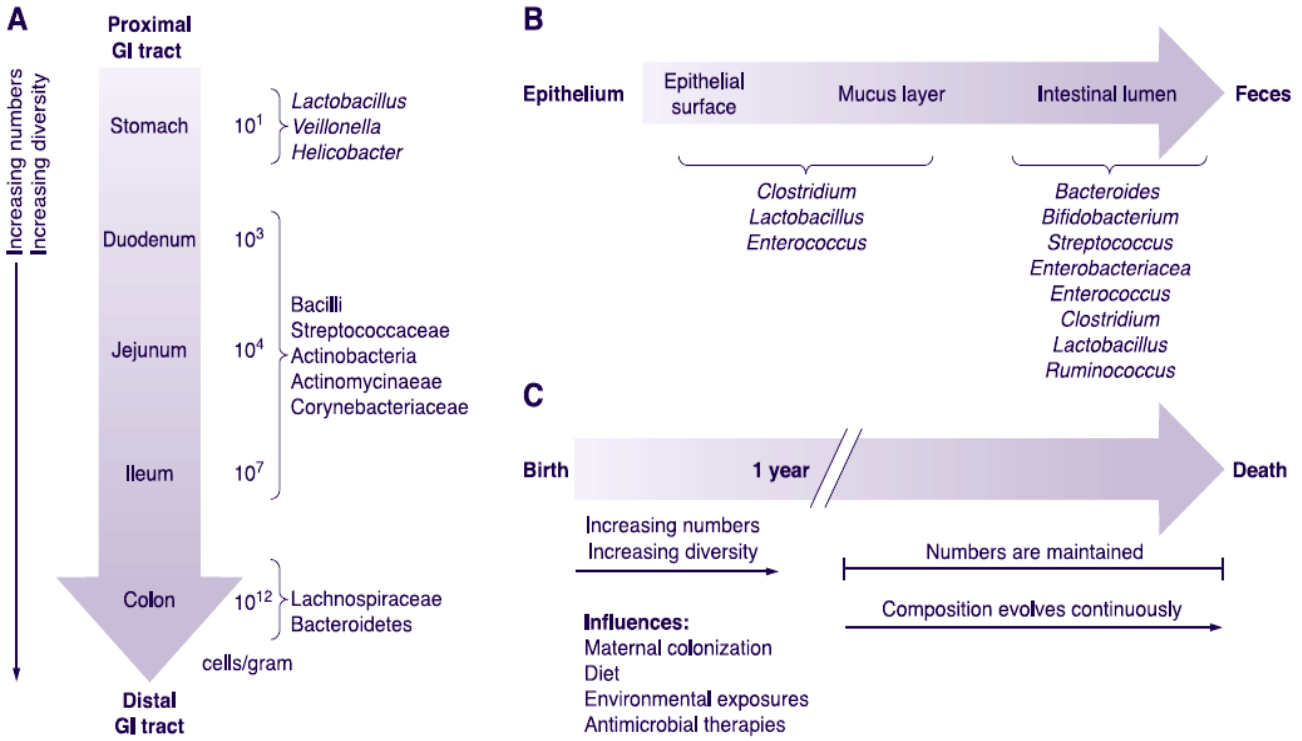


Fig. Spatial and temporal aspects of intestinal microbiota composition [Sekirov et al. 2010]
A: variations in microbial numbers and composition across the length of the gut. B: longitudinal variations in microbial composition in the intestine. C: temporal aspects of microbiota establishment and maintenance and factors influencing microbial composition

The introduction of solid food profoundly impacts on the microbial ecology of breast-fed infants. Once dietary supplementation begins, microbiota profile of breast-fed infants changes toward formula-fed-infants profile, with the significant increase in the count of Enterococci, Enterobacteria, Bacteroides, Clostridia, and anaerobic Streptococci. Between the first and the second year of life, differences between breast- and formula-fed infants are lost. By the age of 2 to 3 years the microbial population stabilizes and starts to resemble that of the adult.

HONEY SHOULD NOT BE FED TO INFANTS YOUNGER THAN 1 YEAR OLD!

It contains spores of Clostridium botulinum that readily grow in baby's intestine and produce toxins. Older children are believed to be less susceptible to botulism due to their mature gastrointestinal tracts, which can excrete the spores before they germinate.

Intestinal motor activity & stools

Intestinal motor activity matures throughout early infancy, with consequent increases in the frequency, amplitude, and duration of propagating contractions.

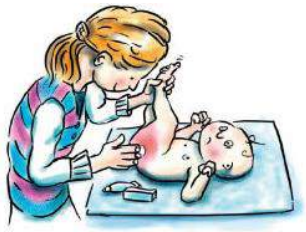
The stools of the newborn (meconium) are odourless, dark green, have a smooth, paste-like appearance and are passed within the first twenty-four hours in about 87 per cent of infants and within 48 hours by 99 per cent. This is not influenced by whether the infant is breast- or formula-fed [Catto-Smith 2005]. After this, the method of feeding will have impact on stool frequency, colour and consistency of the stool.

- *The normal stools of breastfed infants are never formed, may be passed at hourly intervals, may contain mucus and may be green. When lactation becomes established between the third and fifth days intestinal hurry is common, resulting in frequent stools. No treatment is needed. Later the stools tend to become less frequent and more pasty and by the age of 3 weeks they may be passed once every 2 or 3 days.*
- *In contrast, the normal stools of formula-fed infants are formed and do not contain fluid or mucus. With certain cow's milk preparations the stools may be dark green, but this has no sinister meaning.*

Defecation requires two coordinated events: pelvic floor relaxation, and an increase in intraabdominal pressure (bearing down to have a bowel movement). Children with infant dyschezia have not yet developed this coordination so they are unable to enjoy easy defecation.

Infant dyschezia is a functional condition characterized by at least 10 minutes of straining and crying before successful passage of soft stools in an otherwise healthy infant less than six months of age.
These episodes, exhausting for the infant and anxiety provoking for the parents, occur several times daily. They may prompt parents to visit their child's clinician during the infant's first 2 to 3 months of life with concerns that their child is constipated. The parents describe a healthy infant who cries for 20 to 30 minutes, turns red in the face, and screams, seemingly in pain, before defecation takes place.

Breastfed babies' stools have a lower pH than babies fed on infant formula milk, due to the fermentative gut flora, which produces neutral and acid metabolic waste products. When the pH drops, the faecal enzymes become less active and thus these breastfed babies usually have less nappy rash.



Nappy rash occurs when urine and faeces mix; the urea splitting organisms in urine raise the pH and this irritates the infant's delicate skin.

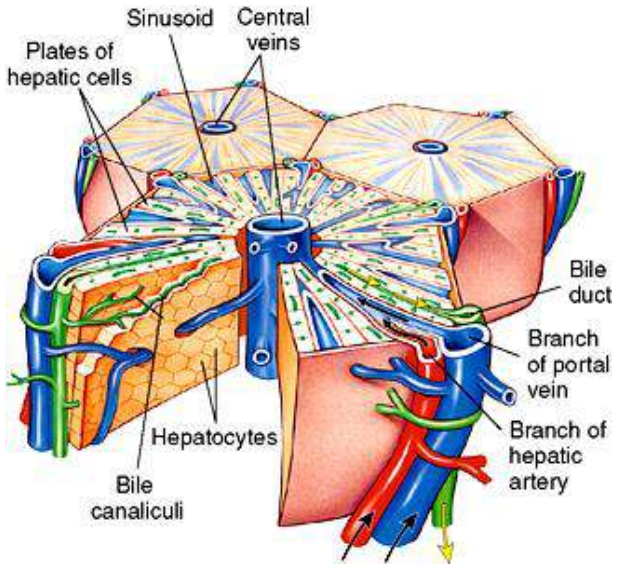
➢ LIVER & BILIARY TRACT

- The liver is relatively larger and is richly vascularised. Liver occupies more of abdominal cavity than in adults. Liver reaches adult size and function by adolescence.

- The liver is functionally immature at birth:
  - *The liver's slow development of glycogen storage capacity makes the infant prone to hypoglycemia. The suckling neonate is entirely dependent on glucose supplied via the milk and on his capacity for an efficient gluconeogenesis to maintain his blood glucose concentration in the normal range*
  - *Decreased synthesis of coagulation factors (prothrombin levels in the neonate are only 20%–40% of adult levels, which affects clotting)*
  - *Decreased synthesis of albumins ⇒ Protein binding of drugs is decreased; high levels of free drug remain in bloodstream, which can lead to toxic level of drug*
  - *Decreased hepatic enzyme function:*
    1) Enzyme systems for biotransformation of drugs are not fully developed, which affects drug dosing; infants and children metabolize drugs more slowly than adults; can easily build up toxic levels of drugs
    2) Liver conjugation reactions are impaired ⇒ neonatal hyperbilirubinemia; long drug half-lives
  - *Immaturity of bile synthesis and secretion ⇒ susceptibility of the sick neonate to develop cholestasis in response to sepsis, administration of parenteral nutrition*

  The composition of bile in the newborn is different to that in the adult, with higher concentrations of **hyocholic acid** as well as some unusual bile acids. Soon after birth, the concentrations of the bile acids cholate and chenodeoxycholate increase rapidly. They are involved in the absorption of long chain fatty acids and fat-soluble vitamins as well as a number of drugs and hormones.

  The ability of the gallbladder to empty in response to a test feed occurs soon after birth, but is reduced in preterm neonates of 27 – 32 weeks' gestation.



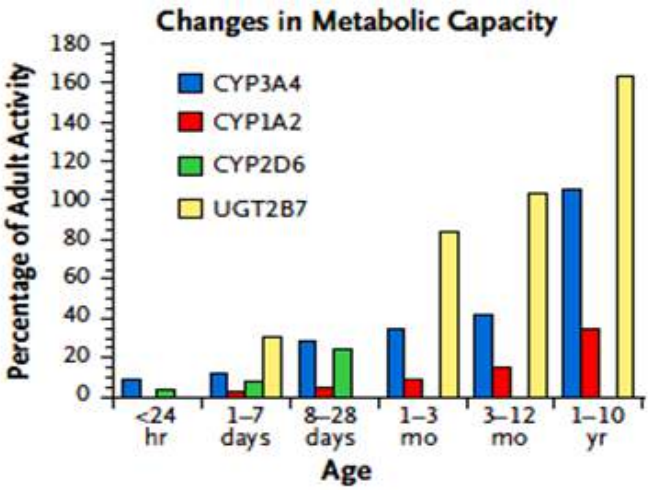


Fig. The activity of many cytochrome P-450 (CYP) isoforms and a single glucuronosyltransferase (UGT) isoform is markedly diminished during the first two months of life.

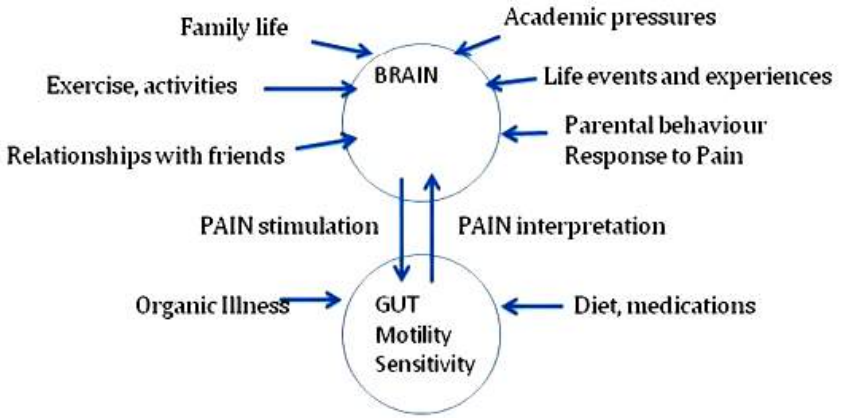
Assessment of the Digestive System in Children

"The colon is the playing field for all human emotions."
- Cyrus Kapadia, MD

General Considerations

- Interactions with other organ systems serve the needs both of the gut and the body. Symptoms apparently related to the gastrointestinal tract may arise fromdisease elsewhere. For example, vomiting may be a symptom of infection, poisoning or head injury, and abdominal pain may occur in a child with pneumonia or diabetic ketoacidosis.
- Subtle alterations in gastrointestinal function may adversely affect growth while causing minimal symptoms. Only careful examination of the child's growth curve may alert the physician to the possibility of underlying gastrointestinal disease.
- The limited ability of the young child to describe his or her symptoms may make diagnosis more difficult.
- Gastrointestinal symptoms are determined by:
  - *Structural changes (eg, inflammation, destruction, impaired gut blood flow, neoplasia)*
  - *Functional changes (eg, impaired digestion and absorption, altered secretion, altered gut motor function)*
  - *Visceral hypersensitivity*
  - *Psychogenic factors*

Fig. A biopsychosocial model of pain: for use with parents and patients



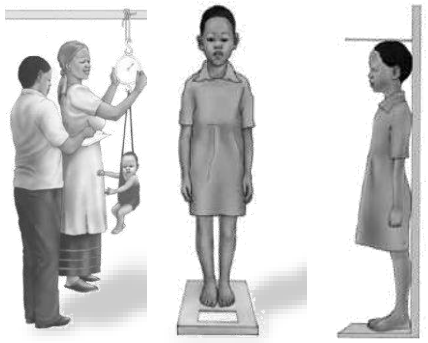
The biopsychosocial model of pain explains how abdominal pain occurs as a result of interplay between multiple factors surrounding the child, including genetic predisposition, life events, the family and the child's coping mechanisms for dealing with stress and pain. These biological, social and psychological factors impact the development and recognition of gut pain through altered gut physiology via the brain–gut axis [Mulak & Bonaz, 2004].

- **Biopsychosocial Approach to GI disorders**

There is a link between "psyche" and "soma" in gut function (**brain–gut axis mechanism**), and this is true in children as it is in adults. Interactions between physiological (e.g., motility, sensation) and psychological factors (e.g., life stress, emotional state, coping, social support) are seen as shaping the nature and outcome of the child's gastrointestinal symptoms. Factors such as the child's adoption of a sick role, their sensitivity to pain, their level of psychological functioning, and the family's ability to deal with the illness can all contribute to differences among children's reaction to illness [Drossman, 1998; Hyams, 1996]. The commonest manifestation is with recurrent abdominal pain, sometimes associated with vomiting ("periodic syndrome"), which occurs in school-age children in association with emotional triggers such as bullying, anxiety over parental stress, or exams. Some adolescents with severe Crohn's disease do not limit their functioning and will not let the illness define them, participating in a wide range of academic and extracurricular activities. However, others with less severe physical symptoms but who are anxious and whose parents have significant concerns about their health status are home schooled and have little peer contact.

➢ NUTRITIONAL ASSESSMENT

Feeding history	24-hour recall, food frequency questionnaire, etc.
Anthropometry	Weight, height, weight-for-height, body mass index (BMI), skinfold thickness, mid-upper arm circumference (MUAC), waist circumference
Clinical	Physical appearance, signs of malnutriution
Biochemical and haematological	Vitamin status tests Lipid status Iron status – haemoglobin, ferritin, etc.



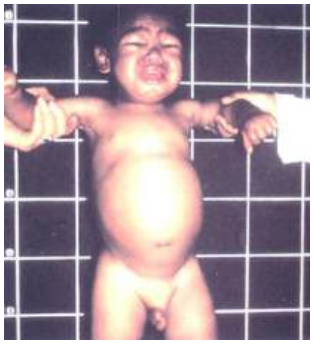


Fig. *Kwashiorkor. This patient has a typical edematous appearance in the periorbital area, extremities, and abdomen.*

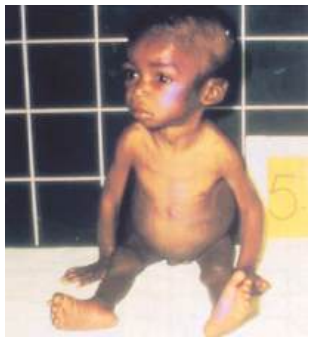


Fig. *Marasmus. Note the profound wasting and sparse hair*

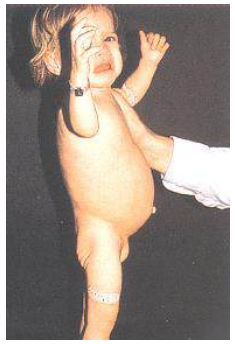


Fig. *Potbelly and muscle wasting in a child with celiac disease*

Infant feeding history

Which milk?	Breast or formula? If formula, note which one and details of reconstitution
How much feed?	In breast-fed infants, does the mother have a good milk supply? In formula-fed infants, note volumes offered and taken
How often?	Note the times of feeds in the previous 24 hours
How long does the feed take to complete?	
Characteristics of feeding?	Hungry, windy, apathetic, slow, sleepy, etc.

➢ CLINICAL EXAMINATION OF THE CHILD'S ORAL CAVITY

Lips, Tongue, and Oral Mucosa

The lips and tongue should be soft, pink, and moist. The oral mucosa may be pink or brown, depending on the infant's or child's skin color. It should be smooth and moist.

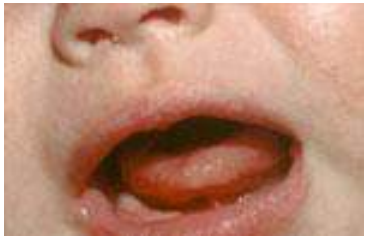


Fig. Healthy Lips and Tongue

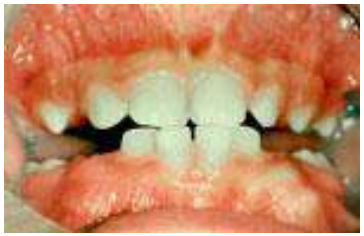


Fig. Healthy Mucosa

Palate

To observe the palate, you should gently bend the infant's or child's head back. Directing the light onto the surface of the palate, observe pink, moist surfaces. The soft, fleshy mass that hangs from the rear of the soft palate is the uvula.

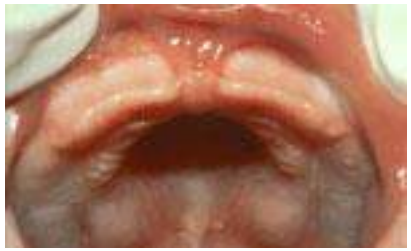
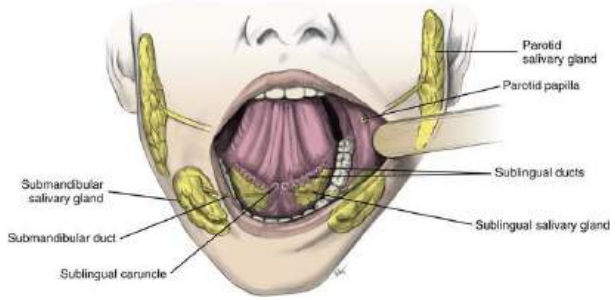


Fig. Healthy Palate

Major Salivary Glands

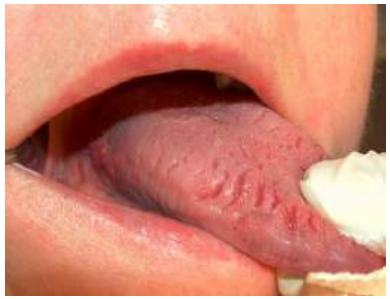
The major salivary glands are located in the cheeks and on the floor of the mouth. The ducts should be raised and pink. Youl should first look at them and then press them lightly. It is common to observe clear secretions from the glands. Pressing the glands should not cause discomfort.



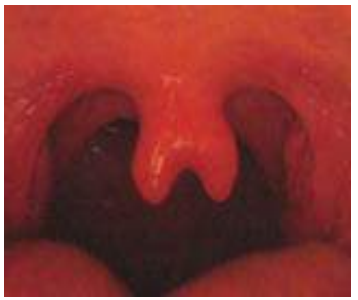
A number of **normal anatomic variations** may be noted in the mouth.

- **A short lingual frenulum ("tongue-tie")** may be worrisome to parents but only rarely interferes with eating or speech, generally requiring no treatment.
- **Fissured tongue (+/-geographic tongue)** is usually a normal finding.
- **A bifid uvula** may be normal or associated with a submucous cleft of the soft palate.

A short lingual frenulum ("tongue-tie")



Fissured tong (+ geographic or scrotal tongue)



A bifid uvula

Abnormalities and complaints related to the mouth and throat

Manifestation	Definition	Causes
Halitosis (fetor oris)	Oral malodor	Poor oral hygiene, tooth decay, gingivitis, oral candidiasis, postnasal drip, sinusitis, tobacco use, xerostomia …
Xerostomia	Dry mouth	Thirst, mouth breathing, allergic rhinitis, adenoiditis, dehydration, diabetes, or mumps; may be associated with drug use
Dysphagia	Dysphagia refers either to the difficulty someone may have with the initial phases of a swallow (usually described as "oropharyngeal dysphagia") or to the sensation that foods and or liquids are somehow being obstructed in their passage from the mouth to the stomach (usually described as "esophageal dysphagia").	Viral or bacterial pharyngitis, peritonsillar or retropharyngeal abscess, epiglottitis, GERD, cleft palate, cerebral palsy …
Stomatitis	Inflammation of the mucous membrane of the mouth. *Inflammation of the lips is known as cheilitis, inflammation of the tongue is glossitis, inflammation of the gums is gingivitis.*	Coxsackievirus (herpangina; hand, foot, and mouth disease), aphthous ulcers, oral candidiasis, herpesvirus 1 or 2, measles …
Tooth decay		Tooth decay associated with sore throat may be caused by self-induced vomiting, poor oral hygiene, or early childhood caries

Candidiasis

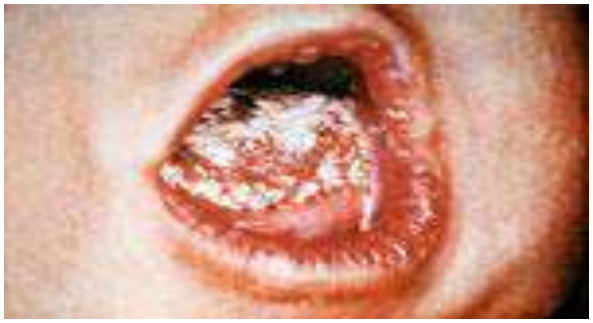


Fig. Candidiasis, a fungal infection that may be present in infancy, appears as a soft white plaque coating the mucosa and palate. When the coating is removed with a gauze pad or tongue blade, the undersurface is red and raw.

Primary herpetic gingivostomatitis

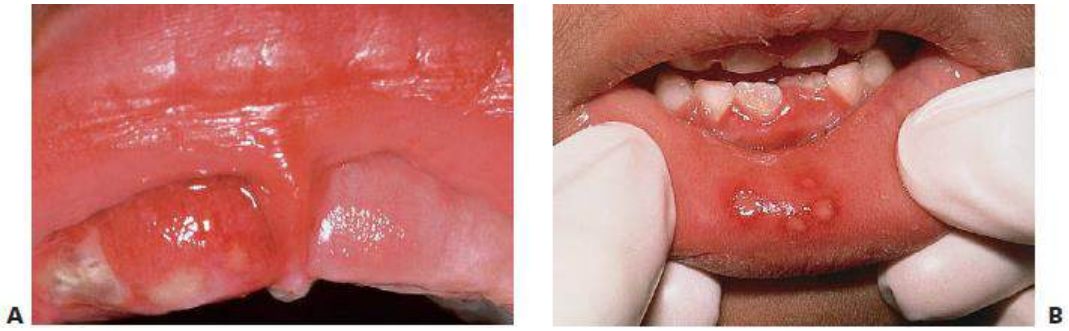


Fig. A, Infection with primary herpes often occurs at the time of eruption of primary teeth. **B,** Common presentation with multiple small ulcers on the lower lip, and gingival swelling and inflammation.

Infections caused by Coxsackie group A viruses

A. Herpangina B. Hand, foot and mouth disease (HFMD)

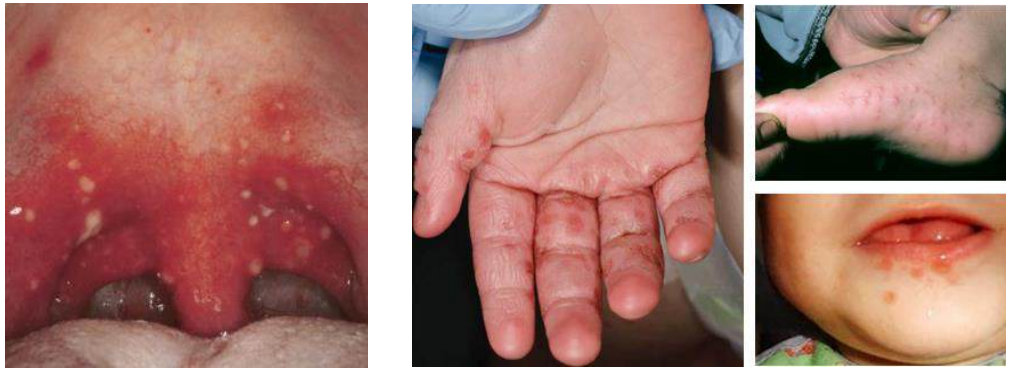
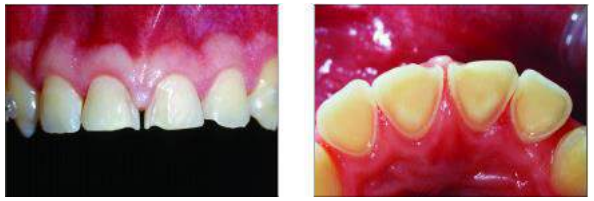
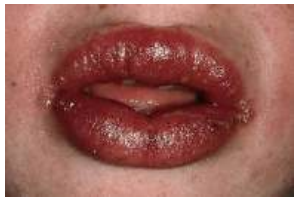
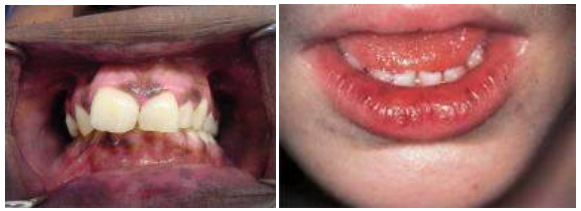


Fig. A, Herpangina with characteristic palatal and pharyngeal ulceration and inflammation. **B,** Cutaneous lesions in hand, foot and mouth disease.

ORAL MANIFESTATIONS OF GASTROINTESTINAL DISEASES		
Gastroesophageal reflux disease (GERD)	It causes enamel erosion due to gastric acid influence.	
Inflammatory bowel disease (IBD)	**1. Crohn disease (CD) –** Oral manifestations of Crohn disease include multifocal, linear, nodular, polypoid or diffuse mucosal thickenings. They are characteristically firm, pink and painless to palpation unless there are ulcerations that may cause pain on touch, or when eating acidic, spicy or hot foods. **2. Ulcerative colitis (UC) –** Rare oral manifestation of ulcerative colitis is *pyostomatitis vegetans*.	 **Painless swelling of the lips (CD)**  **Pyostomatitis - tiny yellow pustules on the oral mucosa (UC)**
Celiac disease	**Oral and dental manifestations of celiac disease:** *enamel defects; delayed eruption; recurrent aphthous ulcers; cheilosis; oral lichen planus; atrophic glossitis*	
Peutz-Jeghers syndrome	– An autosomal dominant disease, characterized by • pigmentation of the skin and mucosals • intestinal polyposis with high risk of malignancy	

➢ ABDOMINAL EXAMINATION

CASE SCENARIO

A 14 year-old boy came to his family physician with a poorly demarcated, indurated, nontender swelling on the left forehead. The patient had no other complaints. Two courses of antibiotics for presumed cellulitis failed to resolve the problem. An experienced pediatrician conducted a thorough physical examination and discovered a large testicular tumor (seminoma). The swelling on the forehead was due to a secondary bony deposit from the malignant tumor. The boy confessed that he had been aware of the testicular mass for some time but was too embarrassed to tell anyone.

- 'Examine the abdomen' is not the same as 'Examine the gastrointestinal system', but is often interpreted as such. Examination of the inguinal region, external genitalia, and perianal area (in select cases) is part of the abdominal examination, especially in infants who cannot localize their symptoms. For example, an infant presenting with acute onset of irritability, poor feeding, and vomiting may have a strangulated inguinal hernia. Examination of external genitalia is especially important in male patients because a variety of testicular and penile lesions can occur. A toddler with testicular torsion may present with severe abdominal pain and be unable to localize the pain. Often physicians are hesitant to examine the external genitalia in children, especially if the complaint is not directly linked to that region. However, serious diagnoses can be missed if the relevant areas are not specifically examined.

- The other common misconception is that the abdomen can be examined with the examiner standing up: this is inappropriate, as the hand and forearm should be at the same level as the abdomen, which can be achieved only by kneeling at the bedside or sitting on a chair. The other point worth noting is that after inspection, when initially palpating, you should look not at the abdomen or examining hand but at the face of the child, as that is the only way to assess if there is any abdominal tenderness.

To describe the location of any abnormality, it helps to divide the abdomen into four quadrants with a horizontal line through the umbilicus and a vertical line from the xiphoid process to the symphysis pubis through the umbilicus. For infants and younger children with smaller abdomens, this division should suffice. For older children and adolescents, the abdomen can be divided into nine regions by including two additional vertical lines from the mid-clavicular area to the mid-inguinal point and two horizontal lines through the subcostal margins and the anterior iliac crests.

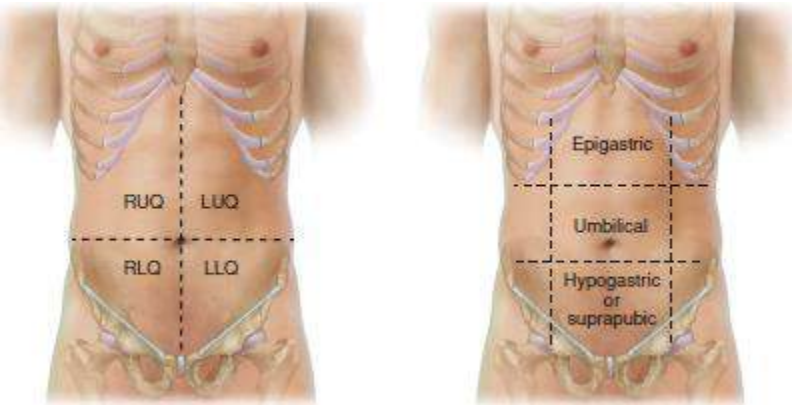
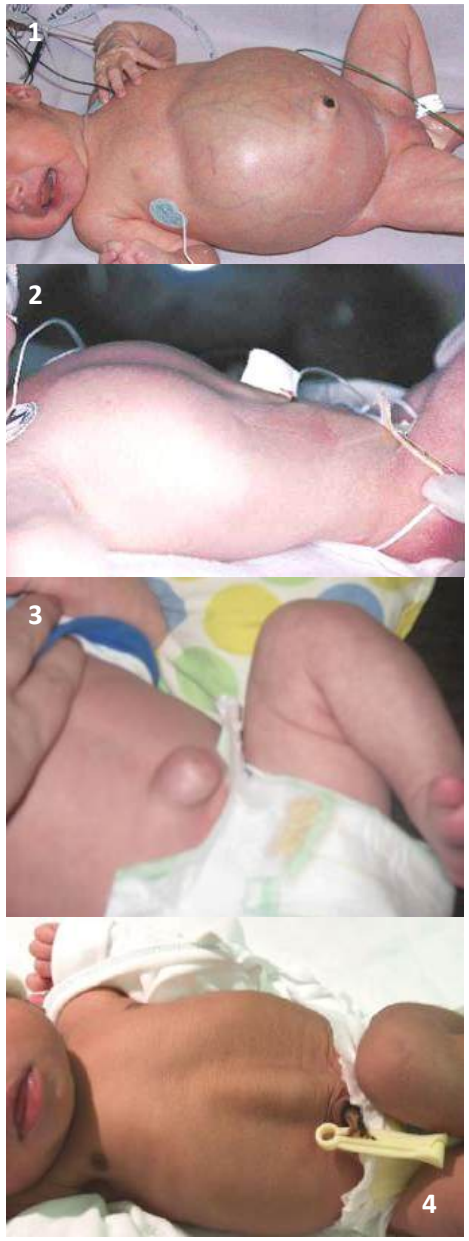


Fig. Quadrants and sections of the abdomen

INSPECTION

Simply looking at the abdomen can provide important clues to the underlying diagnosis.

- **The abdominal wall normally moves with respiration**, especially in infants. Loss of this movement secondary to pain can be an important indicator of abdominal inflammation, such as peritonitis.
- **Abdominal symmetry** is best assessed by inspection from the foot of the bed. Asymmetry can result from an intraabdominal mass. Bulging of the flanks can occur in patients with ascites.
- **Distention** [1] can be caused by air in the intestine, fluid in the abdominal cavity (ascites), or solid organ enlargement.
  Until about 4 years of age, the abdomen continues to protrude in both the supine and standing positions. After 4 years of age, the abdomen still protrudes with standing due to lumbar lordosis, but it is flat when the child is lying down. Do not mistake this appearance for pathologic distention.
  Abdominal distention is an important sign of intestinal obstruction. The lower the obstruction in the gut, the more marked the distention. Also, associated symptoms will be present, including vomiting and abdominal pain/irritability. Peristalsis may be visible through the abdominal wall in patients with intestinal obstruction. This peristalsis is most commonly observed in the upper abdomen in infants with hypertrophic pyloric stenosis.
- **A depressed (scaphoid) abdomen** [2] in a newborn suggests a diaphragmatic hernia with some abdominal organs sitting in the chest cavity.
- **Umbilical hernias** [3] are common in infants. In some ethnic groups, they are virtually universal. Umbilical hernias are reducible and, although they are sometimes quite large in size, they typically resolve without treatment during the first few years of life.
- Slight separation of the rectus abdominis muscle (**diastasis recti**) [4] is normal in children, especially in premature infants.
- **Examine the inguinal area** for swelling. Indirect inguinal hernias are common in children and always require surgical correction. A reducible hernia may not be obvious in the supine position. Older children should be examined standing up. Increasing the intraabdominal pressure by coughing or straining makes the swelling more obvious. Small, nontender, soft, mobile inguinal lymph nodes are common in children. They can be bilateral and often are benign. Check for abnormal lymphadenopathy elsewhere (e.g., the axilla).
- **Examine the back**, because diseases of the spine may present with abdominal symptoms. A tuft of hair in the midline often is a clue to an underlying congenital spinal abnormality (e.g., diastematomyelia) in a child with chronic constipation.



PERCUSSION

Indirectly percuss all areas of the abdomen. Normal findings include dullness along the costal margins and tympany over the remainder of the abdomen. A full bladder may yield dullness to percussion. Percussion can be useful in delineating the edge of the liver or spleen and in examining for ascites.

PALPATION

Palpate the abdomen with the child in a supine position. If the child's legs are small enough, the knees may be brought up with the nondominant hand to flex the hips and relax the abdomen. The examiner is always at the patient's right side.

Look at the child's face while palpating the abdomen. Start palpating at a point furthest away from any tenderness. A reluctant child may be put at ease if their own hand is used, with the examiner 's hand overlying.

Palpate all four quadrants of the abdomen in a systematic fashion, first lightly and then deeply.

- Apply light pressure with the fingertips to perform light palpation, assessing for tenderness and muscle tone.
- Note skin turgor by gently elevating a piece of skin and allowing it to fall back into place.
- Perform deep palpation to assess the organs and any masses. Place one hand on top of the other and palpate from the lower quadrants to the upper.
  - *The edge of the liver may be felt at the right costal margin, and the tip of the spleen can be felt at the left costal margin. The liver often is palpable 1 to 2 cm below the right costal margin in normal infants and toddlers. Its edge is usually soft, and it moves downward with respiration. The liver edge is often palpable in healthy children and adolescents [Goldbloom RB, 2010].*
  - *The descending colon may be felt in the left lower quadrant as a small column and the bladder as a soft balloon below the umbilicus.*
  - *The kidneys are rarely palpable.*
  - *The abdomen should be soft and nontender to palpation. Report firmness, tenderness, or masses.*

- Palpate the inguinal area for the presence of hernia or enlarged lymph nodes.

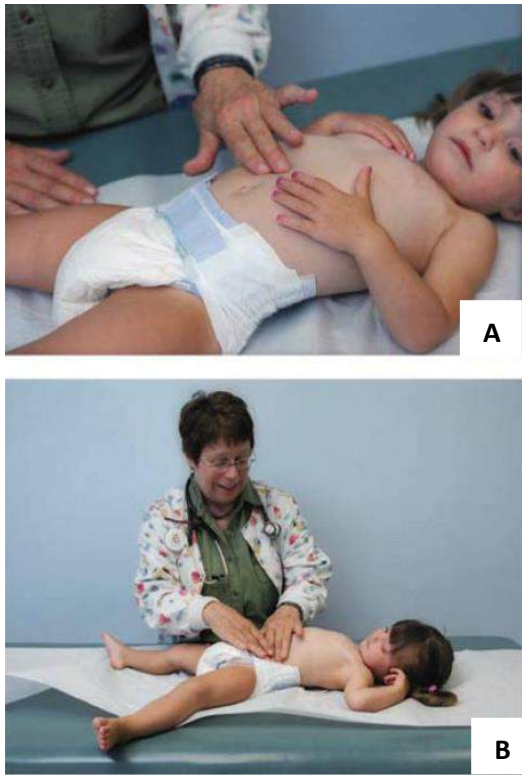
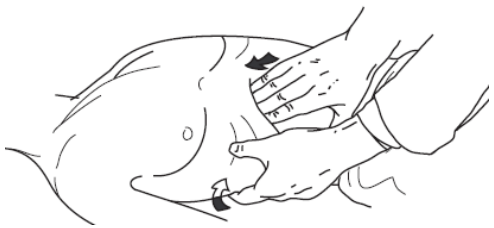


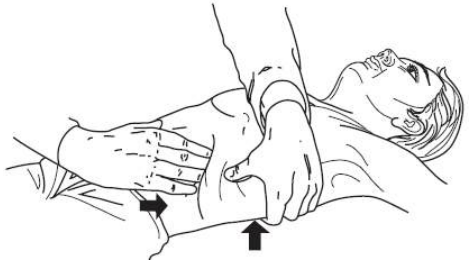
Fig. (A) Light and **(B)** deep palpation of the abdomen.

- **Bimanual Palpation of the Right Upper Quadrant**



Proper palpation of the right upper quadrant consists of placing the right hand at the right costal margin and the left hand under the patient's right flank, lifting it toward the examiner.

- **Bimanual Palpation of the Left Upper Quadrant**



Palpate the left upper quadrant by placing the right hand toward the patient's left costal margin while the left hand is placed at the patient's left flank, pushing the spleen anteriorly.

On palpation of either upper quadrant, it is advisable to have the patient take a deep breath. Palpate the lower quadrants with similar technique to evaluate the kidneys for enlargement. Palpation of the right lower quadrant is a critical part of the evaluation for appendicitis, with the classic finding of tenderness over McBurney's point.

Table. Physical signs and clinical significance on abdominal examination

Physical sign	*Clinical significance*
Abdominal mass	Fecal mass in constipation Hydronephrosis Renal/suprarenal tumor Crohn disease
Splenomegaly	Hemolytic anemia Neoplastic disease Portal hypertension
Hepatomegaly	Chronic liver disease Neoplastic disease Storage disease Congestive heart failure
Ascites	Liver cirrhosis Nephrotic syndrome Congestive heart failure
Anal fissure	Chronic constipation Crohn disease

RECTAL EXAMINATION IN CHILDHOOD

This is never a routine examination and is rarely helpful. Careful thought must be given to undertaking this examination in any child.

In older children, a rectal examination is best performed with the child in the left lateral position with the spine and knees fully flexed. Infants and younger children can be examined in a knee-chest position.
Examine the **perianal area** for excoriations, skin tags, or fistulae. Sentinel skin tag(s) overlying a chronic anal fissure in older children are pathognomonic of Crohn disease.

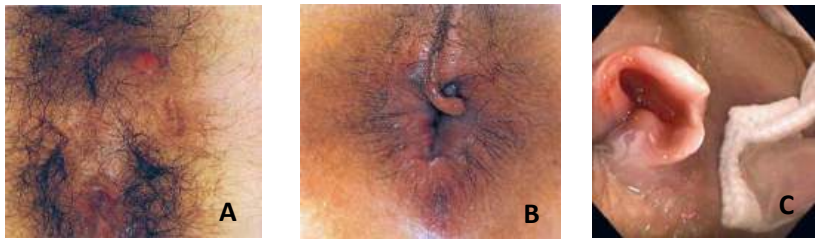


Fig. Crohn disease. (A) Perianal abscess, (B) sentinel skin tags, (C) draining perianal fistula.

CASE SCENARIO

15-year-old Emily was diagnosed with an eating disorder by her family doctor and pediatrician. She had presented with severe weight loss. Her appetite had decreased but she denied abdominal pain, vomiting, or diarrhea. She was markedly wasted. She was admitted to the psychiatric ward of a pediatric tertiary care hospital for further management. A referral was made to the gastroenterology service. Physical examination revealed large perianal skins tags and an underlying anal fissure. A perianal examination had not been performed previously, delaying the diagnosis of Crohn's disease by months.

➢ COMMON PRESENTATIONS OF ABDOMINAL CONDITIONS. FUNCTIONAL VS ORGANIC DISORDERS

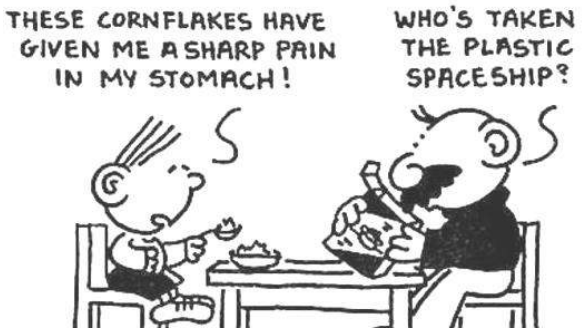
ABDOMINAL PAIN

Quick Quiz

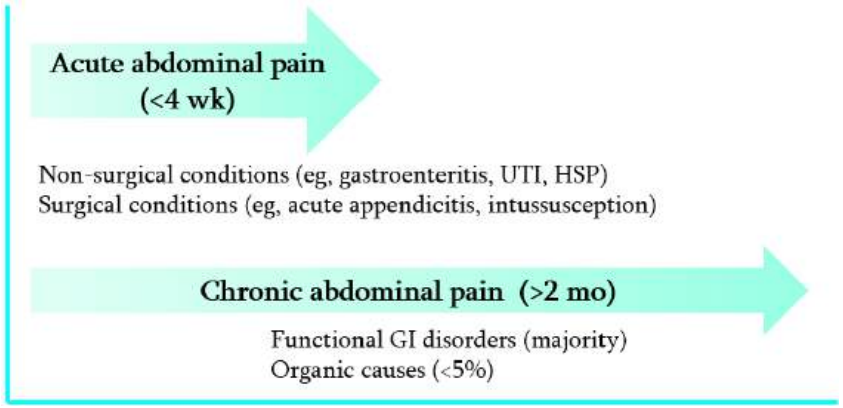
- My 3-year-old girl has fever and abdominal pain with smoky coloured urine.
- My 9-year-old daughter has been thirsty for days and passing lots of urine. Now she has tummy ache and is drowsy.
- My 13-month-old child is getting thinner, with frequent tummy aches and diarrhoea.
- My 7-year-old son keeps getting tummy ache on the way to school.
- My 10-year-old daughter is constipated, and this is very distressing. Can you give her something?

Questions

1. What types of abdominal pain occur in children?
2. What characteristics distinguish functional from organic abdominal pain?
3. What are the common organic causes of recurrent abdominal pain in children?
4. What functional gastrointestinal disorders manifest with recurrent abdominal pain in children?



1. What types of abdominal pain occur in children?



- **Acute abdominal pain** resolves within 4 weeks since onset of symptoms. Common causes of acute abdominal pain include:
  - *non-surgical conditions, e.g. gastroenteritis, urinary tract infection (UTI), Henoch–Schönlein purpura (HSP)*
  - *surgical pathology, e.g. appendicitis, intussusception*
- **Chronic abdominal pain** is characterized by intermittent or persistent pain that occurs over a period greater than 2 months. The majority of children with chronic abdominal pain have so-called functional abdominal pain (FAP).

Table. Common causes of abdominal pain in accordance with the patient's age

Approximate age	Pathology
0–2 years	Gastroenteritis UTI Intussusception Hernia
3–12 years	Gastroenteritis Constipation UTI Pneumonia Diabetic ketoacidosis Mesenteric adenitis Testicular torsion
Adolescence	Testicular pathology Acute appendicitis Ovarian disorders Trauma Pregnancy Inflammatory bowel disease

The sensation of abdominal pain is transmitted to the central nervous system via somatic and visceral afferent fibers.

- *The visceral afferent system innervates the visceral peritoneum and its structures. Visceral pain localizes poorly.*
- *Pain originating from the parietal peritoneum from inflammation or abdominal wall pain is well localized (parietal or somatic pain).*
- ***Referred pain** results from the **convergence of visceral and somatic pain pathways in the spinal cord**, so pain originating in abdominal viscera may be perceived as originating at a distant, well-isolated somatic location. For example:*
  - *Diaphragmatic irritation secondary to pancreatitis, a bleeding spleen, cholecystitis, or liver abscess may be interpreted as pain arising in the vicinity of the lower neck and shoulders because the diaphragm and shoulder pain pathways converge in the spinothalamic tracts at C4. Similarly, gallbladder inflammation may be sensed in the right infrascapular region, a migrating ureteral stone may be felt progressing toward the ipsilateral groin, and rectal and gynecologic discomfort may be sensed in the vicinity of the sacrum.*
  - *Conversely, pain originating in somatic locations, such as the right pleural surface with pneumonia, may be perceived as originating in the lower abdomen because pain afferents from both regions converge at T10-11.*

2. What characteristics distinguish functional from organic abdominal pain?

Chronic or recurrent abdominal pain (RAP) is reported to occur in 10% to 15% of children between the ages of 4 and 16 years. RAP is not a diagnosis but is a descriptive term that applies to intermittent, severe, episodic pain.

- In most cases, the pain is functional, without demonstrable evidence of a pathological condition.
- Multiple studies have demonstrated that less than 5% of these children have an organic disorder.

Clues to ORGANIC disease	Clues to FUNCTIONAL disease
▪ Age younger than 4 years ▪ Localized abdominal pain ▪ Nocturnal pain, eg, awakening from sleep to pass loose stool at night ▪ Recurrent emesis ▪ Chronic diarrhea ▪ Heme-positive stools ▪ Weight loss ▪ Abnormal physical examination findings — clubbing, perianal skin tags, abdominal mass ▪ Abnormal screening laboratory test results — decreased albumin, increased ESR/CRP, anemia, abnormal liver or kidney function tests, elevated amylase or lipase	▪ Typically the pain is episodic, unrelated to meals, and periumbilical in location lasting a few hours to several days with intervening symptom-free intervals lasting days to months. Pain may be severe enough to cause significant school absenteeism ▪ History of irritable bowel syndrome (IBS) in first-degree relative. IBS is characterized by an abnormal frequency and/or consistency of stools (diarrhea or constipation), straining, urgency, relief of pain with defecation, a feeling of incomplete evacuation, passage of mucus, or a feeling of bloating or abdominal distention. Commonly associated symptoms include headache, pallor, dizziness, and fatigue. ▪ Although many children complain of pain at the time of office visits, their behavior, affect, and activity are seldom consistent with the degree of expressed discomfort. Poorly localized pressure tenderness is frequently elicited during abdominal palpation. Between episodes, the abdominal examination is normal

3. What are the common organic causes of recurrent abdominal pain in children?

Cause	*Clinical clues*
Food allergy (eg, cow's milk protein allergy)	*Vomiting, diarrhea, Hemoccult-positive stools, failure to thrive, rhinitis, eczema, pallor, irritability, and a positive family history of allergies*
Lactose intolerance	*Crampy pain and/or bloating and/or intestinal gas related to meals, dairy products and foods containing dairy products*
Giardiasis	
Peptic origin	*Early morning pain, pain awakens at night. Early satiety, nausea, sour breath, belching*
Genitourinary problems	*Back pain, dysuria, cervical motion tenderness, adnexal tenderness, or adnexal mass on pelvic examination*
Familial Mediterranean fever (FMF)	*Recurrent episodes of fever and serositis, resulting in pain in the abdomen, chest, joints and muscles*
Inflammatory bowel disease (IBD)	*Fever, weight loss, no increase in height, joint complaints and rash, blood in stool*

4. What functional gastrointestinal disorders manifest with recurrent abdominal pain in children?

The Rome III diagnostic criteria for abdominal pain-related functional gastrointestinal disorders

Characteristics of pain	Other diagnostic criteria
Functional dyspepsia	
Persistent or recurrent pain or discomfort centred in the upper abdomen	Not relieved by defecation or associated with the onset of a change in stool frequency or stool form (ie, not irritable bowel syndrome) No evidence of an inflammatory, anatomic, metabolic or neoplastic process that explains the child's symptoms
Irritable bowel syndrome	
Abdominal discomfort* or pain associated with two or more of the following at least 25% of the time	A. Improvement with defecation B. Onset associated with a change in frequency of stool C. Onset associated with a change in form (appearance) of stool
Abdominal migraine	
1. Paroxysmal episodes of intense, acute periumbilical pain that lasts for 1 h or more 2. Intervening periods of usual health lasting weeks to months 3. The pain interferes with normal activities	Pain associated with two of the following: A. Anorexia B. Nausea C. Vomiting D. Headache E. Photophobia F. Pallor
Functional abdominal pain	
Episodic/continuous abdominal pain	Insufficient criteria for other functional gastrointestinal disorders
Functional abdominal pain syndrome	
Must satisfy criteria for childhood FAP and be present for at least 25% of the time	1. Some loss of daily functioning 2. Additional somatic symptoms such as headache, limb pain or difficulty sleeping

*For all syndromes, the following criteria apply: no evidence of an inflammatory, anatomic, metabolic or neoplastic process considered that explains the subject's symptoms. The most recent iteration of the Rome criteria reduced the duration of pain required for diagnosis from 3 to 2 months, except abdominal migraine: described as acute episodic pain occurring over 1 year.

CONSTIPATION AND FECAL INCONTINENCE (ENCOPRESIS)

Average stooling frequency is 3 to 4 per day during the first weeks of life and decreases to 1 to 2 per day with introduction of table foods by 1 year of age. After age 4 and into adulthood, normal stool frequency can range from 3 per day to 3 per week.

Constipation is defined as infrequent passage of stool associated with pain and difficulty, or delay in defaecation. The majority of children with chronic constipation have no clearly identifiable disorder, and their condition is therefore labeled **functional or idiopathic constipation**.

Table. Causes of constipation

Idiopathic	*Gastrointestinal*	*Non-gastrointestinal*
Commonest due to a combination of: • Low fibre diet • Lack of mobility and exercise • Poor colonic motility (55% have a positive family history)	• Meconium plug syndrome (often in preterm babies) • Hirschsprung's disease • Anal disease (infection, stenosis, ectopic, fissure, hypertonic sphincter) • Partial intestinal obstruction • Coeliac disease	• Hypothyroidism • Hypercalcaemia • Neurological disease, e.g. spinal disease • Chronic dehydration, e.g. diabetes insipidus • Drugs, e.g. opiates and anticholinergics • Sexual abuse

Children with constipation may present with decreased frequency of defecation and hard pellet-like or large torpedo-like stools that are difficult to pass, often causing pain and fresh blood per rectum. Repeated painful experiences can scare the child and prompt **stool-avoidance behavior**.

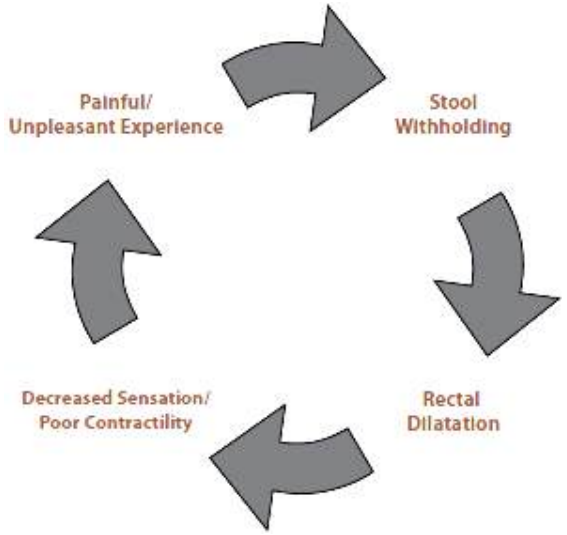


Fig. The vicious cycle of constipation

Rome III criteria for functional constipation*

1) Defecation frequency 2 times or fewer per week
2) Fecal incontinence (fecal soiling in undergarments)
3) Episodes of retentive posturing during which the child crosses legs and screams
4) Pain during defecation
5) Large-diameter stools that sometimes clog the toilet
6) Palpable rectal fecal mass

* ***Children younger than 4 years*** *need to meet 2 criteria for at least 1 month*
Children older than 4 years *need to meet 2 criteria for at least 2 months*

Fig. Child exhibiting retentive posture

Younger children often develop a **stool-withholding behavior** without pre-existing constipation (some children can withhold stool for up to 2 to 3 weeks), crouching down to prevent their bowels opening.

Stool-withholding behavior can lead to a very impacted rectum. Liquid stool from above can leak out into their underwear (**overflow incontinence**), often causing diagnostic confusion.

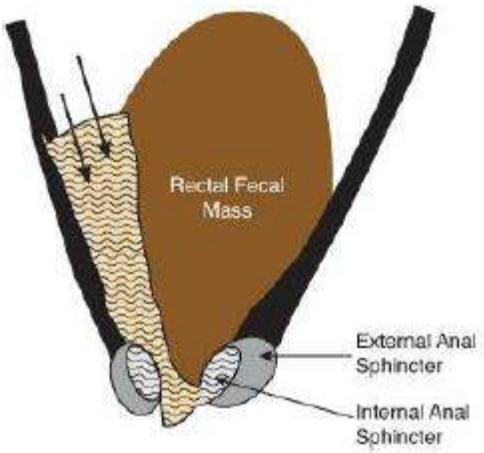


Fig. Fecal incontinence results from the rectal fecal mass stretching open the anal sphincter; the liquid stool seeps around it and leaks out of the anal canal

It is important to distinguish between the common problem of functional constipation and less common organic causes of constipation, including Hirschsprung disease. **Organic cause of constipation** is more likely if: delayed passage of meconium beyond 24hr of age; onset in infancy; severe; associated with faltering growth or abnormal physical signs (include per anal examination).

A diagnosis of Hirschsprung disease is suggested by small-caliber soft stool, episodes of explosive soft stool preceded by a lack of stool passage and abdominal distension, and history of delayed meconium passage in the first few days of life. If Hirschsprung disease is suspected, suction rectal biopsy should be considered as the next step in evaluation.

A newborn without a bowel movement? It could be Hirschsprung's Disease

Constipation complications

- **Overflow incontinence** - this should be distinguished from fecal incontinence secondary to fecal urgency seen in patients with irritable bowel syndrome, neurologic disorders, and spinal disorders. Children with behavioral disorders and sexual abuse can also present with fecal incontinence.
- **Anal fissures**.
- **Urinary tract infection** occurs in 5% to 10% of chronically constipated children, probably secondary to partial urethral obstruction or ascending infection from chronically soiled underwear.
- **Chronic anorexia and failure to thrive.**
- **Affected psychosocial functioning** (poor self-esteem, poor school performance, and family stress and conflict).

VOMITING

Definitions

- **Vomiting**: forceful expulsion of gastric contents from the mouth
- **Regurgitation**: effortless flow of gastric contents from the mouth (also referred to as infant gastroesophageal reflux [GER], spitting, posseting)

Although the end result of vomiting and regurgitation is similar, they have completely different characteristics. Vomiting is usually preceded by nausea and is accompanied by forceful gagging and retching. Regurgitation, on the other hand, is effortless and not preceded by nausea.

Physiologic GER is common in normal infants. It presents between 1 and 2 months of age, increases over the next few months, and resolves spontaneously. The emesis is gastric contents without blood or bile. GER does not cause excessive crying, poor eating, slow weight gain, or apnea. If such symptoms or signs are being evaluated, alternative explanations should be sought. Physiologic GER requires no intervention (i.e., no dietary change in infant or mother, no suppression of gastric acid, etc.). Multiple studies document the absence of esophagitis or other complications in such infants. Acid suppression may result in increased risk of pneumonia or gastroenteritis [Smith et al. 2013].

The most common causes of vomiting:	Less common and serious diseases that present with vomiting:
• *Gastrointestinal infections (eg, viral, bacterial, and parasitic gastroenteritis)* • *Non-gastrointestinal infections* (eg, pyelonephritis, sepsis, streptococcal pharyngitis, otitis media)* • *Acid-peptic disorders (eg, GERD, Helicobacter pylori gastritis)* • *Allergic disorders (eg, formula protein sensitivity, eosinophilic esophagitis)* • *Cyclic vomiting syndrome: severe, discrete episodes associated with pallor, lethargy +/– abdominal pain. The child is well in between episodes. Often there is a family history of migraine or vomiting* * In young children a simple fever can cause vomiting, as can almost any infection of any system.	○ **Small bowel obstruction** due to anatomic abnormality or prior intestinal surgery with adhesions presents with repeated bilious emesis, abdominal pain, and, often, distension with tympany. Urgent evaluation should proceed. Intussusception produces reflex vomiting prior to evolution to obstruction. ○ **Posterior fossa tumor:** In all children and adolescents, acute onset of daily vomiting with any associated neurologic symptom (headache, irritability, lethargy, ataxia, decreased activity, diplopia) should prompt careful neurologic exam for cerebellar signs of nystagmus, dysmetria, and ataxia. Fundoscopic exam should be attempted and imaging considered. Posterior fossa brain tumors produce vomiting with or without increased intracranial pressure. ○ **Caustic ingestion:** Acute vomiting, dysphagia, refusal to swallow, and drooling characterize esophageal injury due to caustic ingestion. Oral burns or erosions are often but not always present. Usually, caregivers recognize or witness the event. ○ **Esophageal foreign body** can present similarly to caustic ingestion, but without evident burns or erosions. A disk battery retained in the esophagus is a medical emergency

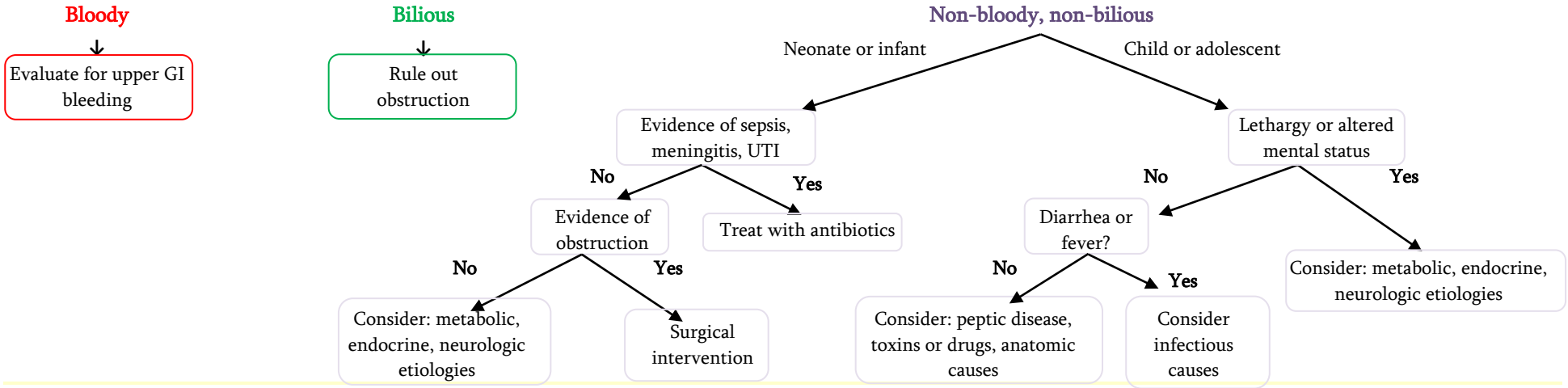
There are some key **red flags** to watch for:

- **persisting vomiting and fever** (of more than 24 hours' duration) but without diarrhoea – this can suggest bacterial meningitis
- **bile-stained vomitus** – in such cases, bowel obstruction (e.g. from a volvulus) must be excluded
- **blood-stained vomit** (see "Gastrointestinal bleeding")

- **Important Disorders Presenting with Vomiting by Age**

Infant Vomiting	Childhood Vomiting
▪ Bilious emesis: intestinal malrotation with or without volvulus ▪ Meconium ileus (nearly always indicates underlying cystic fibrosis) ▪ Hirschsprung disease ▪ Pyloric stenosis	▪ Bilious emesis ▪ Prior abdominal surgery (intraabdominal adhesions and associated obstruction) ▪ Other acquired small bowel obstructions (e.g., intussusception, HSP) ▪ Nonbilious emesis *Gastroenteritis is the most common cause of acute nonbilious emesis. Many other GI illnesses (e.g., pancreatitis, chole(docho)lithiasis, peptic ulcer disease, and others) have vomiting as a component.*

AN APPROACH TO EVALUATION OF THE PATIENT WITH VOMITING



DIARRHEA

Normally, a young infant has approximately 5 mL/kg/day of stool output; the volume increases to 200 g/24 hr in an adult.

Diarrhea is best defined as excessive loss of fluid and electrolyte in the stool. **Acute diarrhea** is defined as sudden onset of excessively loose stools of >10 mL/kg/day in infants and >200 g/24 hr in older children, which lasts <14 days (*see* "Acute diarrheal diseases in children"). When the episode lasts longer than 14 days, it is called **chronic diarrhea**.

In general, the approach to the child with chronic diarrhea involves first trying to determine the primary underlying mechanism (malabsorptive, secretory, osmotic, inflammatory, dysmotility) and then the specific cause.

- **Important Disorders Presenting with Chronic Diarhea by Age**

Infant	Child	Adolescent
• Postinfectious lactase deficiency • Milk/soy intolerance • Chronic diarrhea of infancy (Toddler diarrhea)* • Cystic fibrosis • Celiac disease (after the introduction of foods that contain gluten)	• Postinfectious lactase deficiency • Irritable bowel syndrome • Celiac disease • Lactose intolerance • *Giardiasis* • Inflammatory bowel disease	• Irritable bowel syndrome • Inflammatory bowel disease • Lactose intolerance • *Giardiasis* • Laxative abuse

* Toddler diarrhea

Toddlers often experience non-specific diarrhoea, probably due to a rapid gastrocolic reflex. Features are drinking excessive fluids, particularly fruit juices, and food particles in the stool. The diagnosis should only be made if the child is thriving. This syndrome generally has its onset between ages 6 and 24 months. It is a self-limiting disorder, usually ceasing spontaneously between ages 2 and 4 years, but occasionally it may persist beyond age 4. Reassurance is all that is required.

UPPER AND LOWER GASTROINTESTINAL BLEEDING

A 2-year-old boy presents with a 1-week history of painless rectal bleeding. Physical examination is unremarkable. The abdomen is soft and nontender. Rectal examination is unremarkable.

- **Upper gastroiuntestinal (UGI) bleeding** refers to a source proximal to the ligament of Treitz (duodenojejunal junction) and may present as:
  - *hematemesis (vomiting of frank blood and suggests a rapidly bleeding lesion)*
  - *coffee-ground vomiting (vomited blood that has been coagulated by gastric acid)*
  - *melena (black, tarry stool produced by the oxidation of heme by intestinal flora)*
  - *hematochezia (from rapid transit of blood through the GI tract)*
- **Lower gastrointestinal (LGI) bleeding**, that is, bleeding distal to the ligament of Treitz, presents with hematochezia or melena. Blood limited to the outside of otherwise unremarkable stool suggests a rectal origin; blood mixed throughout the stool suggests a colonic source.
- **Occult GI bleeding** can present with pallor, fatigue, or microcytic (iron deficiency) anemia.
- Bleeding that is apparently **painful** may be associated with infectious colitis, malrotation with volvulus, anal fissure, and intussusception.
- **Painless bleeding** may be seen with a Meckel diverticulum, intestinal duplication, or lymphonodular hyperplasia.

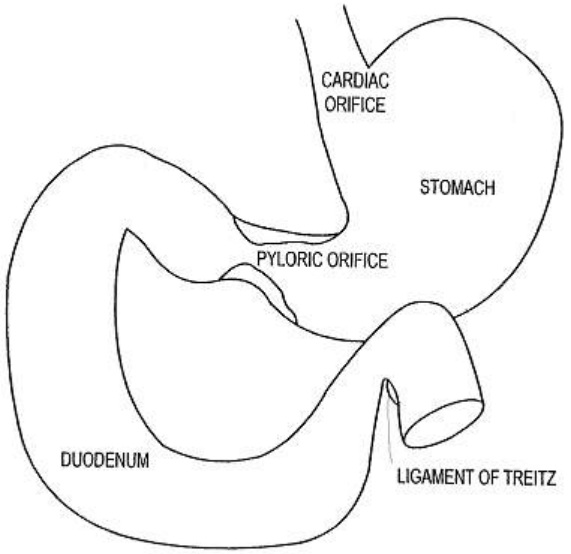


Table. Probable source of GI bleeding within the gut

Clinical Indicator	Probability of Upper GI Source	Probability of Lower GI Source
Hematemesis	Almost certain	Rare
Melena	Probable	Possible
Hematochezia	Possible	Probable
Blood-streaked stool	Rare	Almost certain
Occult blood in stool	Possible	Possible

➢ Common Laboratory and Instrumental Studies Used to Evaluate Digestive Conditions

Laboratory and instrumental investigations are done in a volume of diagnoses supposed.

SCREENING TESTS

A **complete blood count** may provide evidence for inflammation (white blood cell [WBC] and platelet count), poor nutrition or bleeding (hemoglobin, red blood cell volume, reticulocyte count), and infection (WBC number and differential, presence of toxic granulation).
Serum electrolytes, blood urea nitrogen (BUN), and creatinine help define hydration status.
Tests of liver dysfunction include total and direct bilirubin, alanine aminotransferase, aspartate aminotransferase for evidence of hepatocellular injury, and γ-glutamyltransferase or alkaline phosphatase for evidence of bile duct injury. **Hepatic synthetic function** can be assessed by coagulation factor levels, prothrombin time, and albumin level.
Pancreatic enzyme tests (amylase, lipase) provide evidence of pancreatic injury or inflammation.

DIAGNOSTIC IMAGING

Radiology	Consultation with a radiologist is often advisable to discuss appropriate imaging, decide what variants of the technique to use, and learn how to prepare the patient for the study. A plain abdominal x-ray to document excessive retained stool when history is consistent with constipation and encopresis is not necessary, as examination alone can confirm the diagnosis.
Endoscopy	Endoscopy permits the direct visualization of the interior of the gut. Video endoscopes may be used even in very small infants by pediatric gastroenterologists. Wireless capsule endoscopy enables visualization of lesions beyond the reach of conventional endoscopes. Consultation with a pediatric gastroenterologist for endoscopy is recommended for further evaluation of suspected esophageal or gastric inflammation unresponsive to medications and to confirm the diagnosis of eosinophilic esophagitis or celiac disease, evaluate gastrointestinal bleeding, evaluate suspected inflammatory bowel disease, and screen for polyp disorders. In addition, a trained endoscopist can remove esophageal and gastric foreign bodies and place feeding tubes.

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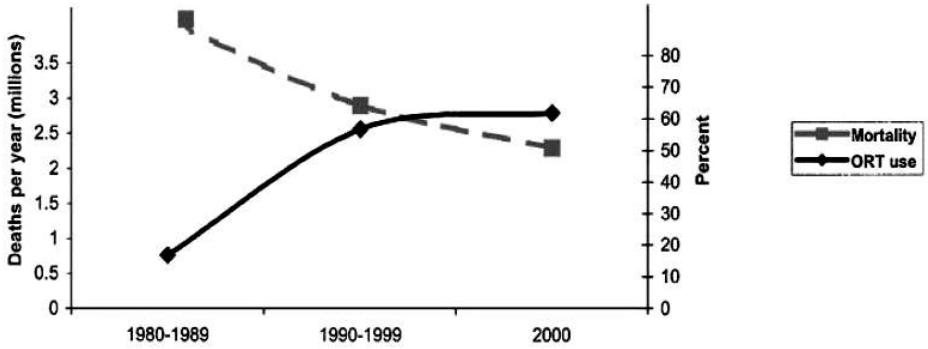
Acute diarrheal diseases in children

Diarrhoeal diseases are a leading cause of sickness and death among children in developing countries. During the past three decades, factors such as the widespread distribution and use of oral rehydration solutions (ORS) combined with zinc supplements, improved rates of breastfeeding, improved nutrition, better sanitation and hygiene, have contributed to a consistent decline in the mortality rate in developing countries.



From 2000 to 2015, the total annual number of deaths from diarrhoea among children under 5 decreased by more than 50 per cent – from over 1.2 million to half a million. Many more children could be saved through basic interventions to improve drinking water, sanitation and hygiene (WASH) for diarrhoea prevention, and the widespread use of a simple solution of oral rehydration salts (ORS) and zinc supplementation during episodes of diarrhoea.

Diarrhoea is usually defined in epidemiological studies as the passage of three or more loose or watery stools in a 24-hour period, a loose stool being one that would take the shape of a container. However, mothers may use a variety of terms to describe diarrhoea, depending, for example, upon whether the stool is loose, watery, bloody or mucoid, or there is vomiting. It is important to be familiar with these terms when asking whether a child has diarrhoea. Exclusively breast-fed infants normally pass several soft, semi-liquid stools each day; for them, it is practical to define diarrhoea as an increase in stool frequency or liquidity that is considered abnormal by the mother.

Three clinical syndromes of diarrhoea have been defined, each reflecting a different pathogenesis and requiring different approaches to treatment.

1. Acute watery diarrhoea

This term refers to diarrhoea that begins acutely, lasts less than 14 days (most episodes last less than seven days), and involves the passage of frequent loose or watery stools without visible blood. Vomiting may occur and fever may be present. Acute watery diarrhoea causes dehydration; when food intake is reduced, it also contributes to undernutrition. When death occurs, it is usually by acute dehydration. The most important causes of acute watery diarrhoea in young children in developing countries are rotavirus, enterotoxigenic Escherichia coli, Shigella, C ampylobacter jejuni, and cryptosporidia. In some areas, Vibrio cholerae 01, Salmonella and enteropathogenic E. coli are also important causes.

2. Dysentery

The term dysentery refers to diarrhoea with visible blood in the faeces. Important effects of dysentery include anorexia, rapid weight loss, and damage to the intestinal mucosa by the invasive bacteria. A number of other complications may also occur. The most important cause of acute dysentery is Shigella; other causes are Campylobacter jejuni and, infrequently, enteroinvasive E. coli or Salmonella. Entamoeba histolytica can cause serious dysentery in young adults but is rarely a cause of dysentery in young children.

3. Persistent diarrhoea

This term refers to diarrhoea that begins acutely but is of unusually long duration (at least 14 days). The episode may begin either as watery diarrhoea or as dysentery. Marked weight loss is frequent. Diarrhoeal stool volume may also be great, with a risk of dehydration. There is no single microbial cause for persistent diarrhoea; enteroadherent E. coli and cryptosporadia may play a greater role than other agents. Persistent diarrhoea should not be confused with **chronic diarrhoea**, which refers to recurrent or long-lasting diarrhoea due to non-infectious causes, such as sensitivity to gluten or inherited metabolic disorders.

CONSEQUENCES OF WATERY DIARRHOEA

Isotonic dehydration	• there is a balanced deficit of water and sodium; • serum sodium concentration is normal (130-150 mmol/l); • serum osmolality is normal (275-295 mOsmol/l); • hypovolaemia occurs as a result of a substantial loss of extracellular fluid.
Hypertonic (hypernatraemic) dehydration	• there is a deficit of water and sodium, but the deficit of water is greater; • serum sodium concentration is elevated (>150 mmol/l); • serum osmolality is elevated (>295 mOsmol/l); • thirst is severe and out of proportion to the apparent degree of dehydration; the child is very irritable; • seizures may occur, especially when the serum sodium concentration exceeds 165 mmol/l.
Hypotonic (hyponatraemic) dehydration	• there is a deficit of water and sodium, but the deficit of sodium is greater; • serum sodium concentration is low (<130 mmol/l); • serum osmolality is low (<275 mOsmol/l); • may lead to cerebral edema.
Base-deficit acidosis (metabolic acidosis)	• the serum bicarbonate concentration is reduced - it may be less than 10 mmol/l; • arterial pH is reduced - it may be less than 7.10; • breathing becomes deep and rapid, which helps to raise arterial pH by causing a compensating respiratory alkalosis; • there is increased vomiting.
Potassium depletion	Patients with diarrhoea often develop potassium depletion owing to large faecal and renal losses of this ion. The signs of hypokalaemia may include: • general muscular weakness; • cardiac arrhythmias; • paralytic ileus.

ASSESSMENT OF DEHYDRATION

Gold standard is measurement of acute weight loss!

- Patients with dehydration are divided into subgroups:
  - mild (3%-5% fluid deficit)
  - moderate (6%-9% fluid deficit)
  - severe (>10% fluid deficit, shock, or near shock)

Studies that have evaluated the correlation of clinical signs of dehydration with post-treatment weight gain indicate that the first signs of dehydration might not be evident until 3%-4%, with more numerous clinical signs evident at 5% and signs indicating severe dehydration not evident until fluid loss reaches 9%-10% (Duggan C et al, 1996). Because of this threshold effect, it is recommended to group together patients with mild to moderate dehydration (or some dehydration) over a relatively wide range of fluid loss (i.e., from 3%-9%).

Practically we rely on clinical assessment. The main signs to be evaluated are as follows:

- ***Condition and behaviour***
- ***Eyes***
- ***Thirst***
- ***Skin pinch (skin turgor)***

*Table 1: Assessment of diarrhoea patients for dehydration**

	A	B	C
LOOK AT:			
CONDITION	Well, alert	Restless, irritable	Lethargic or unconscious
EYES	Normal	Sunken	Sunken
THIRST	Drinks normally, not thirsty	Thirsty, drinks eagerly	Drinks poorly, or not able to drink
FEEL: SKIN PINCH	Goes back quickly	Goes back slowly	Goes back very slowly (≥ 2 s)
DECIDE	Fluid deficit <3% or <30 ml/kg **(MINIMAL OR NO DEHYDRATION)**	Fluid deficit 3-9% or 30-90 ml/kg **(MILD TO MODERATE OR SOME DEHYDRATION)**	Fluid deficit >9% or >90 ml/kg **(SEVERE DEHYDRATION)**
TREAT	**Plan A**	**Plan B**	**Plan C**

* *Adapted from Caleb et al. Managing acute gastroenteritis among children. MMWR 2003; 52: 1–16; and World Health Organization. The treatment of diarrhea: a manual for physicians and other senior health workers. Geneva, Switzerland: World Health Organization, 2005.*

This clinical approach to the diagnosis and management of diarrhea in young children is a critical component of the **Integrated Management of Childhood Illnesses (IMCI)** package that is being implemented in developing countries that have a high burden of diarrhea mortality.

MANAGEMENT OF ACUTE DIARRHOEA AND DEHYDRATION IN CHILDREN (WHO/IMCI RECOMMENDATIONS)

Plan A

Counsel the mother 4 rules of HOME TREATMENT

1. Give Extra fluid (as much as the child takes)
2. Give Zinc supplements
3. Continue Feeding
4. Advise mother when to return immediately (*see* page 8)

Plan B

Treat Some Dehydration with ORS

1. Calculate the amount of ORS required in some dehydration: 30-90 ml/kg (average 75 ml/kg).
2. Advise the mother to give calculated amount in 4 hrs in small quantities at a time either with a spoon or in small sips. *Never give large amounts with a bottle or cup. This may be vomited out or may stimulate gastro-colic reflex and result in a large watery stool.*

– If the child vomits, wait 10 min, then continue, but more slowly.
– Continue breastfeeding whenever the child wants.

When you do not know the weight, use the child's age.

Age[a]	≤ 4 months	4 to ≤ 12 months	12 months to ≤ 2 years	2 years to ≤ 5 years
Weight	< 6 kg	6–< 10 kg	10–< 12 kg	12–19 kg
	200–400 ml	400–700 ml	700–900 ml	900–1400 ml

3. Replenish ongoing losses by advising the mother to give 50-100 ml of ORS to a child < 2 yrs and 100-200 ml in children between 2-10 yrs. after passage of each diarrhoea stool.

- **After 4 h:**

– Reassess the child and classify him or her for dehydration.
– Select the appropriate plan to continue treatment.
– Begin feeding the child in the clinic.

5. Give Zinc supplements

When is oral rehydratin therapy (ORT) ineffective ?

- High stool purge rate
- Persistent vomitings
- Incorrect preparation of ORS
- Abdominal distension
- Glucose malabsorption

Plan C

Start IV fluids immediately

The best IV fluid solutions for rehydration are isotonic solutions: Ringer's lactate solution (called Hartmann's solution for Injection) and normal saline solution (0.9% NaCl). Do not use 5% glucose (dextrose) solution or 0.18% saline with 5% dextrose solution, as they increase the risk for hyponatraemia, which can cause cerebral oedema.

- Give 100 ml/kg of the chosen solution, divided as shown in Table:

Age (months)	*First, give 30 ml/kg in:*	*Then, give 70 ml/kg in:*
< 12	**1 h**	**5 h**
≥ 12	**30 min**	**2.5 h**

- Reassess the child every 15–30 min. If hydration status is not improving, give the IV drip more rapidly. Also watch for over-hydration.
- Also give ORS (about 5 ml/kg per h) as soon as the child can drink: usually after 3–4 h (infants) and 1–2 h (children).
- Reassess an infant after 6 h and a child after 3 h. Classify dehydration. Then choose the appropriate plan (A, B or C) to continue treatment.

WHEN IS TESTING INDICATED IN CHILDREN WITH DIARRHEA?

Most children with acute diarrhea have viral gastroenteritis. Microbiological examination is not helpful in the majority of cases and should be reserved for special circumstances. In fact, regardless of etiology, most children do not require any etiology-based treatment and therefore identification of a specific pathogen is not generally needed. Microbiological investigation should however be performed during outbreaks, especially in childcare settings, schools, hospitals, or residential settings to identify the pathogen and establish its source in the attempt to reduce transmission. Stool samples should also be taken from children with **bloody diarrhea**, a history of recent foreign travel, and from young or immunocompromised children with high fever for whom antibiotic treatment is considered. Finally, it is also recommended to investigate children in whom diarrhea persists for more than 10–14 days, or when a noninfectious etiology for diarrhea is suspected, such as inflammatory bowel disease (IBD).

Several techniques are available to identify the specific etiology of viral diarrhea. The gold standard is viral culture but its clinical application is limited, due to the costs, the delay in the results and the complexity of the procedures. Immunofluorescence or latex agglutination is widely used to identify fecal viruses. Polymerase chain reaction (PCR) is becoming a common diagnostic tool for virus identification. Specific PCR are currently available for norovirus, rotavirus, adenovirus, cytomegalovirus, and other less common viruses.

ANTIBIOTIC THERAPY OF BACTERIAL GASTROENTERITIS

Pathogen	Indication for antibiotic therapy	Drug of choice*	Alternative agents
Shigella spp	Proven or suspected shigellosis	Oral: azithromycin (12 mg/kg on day 1, followed by 6 mg/kg for 4 days); parenteral, IV, IM: ceftriaxone (50 mg/kg for 2–5 days)†	Cefixime (8 mg · kg^{-1} · day^{-1}); ciprofloxacin‡ PO (20–30 mg · kg^{-1} · day^{-1}). For a known susceptible strain: TMP/SMX† (8 mg · kg^{-1} · day^{-1} of TMP) or ampicillin (100 mg · kg^{-1} · day^{-1}) or nalidixic acid (55 mg · kg^{-1} · day^{-1})
Salmonella spp (nontyphoidal)	Antibiotic therapy is indicated only in high-risk children§ to reduce the risk of bacteremia and extraintestinal focal infections	Ceftriaxone (50–100 mg · kg^{-1} · day^{-1})	Azithromycin (10 mg · kg^{-1} · day^{-1}); ciprofloxacin‡ PO (20–30 mg · kg^{-1} · day^{-1}); for a known susceptible strain, TMP/SMX§ (8 mg · kg^{-1} · day^{-1} of TMP).
Campylobacter spp	Antibiotic therapy is recommended mainly for the dysenteric *Campylobacter* gastroenteritis and most efficacious when started within 3 days after onset of the disease	Azithromycin (10 mg · kg^{-1} · day^{-1} for 3 days, or a single dose of 30 mg/kg)	Doxycycline (>8 years) or ciprofloxacin (>17 years), when susceptible)
Shiga toxin-producing *Escherichia coli*	Antibiotic therapy is not recommended	—	—
Enterotoxigenic; *Escherichia coli*	Antibiotic therapy is recommended, mainly for traveler's diarrhea	Azithromycin (10 mg · kg^{-1} · day^{-1} for 3 days)	Cefixime (8 mg · kg^{-1} · day^{-1} for 5 days); TMP/SMX§ (8 mg · kg^{-1} · day^{-1} of TMP); ciprofloxacin§ PO (20–30 mg · kg^{-1} · day^{-1}); rifaximin (>12 years, 600 mg/day, for 3 days)
Vibrio cholerae	Antibiotic therapy is recommended for confirmed or suspected case by travel history	Azithromycin (10 mg · kg^{-1} · day^{-1} for 3 days, or a single 20 mg/kg dose)	Doxycycline (>8 years), Ciprofloxacin (>17 years), or TMP/SMX§ (when susceptible)
Clostridium difficile	Antibiotic therapy is recommended for moderate and severe cases	Metronidazole (30 mg · kg^{-1} · day^{-1} for 10 days)	Vancomycin PO (40 mg · kg^{-1} · day^{-1})

Zinc supplements

Zinc is an important micronutrient for a child's overall health and development but is lost in greater quantities during diarrhoea. Replacement helps the child's recovery, reduces the duration and severity of the episode, and lowers the incidence of diarrhoea in the following 2–3 months.

_ Give zinc and advise the mother how much to give:

≤ 6 months: half tablet (10 mg) per day for 10–14 days

≥ 6 months: one tablet (20 mg) per day for 10–14 days

Feeding

Continuation of nutritious feeding is an important element in the management of diarrhoea.

_ In the initial 4-h rehydration period, do not give any food except breast milk.

Breastfed children should continue to breastfeed frequently throughout the episode of diarrhoea. If they cannot suck from the breast, consider giving expressed breast milk either orally from a cup or by nasogastric tube.

_ After 4 h, if the child still has some dehydration and ORS continues to be given, give food every 3–4 h.

_ All children > 6 months should be given some food before being sent home.

If the child is not normally breastfed, explore the feasibility of **relactation** (i.e. restarting breastfeeding after it was stopped) or give the usual breast milk substitute. If the child is ≥ 6 months or already taking solid food, give freshly prepared foods – cooked, mashed or ground. The following are recommended:

• cereal or another starchy food mixed with pulses, vegetables and meat or fish, if possible, with 1–2 teaspoons of vegetable oil added to each serving

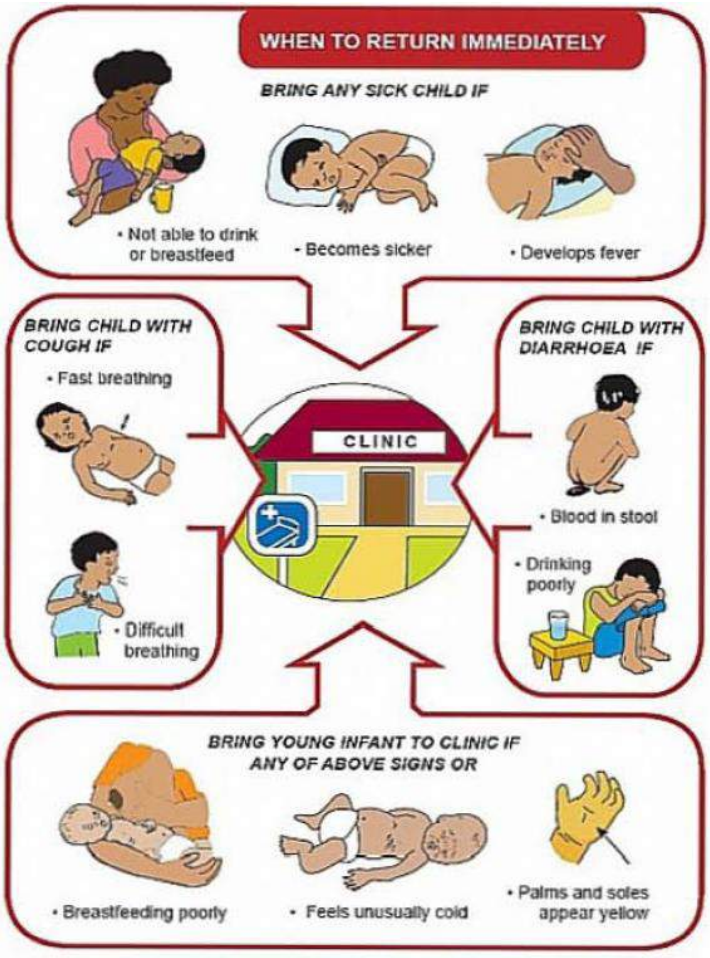
• fresh fruit juice or mashed banana to provide potassium.

_ Encourage the child to eat by offering food at least six times a day. Give the same foods after the diarrhoea stops, and give an extra meal a day for 2 weeks.

Additional therapies

The use of **probiotic nonpathogenic bacteria** for prevention and therapy of diarrhea has been successful in some settings although the evidence is inconclusive to recommend their use in all settings. In addition to restoring beneficial intestinal flora, probiotics can enhance host protective immunity such as downregulation of proinflammatory cytokines and upregulation of antiinflammatory cytokines. A variety of organisms (*Lactobacillus, Bifidobacterium*) have a good safety record; therapy has not been standardized and the most effective (and safe) organism has not been identified. *Saccharomyces boulardii* is effective in antibiotic-associated and in C. difficile diarrhea, and there is some evidence that it might prevent diarrhea in daycare centers. *Lactobacillus rhamnosus GG* is associated with reduced diarrheal duration and severity, which reduction is more evident in cases of childhood rotavirus diarrhea.

Antimotility agents (loperamide) are contraindicated in children with dysentery and probably have no role in the management of acute watery diarrhea in otherwise healthy children. Similarly, **antiemetic agents**, such as the phenothiazines, are of little value and are associated with potentially serious side effects (lethargy, dystonia, malignant hyperpyrexia). Nonetheless, **ondansetron** is an effective and less-toxic antiemetic agent and as indicated previously, is a useful adjunct to the treatment of vomiting in ambulatory settings with reduced risk of intravenous fluid requirements and hospitalization. Because persistent vomiting can limit oral rehydration therapy, a single sublingual dose of an oral dissolvable tablet of ondansetron (4 mg 4-11 yr and 8 mg for children older than 11 yr [generally 0.2 mg/kg]) may be given. However, most children do not require specific antiemetic therapy; careful oral rehydration therapy is usually sufficient.



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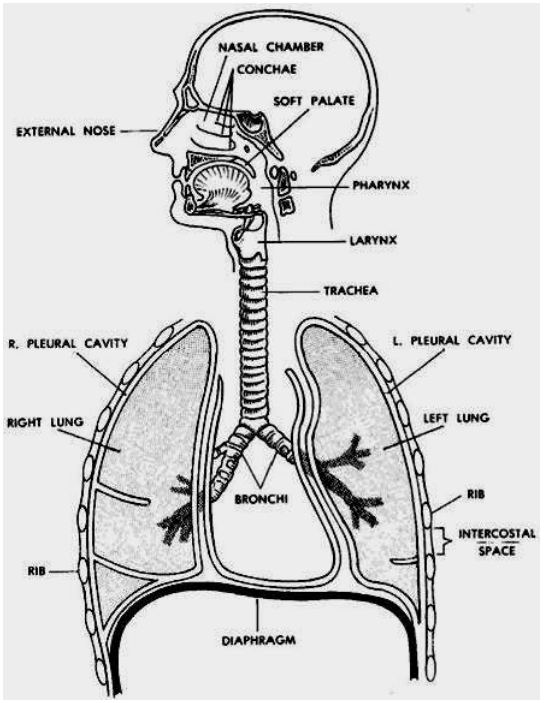
The Respiratory System

Upper Respiratory Tract

- Nose
- Paranasal Sinuses
- Pharynx
- Larynx
- Trachea



Lower Respiratory Tract

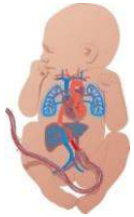
- Bronchi
- Bronchioles
- Alveoli

COMPETENCIES

You must…

Know	Be able to	Appreciate
• The normal and abnormal development of the respiratory system • How to diagnose and manage the common and serious respiratory conditions • How to read a chest X – ray	• Examine the respiratory system competently • Interpret pulmonary function tests • Recognise the signs of respiratory distress • Carry out peak flow measurements • Carry out the Heimlich procedure • Show a child how to use an inhaler	• The principles involved in managing chronic respiratory disorders

Breathing in utero

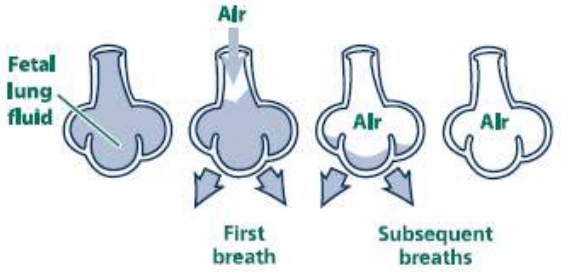


The fetus is fully immersed in amniotic fluid within the uterus. Consequently, fetal lungs do not function as blood gas exchangers. The placenta enables gas exchange to occur between maternal and fetal blood. Just before birth, approximately one-half of the cardiac output passes to the placenta for gas exchange.

Breathing at birth

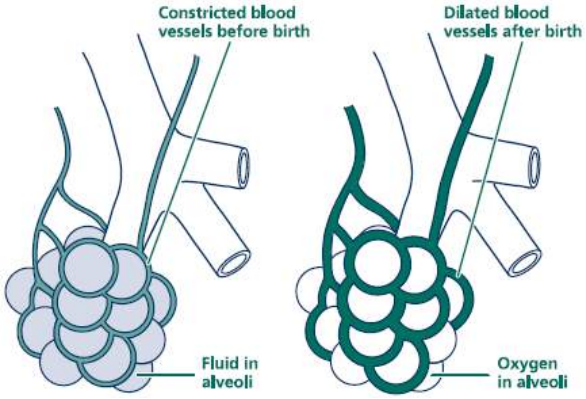
Normally, 3 major changes begin immediately after birth.

1. The fluid in the alveoli is absorbed into pulmonary lymphatics and replaced by air.
At term, the lungs contain about 50 ml of fluid, about a quarter of this fluid is thought to be expelled as the chest wall is compressed during passage through the birth canal (Bhutani, 1997, Rudolph et al., 2003). After delivery, half is absorbed by the pulmonary lymphatics and the rest by the pulmonary capillaries. The amount of remaining lung fluid helps to partially distend the alveoli so that the opening pressure of the first breath can effectively expand the lungs.



2. The umbilical arteries constrict and then the umbilical arteries and vein are closed when the umbilical cord is clamped. This removes the low resistance placental circuit and results in an increase in systemic blood pressure.

3. As a result of the distention of the alveoli with oxygen-containing gas and subsequent increased oxygen levels in the alveoli, the blood vessels in the lung tissue relax, decreasing resistance to blood flow.



A number of structural characteristics of the pulmonary system influence the way in which infants and children respond to respiratory disturbances. These include *structural characteristics of the upper and lower respiratory tracts, chest wall and lung dynamics, metabolic requirements, immunologic immaturity, and physiologic control of respiration*.

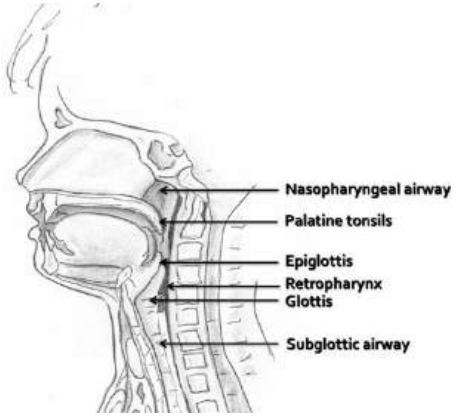
I. Upper Airway

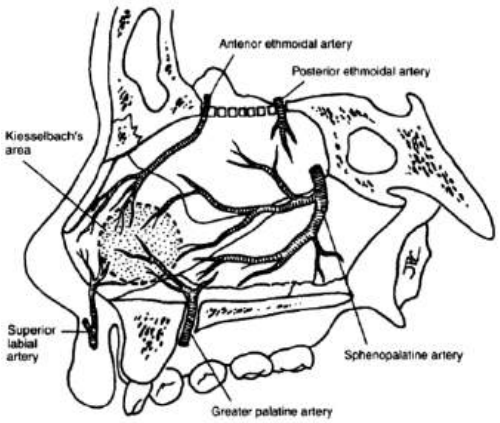
All conducting airways are present at birth and change only in size throughout childhood.
Because infants and children naturally have smaller-diameter airways than adults, they suffer more obstruction for a given degree of mucosal edema or secretion accumulation. The relative sizes of tonsils, adenoids, and epiglottis likewise are proportionately greater in the young child and with swelling can impose a significant site of obstruction.

➢ NOSE AND PHARYNX

CASE STUDY

A 2-hour-old full-term newborn infant is noted by the nursing staff to be having episodes of cyanosis and apnea. Per nursery protocol they place an oxygen saturation monitor on him. When they attempted to feed him, his oxygen levels drop into the 60s. When he is stimulated and cries, his oxygen levels increase into the 90s. What is the most important next step to quickly establish the diagnosis?





In neonates and infants even nasal blocking can cause respiratory distress!

Children and adults preferentially breathe through their nose unless nasal obstruction interferes. Most newborn infants are obligate nasal breathers and significant nasal obstruction presenting at birth, such as choanal atresia, may be a life-threatening situation for the infant unless an alternative to the nasal airway is established. Nasal congestion with obstruction is common in the 1st year of life and can affect the quality of breathing during sleep; it may be associated with a narrow nasal airway, viral or bacterial infection, enlarged adenoids, or maternal estrogenic stimuli similar to rhinitis of pregnancy. The internal nasal airway doubles in size in the 1st 6 mo of life, leading to resolution of symptoms in many infants. Supportive care with a bulb syringe and saline nose drops, topical nasal decongestants, and antibiotics, when indicated, improve symptoms in affected infants.

Epistaxis

Nosebleeds are rare in infancy and common in childhood. Their incidence decreases after puberty and rises again after age 50 yr. Diagnosis and treatment depend on the location and cause of the bleeding.

The most common site of bleeding is the **Kiesselbach plexus**, an area in the anterior septum where vessels from both the internal carotid (anterior and posterior ethmoid arteries) and external carotid (sphenopalatine and terminal branches of the internal maxillary arteries) converge. The thin mucosa in this area, as well as the anterior location, makes it prone to exposure to dry air and trauma. In children under 6 the Kiesselbach plexus is underdeveloped.

The nose, mouth, and pharynx are exposed to circulating viruses and are normally colonized by large numbers of bacteria including potential pathogens such as S. aureus, S. pneumoniae, H. influenzae, and group A streptococci (Fig). Mucosal damage caused by viral infection, allergy, or other factors compromises the mucociliary barriers designed to maintain sterility of the middle ears, paranasal sinuses, and lungs. Most URIs are self-limited but progression to life-threatening acute illness occurs and progression to chronic disease is common.

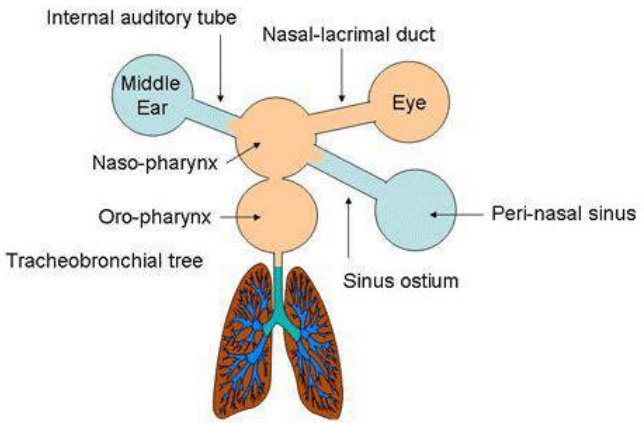


Fig. Anatomic predispositions to upper respiratory tract infections (orange = normal colonizing flora)

➢ PARANASAL SINUSES

Both the **ethmoidal** and **maxillary** sinuses are present at birth, but only the ethmoidal sinuses are pneumatized. The maxillary sinuses are not pneumatized until 4 yr of age (Fig). The **sphenoidal** sinuses are present by 5 yr of age, whereas the **frontal sinuses** begin development at age 7-8 yr and are not completely developed until adolescence. The ostia draining the sinuses are narrow (1-3 mm) and drain into the ostiomeatal complex in the middle meatus. The **paranasal sinuses** are normally sterile, maintained by the mucociliary clearance system.

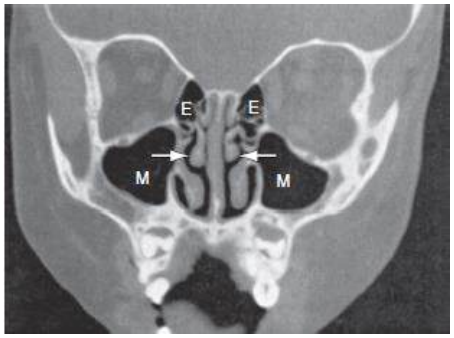
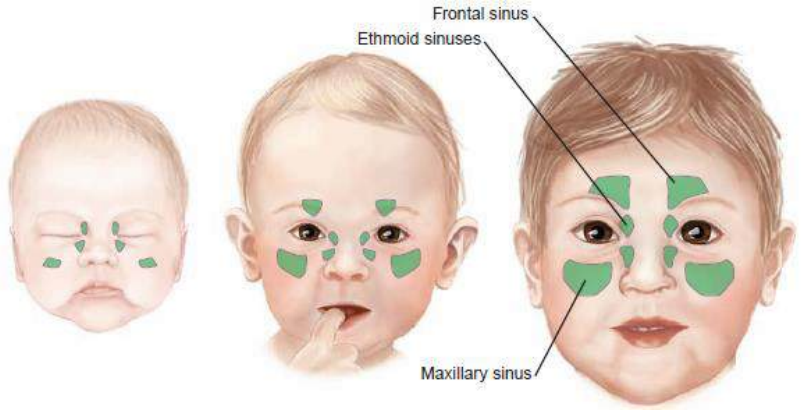
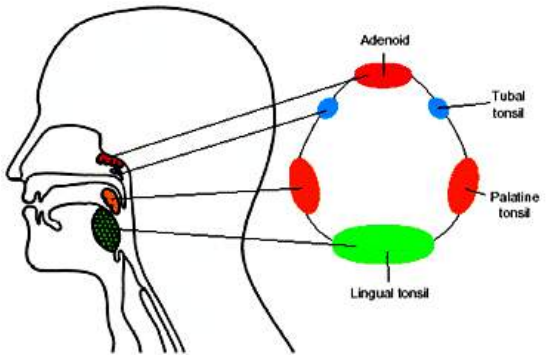


Fig. Coronal CT scan of a normal 3 yr old child. *Arrows* point to middle meatus. E, ethmoid sinuses; M, maxillary sinuses. (From Isaacson G: Sinusitis in childhood, *Pediatr Clin North Am* 43:1297–1317, 1996.)



Sinusitis is a common illness of childhood and adolescence with significant acute and chronic morbidity as well as the potential for serious complications. There are 2 types of acute sinusitis: viral and bacterial. The common cold produces a viral, selflimited rhinosinusitis. Approximately 0.5-2% of viral upper respiratory tract infections in children and adolescents are complicated by acute bacterial sinusitis. Some children with underlying predisposing conditions have chronic sinus disease that does not appear to be infectious.

➢ TONSILS AND ADENOIDS



Waldeyer ring refers to the lymphoid tissue that surrounds the opening of the oral and nasal cavities into the pharynx. It is composed of the palatine tonsils, the pharyngeal tonsil or adenoid, lymphoid tissue surrounding the eustachian tube orifice in the lateral walls of the nasopharynx, the lingual tonsil at the base of the tongue, and scattered lymphoid tissue throughout the remainder of the pharynx, particularly behind the posterior pharyngeal pillars and along the posterior pharyngeal wall. Lymphoid tissue of Waldeyer ring is most immunologically active between 4 and 10 yr of age, with a decrease after puberty. No major immunologic deficiency has been demonstrated after removal of either or both of the tonsils and adenoid.

PATHOLOGY

Acute Infection

Most episodes of acute pharyngotonsillitis are caused by viruses. Group A beta-hemolytic streptococcus (GABHS) is the most common cause of bacterial infection in the pharynx.

Chronic Infection

The tonsils and adenoids can be chronically infected by multiple microbes, which can include a high incidence of beta-lactamase–producing organisms. Both aerobic species, such as streptococci and *Haemophilus influenzae,* and anaerobic species, such as *Peptostreptococcus, Prevotella,* and *Fusobacterium,* predominate. The tonsillar crypts can accumulate desquamated epithelial cells, lymphocytes, bacteria, and other debris, causing cryptic tonsillitis. With time, these cryptic plugs can calcify into tonsillar concretions or tonsillolith. There is growing evidence that biofilms might also play a role in chronic inflammation of the tonsils.

Airway Obstruction

Both the tonsils and adenoids are a major cause of upper airway obstruction in children. Airway obstruction in children is typically manifested in sleep-disordered breathing, including obstructive sleep apnea, obstructive sleep hypopnea, and upper airway resistance syndrome. Sleep-disordered breathing secondary to adenotonsillar breathing is a cause of growth failure.

Tonsillar Neoplasm

Rapid enlargement of one tonsil is highly suggestive of a tonsillar malignancy, typically lymphoma in children.

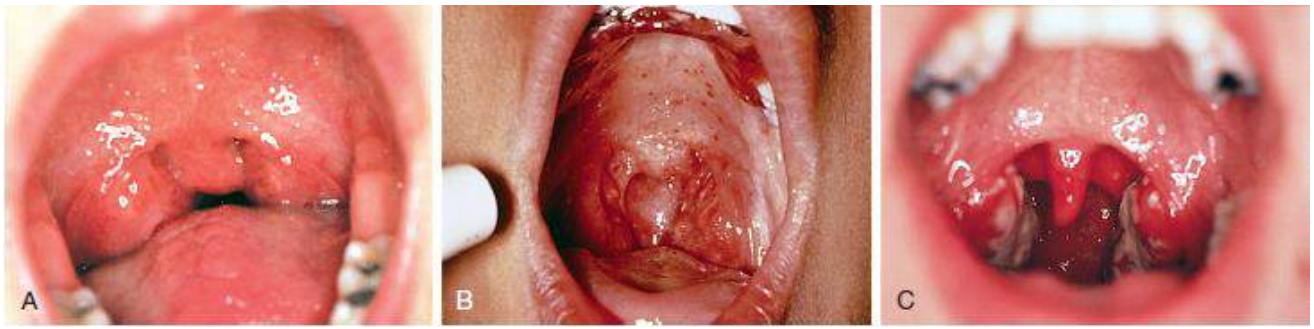
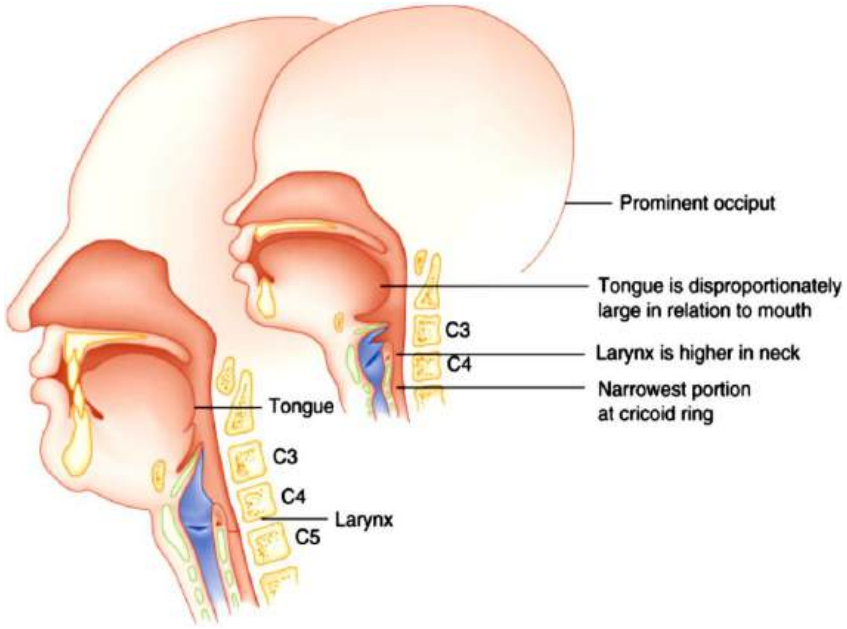
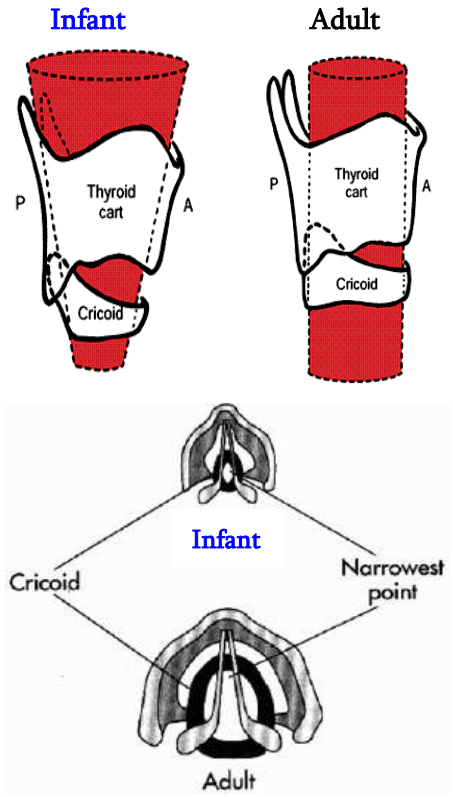


Fig. Pharyngotonsillitis. This common syndrome has a number of causative pathogens and a wide spectrum of severity.
A, The diffuse tonsillar and pharyngeal erythema seen here is a nonspecific finding that can be produced by a variety of pathogens.
B, This intense erythema, seen in association with acute tonsillar enlargement and **palatal petechiae**, is highly suggestive of GABHS infection, though other pathogens can produce these findings.
C, This picture of exudative tonsillitis is most commonly seen with either group A streptococcal or Epstein-Barr virus infection.

➢ LARYNX AND TRACHEA

- Larynx and trachea are funnel shaped
- Larynx located higher in neck (at C4 vs. C6 in adults)
- Epiglottis is relatively large and floppy
- Narrowest part of the pediatric upper airway is at cricoid cartilage (until age 5). In adults the narrowest part is at the level of vocal cords
- Well vascularized

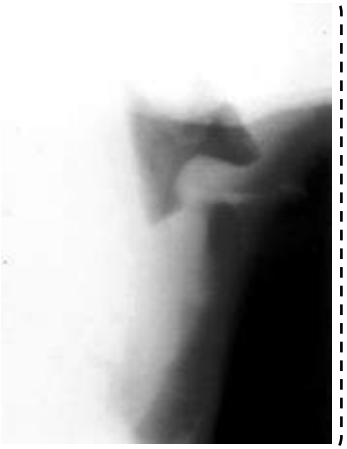




Major adjustments in the relative positions of upper respiratory structures begin to take place by the second year of life. The posterior third of the tongue descends into the neck and forms the upper anterior wall of the pharynx. The epiglottis descends from C1 as the neck elongates until it rests between C4 and C7 in adulthood.

CASE STUDY

A 3-year-old boy with incomplete immunization presents with respiratory distress, drooling, and stridor on inspiration. On examination, he is toxic-appearing, extending his neck with an open mouth and leaning forward. A lateral radiograph of his neck is shown in figure. What is the next step in treatment?



II. Lower Airways and Lung Parenchyma

- During fetal development the lung is transformed from a somewhat dense organ to one that is more delicately structured to facilitate air exchange. Beginning in the second trimester, there is loss of interstitial (mesenchymal) tissue with concomitant expansion of the future air spaces. Capillaries grow into the distal respiratory units that keep subdividing (alveolarization) to maximize surface area for gas exchange.
- In addition to the structural development of the lung in utero, there is accompanying functional maturation during which specialized cell types, such as type II cells, manifest.

  Surfactant *is a lipid-protein mix that is produced by type II alveolar cells and is critical for maintaining alveolar expansion (thus allowing normal gas exchange). It lines alveoli and reduces surface tension, preventing alveolar collapse at the end of each exhalation. Without surfactant the alveoli tend to stay closed, demanding greater inspiratory force and work of breathing to reexpand on the next breath. Deficiency of surfactant is often seen in premature infants and causes respiratory distress syndrome (RDS), also known as hyaline membrane disease. Surfactant is produced by 20 to 24 weeks of gestation and is secreted into the fetal airways by 30 weeks. The more premature the infant, the higher the risk of RDS.*

- Lungs aren't fully developed at birth. The number of alveoli continues to increase during the first 5 to 8 years of life, after which the alveoli increase in size and complexity. Newborns have 25 million alveoli (adults – 300 million). Newborns from 32 to 36 wks gestation have enough alveoli to maintain gas exchange.

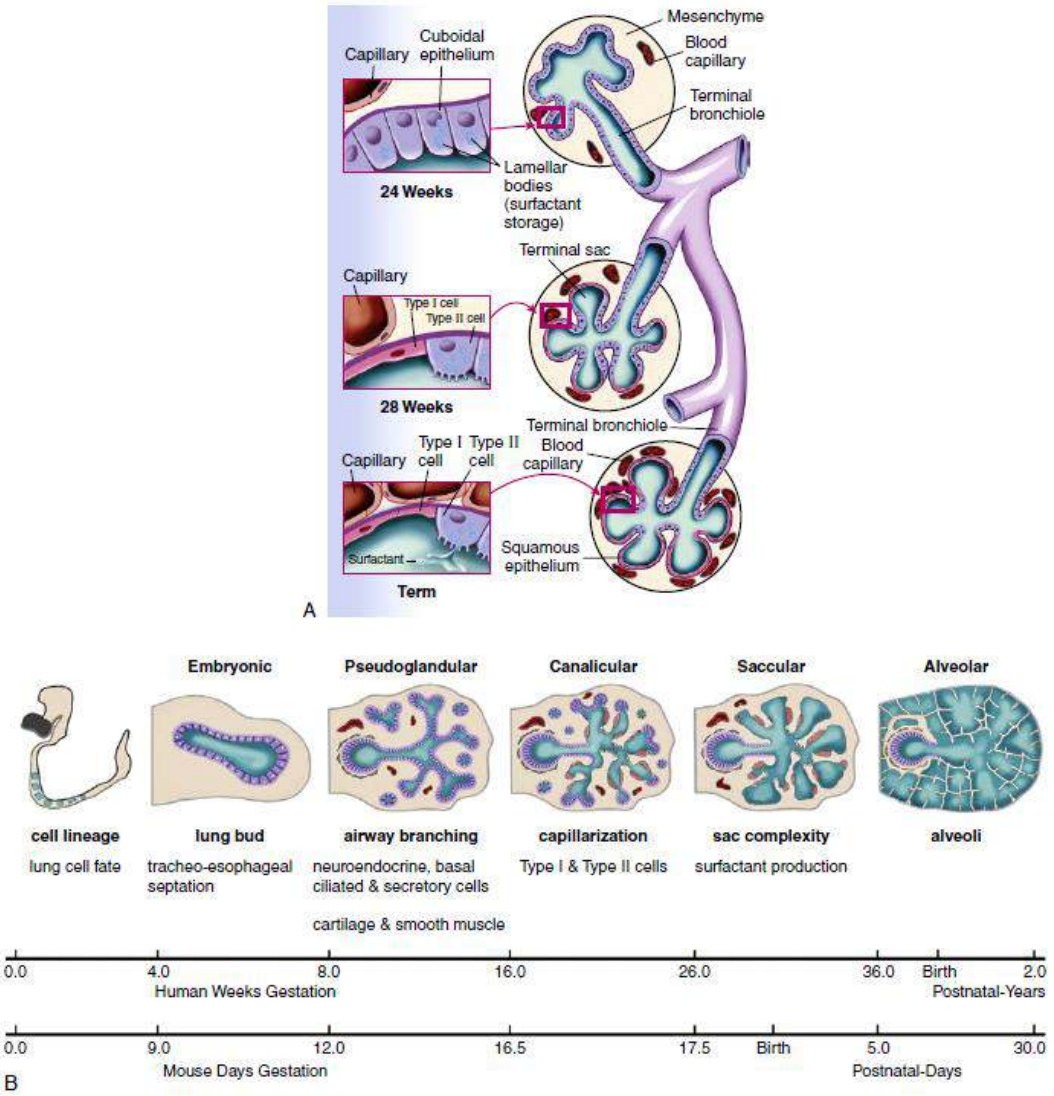


FIG. Alveolar development and stages of fetal lung development

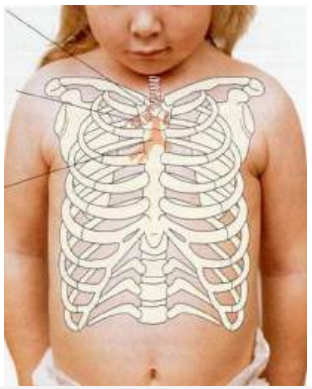
A, Epithelial cells differentiate into type II and type I cells. Mature type II cells are cuboidal, have apical microvilli, and contain lamellar bodies for surfactant storage and secretion. Type I cells are derived from type II cells and consist of flattened epithelium overlying capillaries, thus forming part of the desired thin air-blood barrier. During fetal development the pulmonary capillaries initially are randomly distributed in mesenchyme. They progressively arrange around the epithelial tubes and establish close contacts to the lining epithelium. Overall the volume of mesenchyme decreases and that of the potential air space increases.

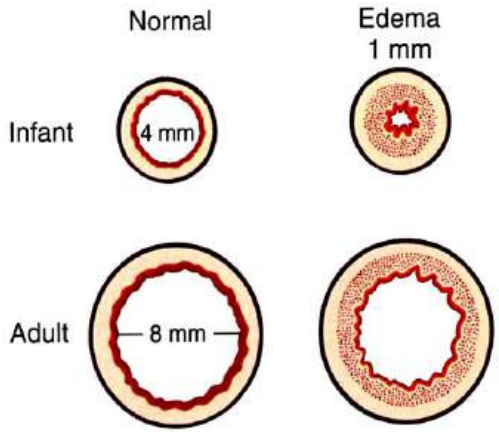
B, Stages of fetal lung development.

Bifurcation of trachea in children is at T_3 level

Right mainstem bronchus in children has a steeper slope, than in adults

Bifurcation of trachea in adults is at T_6 level





- The narrow airway makes the young child prone to airway obstruction and respiratory distress from inflammation, mucus secretion, or a foreign body.
- Newborns lower airways don't have enough smooth muscle bundles to trap airway invaders; by 5 months bundles increase.
- Elastic connective tissue becomes more abundant with age in the peripheral part of the lung.
- Children have a more complaint trachea, larynx, and bronchi due to poor cartilaginous integrity. This in turn allows for **dynamic airway compression**, i.e. a greater negative inspiratory force "sucks in" the floppy airway and decreases airway diameter. This in turn increases the work of breathing by increasing the negative inspiratory pressure generated.

Normal pulmonary function values

[Adapted from Rennie JM, Robertson NRC, eds. A manual of neonatal intensive care, 4th edn. London: Hodder Education, 2002.]

Measurement	Preterm neonate	Term neonate	Adult
Total lung capacity (ml/kg)	55–70	55–70	80–85
Tidal volume (ml/kg)	5–7	5–7	7
Functional residual capacity (ml/kg)	20–25	27–30	30
Vital capacity (ml/kg)	35–40	35–40	60
Respiratory rate (breaths/min)	30–50	30–50	12–16
Alveolar ventilation (ml/kg/min)		100–150	60

*The neonate has a **reduced inspiratory reserve** volume compared with adults, indicated by similar tidal volume and functional residual capacity values with a diminished total lung capacity. Significant increases in minute volume must be achieved by an increase in respiratory rate rather than tidal volume.*

III. Chest Wall and Lung Dynamics

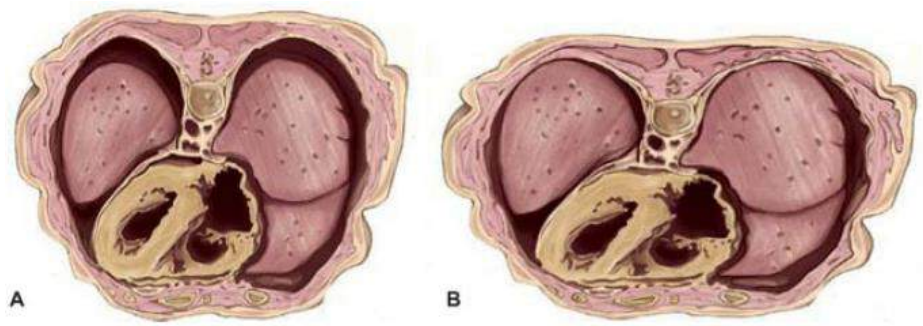


FIG. **(A)** The newborn's chest is round. **(B)** The adult chest has an anterior-posterior diameter about half the transverse diameter.

The newborns' chest should be smooth and round, with the transverse diameter nearly equal to the anterior-posterior diameter.The shape of the chest progresses to that of the adult by age 5 to 6 years. At that time the anterior-posterior diameter is about half the transverse diameter. At the point where the xiphoid process and the right and left costal margins meet, the costal angle should measure 90 degrees or less.

Children's ribs lie more horizontally and do not contribute as much to expansion of their chests.

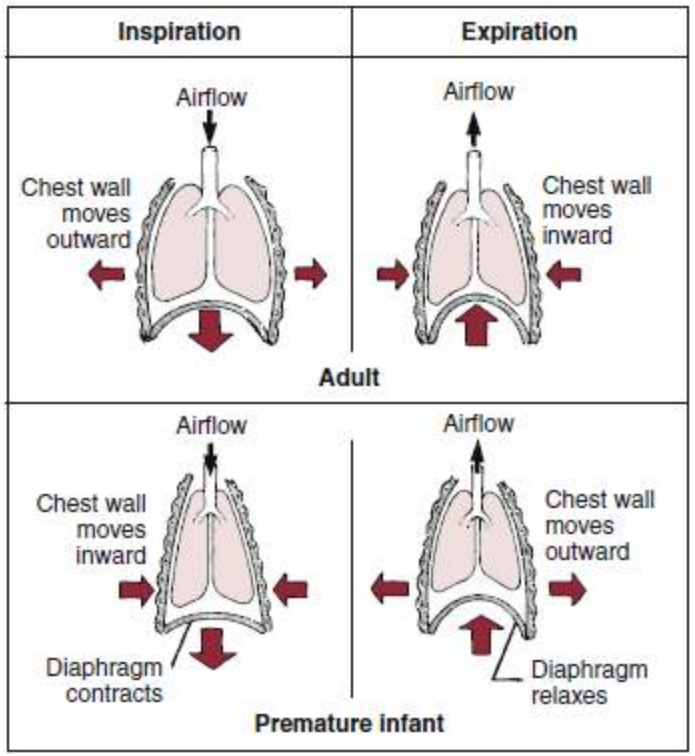


FIG. Differences in lung mechanics caused by differences in chest wall compliance (degree of rigidity) in premature infants and adults.

Chest wall compliance is high in infants, particularly premature infants. The cartilaginous structures of the thoracic cage are not yet well ossified (ossification continues to occur throughout childhood), and the chest wall is easily collapsible. During inspiration in the young child, air is drawn in by the downward movement of the diaphragm, but the resulting negative pressure causes the "soft" chest wall to be drawn inward; this produces so-called ***paradoxic breathing, or diaphragmatic breathing****. Paradoxic breathing is especially seen during rapid eye movement (REM) sleep of premature infants.*

With pulmonary compromise the accessory muscles are drawn inward, creating retraction of the intercostal and supraclavicular spaces. Resting lung volume, or functional residual capacity (FRC), represents the balance point between the natural elastic recoil of the lungs (to collapse) and the elastic recoil of the chest wall (to expand). In the face of an overly compliant chest wall, infants up to about 1 year of age are thought to maintain their FRC and avoid atelectasis by muscular "braking" of their expiration. This may occur either by active glottic narrowing or by increased activity of the inspiratory intercostal muscles.

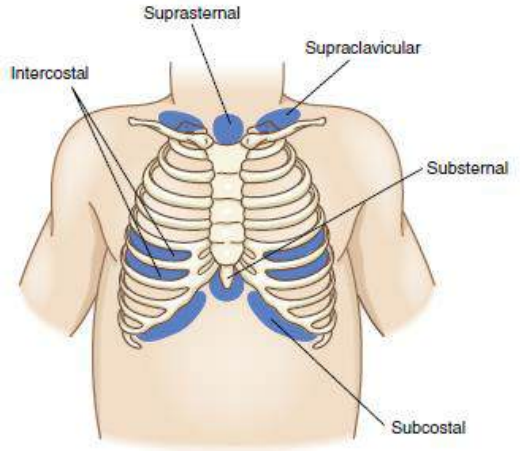


FIG. Areas of Chest Muscle Retraction.

Infants are dependent on functional diaphragms for adequate ventilation. The accessory muscles contribute less to the overall work of breathing in infants as compared to older children and adults. Therefore, a non-functional diaphragm often leads to respiratory failure. Diaphragmatic fatigue is one amongst several potential causes of respiratory failure and apnea in young patients with RSV bronchiolitis. Finally, the respiratory muscles themselves have a significant oxygen and metabolite requirement in children. In pediatric patients the work of breathing can account for up to 40% of the cardiac output, particularly in stressed conditions.

IV. Metabolic Characteristics

The basal metabolic rate of a child is greater than that of an adult, and thus oxygen consumption (VO_2) is greater per unit of body weight. The VO_2 of the child's normal breathing accounts for up to 25% of the total VO_2. The work of breathing increases VO_2 exponentially with respiratory distress. Children have less muscle glycogen reserve, which limits the efficiency of accessory muscles, such that fatigue with lactic acidosis can occur quickly. Children also have a high proportion of extracellular fluid and therefore more quickly lose fluid and become dehydrated as a result of fever, from environmental heat, or in association with tachypnea (which causes evaporation from the respiratory tract).

CASE STUDY

A 3-day-old infant, born at 32 weeks' gestation and weighing 1700 g, has three episodes of apnea, each lasting 20 to 25 seconds and occurring after a feeding. During these episodes, the heart rate drops from 140 to 100 beats per minute, and the child remains motionless; between episodes, however, the child displays normal activity. Blood sugar is 50 mg/dL and serum calcium is normal. Give an explanation of the child's apneic periods.

V. Physiologic Control of Respiration

For up to 3 weeks of age, the newborn has a blunted ventilatory response to hypoxia compared with older children and adults. The mechanisms for this are not well understood but may reflect reduced activity of the peripheral chemoreceptors (in the carotid body) and nonadaptive responses in the respiratory center (in the brainstem). Ventilatory response to hypercarbia is normal in term infants but may be reduced in premature infants. Congenital or acquired lesions of the central nervous system may cause hypoventilation or apnea.
Periods of apnea are generally thought to be secondary to an incompletely developed respiratory center, particularly when they are seen, as is common, associated with prematurity.

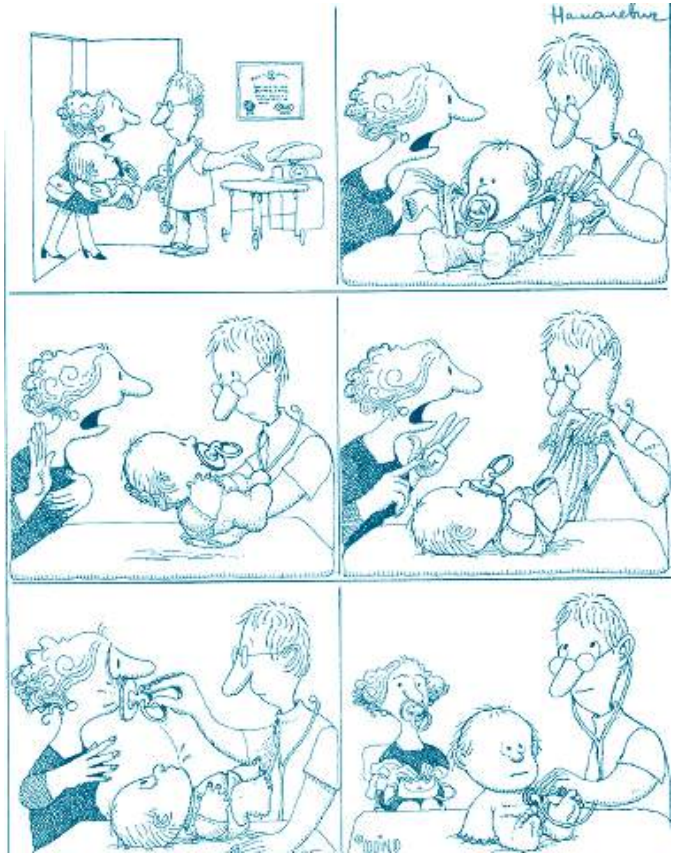
Pediatric Respiratory Assessment

Collecting the health history and performing the physical assessment of the child with a respiratory system disturbance is the first step in the diagnostic process.

HISTORY

Diagnosis of respiratory disease is typically based on a careful history, focusing on the following questions:

1. What are the symptoms?	(I) Presence of a cough and its characteristics (2) Labored or noisy breathing and its interference with activities *(see "Common Manifestations of the Respiratory Disorders", p. 20)*
2. Is the disorder acute, chronic, or recurrent?	The physician must determine whether the condition is acute and self-limited; chronic (i.e., with symptoms occurring daily for more than 4 weeks); or recurrent (i.e., with disease-free intervals).
3. Is the disorder immediately or eventually life threatening?	(1) Cyanosis, respiratory distress, or severe stridor indicate the need for immediate action. (2) Problems such as progressive weight loss or a progressive pulmonary opacification imply a serious long-term outlook.
4. What factors affect the severity of symptoms?	Identify factors that improve or worsen symptoms. Asthma is suggested when symptoms are exacerbated by changes in weather, viral infections (e.g., common colds), exercise, laughing or crying, or exposure to allergens.
5. **Is there a family history of pulmonary disease?**	Some diseases such as cystic fibrosis and asthma have a genetic or familial basis.
6. Have any treatments been given?	Inquire about types, dosages, and duration of therapy the child has received, and response of symptoms to treatment.



PHYSICAL EXAMINATION

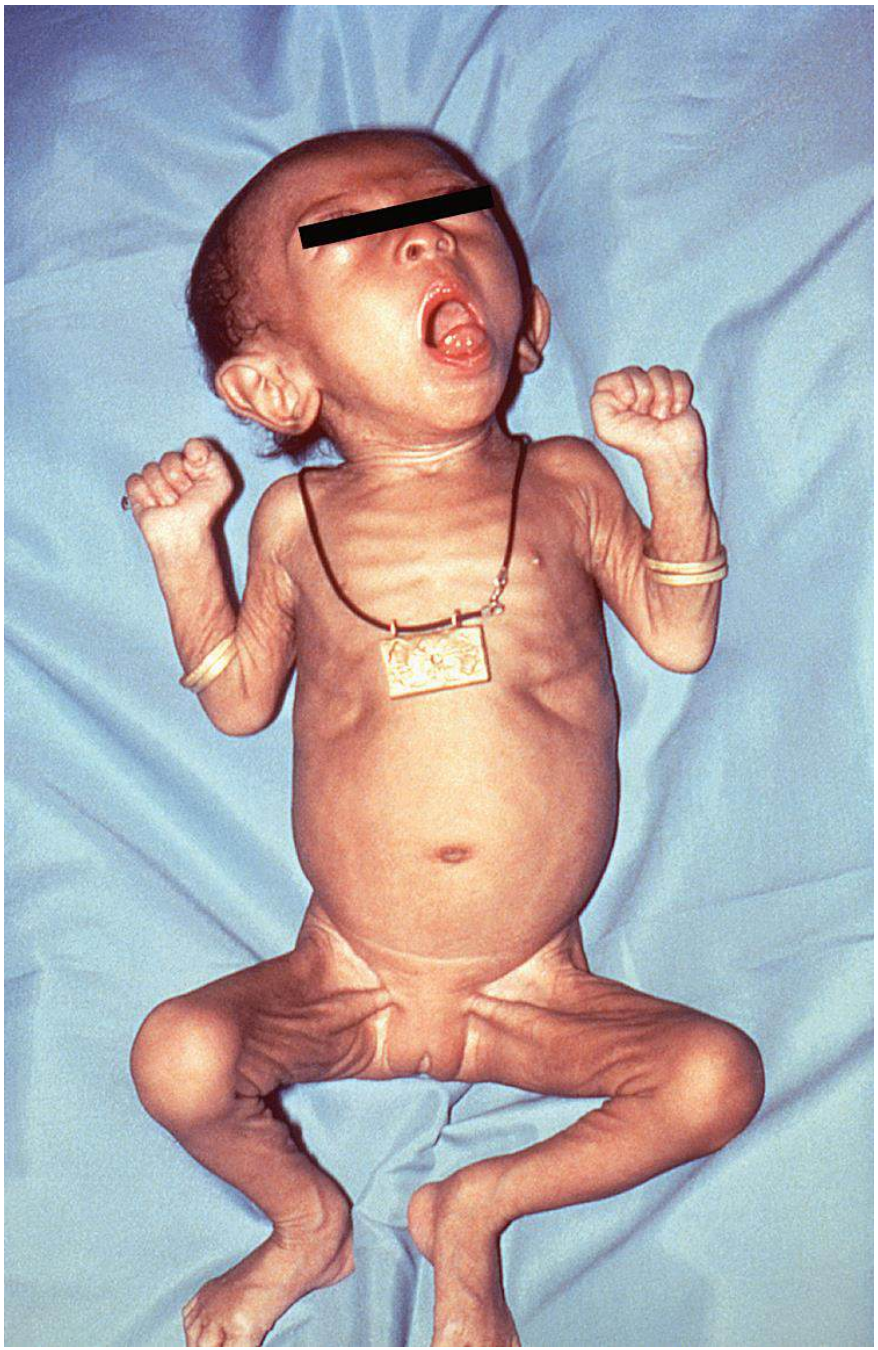
1. Vital signs – respiratory rate, heart rate, blood pressure and temperature.

Respiratory rate is the best indicator of pulmonary function in young infants. As the respiratory rate is influenced by activity when the child is awake, the most reliable and reproducible rate is the sleeping respiratory rate. A child's respiratory rate decreases as body size increases.

Normal respiratory rate (RR) and heart rate (HR) at rest

[From Soghier L. Reference Range Values for Pediatric Care, first ed. AAP 2014]

	Respiratory Rate (breaths/min)	Heart Rate (beats/min)
Newborn	40–60	100-160
1 – 12 mo	35–40	
1 – 3 y	25–30	70-110
4 – 6 y	21–23	
7 – 12 y	19–21	
13 – 19 y	16–18	55-90



2. Visual assessment of the signs of respiratory distress:

- Increases in respiratory rate (tachypnea) and work of breathing: dyspnea, chest retractions (suprasternal, supraclavicular, intercostal, subcostal), grunting, nasal flaring, head bobbing, thoracoabdominal asynchrony,
- Signs of poor oxygenation include alterations in mental status, and change in skin color: pallor, mottling, and cyanosis. They are often late signs indicating respiratory failure and shock.

3. Anatomic changes of significance include the following:

(1) *A change in tracheal position* signals mediastinal shift and an inequality between the two sides of the chest, as with a pneumothorax or atelectasis.
(2) *A change in thoracic configuration.* A barrel-chest deformity suggests hyperinflation and overdistention of the lungs due to chronic airway obstruction.
(3) *Clubbing of the fingers and toes* is caused by lifting of the nail base by tissue proliferation on the dorsal surface of the terminal phalanx. As a sign of pulmonary disease in children, clubbing most often is caused by cystic fibrosis.

CAUSES OF CLUBBING

Cardiac	Respiratory	Gastrointestinal	Other
Cyanotic congenital heart disease *Bacterial endocarditis*	*Bronchiectasis* *Cystic fibrosis/ciliary dyskinesia* *Tuberculosis* *Empyema/abscess, malignancy*	*Inflammatory bowel disease* *Chronic liver disease (CLD)* *Primary sclerosing cholangitis*	*Familial*

4. Ears, nose and throat (ENT) examination

A successful ENT examination requires younger children to be held gently but firmly by the parents.

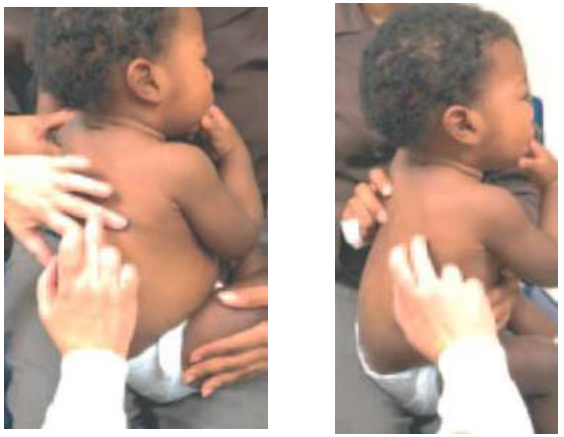
Ears
Ask the parents to sit the child on their lap at 90° to their chest. With one arm, ask them to gently hold the child's head against their chest. Their other arm should hold onto the child's free arm. Gentle traction should be applied to the ear. The pinna should be pulled in an upward and outward direction. The auriscope should be gently held in a pincer grip. The ring finger of this hand should rest on the cheek of the child while the auriscope is within the ear. This allows the examiner's hand to quickly follow any sudden movements the child may make.

Throat
This is an unpleasant examination. It should be left until last. A tongue depressor is necessary for a complete examination. If throat disease is suspected, it is useful to have a swab to hand. A child may comply with throat examination once. They may resist a further request a few minutes later for a throat swab.

Fig. Positions for the ear and throat in the ENT examination

5. Percussion

Percussion of the chest wall assesses acoustic response to a vibratory force applied to lung tissue. The technique requires practice and consists of tapping of the middle finger of one hand with the middle finger of the other while it is applied to the chest wall. It is essential that one does this symmetrically and that the response is assessed for resonance (hollowness) and dullness (flatness). This is often not useful in young infants and frequently will elicit poor cooperation and crying. The technique is of more use in older children.



6. Auscultation of the lungs

Auscultation of the lungs is always necessary for evaluating the child's respiratory status. Use the diaphragm of the stethoscope to auscultate the lung fields (front, back, and axillary areas) by systematically and symmetrically (comparing one side with another), listening for breath sounds as the child takes a deep breath in and blows out. Pretending to blow out the light of an otoscope or penlight is a useful game that encourages deep breathing in younger children.
In infants and young children, lack of subcutaneous fat and smaller distances between structures may make breath sounds readily transmitted across lung fields. Keep this in mind when assessing the presence, location, and nature of breath sounds in infants and young children. To detect **transmitted sounds** from the upper airways, place the diaphragm next to the child's mouth or nose to determine whether what is heard in the lung fields is just like the sound as heard near the mouth or nose. Referred sounds are loudest near their origin.

Respiratory sounds are related to chest air movement, either normal or adventitious, heard at the mouth, the trachea and the chest; they include sounds produced by cough, snoring, sneezing or respiratory muscle contraction, but exclude voiced sounds. Lung sounds are the respiratory sounds heard (or otherwise detected) over the chest.

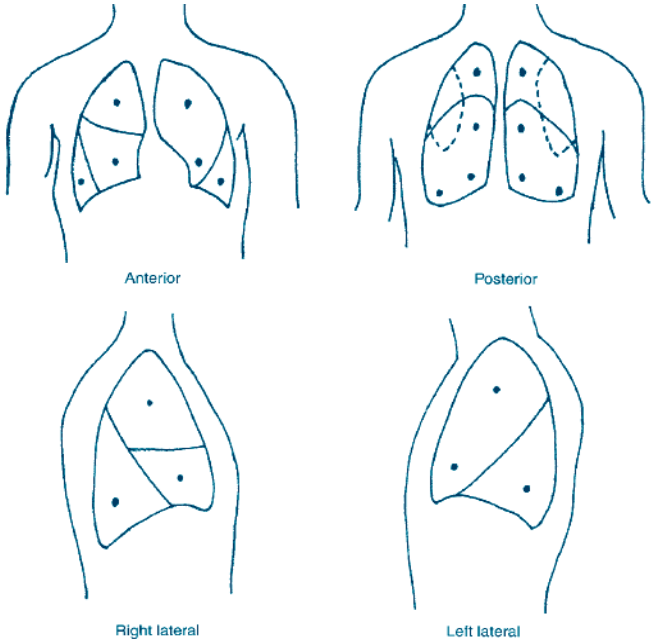
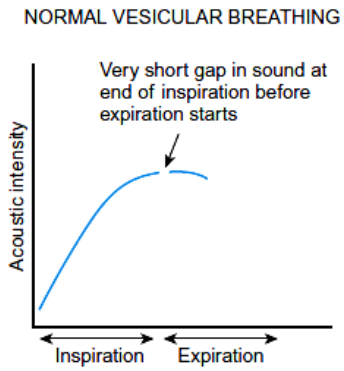
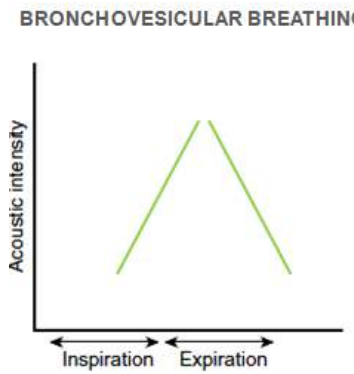
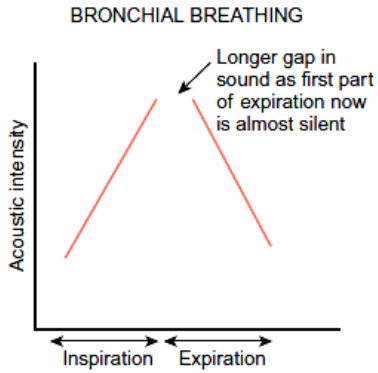


Fig. Surface anatomy of the pulmonary lobes and suggested auscultation sites

Characteristics of Normal Breath Sounds

Sound	Vesicular *	Bronchovesicular	Bronchotubular/ bronchial/ tracheal
Quality	Soft, swishing	Louder and higher pitch than vesicular; mixed	Tubular, harsh, hollow
Relationship of Inspiration (I) to Expiration (E)	I is longer, louder, and higher pitched than E (I > E)	I and E are equal (I = E)	I is short; E is long (I < E)
Diagram			
Normal Location	Throughout lung field	Over manubrium and upper intrascapular region where trachea and bronchi bifurcate (in older children)	Over trachea
Pediatric Considerations	Usually heard in older children but not in infants and young children	Heard throughout lung field in infants and young children	

* Vesicular breath sound is a misnomer, as it does not originate in vesicles, i.e. the alveoli
I – inspiration; E - expiration

Breath sounds normally have equal intensity, pitch, and rhythm bilaterally. Absent or diminished breath sounds generally indicate a partial or total obstruction, such as from a foreign body or mucus, that does not permit airflow.

Adventitious sounds are additional sounds superimposed on normal breath sounds; they are usually associated with pulmonary disorders. Adventitious sounds are primarily divided into continuous and discontinuous sounds.

Characteristics of Adventitious Breath Sounds

Continuous sounds (whezes, ronchi, stridor)	Discontinuous sounds (crackles)
• Sinusoidal, musical, prolonged (but not necessarily persisting throughout the respiratory cycle) • Like dashes in time — — — — — —	• Intermittent, nonmusical, and brief. Crackles (other terms in use are "crepitations" or "rales") are usually auscultated during inspiration, that represent local phenomena. • Like dots in time ……
1. Wheezes: relatively high-pitchet (≥400 Hz) with hissing or shrill quality (>80 ms).  *They usually are expiratory in origin but can be inspiratory when the airway obstruction is fixed and rigid, as in airway edema.* *2. Ronchi:* relatively low-pitched (150-200 Hz) with snoring quality.  *Rhonchi are generated by intraluminal secretions and collapse of large airways.* *2. Stridor: see p. 23*	*1. Fine crackles (subcrepitant crackles):* soft, high-pitched (≈ 650 Hz), very brief (5-10 ms). ° ° ° ° ° ° ° *They are produced by the explosive opening of small airways collapsed by surface forces (increased elastic lung recoil pressure or inflammation/oedema in the lung); they are gravity dependent and the sound is rarely transmitted to the mouth. Fine, late inspiratory crackles are typical of interstitial/fibrotic lung disease. However, they may also be present in normal subjects who inhale slowly from their residual lung volume.* *2. Coarse crackles (crepitant crackles):* somewhat louder, lower in pitch (≈ 350 Hz), brief (15-30 ms) sounds. o o o o o o o *They are generated by a different mechanism to that of fine crackles, i.e. movement of thin secretions in the bronchi or the bronchioles. They start early and continue until mid-inspiration but may be heard during expiration. A typical example of coarse crackles can be heard in bronchiectasis and chronic airway obstruction (e.g. CF). Similar auscultatory findings can be found focally early in pneumonia but shift into more endinspiratory crackles of variable duration that progress to fine crackles during recovery. Acoustic analysis has characterised the crackles of cardiac failure as coarse, of long duration during inspiration and appearing late in the course of the disease.*

Other adventitious sounds are squawk and the pleural friction sound.

- A squawk (sometimes classified as a type of wheeze) is a "composite", short (50–400 ms), inspiratory adventitious sound with a musical character (short inspiratory wheeze) that is preceded by a crackle. It is not associated with airway obstruction but rather with pulmonary fibrosing (restrictive) disease. It is thought to result from the vibrations set in motion by the sudden opening of a collapsed airway.
- Pleural friction sound (or friction rub) is coarse crackles (often described as "leathery") produced by inflamed parietal and visceral pleura that cause vibration of the chest wall and local pulmonary parenchyma. It can be auscultated during inspiration or in both phases of breathing. Pleural friction precedes pleural effusion and disappears when fluid is formed. The "rub" is synchronous with breathing and does not disappear with cough, but is modified by the breathing pattern and posture.

IMAGING PROCEDURES

(1) **Chest X-ray.** This simple investigation is easily obtained in hospital but may be overused. Consider what you hope to learn before requesting a radiograph. It is not necessary, for instance, to X-ray every wheezy child, unless the episode is moderate or severe, or there are focal signs. Do not send an unstable child, particularly with upper airway obstruction, across the hospital to the X-ray department – stabilize the child first or request a portable X-ray. If there is any question of an inhaled foreign body, a single film is never sufficient. Except in those who require immediate bronchoscopy, X-ray screening in the young child, or inspiratory and expiratory films in the cooperative older child, are needed to confidently exclude or confirm a foreign body.

(2) **Fluoroscopy** is useful for dynamic studies (e.g., to evaluate diaphragmatic movements, identify tracheal collapse).

(3) **Ultrasonography** is used to confirm pleural effusion and to guide thoracentesis; it can be used instead of fluoroscopy to evaluate diaphragmatic motility.

(4) **Chest computed tomography:** useful for assessing abnormalities in airways as well as abnormalities in parenchymal tissue density.

(5) **Thoracic MRI**: useful for looking at airway–blood interface, and vascular and mediastinal anatomy.

(6) **Nuclear imaging**: useful for assessing regional ventilation (V) and perfusion (Q), as well as V/Q matching.

ENDOSCOPIC EVALUATION OF THE AIRWAYS

Endoscopic evaluation of the upper airways (**nasopharyngoscopy**) is performed with a flexible fiberoptic nasopharyngoscope to assess adenoid size, patency of the nasal passages, and abnormalities of the glottis. It is especially useful in evaluating stridor and assessing vocal cord motion/function, and it does not require sedation.

Endoscopic evaluation of the subglottic space and intrathoracic airways can be done with either a flexible or rigid bronchoscope under anesthesia. **Bronchoscopy** is useful in identifying airway abnormalities (stenosis, malacia, endobronchial lesions, excessive secretions) and in obtaining airway samples for culture (bronchoalveolar lavage), especially in immunocompromised patients. Rigid bronchoscopy is the method of choice for removing foreign bodies from the airways and performing other interventions, and flexible bronchoscopy is most useful as a diagnostic tool and for obtaining lower airway cultures. Transbronchial biopsies are rarely performed in children. There are few absolute contraindications to bronchoscopy. Relative contraindications include bleeding diatheses, thrombocytopenia (<50,000/cm3), and clinical conditions when the patient is too unstable to tolerate the procedure.

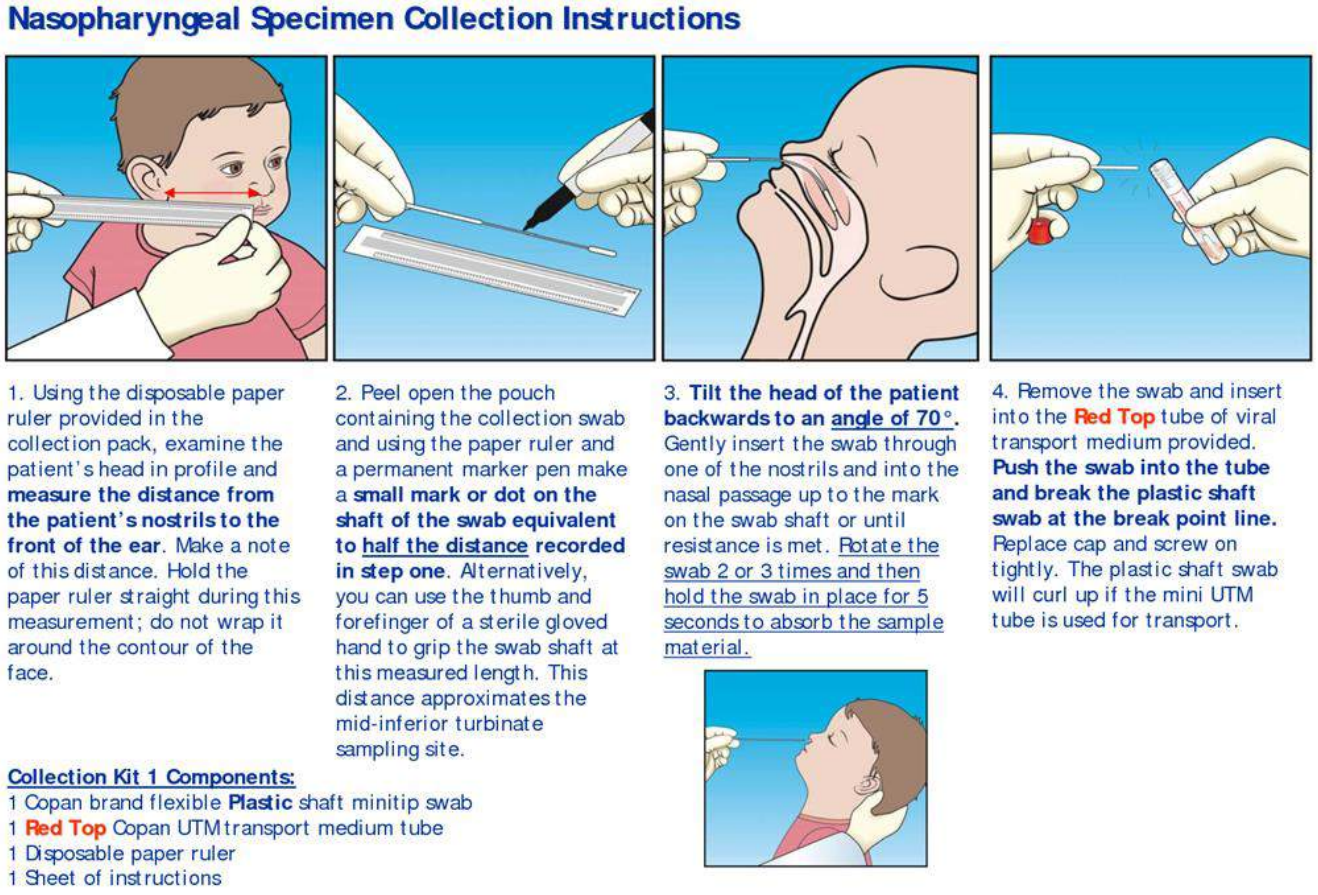
BLOOD TESTS

Blood tests are generally over-used.

- A blood count and C-reactive protein measurements in children with fever and cough are unhelpful at distinguishing common viral infections from more significant bacterial lower respiratory tract infections.
- A high lymphocyte count will help corroborate a diagnosis of whooping cough
- Urea and electrolyte measurement is really only needed if there is coexistent severe vomiting or dehydration, or in children requiring intravenous fluids.
- Blood cultures are necessary if a child with pneumonia is very toxic and there are concerns about associated bacteremia.
- IgE and blood allergy tests may help confirm atopy in the child with probable asthma. Only occasionally does it directly influence management, e.g. the wheezy baby with eczema and milk allergy.
- Rarely, immune function testing may be required in children with true recurrent bacterial lower respiratory tract infections.

RESPIRATORY SECRETIONS

These are under-used. They are often forgotten as young children either cannot or will not produce sputum. Sputum culture, if available, is more helpful than blood culture. If persistent bacterial bronchitis is suspected a cough swab is a useful alternative to sputum culture and is invaluable in monitoring conditions such as cystic fibrosis and other forms of bronchiectasis. Immunofluorescence testing of nasopharyngeal aspirates is useful in infants with bronchiolitis to confirm or exclude respiratory syncytial virus (RSV) infection. A nasopharyngeal aspirate or pernasal swab is used to test for whooping cough.



PULMONARY FUNCTION TESTING

TEST	MEASUREMENTS	KEY RESULTS
Spirometry	Assessment of dynamic lung volumes and ventilation: *The patient inhales to total lung capacity and then forcibly exhales until no more air can be expelled. During the forced expiratory maneuver, forced vital capacity (**FVC**), forced expired volume in the first second (**FEV1**), and **peak expiratory flow rate (PEFR)** are measured. These are compared to **predicted values** based on patient age, gender, and race, but rely mostly on height.* *Most children above 6 years of age can perform spirometry. Infant pulmonary function testing is possible, using sedation and sophisticated equipment.*	• **Forced vital capacity (FVC)** - the volume of air expired in a complete expiration • **Forced expiratory volume in 1 second (FEV1)** - the volume of air that can be expired in 1 second • **Ratio of FEV1 to FVC (FEV1/FVC)** - *this test can be used to distinguish between obstructive airway disease (eg asthma, COPD) and restrictive lung disease (eg pulmonary fibrosis). In an obstructive defect, the FEV1/FVC will be less than 70%. The percentage is greater than 80% with a restrictive defect. But, spirometric restrictive defect ≠ restrictive lung disease.*
Body plethysmography	Assessment of static lung volumes: *TLC (total lung capacity), FRC (functional residual capacity), RV (residual volume), and SVC (slow vital capacity)*	Static lung volumes are reduced in restrictive lung disease. They cannot be measured with spirometry.
	*Abnormal results on pulmonary function testing can be used to categorize **obstructive airway disease** (low flow rates and increased RV or FRC) or a **restrictive defect** (low FVC and TLC, with relative preservation of flow rates and FRC).* *Pulmonary function testing can detect **reversible airway obstruction** characteristic of asthma with a significant improvement in FEV1 (>12%-15%) or in FEF25–75% (>25%) following inhalation of a bronchodilator. Spirometry is also useful for longitudinal patient management.* *The **peak expiratory flow rate (PEFR)** can also be obtained with a simple handheld device (**peak flow meter**) and may be useful for home monitoring of older children with asthma. However, it is highly dependent on patient effort, and values must be interpreted with caution.* ***Inhalation challenge tests** using methacholine, histamine, or cold, dry air are used to assess airway hyperreactivity, but require sophisticated equipment and special expertise and should be performed only in a pulmonary function laboratory with experienced technicians.*	
Arterial blood gases (ABGs) and gas exchange tests	ABGs provide 3 assessments of the function of the respiratory system: • *evaluation of **oxygenation** (PaO2, SaO2, SpO2)* • *evaluation of the **adequacy of ventilation** (PaCO2)* • *evaluation of the lung's role in **acid-base balance** of the arterial blood (pH, PaCO2)*	**Normal Arterial Blood Gas Values** pH: 7.4 (7.38 to 7.42) PO2: 80 to 100 mm Hg PCO2: 35 to 45 mm Hg O2 Saturation: 95% on room air HCO3: 22 to 26 mEq/L Base Excess: - 2 to + 2 mEq/L
Diffusing capacity of the lung (DLCO)	Assessment of the ability of the lungs to transfer gas.	DLCO is reduced in restrictive diseases with diminished pulmonary blood flow.

Common Manifestations of the Respiratory Disorders

The lungs have a limited repertoire of responses to disease. The key presentations in pediatrics are:
- Sore throat
- Cough
- Noisy breathing (e.g., stridor, wheeze)
- Respiratory distress

COUGH

Cough is a very non-specific symptom and can occur as a result of any pathology at any site in the respiratory tract – cough is one of the clinical features of most respiratory pathologies. However, the timing of the cough and its associated features (such as the age of the patient and other symptoms) can give clues to the diagnosis.

It is often informative to hear a cough (or see video recording of a cough), allowing one to distinguish between dry and wet coughs and wheezy or brassy coughs.

Cough type	Suggested underlying process
Barking or brassy cough	Croup, tracheomalacia, habit cough
Honking	Psychogenic
Paroxysmal (with or without inspiratory 'whoop')	Pertussis and parapertussis
Staccato	Chlamydia in infants
Cough productive of casts	Plastic bronchitis/asthma
Chronic wet cough in mornings only	Suppurative lung disease

Based on Chang AB, Landau LI, Van Asperen PP etâ·¯al, Med J Aust 2006; 184(8): 398–403; with permission.

The **duration of the cough** also suggests its possible cause. Most acute coughs are infectious in origin. Upper respiratory infections can initiate an acute cough through stimulation of the cough receptors in the nose and posterior pharynx. If nasal congestion and cough persist, a diagnosis of **allergic rhinitis or sinusitis** should be considered. **Serous otitis media** can also cause a persistent cough and may occur in children with chronic congestion.

Acute cough

In upper respiratory tract infection with bronchitis, cough usually lasts more than 2–3 weeks in 10% of normal children. Provided the child is otherwise well with no pyrexia, tachypnoea or crackles, it is likely best to wait for resolution as aetiology is most often viral. There is limited evidence that any therapy is beneficial.

- Erythromycin is useful for early pertussis cases.
- Honey medications and vapour rub may reduce the severity of acute cough.
- Antibiotics may be beneficial for acute bacterial bronchitis but most bacterial cases resolve naturally anyway.

An inhaled foreign body is a possibility when there is a sudden onset of cough with no upper respiratory tract infection or after a choking episode; bronchoscopy is needed to remove the foreign body. In allergic rhinitis and post-nasal drip syndrome (throatclearing type cough), intranasal steroids and/or antihistamines may be beneficial. 10% of normal children with acute cough due to upper respiratory tract infections are still coughing 3–4 weeks later. Some children with a ‘‘post-infectious cough’’ (prolonged acute coughing after an obvious upper respiratory infection) cough for much longer and this is especially true for those with pertussis (Hay et al., 2005). Providing the child is otherwise well, waiting for a period of time allows natural resolution of post-infectious coughing and pertussis to occur.

Do not use a wait-and-see approach if there is:

- weight loss
- night sweats
- haemoptysis
- sudden-onset cough or cough after a choking episode
- relentlessly progressive coughing (e.g. TB, expanding intrathoracic mass, retained foreign body, collapsed lobe or pertussis)
- clinical history of symptoms or signs (or are at risk) of underlying chronic lung disease (e.g. finger clubbing, barrel-shaped chest, Harrison’s sulci, recurrent pneumonia and immunodeficiency)

Chronic cough

A chronic cough is one that lasts ≥ 14 days (WHO, 2013).
Chronic cough is very common and **often there are no pointers to a specific diagnosis** (e.g. normal chest radiograph, normal lung function and dry isolated cough in otherwise well child). In such cases often a **“trial of treatment”** is used to confirm a diagnosis as it is neither feasible nor desirable to extensively investigate all such children. However, it is important to realise that natural resolution typically occurs with the passage of time and, therefore, a response to treatment must not be taken as confirming a diagnosis. Children responding to a trial of therapy should have the treatment stopped and only a second clearcut response should be used to suggest a diagnosis.
There is little evidence that either nonspecific isolated cough or postinfectious coughing responds to any currently available treatment (inhaled corticosteroids (ICS), b2-agonists, leukotriene antagonists, anti-gastrooesophageal reflux therapy, cromones and environmental modification). Most of these coughs resolve naturally but over a considerable period of time. Ultra-high-dose ICS may have a small benefit but the sideeffects seem to outweigh the benefits.

There is good evidence that children with protracted or persistent productive (moist or wet) cough benefit from treatment with antibiotics to cover the organisms associated with protracted bacterial bronchitis (e.g. Haemophilus influenzae, Pneumococcus and Moraxella), such as coamoxiclav [Chang et al., 2008]. It is important that a full 14-day course is given and, sometimes, a prolonged course is needed for 4–6 weeks along with intensive physiotherapy before the persistent endobronchial infection is eradicated. A positive response to a full course of an appropriate antibiotic and the child returning to completely good health confirms the diagnosis. Failure to respond or other features of chronic disease should trigger further investigations as to an underlying cause, such as:

- persistent bacterial bronchitis
- CF
- immune deficiencies
- primary ciliary disorders
- recurrent pulmonary aspiration
- retained inhaled foreign body

Care needs to be taken, especially in children with neurological or neuromuscular disabilities, to ensure dysfunction of swallowing and gastro-oesophageal reflux is treated to prevent recurrent pulmonary aspiration.

Psychogenic or habit coughing can be difficult to treat if there is some secondary gain associated with an underlying stressor and psychotherapy may be needed. More often behavioural therapies can be employed to empower the child to be able to resist the urge to cough on his/her own (e.g. the child takes a sip of hot lemon drink with each urge to cough).

Differential diagnosis in a child presenting with chronic cough

Diagnosis	In favour
TB	– Weight loss or failure to thrive – Anorexia – Night sweats – Enlarged liver and spleen – Chronic or intermittent fever – History of exposure to infectious TB – Abnormal chest X-ray
Asthma	– History of recurrent wheeze – Hyperinflation of the chest – Prolonged expiration – Reduced air entry (in very severe airway obstruction) – Good response to bronchodilators
Foreign body	– Sudden onset of choking or stridor – Unilateral chest signs (e.g. wheezing or hyperinflation) – Recurrent lobar consolidation – Poor response to medical treatment
Pertussis	– Paroxysms of cough followed by whoop, vomiting, cyanosis or apnoea – Sub-conjunctival haemorrhages – No history of DPT vaccination – No fever
HIV	– Known or suspected maternal or sibling HIV infection – Failure to thrive – Oral or oesophageal thrush – Chronic parotitis – Skin infection with herpes zoster (past or present) – Generalized lymphadenopathy – Chronic fever – Persistent diarrhoea – Finger clubbing
Bronchiectasis	– History of severe pneumonia, TB or aspirated foreign body – Poor weight gain – Purulent sputum, bad breath – Finger clubbing – Localized signs on X-ray
Lung abscess	– Reduced breath sounds over abscess – Poor weight gain or chronically ill child – Cystic or cavitating lesion on chest X-ray

NOISY BREATHING

The term "noisy breathing" is used to describe respiratory sounds that are audible to the "naked ear" without the use of a stethoscope.

Table. Different kinds of noisy breathing

Noise	Description	Site of origin	Common causes
Stertor	It is a snuffly or snoring sound	Oro/nasopharyngeal airway	
Snuffles		Blocked nasal passages	Upper respiratory tract infections Allergic rhinitis
Snoring	Snoring is produced during sleep and is due to obstructed air movement in the naso- and oropharynx; children who snore tend to have more collapsible airways and/ or increased size of adenotonsillar tissue	Oro/nasopharyngeal airway	Collapsible airways with increased size of adenotonsillar tissue Obesity Craniofacial disorders
Grunting		Glottis	Respiratory distress syndrome (neonates) Pneumonia Bacterial infection
Rattle	Rattle is created by the movement of excessive secretions during normal airflow in the central and extrathoracic airways; it has a "rattling", noncontinuous quality, but quite commonly is mislabelled by parents as wheezing	Intra- and extrathoracic airways	Acute viral bronchitis Protracted bacterial bronchitis Neurologic disorders with swallowing dysfunction and/or chronic aspiration
Stridor	Stridor is a musical, monophonic, high-pitched sound that can be heard without a stethoscope; its presence suggests significant obstruction of airflow in the larynx and trachea	Larynx and trachea	Croup Inhaled foreign body – toys, food Epiglottitis Bacterial tracheitis Laryngomalacia/Tracheomalacia Vocal cord dysfunction Vascular ring
Wheezing (wheeze)	Wheeze is a continuous, usually highpitched whistling sound that is accompanied by prolongation of the expiratory phase; it is believed to originate from oscillation of large airways in response to turbulent airflow in partially blocked intrathoracic airways.	Intrathoracic airways (primarily expiratory)	Asthma Viral wheeze Bronchiolitis Foreign body Protracted bacterial bronchitis Tracheo/bronchomalacia

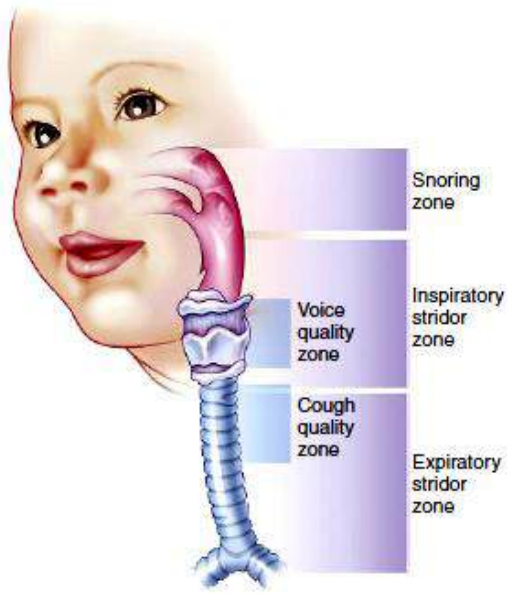


FIG. Listening Can Help Locate the Site of Airway Obstruction. *[Eavey RD, 1986]*

A loud, gasping **snore** suggests enlarged tonsils or adenoids.

Stridor during inspiration **(inspiratory stridor)** suggests the airway is compromised at the level of the supralaryngeal structures (epiglottis and arytenoid cartilages), vocal cords, subglottic region, or upper trachea. With forced inspiration, intrathoracic pressure becomes quite negative and is less than atmospheric pressure, promoting collapse at or just above the site of obstruction.

Expiratory stridor or central wheeze results from narrowing or collapse of the lower trachea or bronchi. During forced exhalation, rising pleural pressure may exceed intratracheal pressure.

Airway noise during both inspiration and expiration (**biphasic stridor**) often represents a fixed obstruction of the vocal cords or subglottic space.

Hoarseness or a weak cry is a byproduct of obstruction at the vocal cords. If a cough is croupy or low pitched, suspect tracheal pathology.

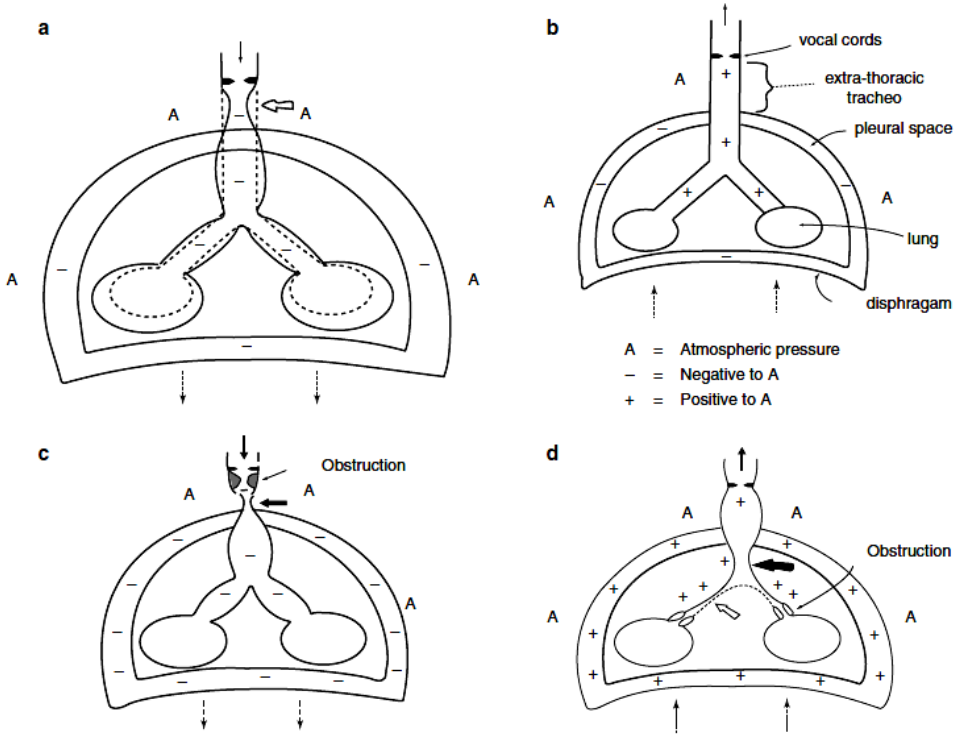


FIG. **(a) Normal Inspiration.** At end-expiration, intrapleural pressure is less than atmospheric pressure, so it should maintain airway patency. In infants the highly compliant chest wall does not provide the support required. Thus airway closure occurs with each breath. Descent of the diaphragm and contraction of the intercostals muscles develop a greater negative intrathoracic pressure relative to intraluminal and atmospheric pressure. The net result is a longitudinal stretching of the larynx and trachea, dilation of the intrathoracic trachea and bronchi, movement of air into the lungs, and some dynamic collapse of the extrathoracic trachea due to the increased compliance of the trachea ad the negative intraluminal pressure in relation to atmospheric pressure.
(b) Normal expiration. Intraluminal pressures are slightly positive in relation to atmospheric pressure, so air is forced out of the lungs.
(c) Extrathoracic obstruction (obstructed inspiration). Respiratory dynamics occurring with upper airway obstruction; note the severe dynamic collapse of the extrathoracic trachea below the level of obstruction. This collapse is greatest at the thoracic inlet, where the largest pressure gradient exists between negative intratracheal pressure and atmospheric pressure.
(d) Intrathoracic obstruction (obstructed expiration). Respiratory dynamics occurring with lower airway obstruction. Breathing through a partially obstructed lower airway (such as occurs in bronchiolitis or asthma) results in greater positive intrathoracic pressures, with dynamic collapse of the intrathoracic airways (prolonged expiration or wheezing) [Zalzal GH, 2003]

Differential diagnosis in a child presenting with stridor

Diagnosis	In favour
Viral croup	– Barking cough – Respiratory distress – Hoarse voice – If due to measles, signs of measles
Retropharyngeal abscess	– Soft tissue swelling in back of the throat – Diffi culty in swallowing – Fever
Foreign body	– Sudden history of choking – Respiratory distress
Laryngomalacia/ Tracheomalacia	– Underdeveloped cartilage in the airway wall, which collapses during inspiration, thereby causing turbulent airflow – Stridor present since birth
Diphtheria	– Bull neck appearance due to enlarged cervical nodes and oedema – Red throat – Grey pharyngeal membrane – Blood-stained nasal discharge – No evidence of DPT vaccination
Epiglottitis	– Soft stridor – 'Septic' child – Little or no cough – Drooling of saliva – Inability to drink
Anaphylaxis	– History of allergen exposure – Wheeze – Shock – Urticaria and oedema of lips and face
Burns	– Swollen lips – Smoke inhalation

Respiratory Distress & Respiratory Failure

CASE STUDY

A 6-month-old boy has been coughing and breathing fast for the past day. This morning he refused feeding and has been irritable. On examination, the infant is fussy. He has an oxygen saturation of 92%, a respiratory rate of 60 breaths/min, a pulse of 140 beats/min, and a normal blood pressure and temperature. In addition, he has nasal flaring, intercostal and supraclavicular retractions, and occasional grunting.

Questions

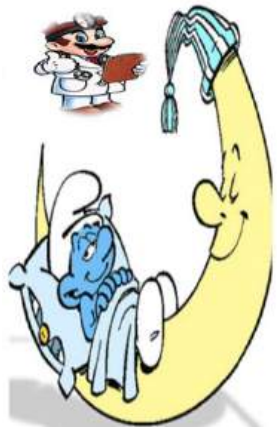
1. What are the causes of respiratory distress in infants and children? 2. What are the signs and symptoms of respiratory distress in infants and children? 3. What are the signs and symptoms of impending respiratory failure in infants and children? 4. What are the critical interventions for infants and children in respiratory distress?

The signs and symptoms of respiratory compromise may be subtle, particularly in small infants. Decompensation may occur rapidly if ventilation or oxygenation is inadequate but may be prevented by prompt recognition and treatment.

Respiratory distress is defined as increased work of breathing, and it usually precedes respiratory failure.

Respiratory failure occurs when ventilation or oxygenation is not sufficient to meet the metabolic demands of the tissues. Thus, oxygenation of the blood is inadequate or carbon dioxide is not eliminated. Respiratory failure may lead to cardiopulmonary arrest if not corrected promptly.

RESPIRATORY DISTRESS	RESPIRATORY FAILURE
• Increased respiratory rate (tachypnea) • Presence of chest retractions • Nasal flaring • Grunting • Diaphoresis • Alterations in mental status • Poor feeding • Inability to speak in sentences • Presence of pale or cyanotic skin • Presence of central cyanosis	Respiratory failure describes any impairment in oxygenation or ventilation in which the arterial oxygen tension falls below 60 mm Hg (hypoxemia), the carbon dioxide tension rises above 50 mm Hg (hypercarbia, hypercapnia) and the pH drops below 7.35, or both. • **PaO2 < 60 mm Hg** • **$PaCO_2$ > 50 mm Hg** • **pH < 7.35**



Common Causes of Respiratory Distress in Infants and Children

Respiratory diseases	NonRespiratory diseases
· Epiglottitis · Croup · Bronchiolitis · Pneumonia · Reactive airway disease (asthma) · Foreign body aspiration	• Cardiac diseases • Metabolic disease with acidosis • Neuromuscular disease

Epidemiology	Respiratory distress continues to be the most common reason for hospital admission. Such admissions usually involve young infants with acute infections such as bronchiolitis or croup. Reactive airway disease (asthma) accounts for respiratory distress–related admission commonly in older children.
Clinical Presentation *(see p. 12)*	Increases in respiratory rate and work of breathing are the most common signs of respiratory disease. Effortless tachypnea may be a sign of respiratory compensation for metabolic acidosis rather than an indication of pulmonary pathology. Similarly, hypoxia that fails to improve with supplemental oxygen may suggest a primary cardiac lesion. Tachycardia is often present, although bradycardia, if present, may be an ominous sign of impending cardiopulmonary failure. Signs of poor oxygenation include alterations in mental status, head bobbing, and change in skin color. Pallor, mottling, and cyanosis are often late signs indicating respiratory failure and shock. Children who are severely hypoxemic may first appear dusky or pale. If children are anemic, cyanosis may not be evident, although oxygen saturation is low.
Pathophysiology	Decrease in tidal volume → Compensatory increase in respiratory rate → Maintaining adequate minute ventilation *If the minute ventilation is still insufficient for adequate gas exchange or the child can no longer sustain the increased work of breathing, respiratory failure ensues. Respiratory failure may then lead to acidosis, myocardial dysfunction, and shock and may progress to complete cardiopulmonary arrest.* Younger children oppose airway collapse by having higher respiratory rates, thus reducing the time allowed for expiration. If this is insufficient to maintain FRC then infants will attempt to reduce expiratory flow rates using partial closure of the glottis or upper airway. This leads to **grunting**, as seen in neonates with respiratory distress, where glottic closure maintains a positive expiratory pressure but reduces expiratory flow.

Different types of respiratory failure

Some clinicians divide respiratory failure into two categories.

- The **hypoxemic type** is generally caused by mismatch of ventilation and perfusion in the lung. Hypoxemic respiratory failure from mismatch of ventilation to perfusion is often associated with normal or low PCO2.
- Other patients with respiratory failure have an overall decrease in alveolar ventilation that is usually the result of upper airway obstruction, neuromuscular disease, thoracic trauma, or muscle fatigue. These patients have increases in PCO2 and relatively proportional decreases in PO2 (**hypercapnic type**).

The physiology in most children with respiratory failure is a combination of these two types, because one type often leads to the other. For instance, an infant with bronchiolitis initially may have hypoxemia from atelectasis and ventilation-perfusion mismatch, but may progress to inadequate alveolar ventilation when airway resistance is high and respiratory muscle fatigue supervenes.

Can respiratory failure be present without respiratory distress?

Absolutely. Children may hypoventilate because of reduced level of consciousness (ingestion, metabolic derangements, and head trauma) or neuromuscular dysfunction. After prolonged respiratory distress, children may become fatigued, and their work of breathing may appear normal in the presence of significant hypoventilation. Elevation of the PCO2 from hypoventilation may signal worsening fatigue and impending respiratory arrest.

MANAGEMENT OF RESPIRATORY DISTRESS

All infants or children in respiratory distress should be managed emergently. As stated earlier, in such situations, assessment and intervention often occur simultaneously. All children in respiratory distress should be reassessed frequently. The highest possible oxygen concentration should be delivered. Children who are able to maintain their own airway should never be forced to use an airway adjunct because this may cause increased anxiety and distress. Patients with clear airways can be maintained with simple interventions such as **oxygen** blown by the face or given by mask or nasal prongs. More advanced airway management such as bagvalve- mask ventilation or endotracheal intubation may be necessary for children who need assisted ventilation, airway protection, or hyperventilation.

Position

Children in respiratory distress who are alert and breathing spontaneously should be allowed to choose a **position of comfort.** Small infants who are incapable of positioning themselves are best placed upright with care taken not to flex or extend the neck. Children and their caregivers should be kept together to reduce anxiety.

The proper position for unconscious children is the "sniffing position," with the neck slightly flexed and the head extended to open the airway. This can be facilitated by placing a towel under the occiput of the head or shoulders. If simple positioning does not relieve an obstruction, the airway should be opened using the chin lift or jaw thrust. If spinal trauma is a possibility, only the jaw thrust should be used. If this fails, **airway adjuncts**, such as nasopharyngeal or oropharyngeal airways, can be placed to help prevent the soft tissue of the oropharynx from collapsing against the posterior pharyngeal wall.

Monitoring

All infants and children in respiratory distress should be carefully monitored. Pulse oximetry will assist the clinician in determining the degree of oxygen saturation, and, if available, a cardiac and respiratory monitor will provide constant readings of respirations and heart rate. Frequent assessments of the patient are critical to ensure a good outcome.

Oxygen Administration

Oxygen should be delivered by any method tolerated by children.

Nasal prongs have 2 advantages: They are noninvasive and allow maintenance of a constant gas flow even when talking and eating. The concentration of oxygen delivered is limited, however, and irritation and drying of the mucous membranes may result. Oxygen masks deliver a higher concentration of humidified oxygen. Disadvantages include obstruction of children's visual field, potential for carbon dioxide retention, and anxiety because the face is covered. Various types of masks are available.

The **simple mask** can deliver 30% to 60% oxygen concentration at flow rates of 6 to 10 L/min. Room air is drawn into the mask through the exhalation ports in the side of the mask.

A **non-rebreathing mask** has valves that allow only oxygen (85%–95%) to flow from the reservoir bag to the patient on inhalation and additional valves on the exhalation ports of the mask that prevent entrapment of room air.

Fig. A non-rebreathing mask can deliver a high concentration of oxygen to a patient in respiratory distres.

The **face tent** is a soft plastic bucket shaped to the chin that is well tolerated by children. The face tent allows up to 40% oxygen to be delivered, and it has the advantage of allowing access to the face and mouth.

Fig. Use of a face tent

A **Venturi mask** is rarely used in children but has the advantage of precisely titrating the oxygen concentration to be delivered from 24% to 60%.

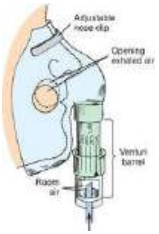


Fig. Venturi mask

Children with potential respiratory failure require **assisted ventilation** with **bag-valve-mask** devices or **endotracheal intubation**. Masks of the proper size should be used. The upper edge of the mask should fit snugly over the bridge of the nose without touching the eyes. The lower edge should rest directly on or just above the mandible. An oropharyngeal airway should be inserted in unconscious children to prevent the tongue from obstructing the upper airway. An appropriately sized oropharyngeal airway should reach from the patient's earlobe to the corner of the mouth. A nasopharyngeal airway may be inserted if the patient has an intact gag reflex to achieve the same goal. Measure the nasopharyngeal airway from the child's earlobe to the tip of the nostril. If a bag-valve-mask is not available, assisted ventilation can be given with a **pocket mask** with a one-way valve. Oxygen can be attached to the mask at the side port. Endotracheal intubation is indicated in those children who require control of the airway, need airway protection, or require hyperventilation.

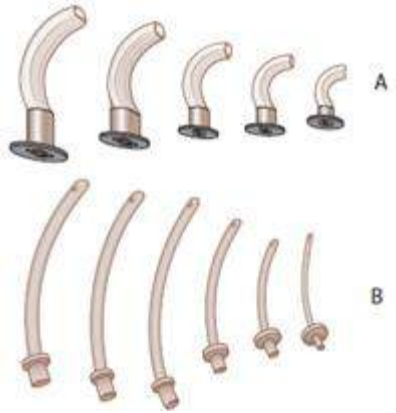


Fig. A, Oropharyngeal airways. B, Nasopharyngeal airways.

Fig. A pocket mask with a one-way valve and side oxygen port that can be used for assisted ventilation in the office setting.

CASE RESOLUTION

The fussy infant discussed in the case history has obvious signs of respiratory distress, including tachypnea, tachycardia, grunting, nasal flaring, and retractions. The differential diagnosis includes foreign body, infection such as croup or bronchiolitis, and reactive airway disease. It is important to place the infant in a position of comfort and provide supplemental oxygen before any diagnostic studies, such as chest radiograph, are performed. Appropriate treatment, such as albuterol, should be initiated while further evaluation proceeds. Pulse oximetry should be monitored. The clinical status of the infant should be reassessed periodically to prevent further deterioration.

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Acute Respiratory Infections (ARIs)

Acute respiratory infection **(ARI) – an acute infection of any part of the respiratory tract and related structures (sinuses, middle ear, pleural cavity), which lasts up to 30 days, except the middle ear infection where the duration of an acute episode is less than 14 days (WHO, 1990).**

Why knowledge of ARI is important?

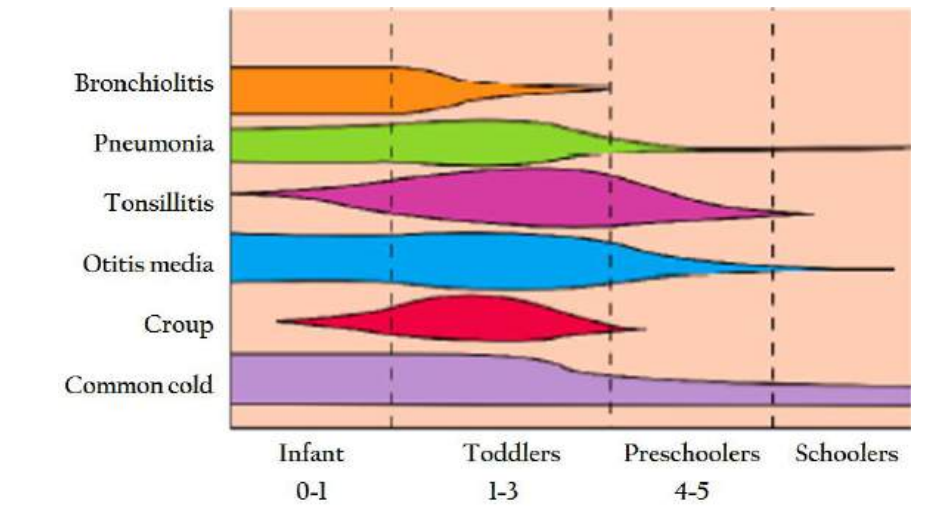
- Most common disease in children and adults
- Large range of diseases with the same clinical findings, but different outcomes
- 2-3% (average) of all cough diseases develops to pneumonia; up to 10% of those may die
- Complications develop soon: average between first signs and fatal outcome is 3 days

UPPER RESPIRATORY TRACT INFECTIONS (URTIs)

Most illnesses of childhood are infections; most childhood infections are respiratory; most are **acute upper respiratory infections**.

URTI	DESCRIPTION	CAUSES
	All may cause fever, vomiting and anorexia	*The great majority are viral*
Common cold (nasopharyngitis)	Cough, rhinorrhea, sneeze	Viral
Tonsillitis/pharyngotonsillitis (sore throat)	Enlarged, inflamed tonsills ± exudate	Viral or bacterial
Acute otitis media	Ear ache, inflamed and bulging tympanic membrane	Viral or bacterial
Sinusitis	Cough occuring after lying down, face pain, morning post-tussive emesis	Viral or bacterial

Incidence and type of respiratory infections varies with age.



Upper respiratory tract infections (URTIs) may be summarized as snuffles, fever and misery.

Viral URTIs are the commonest conditions encountered in primary care. Adults are immune to most of the upper respiratory tract viruses in their immediate environment – they only produce symptoms when they contract a new virus. Children have to acquire immunity to a host of viruses in their first few years, and have, on average, **six to ten episodes of infection annually**. Changes of environment – such as starting at the nursery or school – will produce an even higher infection rate. Although often trivial illnesses in medical terms, the symptoms of snuffles, fever and sore throat may make young children thoroughly miserable.

Nasal obstruction may cause feeding problems in babies as they are obligate nose breathers.

Symptomatic treatment includes paracetamol for the relief of discomfort and fever. Decongestant nose drops and oral decongestants are ineffective and best avoided. Saline nose drops are probably as effective as more expensive proprietary remedies.

Tonsillitis

Tonsillitis is a form of pharyngitis where there is intense inflammation of the tonsils, often with a purulent exudate. Common pathogens are group A β-haemolytic streptococci and the Epstein–Barr virus (infectious mononucleosis). Group A β-haemolytic streptococcus can be cultured from many tonsils; however, it is uncertain why it causes recurrent tonsillitis in some children but not in others.

Although the surface exudates seen in infectious mononucleosis are reported to be more membranous in appearance compared to bacterial tonsillitis, in reality it is not possible to distinguish clinically between viral and bacterial causes. Marked constitutional disturbance, such as headache, apathy and abdominal pain, white tonsillar exudate and cervical lymphadenopathy, is more common with bacterial infection.

Antibiotics (often penicillin, or erythromycin if there is penicillin allergy) are often prescribed for severe pharyngitis and tonsillitis even though only a third are caused by bacteria. They may hasten recovery from streptococcal infection. In order to eradicate the organism to prevent rheumatic fever, 10 days of treatment is required, but this is not indicated in the developed countries, where rheumatic fever is now exceedingly rare. In severe cases, children may require hospital admission for intravenous fluid administration and analgesia if they are unable to swallow solids or liquids. Amoxicillin is best avoided as it may cause a widespread maculopapular rash if the tonsillitis is due to infectious mononucleosis – look for generalized lymphadenopathy or hepatosplenomegaly.

> ***Patient Started Antibiotics Prior to Diagnosis***
>
> *Occasionally, patients may have started "leftover" antibiotics at home on the assumption that the diagnosis is group A beta streptococcal pharyngitis prior to presenting for diagnosis. This can make the diagnosis of group A beta streptococcal more difficult. Snellman et al. have reported that cultures of patients on anti-group A beta streptococcal active antibiotics may remain positive for a short period of time.*
>
> *If the patient has started antibiotics (two or more doses) before a laboratory test is done, the laboratory test results may be invalidated; therefore, a clinician should be consulted (Snellman, 1993 [High Quality Evidence]).*

Sore Throat for More Than Five Days Duration

Patients with pharyngitis persisting over five days are less likely to have group A beta streptococcal pharyngitis and should be seen to be evaluated. Infectious mononucleosis can be difficult to differentiate from group A beta streptococcal pharyngitis on clinical grounds, and some patients with infectious mononucleosis may have a positive throat culture for group A beta streptococcal. Serologic evidence of infectious mononucleosis should be sought in patients when splenomegaly is present or if pharyngitis symptoms persist over five to seven days. Other possibilities include other viral etiologies, bacterial sinusitis and other causes of postnasal drip.

Persistent Infection/Treatment Failure

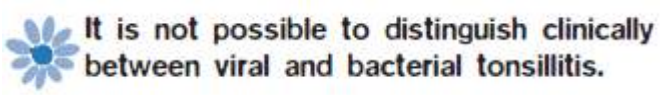
Patients who have been treated with antibiotics for streptococcal pharyngitis within the last month may represent a treatment failure, recurrent disease or carrier state, and further evaluation may be necessary.

Treatment failure is defined as recurrence of symptoms within seven days of completing antibiotic therapy. Possible reasons include: medication non-compliance, and pharyngeal flora producing beta-lactamase.

Recurrent Strep Pharyngitis

Recurrent strep pharyngitis is defined as recurrence of culture-positive group A beta streptococcal pharyngitis greater than seven days but within four weeks of completing antibiotic therapy. The patient is likely to be experiencing recurrent episodes of acute group A beta streptococcal pharyngeal infection when:

- *clinical findings suggest group A beta streptococcal as the etiology,*
- *epidemiologic findings suggest group A beta streptococcal as etiology (e.g., age 5-15 and winter/spring season),*
- *there is a repeated marked clinical response to antibiotic therapy,*
- *throat cultures are negative between episodes of pharyngitis, and*
- *there is a serologic response to group A beta streptococcal extra cellular antigens (ASO, anti-DNAase B) if measured.*



Tonsillectomy and adenoidectomy

Children with recurrent tonsillitis are often referred for removal of their tonsils, one of the commonest operations performed in children. Many children have large tonsils but this in itself is not an indication for tonsillectomy, as they shrink spontaneously in late childhood. The indications for tonsillectomy are controversial, and must be balanced against the risks of surgery, but include:

- *Recurrent severe tonsillitis (as opposed to recurrent URTIs) – tonsillectomy reduces the number of episodes of tonsillitis by a third, e.g. from three to two per year, but is unlikely to benefit mild symptoms.*
- *A peritonsillar abscess (quinsy)*
- *Obstructive sleep apnoea (the adenoids will also normally be removed).*

Like the tonsils, adenoids increase in size until about the age of 8 years and then gradually regress. In young children, the adenoids grow proportionately faster than the airway, so that their effect of narrowing the airway lumen is greatest between 2 and 8 years of age. They may narrow the posterior nasal space sufficiently to justify adenoidectomy. Indications for the removal of both the tonsils and adenoids are controversial but include:

- *Recurrent otitis media with effusion with hearing loss, where it gives a significant long-term additional benefit, especially if reinsertion of grommets is considered*
- *Obstructive sleep apnoea (an absolute indication).*

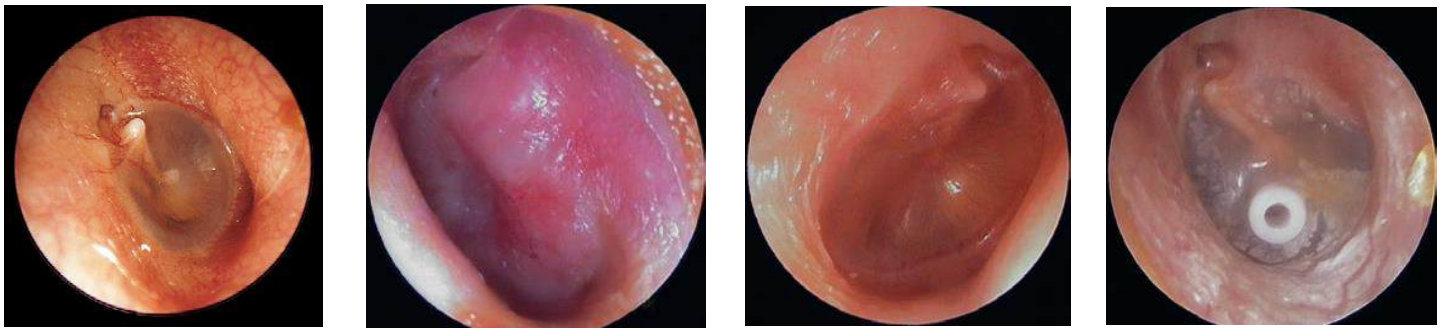
Otitis media

This presents with fever, misery and acute pain in the involved ear. Any viral URTI may produce a pink or red drum, but check for pain and look for evidence of loss of light reflex and bulging of the drum. Pathogens include viruses, especially RSV and rhinovirus, and bacteria including pneumococcus, nontypeable H. influenzae and Moraxella catarrhalis.

Serious complications are mastoiditis and meningitis, but are now uncommon. Pain should be treated with an analgesic such as paracetamol or ibuprofen. Regular analgesia is more effective than intermittent (as required) and may be needed for up to a week until the acute inflammation has resolved. Most cases of acute otitis media resolve spontaneously. Antibiotics marginally shorten the duration of pain but have not been shown to reduce the risk of hearing loss. It is often useful to give the parents a prescription, but ask them to use it only if the child remains unwell after 2–3 days. Amoxicillin is widely used. Neither decongestants nor antihistamines are beneficial.

Sometimes the tympanic membrane perforates during an acute infection, releasing a little pus which discharges from the ear. Perforation produces dramatic relief of symptoms and the damaged tympanic membrane usually heals spontaneously. Provided the ear discharge is transient and other symptoms resolve promptly no additional measures are needed. Glue ear may be a chronic consequence of otitis media or occur without acute infection. Hearing loss is the commonest symptom, and evidence suggests that prophylactic antibiotics for a few months can reduce the need for grommets or other surgery.

Fig. Appearance of the eardrum



Normal **Acute otitis media** **Otitis media with effusion** **Grommet**

Sinusitis

Infection of the paranasal sinuses may occur with viral URTIs. Occasionally there is secondary bacterial infection, with pain, swelling and tenderness over the cheek from infection of the maxillary sinus. As the frontal sinuses do not develop until late childhood, frontal sinusitis is uncommon in the first decade of life. Antibiotics and analgesia are used for acute sinusitis in addition to topical decongestants. There is some recent evidence that the concurrent use of intranasal corticosteroids or antihistamines together with antibiotics hasten recovery.

CROUP (LARYNGOTRACHEOBRONCHITIS)

Croup is the most common infectious cause of acute stridor and upper airway obstruction seen in children. Croup is usually considered to exist in two forms:
• viral croup
• recurrent (or spasmodic) croup.

Viral Croup

The term **laryngotracheobronchitis** refers to viral infection of the glottic and subglottic regions. Some clinicians use the term **laryngotracheitis** for the most common and most typical form of croup and reserve the term **laryngotracheobronchitis** for the more severe form that is considered an extension of laryngotracheitis associated with bacterial superinfection that occurs 5-7 days into the clinical course.
It is seen in the early fall and winter months, when viral upper respiratory tract infections reach their peak. The age group most frequently affected is between 6 months and 6 years of age, and it is seen in males more than in females.

Several viruses can cause croup; however, parainfluenza type I is the most common organism. Parainfluenza types II and III, respiratory syncytial virus, adenovirus, and influenza can also cause croup. Mycoplasma pneumoniae has also been implicated in croup.

Many children have a 1- to 3-day history of viral prodrome consisting of nasal symptoms such as congestion or rhinorrhea and possibly fever. Subsequently, there is development of a harsh, barky cough that is often described to be similar to “a barking seal or dog.” They may also have inspiratory stridor as well as respiratory distress indicated by nasal flaring and suprasternal and subcostal retractions. Stridor is often worsened with activity, crying, and increased anxiety or agitation. Typically, the course of illness lasts for no more than 1 week.

Croup is diagnosed clinically by history and physical examination. An x-ray of the upper airway can be useful to distinguish croup from other entities such as a retropharyngeal abscess or foreign body. In croup, a “steeple sign”, which is the tapering of the subglottic airway, may be seen, but many patients will also have normal x-rays.

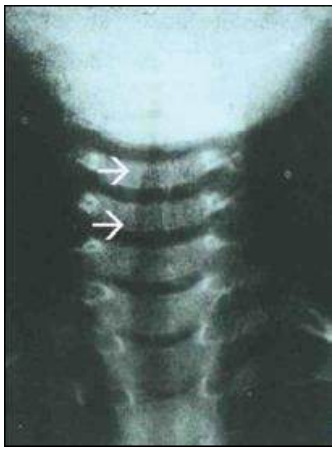


Fig. The classic ‘steeple sign’ of croup as shown on posterior-anterior neck radiography, resulting in a narrowed column of subglottic air (top arrow) and an enlargement of the column (bottom arrow).

Diagnosis

Mild croup is characterized by:
- fever
- a hoarse voice
- a barking or hacking cough
- stridor that is heard only when the child is agitated.

Severe croup is characterized additionally by:
- stridor even when the child is at rest
- rapid breathing and lower chest indrawing
- cyanosis or oxygen saturation ≤ 90%.

Because croup is a disease of the upper airway and gas exchange in the alveoli is usually unaffected, decreased oxygen saturation is a late sign of severity. Oxygenation may be maintained even in severe croup.

The differential diagnosis of croup includes retropharyngeal abscess, epiglottitis, foreign body, angioedema, and structural abnormalities such as laryngomalacia or subglottic stenosis. Obtaining a thorough and careful history greatly helps to differentiate croup from these other conditions.

Children who have recurrent croup should be investigated for other problems beyond simply recurring viral infections, such as anatomic abnormalities or GERD.

Treatment

Mild croup can be managed at home with supportive care, including encouraging oral fluids, breastfeeding or feeding, as appropriate.

A child with **severe croup** should be admitted to hospital. Try to avoid invasive procedures unless undertaken in the presence of an anaesthetist, as they may precipitate complete airway obstruction.

_ **Steroid treatment.** Give one dose of oral dexamethasone (0.6 mg/kg) or equivalent dose of some other steroid: dexamethasone or prednisolone. If available, use nebulized budesonide at 2 mg. Start the steroids as soon as possible. It is preferable to dissolve the tablet in a spoonful of water for children unable to swallow tablets. Repeat the dose of steroid for children who vomit.

_ **Adrenaline.** As a trial, give the child nebulized adrenaline (2 ml of 1:1000 solution). If this is effective, repeat as often as every hour, with careful monitoring. While this treatment can lead to improvement within 30 min in some children, it is often temporary and may last only about 2 h.

_ **Antibiotics.** These are not effective and should not be given.

_ Monitor the child closely and ensure that facilities for an emergency intubation and/or tracheostomy are immediately available if required, as airway obstruction can occur suddenly.

In a child with severe croup who is deteriorating, consider the following:

_ **Intubation and/or tracheostomy:** If there are signs of incipient complete airway obstruction, such as severe lower chest wall indrawing and restlessness, intubate the child immediately.
_ If this is not possible, transfer the child urgently to a hospital where intubation or emergency tracheostomy can be done. Tracheostomy should be done only by experienced staff.
_ Avoid using oxygen unless there is incipient airway obstruction. Signs such as severe lower chest wall indrawing and restlessness are more likely to indicate the need for intubation or tracheostomy than oxygen. Nasal prongs or a nasal or nasopharyngeal catheter can upset the child and precipitate obstruction of the airway.

_ However, oxygen should be given if there is incipient complete airway obstruction and intubation or tracheostomy is deemed necessary. **Call for help** from an anaesthetist and surgeon to intubate or perform a tracheostomy.

Supportive care

_ Keep the child calm, and avoid disturbance as much possible.
_ If the child has fever (≥ 39 °C or ≥ 102.2 °F) that appears to be causing distress, give paracetamol.
_ Encourage breastfeeding and oral fluids. Avoid parenteral fl uids, as this involves placing an IV cannula, which can cause distress that might precipitate complete airway obstruction.
_ Encourage the child to eat as soon as food can be taken. Avoid using mist tents, which are not effective, which separate the child from the parents and which make observation of the child's condition difficult. Do not give sedatives or antitussive medicines.

Monitoring

The child's condition, especially respiratory status, should be assessed by nurses every 3 h and by doctors twice a day. The child should occupy a bed close to the nursing station, so that any sign of incipient airway obstruction can be detected as soon as it develops.

Spasmodic croup, an entirely different disease, is common, frequently occurs at night, and may be recurrent. It is characterized by the sudden onset of hoarseness, barking cough, and stridor. This condition may resolve when children are exposed to humid air. The etiology is unknown but is probably either a reaction to a viral infection or an allergic phenomenon. Gastroesophageal reflux (GER) has also been associated with recurrent croup. There may be a family history of recurrent stridor in children with spasmodic croup and it tends to occur in older aged children. Parents can attempt supportive care at home, such as exposure to cool night air to improve symptoms. Treatment with racemic epinephrine and steroids is helpful, as in viral croup. If symptoms are frequent and recurrent, structural abnormalities of the airway should also be considered.

Bacterial tracheitis (pseudomembranous croup)

This rare but dangerous condition is similar to severe viral croup except that the child has a high fever, appears toxic and has rapidly progressive airways obstruction with copious thick airway secretions. It is caused by infection with Staphylococcus aureus. Treatment is by intravenous antibiotics and intubation and ventilation if required.

Acute epiglottitis

Acute epiglottitis is a life-threatening emergency due to the high risk of respiratory obstruction. It is caused by H. influenzae type b. In many countries, the introduction of universal Hib immunisation in infancy has led to a >99% reduction in the incidence of epiglottitis and other invasive H. influenzae type b infections. There is intense swelling of the epiglottis and surrounding tissues associated with septicaemia. Epiglottitis is most common in children aged 1–6 years but affects all age groups. It is important to distinguish clinically between epiglottitis and croup, as they require quite different treatment.

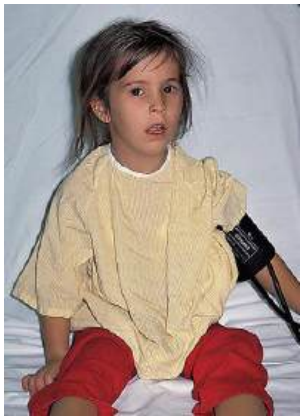
The onset of epiglottitis is often very acute, with:

- *high fever in an ill, toxic-looking child*
- *an intensely painful throat that prevents the child from speaking or swallowing; saliva drools down the chin*
- *soft inspiratory stridor and rapidly increasing respiratory difficulty over hours*
- *the child sitting immobile, upright, with an open mouth to optimise the airway.*

If the diagnosis of epiglottitis is suspected, urgent hospital admission and treatment are required. A senior anaesthetist, paediatrician and ENT surgeon should be summoned and treatment initiated without delay. The child should be transferred directly to the intensive care unit or an anaesthetic room, and must be accompanied by senior medical staff in case respiratory obstruction occurs. The child should be intubated under controlled conditions with a general anaesthetic. Rarely, this is impossible and urgent tracheostomy is life-saving. Only after the airway is secured should blood be taken for culture and intravenous antibiotics such as cefuroxime started. The tracheal tube can usually be removed after 24 h and antibiotics given for 3–5 days. With appropriate treatment, most children recover completely within 2–3 days. As with other serious H. influenzae infections, prophylaxis with rifampicin is offered to close household contacts.

CASE STUDY

This 5-year-old girl developed a severe sore throat, drooling of saliva, a high fever and increasing difficulty breathing over 8 h. Epiglottitis was diagnosed and her airway was guaranteed with a nasotracheal tube. Antibiotics were started immediately. She made a full recovery.



At presentation

At 16 h, with nasotracheal and nasogastric tubes and an indwelling cannula for intravenous antibiotics

At 36 h, following removal of the nasotracheal and nasogastric tubes

Minutes count in acute epiglottitis.

LOWER RESPIRATORY TRACT INFECTIONS (LRTIs)

BRONCHITIS

Nonspecific bronchial inflammation is termed **bronchitis** and occurs in multiple childhood conditions. **Acute bronchitis** is a syndrome, usually viral in origin, with cough as a prominent feature.

Acute tracheobronchitis is a term used when the trachea is prominently involved. Nasopharyngitis may also be present, and a variety of viral and bacterial agents, such as those causing influenza, pertussis, and diphtheria, may be responsible. Isolation of common bacteria such as pneumococcus, *Staphylococcus aureus,* and *Streptococcus pneumoniae* from the sputum might not imply a bacterial cause that requires antibiotic therapy.

- The tracheobronchial epithelium can become significantly damaged or hypersensitized, leading to a protracted cough lasting 1-3 wk.
- The principal objective of the clinician is to **exclude pneumonia**, which is more likely caused by bacterial agents requiring antibiotic therapy.
- There is no specific therapy for acute bronchitis. The disease is self-limited, and antibiotics, although often prescribed, do not hasten improvement. Frequent shifts in position can facilitate pulmonary drainage in infants. Older children are sometimes more comfortable with humidity, but this does not shorten the disease course. Cough suppressants can relieve symptoms but can also increase the risk of suppuration and inspissated secretions and, therefore, should be used judiciously. Antihistamines dry secretions and are not helpful; expectorants are likewise not indicated.

PLASTIC BRONCHITIS

Plastic bronchitis is a rare condition characterized by recurrent episodes of airway obstruction secondary to the formation of large proteinaceous branching casts that take on the shape of and obstruct the tracheobronchial tree. It is not a single disease entity, but rather represents an altered state of respiratory epithelial function and is most frequently encountered in the setting of underlying pulmonary or congenital cardiac disease, although there have been reports of plastic bronchitis complicating lymphangitic disorders, pulmonary infections, and the acute chest syndrome of sickle cell disease. In comparison to the smaller bronchial and bronchiolar casts seen with mucus plugging, the lesions of plastic bronchitis are more extensive, with casts that can outline large segments of the airway to the level of the terminal bronchioles.

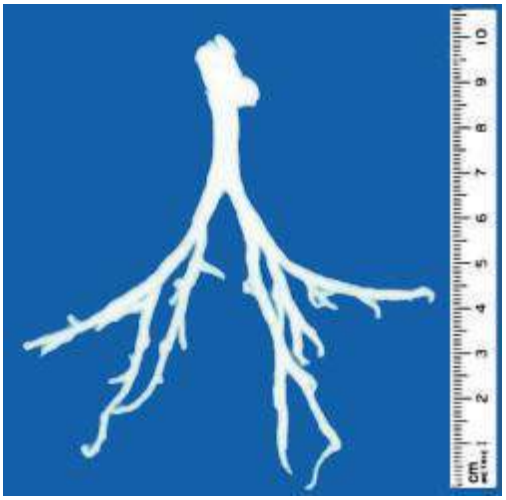


Fig. Tracheobronchial casts following bronchoscopic extraction. Casts show branched architecture corresponding to the bronchial tree.

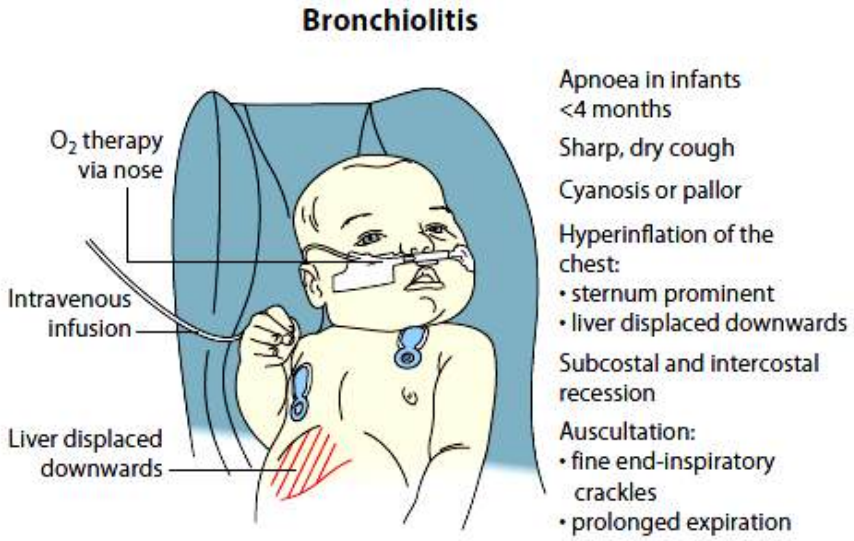
These casts may be spontaneously expectorated or may require bronchoscopic removal for relief of potentially fatal airway obstruction.

BRONCHIOLITIS

Bronchiolitis is a lower respiratory viral infection, which is typically most severe in young infants, occurs in annual epidemics and is characterized by airways obstruction and wheezing. It is most commonly caused by **respiratory syncytial virus** (RSV). Secondary bacterial infection may occur.
The management of bronchiolitis associated with fast breathing or other sign of respiratory distress is therefore similar to that of pneumonia. Episodes of wheeze may occur for months after an attack of bronchiolitis (post-RSV reactive airway disease), but will eventually stop.

Diagnosis

Typical features of bronchiolitis, on examination, include:
■ wheezing that is not relieved by up to three doses of a rapid-acting bronchodilator
■ hyperinflation of the chest, with increased resonance to percussion
■ lower chest wall indrawing
■ fine crackles and wheeze on auscultation of the chest
■ difficulty in feeding, breastfeeding or drinking owing to respiratory distress
■ nasal discharge, which can cause severe nasal obstruction.



Treatment

Most children can be treated at home, but those with the following signs of severe pneumonia should be treated in hospital:
■ oxygen saturation < 90% or central cyanosis
■ apnoea or history of apnoea
■ inability to breastfeed or drink, or vomiting everything
■ convulsions, lethargy or unconsciousness
■ gasping and grunting (especially in young infants).

Oxygen

- Give oxygen to all children with severe respiratory distress or oxygen saturation ≤ 90%. The recommended method for delivering oxygen is by nasal prongs or a nasal catheter.
- The nurse should check, every 3 h, that the prongs are in the correct position and not blocked with mucus, and that all connections are secure.

Antibiotic treatment is indicated only if the child has signs of pneumonia (fast breathing and lower chest wall indrawing).

Supportive care

If the child has fever (≥ 39 °C or ≥ 102.2 °F) that appears to be causing distress, give paracetamol.

Ensure that the hospitalized child receives daily maintenance fluids appropriate for age, but avoid overhydration. Encourage breastfeeding and oral fluids.

Encourage the child to eat as soon as food can be taken. Nasogastric feeding should be considered in any patient who is unable to maintain oral intake or hydration (expressed breast milk is the best).

Gentle nasal suction should be used to clear secretions in infants where nasal blockage appears to be causing respiratory distress. Monitoring A hospitalized child should be assessed by a nurse every 6 h (or every 3 h if there are signs of very severe illness) and by a doctor at least once a day. Monitor oxygen therapy. Watch for signs of respiratory failure, i.e. increasing hypoxia and respiratory distress leading to exhaustion.

Complications

If the child fails to respond to oxygen therapy or the child's condition worsens suddenly, obtain a chest X-ray to look for evidence of pneumothorax. Tension pneumothorax associated with severe respiratory distress and shift of the heart requires immediate relief by placing a needle to allow the air that is under pressure to escape (needle thoracocentesis). Following this, a continuous air exit should be assured by inserting a chest tube with an underwater seal until the air leak closes spontaneously and the lung expands. If respiratory failure develops, continuous positive airway pressure may be helpful.

Infection control

Bronchiolitis is very infectious and dangerous to other young children in hospital with other conditions. The following strategies may reduce cross-infection:

- hand-washing by personnel between patients
- ideally isolate the child, but maintain close observation
- during epidemics, restrict visits to children by parents and siblings with symptoms of upper respiratory tract infection.

Discharge

An infant with bronchiolitis can be discharged when respiratory distress and hypoxaemia have resolved, when there is no apnoea and the infant is feeding well. Infants are at risk for recurrent bronchiolitis if they live in families where adults smoke or if they are not breastfed. So, advise the parents against smoking. Follow-up Infants with bronchiolitis may have cough and wheeze for up to 3 weeks. As long as they are well with no respiratory distress, fever or apnoea and are feeding well they do not need antibiotics.

WHEEZING DISORDERS (LOWER AIRWAY OBSTRUCTION) IN CHILDREN

Wheeze is a high-pitched whistling sound on expiration. To hear a wheeze, even in mild cases, place your ear next to the child's mouth and listen to the breathing while the child is calm, or use a stethoscope.

Increased resistance to air ow can be caused by conditions (1) inside the lumen, (2) in the wall of the airway, and (3) in the peribronchial region.

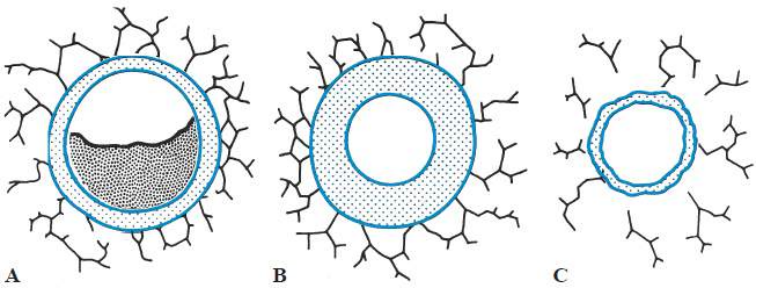


Fig. Mechanisms of airway obstruction.
A. *The lumen is partly blocked, for example, by excessive secretions.*
B. *The airway wall is thickened , for example , by edema or hypertrophy of smooth muscle.*
C. *The abnormality is outside the airway; in this example, the lung parenchyma is partly destroyed and the airway has narrowed because of the loss of radial traction.*

In the first 2 years of life, wheezing is most commonly caused by acute viral respiratory infections such as **bronchiolitis** or **coughs and colds**. After 2 years of age, most wheezing is due to asthma. Some children with pneumonia present with wheeze. It is important always to consider treatment for pneumonia, particularly in the first 2 years of life. Children with wheeze but no fever, chest indrawing or danger signs are unlikely to have pneumonia and should therefore not be given antibiotics.

Causes of wheezing

Infection	Reactive Airways Disease	Congenital Structural Anomalies	Chronic Aspiration	Other Causes
• Bronchiolitis • Pneumonia • Bronchitis • Laryngo-tracheobronchitis • Bacterial tracheitis • Toxocariasis • Ascariasis	• Asthma • Exercise-induced asthma • Anaphylaxis • Nighttime cough asthma • Toxic exposure (smoke, organophosphate poisoning) • Allergic aspergillosis	• Vascular rings • Bronchiectasis • Lung cysts • Laryngotracheo-esophageal cleft • Tracheobroncho-malacia	• Gastro-esophageal reflux • Bulbar palsy • Tracheo-esophageal fistula	• ***Foreign Body*** • ***Cardiac Disease*** • Bronchopulmonary dysplasia • α1-Antitrypsin deficiency • Laryngeal Dysfunction • Cystic fibrosis • Immotile cilia syndrome • Mediastinal tumors (lymphoma, teratoma, neuroblastoma, thymoma) • Pulmonary hemosiderosis • Sarcoidosis

Reactive airways disease is the most common cause of wheezing in childhood. Childhood asthma typically falls into 1 of 3 categories.

Transient wheezers are infants who wheeze when ill with lower respiratory tract infections but experience no further wheezing after age 3 years. More than 80% of infants with a history of wheezing in their first 12 months fall into this category.

Nonatopic wheezers are children with somewhat more reactive airways, a history of previous respiratory syncytial virus (RSV) infections, and persistent wheezing beyond 3 years of age, but symptoms may still resolve over time.

Atopic wheezers are those children who are most likely to develop persistent asthma.

Differential diagnosis in a child presenting with wheeze

Diagnosis	In favour
Asthma	– History of recurrent wheeze, chest tightness, some unrelated to coughs and colds or induced by exercise – Hyperinflation of the chest – Prolonged expiration – Reduced air entry (if very severe, airway obstruction) – Good response to bronchodilators, unless very severe
Bronchiolitis	– First episode of wheeze in a child aged < 2 years – Wheeze episode at time of seasonal bronchiolitis – Hyperinflation of the chest – Prolonged expiration – Reduced air entry (if very severe, airway obstruction) – Poor or no response to bronchodilators – Apnoea in young infants, especially if born preterm
Wheeze associated with cough or cold	– Wheeze always related to coughs and colds – No family or personal history of asthma, eczema, hay-fever – Prolonged expiration – Reduced air entry (if very severe, airway obstruction) – Good response to bronchodilators – Tends to be less severe than wheeze associated with asthma
Foreign body	– History of sudden onset of choking or wheezing – Wheeze may be unilateral – Air trapping with hyper-resonance and mediastinal shift – Signs of lung collapse: reduced air entry and impaired breathing – No response to bronchodilators
Pneumonia	– Fever – Coarse crackles – Grunting

MANAGEMENT OF ACUTE RESPIRATORY ILLNESSES ACCORDING TO WHO/IMCI GUIDELINES

Patients and/or parents of children presenting or calling with symptoms suggestive of the common cold should be evaluated for other symptoms and the presence of more serious illness.

THE PRINCIPAL OBJECTIVE OF THE CLINICIAN IS TO EXCLUDE PNEUMONIA!

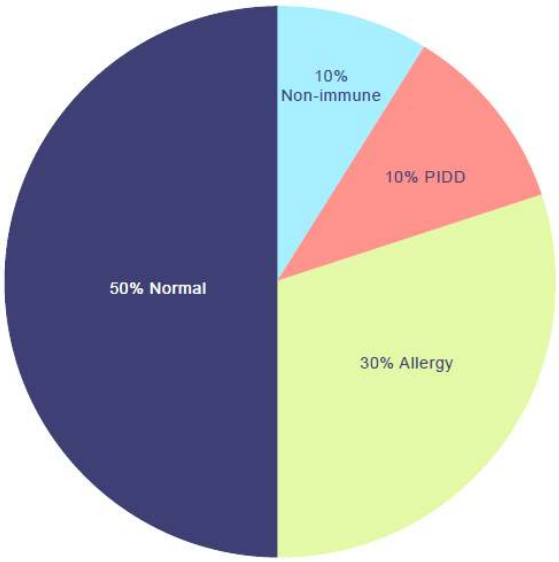
ASSESS	CLASSIFY	IDENTIFY TREATMENT
▪ Cough or difficulty in breathing with: – *Oxygen saturation < 90% or central cyanosis* – *Severe respiratory distress (e.g. grunting, very severe chest indrawing)* – *Signs of pneumonia with a general danger sign (inability to breastfeed or drink, lethargy or reduced level of consciousness, convulsions)* ▪ Stridor in calm child	SEVERE PNEUMONIA OR VERY SEVERE DISEASE	– Admit to hospital – Give oxygen if saturation < 90%. – Manage airway as appropriate – Give recommended antibiotic – Treat high fever if present
▪ Fast breathing: – *≥ 50 breaths/min in a child aged 2–11 months* – *≥ 40 breaths/min in a child aged 1–5 years* ▪ Chest indrawing	PNEUMONIA	– Home care – Give appropriate antibiotic – Advise the mother when to return immediately if symptoms of severe pneumonia – Follow up after 3 days
No signs of pneumonia or very severe disease	No pneumonia: cough or cold	– Home care – Soothe the throat and relieve cough with safe remedy – Advise the mother when to return. – Follow up after 5 days if not improving – If coughing for more than 14 days, refer to chronic cough

Recurrent Respiratory Infections (RRI) in Children

In the clinical practice, most of the children suffer from the recurrent infections of the upper airways, but in approximately 10-30%, the lower tract is also affected. There are two peaks of the incidence of RRI [Couriel, 2002]:

- *6-12 months of age → after consumption of the maternal passively transferred immunoglobulins with concomitant postponed synthesis of own antibodies,*
- *the involvement of the child in to the group of children at nursery or school.*

Approximately 50% of the children who present with recurrent infection, are actually "normal" children. A further 30% of recurrences result from underlying allergic inflammation, 10% from the primary immunodeficiency (PID) and the remaining 10% are caused by a variety of non-immune related chronic conditions [Stiehm et al, 2015].



The most frequent PID (selective IgA deficiency; mannose-binding lectin deficiency) are usually asymptomatic or have only mild clinical symptoms.

An underlying immunodeficiency is more likely when some of the following "warning" symptoms or signs occur [Champi et al., 2002; Slatter & Gennery, 2008]:

- *eight or more new ear infections (otitis media) within 12 months*
- *two or more serious sinus infections within 12 months*
- *two or more episodes of pneumonia within 12 months*
- *two or more invasive infections in the history (meningitis, cellulitis, osteomyelitis, septicaemia)*
- *failure of an infant to gain weight or grow normally ± chronic diarrhoea*
- *recurrent deep skin or organ abscesses*
- *persistent superficial candidiasis after age 1 year*
- *two or more months on antibiotics with little or no effect*
- *need for intravenous antibiotics to clear infections*
- *a family history of primary immunodeficiency.*

A pattern of recurrent or persistent infection is the major manifestation of primary immunodeficiencies. While most children with RRI have normal immunity, it is essential to recognise the child with underlying PID and investigate and treat appropriately. Prompt, accurate diagnosis of PID helps to direct the most appropriate treatment, predict prognosis and facilitate genetic counselling for the family.

There are also overlaps between allergy and PID with coexisting allergy in 31% of PID patients. Allergic features may be a componentt of selective IgA deficiency, common variable immunodeficiency (CVID), chronic granulomatous disorder (CGD) and Di George syndrome. Elevated IgE is seen in the hyper-IgE syndrome (HIES), Wiskott Aldrich syndrome, Omenn syndrome and immunodysregulation polyendocrinopathy enteropathy X-linked syndrome (IPEX).

Table. NON-IMMUNE RELATED CAUSES AND RRI

MECHANISM	CONDITION	
Ineffective mucus clearance	Primary ciliary dyskinesia (PCD) Cystic fibrosis (CF) Nervous system and muscular abnormalities with ineffective cough Bronchiectasis	
Airway obstruction	Eustachian tube dysfunction Sinus ostia obstruction Tonsil and adenoid hypertrophy Lymph node hyperplasia	Tumours Foreign body aspiration Vascular rings Airway malacia
Increased pulmonary blood flow	Cardiovascular abnormality	
Congenital airway abnormality	Developmental abnormalities of the airways and lungs	
Chronic infection	Mycobacterium tuberculosis Persistent bacterial bronchitis (PBB)	
Recurrent re-infection	Day-care attendance	
Exposure to irritants	Cigarette smoke GERD	

Protracted bacterial bronchitis (PBB) has recently been recognised as an important entity and cause for RRI. It often follows after an initial viral airway infection in younger children and manifests with an isolated wet cough that lasts for longer than 4 weeks. The cough is usually more prominent on reclining, in the early morning hours and during exercise. PBB patients may cough for the entire night and suffer from disrupted sleep. It is a neutrophil disease with associated biofilm production in the airway. Non-typable H. influenzae, S. pneumoniae and Moraxella catarrhalis are the most frequent colonising bacteria. PBB patients are commonly misdiagnosed as being asthmatic. Associated findings include wet rattles in both lung fields, stained sputum and other biofilm manifestations like chronic middle ear effusion and sinusitis. It remains a diagnosis of exclusion and should be differentiated from bronchiectasis and chronic suppurative lung disease. Recurrent PBB raises concern, as underlying risk factors to PBB may be present. Detailed investigation is needed in children who present with recurrent PBB.

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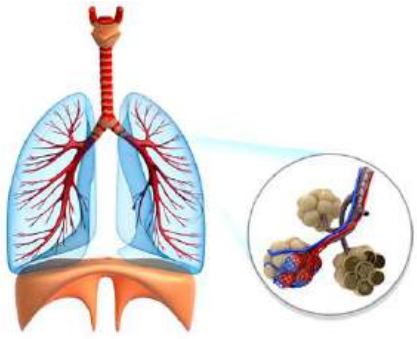
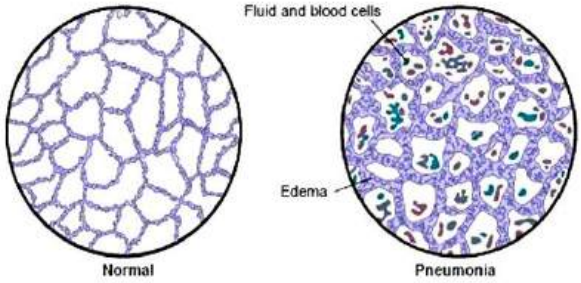
Pediatric Pneumonia

Pneumonia is a generic term that refers to acute inflammation and consolidation (solidification) of the pulmonary parenchyma, including alveoli and interstitial tissue*.



There are two major types of parenchymal lung disease:
- alveolar (airspace) disease
- interstitial disease

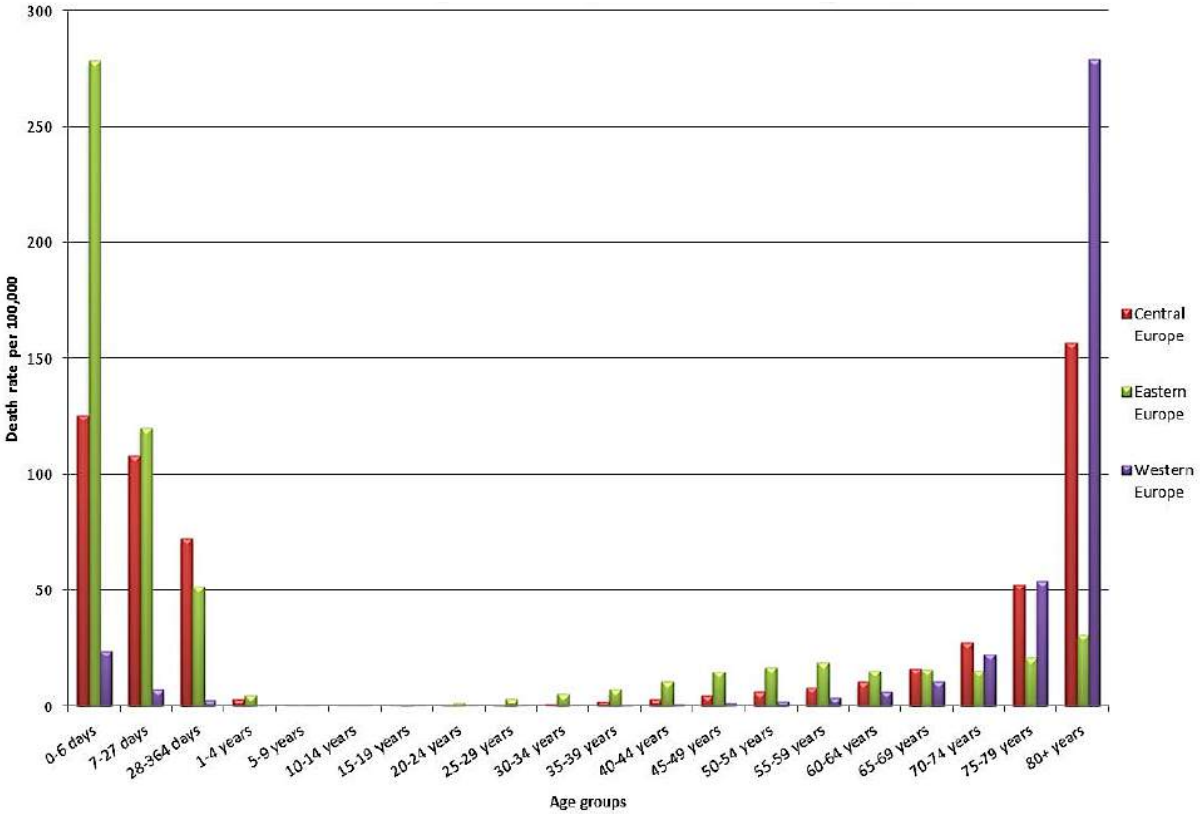


Pneumonia often occurs in three settings:

- **Community-acquired pneumonia (CAP)**: occurs in persons with no primary disorder of the immune system
- **Nosocomial pneumonia**: caused by organisms spread in a hospital environment to susceptible persons
- **Opportunistic pneumonia**: affects immunocompromised persons

Pneumonia is a severe form of acute lower respiratory infection, and is a major cause of childhood mortality under 5 years.

Death rates caused by pneumonia by European region and age group
[Institute of Health Metrics and Evaluation 2010]



WHAT AGENTS CAUSE COMMUNITY-ACQUIRED PNEUMONIA (CAP) IN CHILDREN ?

The etiology of community-acquired pneumonia in pediatrics is highly dependent on the age of the child (Table 1). Most studies cannot determine an etiology in about 50% of patients.

• **Newborn** – organisms from the mother's genital tract, particularly group B streptococcus, but also Gram-negative enterococci.
• **Infants and young children** – respiratory viruses, particularly RSV, are most common, but bacterial infections include *Streptococcus pneumoniae* or *Haemophilus influenzae*. *Bordetella pertussis* and *Chlamydia trachomatis* can also cause pneumonia at this age. An infrequent but serious cause is *Staphylococcus aureus.*
• **Children over 5 years** – *Mycoplasma pneumoniae, Streptococcus pneumoniae* and *Chlamydia pneumoniae* are the main causes.
• **At all ages *Mycobacterium tuberculosis* should be considered.**

Table 1 . ETIOLOGIC AGENTS OF CAP GROUPED BY AGE OF THE PATIENT

[Kliegman RM et al: Nelson textbook of pediatrics, ed 20, p2090]

AGE GROUP	FREQUENT PATHOGENS (IN ORDER OF FREQUENCY)
Neonates (<3 wk)	Group B streptococcus, *Escherichia coli,* other Gram-negative bacilli, *Streptococcus pneumoniae, Haemophilus influenzae* (type b,* nontypeable)
3 wk-3 mo	Respiratory syncytial virus, other respiratory viruses (rhinoviruses, parainfluenza viruses, influenza viruses, adenovirus), *S. pneumoniae, H. influenza* (type b,* nontypeable); if patient is afebrile, consider *Chlamydia trachomatis*
4 mo-4 yr	Respiratory syncytial virus, other respiratory viruses (rhinoviruses, parainfluenza viruses, influenza viruses, adenovirus), *S. pneumoniae, H. influenza* (type b,* nontypeable), *Mycoplasma pneumoniae,* group A streptococcus
≥5 yr	*M. pneumoniae, S. pneumoniae, Chlamydophila pneumoniae, H. influenzae* (type b,* nontypeable), influenza viruses, adenovirus, other respiratory viruses, *Legionella pneumophila*

**H. influenzae* type b is uncommon with routine *H. influenzae* type b immunization.

The cause of pneumonia in an individual patient is often difficult to determine because direct culture of lung tissue is invasive and rarely performed. Cultures performed on specimens obtained from the upper respiratory tract or "sputum" often do not accurately reflect the cause of lower respiratory tract infection. Healthy children may be colonized with a wide variety of potentially pathologic bacteria (e.g., *Staphylococcus aureus, Haemophilus influenzae*), which can be considered part of the normal flora; *Bordetella pertussis* is an exception. Cultures or antigen detection systems to identify respiratory viruses or chlamydia, however, are highly informative because these organisms are rarely carried asymptomatically.

PATHOGENESIS

The lungs have far greater contact with the surrounding environment and its microbial threats than any other part of the body. An average newborn baby has a body surface area of 0.2 m^2. The surface area of the infant's lungs is 3–4 m^2, as much as 20 times greater. As the infant matures, the disparity increases. An adult with a body surface of 2 m^2 has a pulmonary surface area of 70 m^2. This huge pulmonary surface area contacts the outside world with every tidal breath, drawing in potential contagion dozens of times each minute. It is no surprise that respiratory illnesses are the most common cause of death for children in the developing world.

The lower respiratory tract is normally kept sterile by physiologic defense mechanisms, including mucociliary clearance, the properties of normal secretions such as secretory immunoglobulin A (IgA), and clearing of the airway by coughing. Immunologic defense mechanisms of the lung that limit invasion by pathogenic organisms include macrophages that are present in alveoli and bronchioles, secretory IgA, and other immunoglobulins. Additional factors that promote pulmonary infection include trauma, anesthesia, and aspiration.

Viral pneumonia usually results from spread of infection along the airways, accompanied by direct injury of the respiratory epithelium, which results in airway obstruction from swelling, abnormal secretions, and cellular debris. The small caliber of airways in young infants makes such patients particularly susceptible to severe infection. Atelectasis, interstitial edema, and ventilation-perfusion mismatch causing significant hypoxemia often accompany airway obstruction. Viral infection of the respiratory tract can also predispose to secondary bacterial infection by disturbing normal host defense mechanisms, altering secretions, and modifying the bacterial flora.

Bacterial pneumonia most often occurs when respiratory tract organisms colonize the trachea and subsequently gain access to the lungs, but pneumonia may also result from direct seeding of lung tissue after bacteremia. When bacterial infection is established in the lung parenchyma, the pathologic process varies according to the invading organism.

- *M. pneumoniae* attaches to the respiratory epithelium, inhibits ciliary action, and leads to cellular destruction and an inflammatory response in the submucosa. As the infection progresses, sloughed cellular debris, inflammatory cells, and mucus cause airway obstruction, with spread of infection occurring along the bronchial tree, as it does in viral pneumonia.
- *S. pneumoniae* produces local edema that aids in the proliferation of organisms and their spread into adjacent portions of lung, often resulting in the characteristic focal lobar involvement.
- *Group A streptococcus* infection of the lower respiratory tract results in more diffuse infection with interstitial pneumonia. The pathology includes necrosis of tracheobronchial mucosa; formation of large amounts of exudates, edema, and local hemorrhage, with extension into the interalveolar septa; and involvement of lymphatic vessels and the increased likelihood of pleural involvement.
- *S. aureus* pneumonia manifests in confluent bronchopneumonia, which is often unilateral and characterized by the presence of extensive areas of hemorrhagic necrosis and irregular areas of cavitations of the lung parenchyma, resulting in pneumatoceles, empyema, or, at times, bronchopulmonary fistulas.

➢ **RECURRENT PNEUMONIA** is defined **as 2 or more** episodes in a single year **or 3 or more** episodes ever, with radiographic clearing between occurrences. An underlying disorder should be considered if a child experiences recurrent pneumonia (Table 2).

Table 2. DIFFERENTIAL DIAGNOSIS OF RECURRENT PNEUMONIA

[Kliegman RM et al: Nelson textbook of pediatrics, ed 20, p2091]

HEREDITARY DISORDERS	DISORDERS OF IMMUNITY	DISORDERS OF CILIA	ANATOMIC DISORDERS
Cystic fibrosis Sickle cell disease	HIV/AIDS Bruton agammaglobulinemia Selective immunoglobulin G subclass deficiencies Common variable immunodeficiency syndrome Severe combined immunodeficiency syndrome Chronic granulomatous disease Hyperimmunoglobulin E syndromes Leukocyte adhesion defect	Immotile cilia syndrome Kartagener syndrome	Pulmonary sequestration Lobar emphysema Gastroesophageal reflux Foreign body Tracheoesophageal fistula (H type) Bronchiectasis Aspiration (oropharyngeal incoordination) Aberrant bronchus

CLINICAL FEATURES

- **Fever** and **difficulty in breathing** are the commonest presenting symptoms, usually preceded by an upper respiratory tract infection. Other symptoms include cough, lethargy, poor feeding and an 'unwell' child.
- **Localised chest, abdominal, or neck pain** is a feature of pleural irritation and suggests bacterial infection.
- Examination reveals signs of respiratory distress - **tachypnoea, nasal flaring, chest indrawing** (Table 3).The best clinical sign of pneumonia in children is increased respiratory rate, and pneumonia can sometimes be missed if the respiratory rate is not measured in a febrile child (so-called 'silent pneumonia').
- There may be end-inspiratory coarse **crackles** over the affected area, but the classic signs of consolidation with dullness on percussion, decreased breath sounds and bronchial breathing over the affected area are often absent in young children. There may also be **wheezing** in children with pneumonia.
- Oxygen saturation readings may be decreased; this is an indication for hospital admission.

Table 3. CRITERIA FOR RESPIRATORY DISTRESS IN CHILDREN WITH PNEUMONIA *[Adapted from WHO criteria]*

1. Tachypnea, RR (breaths/min)
Age 0-2 months ≥ 60
Age 2-11 months ≥ 50
Age 1-5 years ≥ 40
2. Dyspnea
3. Chest retractions
4. Grunting
5. Nasal flaring
6. Apnea
7. Altered mental status
8. Pulse oximetry measurement <90% on room air

DIAGNOSIS

- An infiltrate on chest radiograph supports the diagnosis of pneumonia (Fig. 1, 2); the film may also indicate a complication such as a pleural effusion or empyema.
- Viral pneumonia is usually characterized by hyperinflation with bilateral interstitial infiltrates and peribronchial cuffing (Fig. 3). Confluent lobar consolidation is typically seen with pneumococcal pneumonia (Fig. 4). The radiographic appearance alone is not diagnostic, and other clinical features must be considered. **A chest X-ray may confirm the diagnosis, but with the exception of a classic lobar pneumonia characteristic of *Streptococcus pneumoniae*, a chest X-ray cannot differentiate between bacterial and viral pneumonia.**
- Routine chest radiographs are not necessary for the confirmation of suspected CAP in patients well enough to be treated in the outpatient setting (after evaluation in the office, clinic, or emergency department setting).
- Chest radiographs, posteroanterior and lateral, should be performed in patients with suspected or documented hypoxemia or significant respiratory distress and in patients with failed initial antibiotic therapy to verify the presence or absence of complications of pneumonia, including parapneumonic effusions, necrotizing pneumonia, and pneumothorax.
- Repeat chest radiographs are not required for proof of cure for patients with uncomplicated pneumonia.
- In younger children, a nasopharyngeal aspirate is useful to identify viral causes, but blood tests, including full blood count and acute phase reactants, are generally unhelpful in differentiating between a viral and bacterial cause.

Radiographic patterns of lobar consolidation and collapse on chest X-ray

It is very useful to understand the patterns of the CXR silhouette:

Consolidation	Increased shadowing, may have air bronchogram but no loss of volume or shift of mediastinum or other lobes
Collapse	Dense increased shadowing, but contracted, loss of lung volume, no bronchogram, shift of fissures and mediastinal structures

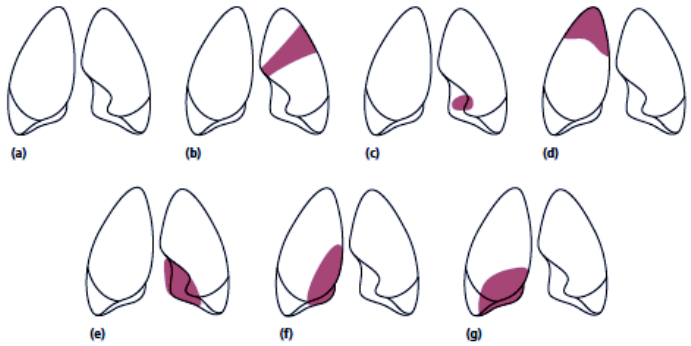


Fig. 1. Pneumonia shadowing patterns seen on chest X-ray. (a) Normal chest X-ray. (b) Left upper lobe segmental consolidation. (c) Lingular consolidation. (d) Right upper lobe consolidation with collapse (horizontal fissure and right hilar pulled up). (e) Left lower lobe collapse and consolidation (left hilar pulled down). (f) Loss of distinct right cardiac border (right middle lobe consolidation). (g) Right cardiac border still distinct. Right hemidiaphragm may be raised (right lower lobe consolidation)

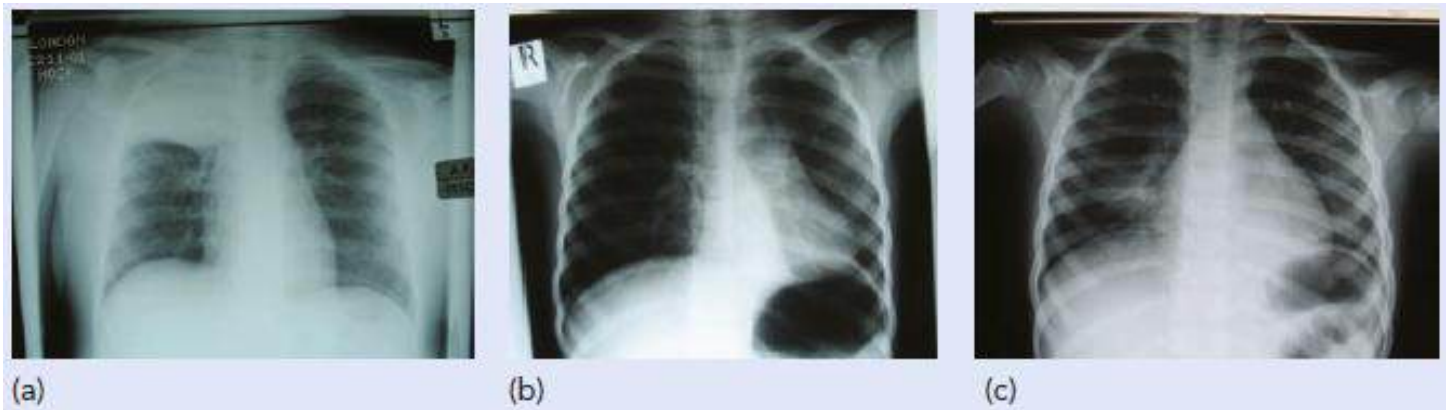


Fig. 2. Pneumonia. (a) Right upper lobe consolidation. (b) Left lower lobe (LLL) collapse consolidation. Note the left hilar is displaced downwards and the LLL is contracted, indicating collapse in addition to consolidation. (c) Right middle lobe consolidation

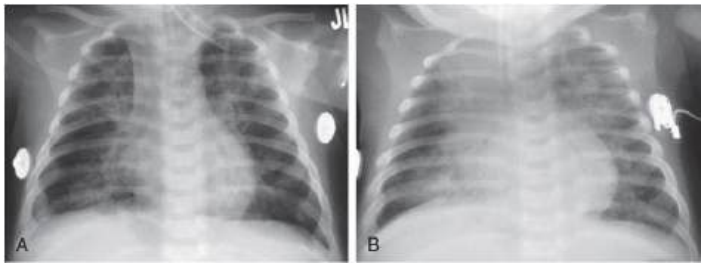


Fig. 3. ***A,*** **Radiographic findings characteristic of respiratory syncytial virus pneumonia in a 6 mo old infant with rapid respirations and fever.**
Anteroposterior radiograph of the chest shows hyperexpansion of the lungs with bilateral fine air space disease and streaks of density, indicating the presence of both pneumonia and atelectasis. An endotracheal tube is in place. *B,* One day later, the AP radiograph of the chest shows increased bilateral pneumonia.

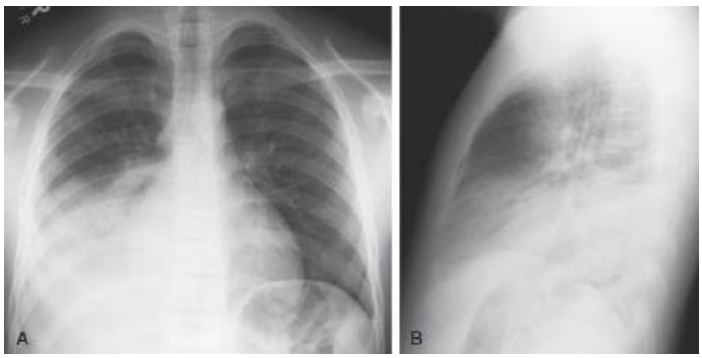


Fig. 4. Radiographic findings characteristic of pneumococcal pneumonia in a 14 yr old boy with cough and fever.
Posteroanterior *(A)* and lateral *(B)* chest radiographs reveal consolidation in the right lower lobe, strongly suggesting bacterial pneumonia.

Accuracy of Clinical Signs and Symptoms in the Diagnosis of Pneumonia in Children

				Likelihood ratio		Posttest probability*	
Study	*Sign/symptom*	*Sensitivity (%)*	*Specificity (%)*	*Positive*	*Negative*	*Positive (%)*	*Negative (%)*
Crain (1991)[1]†	Rales	15	99	15	0.86	63	9
	Retractions	26	98	13	0.76	59	8
	Rhonchi	26	98	13	0.76	59	8
	Respiratory rate ≥ 60 breaths per minute	50	95	8.3	0.53	48	6
	Rhinorrhea	74	87	5.7	0.3	39	3
	Wheezing	4	98	2	0.98	18	10
Lynch (2004)[2]‡	Tachypnea (age-specific)	13	95	2.6	0.92	22	9
	Crackles	43	73	1.6	0.78	15	8
	Fever on examination	47	68	1.5	0.78	14	8
	Tachycardia (age-specific)	51	60	1.3	0.82	13	8
	History of fever	92	21	1.2	0.38	12	4
	Decreased breath sounds	54	55	1.2	0.84	12	9
	Cough	88	16	1	0.75	10	8
Mahabee-Gittens (2005)[3]§	Nasal flaring (in infants 12 months and younger)	33	94	5.5	0.71	38	7
	Oxygen saturation ≤ 94%	26	93	3.7	0.80	29	8
	Oxygen saturation ≤ 96%	63	77	2.7	0.48	23	5
	Respiratory rate ≥ 50 breaths per minute	50	71	1.7	0.70	16	7
	Age > 12 months	66	57	1.5	0.60	14	6
	Respiratory rate ≥ 40 breaths per minute	77	43	1.4	0.53	13	6

*—Posttest probability is based on 10 percent pretest probability of pneumonia.
†—Study included infants younger than eight weeks (n=242) with fever >100.4°F (38.0°C). Reference standard was radiographic evidence of pneumonia.
‡—Study included children one to 16 years of age (n = 570) with clinically suspected pneumonia in whom radiography was performed in the emergency department. Critically ill children and those with chronic illness were excluded; only 3 percent were admitted to the hospital. Because cough, fever, or crackles led to inclusion in the study, the accuracy of these symptoms is underestimated. Reference standard was radiographic evidence of pneumonia, as evaluated by blinded radiologist.
§—Study included children two to 59 months of age (n = 510) presenting to the emergency department with cough and at least one other symptom of lower respiratory tract infection. Reference standard was a chest radiograph read by two blinded radiologists.

1. Crain EF, Bulas D, Bijur PE, Goldman HS. Is a chest radiograph necessary in the evaluation of every febrile infant less than 8 weeks of age? Pediatrics. 1991;88(4):821-824.
2. Lynch T, Platt R, Gouin S, Larson C, Patenaude Y. Can we predict which children with clinically suspected pneumonia will have the presence of focal infiltrates on chest radiographs? Pediatrics. 2004;113(3 pt 1):e186-e189.
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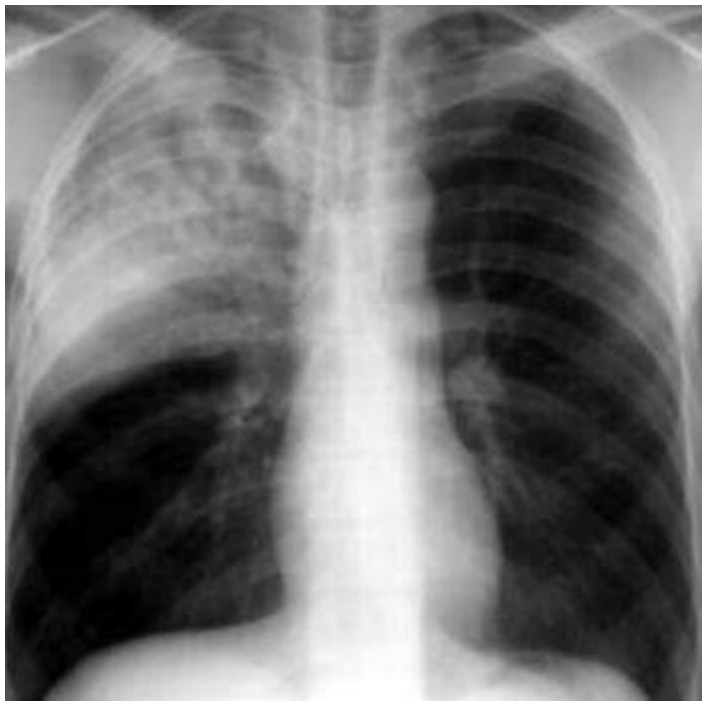
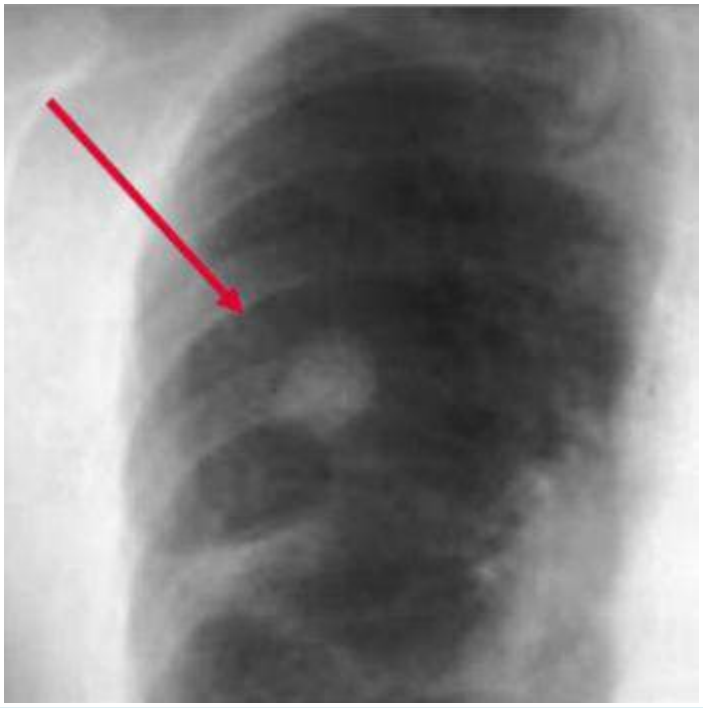
AIRSPACE VERSUS INTERSTITIAL DISEASE

These patterns often overlap, but recognition of one or the other helps with the differential diagnosis.

Airspace Disease	Interstitial Lung Disease (ILD)
	
Soft tissue opacities with hazy and indistinct margins	Discrete particles. Made up of dots (nodular) or lines (reticular) or both (reticulonodular)
Tend to respect segmental or lobar boundaries	Does not respect lobar boundaries
May contain air bronchograms *Bronchi are usually not visible, as their walls are thin, they contain air and are surrounded by air. When something of fluid dencity fills alveoli, air in bronchus becomes visible*	Usually no air bronchograms
Common airspace diseases: ▪ Pneumonia ▪ Pulmonary edema ▪ Pulmonary hemorrhage ▪ Aspiration – gastric juice	Common ILDs: ▪ Acute interstitial pneumonitis ▪ Cystic fibrosis ▪ Miliary tuberculosis ▪ Sarcoidosis ▪ Lung cancer – primary or metastatic

TREATMENT

Treatment of suspected bacterial pneumonia is based on the presumptive cause and the age and clinical appearance of the child.

- For mildly ill children who do not require hospitalization, **amoxicillin** is recommended. In communities with a high percentage of penicillin-resistant pneumococci, high doses of amoxicillin (90 mg/kg/24 hr) should be prescribed. Therapeutic alternatives include *cefuroxime axetil and amoxicillin/clavulanate*.
- For school-aged children and in children in whom infection with *M. pneumoniae* or *C. pneumoniae* is suggested, a **macrolide antibiotic** such as azithromycin is an appropriate choice.
- In adolescents, a **respiratory fluoroquinolone** (levofloxacin, moxifloxacin, gemifloxacin) may be considered as an alternative.
- The empiric treatment of suspected bacterial pneumonia in a hospitalized child requires an approach based on the clinical manifestations at the time of presentation. *Parenteral cefotaxime or ceftriaxone* is the mainstay of therapy when bacterial pneumonia is suggested.
- If clinical features suggest staphylococcal pneumonia (pneumatoceles, empyema), initial antimicrobial therapy should also include *vancomycin or clindamycin*.
- If viral pneumonia is suspected, it is reasonable to withhold antibiotic therapy, especially for those patients who are mildly ill, have clinical evidence suggesting viral infection, and are in no respiratory distress. Up to 30% of patients with known viral infection may have coexisting bacterial pathogens. Therefore, if the decision is made to withhold antibiotic therapy on the basis of presumptive diagnosis of a viral infection, deterioration in clinical status should signal the possibility of superimposed bacterial infection, and antibiotic therapy should be initiated.
- Indications for admission to a hospital are noted in Table 4.
- Empiric outpatient antibiotic therapy for pediatric CAP is noted in Table 5.

Table 4. FACTORS SUGGESTING NEED FOR HOSPITALIZATION OF CHILDREN WITH PNEUMONIA

[Adapted from Baltimore RS: Pneumonia. In Jenson HB, Baltimore RS, editors: *Pediatric infectious diseases: principles and practice,* Philadelphia, 2002, WB Saunders, p 801]

- **Age <6 mo**
- **Sickle cell anemia with acute chest syndrome**
- **Multiple lobe involvement**
- **Immunocompromised state**
- **Toxic appearance**
- **Moderate to severe respiratory distress**
- **Requirement for supplemental oxygen**
- **Complicated pneumonia***
- **Dehydration**
- **Vomiting or inability to tolerate oral fluids or medications**
- **No response to appropriate oral antibiotic therapy**
- **Social factors (e.g., inability of caregivers to administer medications at home or follow-up appropriately)**

- In developing countries, **oral zinc (20 mg/day)** helps accelerate recovery from severe pneumonia.
- The optimal duration of antibiotic treatment for pneumonia has not been well-established in controlled studies. For pneumococcal pneumonia, antibiotics should probably be continued until the patient has been afebrile for 72 hours, and the total duration should not be less than 10 to 14 days (or 5 days if azithromycin is used). Available data do not support prolonged courses of treatment for uncomplicated pneumonia.

Table 5. EMPIRIC OUTPATIENT ANTIBIOTIC THERAPY FOR PEDIATRIC CAP

Duration of treatment is 10 days unless otherwise noted

Patient age	Presumed bacterial pneumonia	Presumed atypical pneumonia
3 mo to <5 y, regardless of immunization status	**Preferred:** amoxicillin 90 mg/kg/d PO in 2 divided doses **Alternative:** amoxicillin clavulanate 90 mg/kg/d PO in 2 divided doses	For all children regardless of age and immunization status: **Preferred:** azithromycin 10 mg/kg PO on Day 1, followed by 5 mg/kg PO once daily on Days 2-5 **Alternative:** clarithromycin 15 mg/kg/d PO in 2 divided doses *OR* In children >7 y: erythromycin 40 mg/kg/d PO in 4 divided doses; or doxycycline 2-4 mg/kg/d PO in 2 divided doses
≥5 y and fully immunized against *Streptococcus pneumoniae* and *Haemophilus influenzae*	**Preferred:*** amoxicillin 90 mg/kg/d PO in 2 divided doses to a maximum 4 g/d, with or without a macrolide antibiotic **Alternatives:** Second- or third-generation cephalosporins such as oral cefpodoxime, cefuroxime, or cefprozil *OR* levofloxacin (5-16 y) 8-10 mg/kg PO once daily (max 750 mg/d)† *OR* linezolid (<12 y) 30 mg/kg/d PO (max 1200 mg/d) in 3 divided doses; or (≥12 y) 20 mg/kg/d (max 1200 mg/d) in 2 divided doses	
≥5 y and NOT fully immunized against *S pneumoniae* and *H influenzae*	**Preferred:*** amoxicillin 90 mg/kg/d PO in 2 divided doses to a max of 4 g/d; or amoxicillin clavulanate 90 mg/kg/d PO in 2 divided doses **Alternatives:** Second- or third-generation cephalosporins such as oral cefpodoxime, cefuroxime, or cefprozil *OR* levofloxacin (5-16 y) 8-10 mg/kg PO once daily (max 750 mg/d)†	

CAP, community-acquired pneumonia.

* Preferred treatments of choice change in areas of high *S pneumoniae* resistance. Refer to the complete guidelines for specific recommendations.

† The guidelines do not fully address the controversy concerning the use of quinolones in children. The use of quinolones in infants and children is considered a risk vs benefit decision.

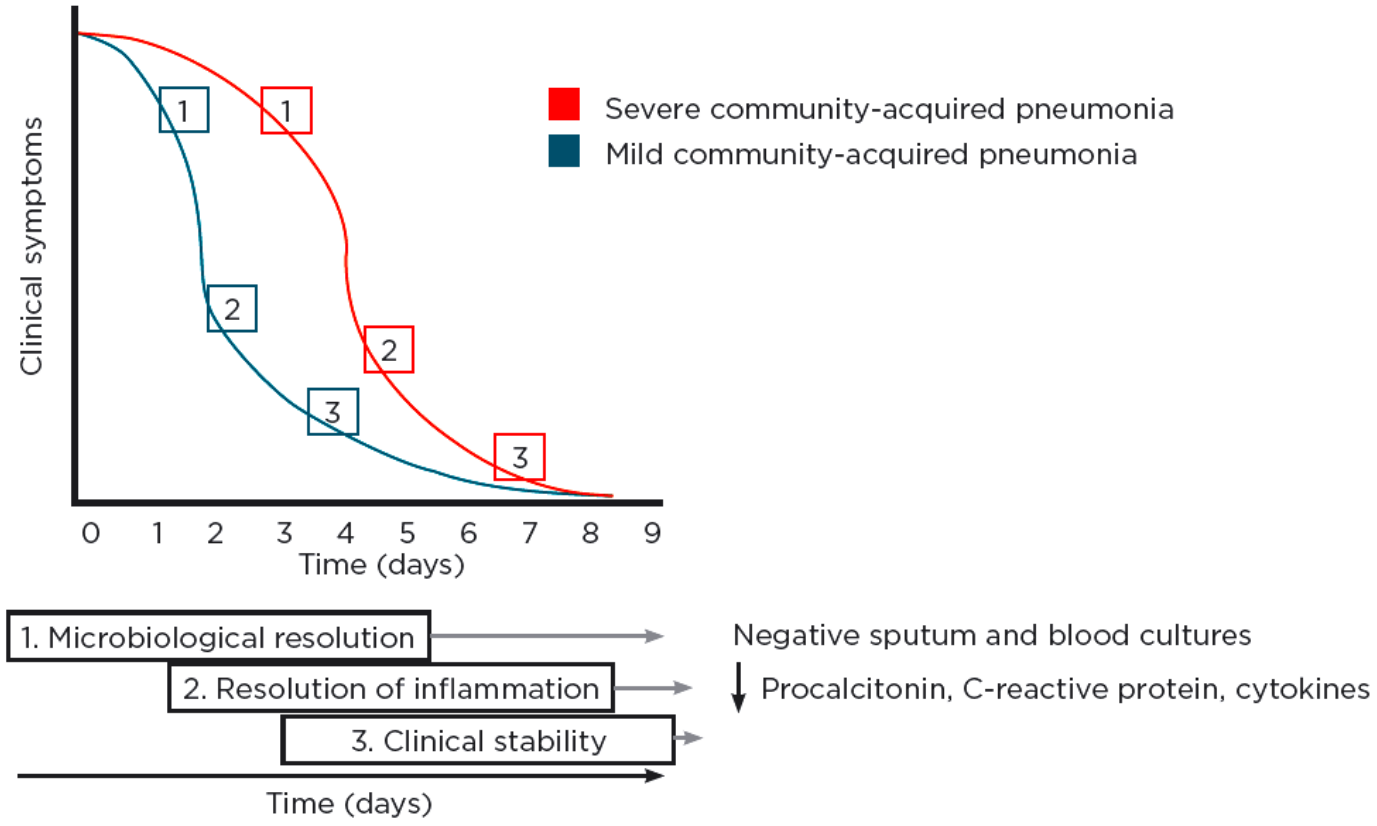
PROGNOSIS

Typically, patients with uncomplicated community-acquired bacterial pneumonia show response to therapy, with improvement in clinical symptoms (fever, cough, tachypnea, chest pain), **within 48-96 hr of initiation of antibiotics** (Fig. 5). Radiographic evidence of improvement lags substantially behind clinical improvement.
Mortality from community-acquired pneumonia in developed nations is rare, and most children with pneumonia do not experience long-term pulmonary sequelae. Some data suggest that up to 45% of children have symptoms of asthma 5 yr after hospitalization for pneumonia; this finding may reflect either undiagnosed asthma at the time of presentation or a propensity for development of asthma after pneumonia.

➢ *NONRESOLVING OR SLOWLY RESOLVING PNEUMONIA*

Treatment response has traditionally been difficult to define because radiographic changes, which are used to define the presence of pneumonia, can take up to 6 weeks to resolve and often lag behind the clinical recovery of patients [Menéndez R et al, 2003].
A number of factors must be considered when a patient does not improve with appropriate antibiotic therapy: (1) complications, such as empyema; (2) bacterial resistance; (3) nonbacterial etiologies such as viruses and aspiration of foreign bodies or food; (4) bronchial obstruction from endobronchial lesions, foreign body, or mucous plugs; (5) pre-existing diseases such as immunodeficiencies, ciliary dyskinesia, cystic fibrosis, pulmonary sequestration, or cystic adenomatoid malformation; and (6) other noninfectious causes (including bronchiolitis obliterans, hypersensitivity pneumonitis, eosinophilic pneumonia, aspiration, and granulomatosis with polyangiitis).
A repeat chest radiograph is the 1st step in determining the reason for delay in response to treatment.

Fig. 5. A schematic representation of recovery from community-acquired pneumonia



➢ *COMPLICATIONS*

Complications of pneumonia (**Table 6**) are usually the result of direct spread of bacterial infection within the thoracic cavity (pleural effusion, empyema, pericarditis) or bacteremia and hematologic spread (Fig. 6). Meningitis, suppurative arthritis, and osteomyelitis are rare complications of hematologic spread of pneumococcal or *H. influenzae* type b infection.

S. aureus, S. pneumoniae, and *S. pyogenes* are the most common causes of parapneumonic effusions and of empyema. The treatment of empyema is based on the stage (exudative, fibrinopurulent, organizing). Imaging studies including ultrasonography and CT are helpful in determining the stage of empyema. The mainstays of therapy include antibiotic therapy and drainage with tube thoracostomy. Additional approaches include the use of intrapleural fibrinolytic therapy (urokinase, streptokinase, tissue plasminogen activator) and selected videoassisted thoracoscopy (VATS) to debride or lyse adhesions, and drain loculated areas of pus. Early diagnosis and intervention, particularly with fibrinolysis or VATS, may obviate the need for thoracotomy and open debridement. Fibrinolysis may be more cost effective than VATS.

Table 6. COMPLICATIONS ASSOCIATED WITH COMMUNITY-ACQUIRED PNEUMONIA

Pulmonary	Metastatic	Systemic
Pleural effusion or empyema Pneumothorax Lung abscess Bronchopleural fistula Necrotizing pneumonia Acute respiratory failure	Meningitis Central nervous system abscess Pericarditis Endocarditis Osteomyelitis Septic arthritis	Systemic inflammatory response syndrome or sepsis Hemolytic uremic syndrome

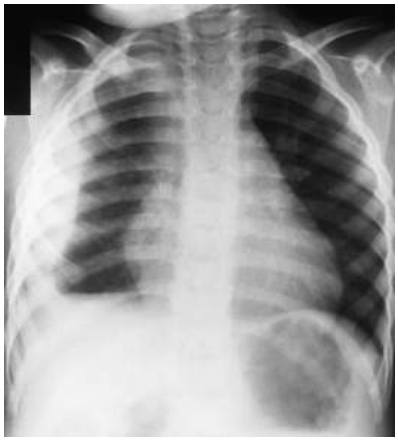


Fig. 6. Pneumococcal empyema on the chest radiography of a 3 yr old child who has had upper respiratory symptoms and fever for 3 days.
A pleural fluid collection can be seen on the right side. The patient had a positive pleural tap and blood culture result for pneumococci. The child recovered completely within 3 wk.

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CASE-BASED LEARNING

CASE 1. Newborn with Pneumonia

A pediatric intern was called to the delivery room to assess a term newborn infant with respiratory difficulty. The infant was less than 2 hours old. His respiratory effort remained labored and he grunted with each exhalation. His mother's prenatal history was unknown, and her labor was too rapid for her to have had any prenatal antimicrobial screening or antibiotics. She reported having had a baby die in the first days of life from an infection. This infant was tachypneic with a respiratory rate of 75 breaths per minute. He had decreased breath sounds bilaterally with rare fine crackles. His airway was intubated for severe respiratory distress and his radiograph demonstrated bilateral "ground-glass" alveolar filling (Fig. 7). His white blood cell count was 2200 cells/hpf and his platelet count was 66,000/ml. His clinical condition deteriorated despite antibiotic therapy. Both initial blood cultures grew group B beta-hemolytic streptococcus (GBBS) within 6 hours. He died before he was 12 hours old.

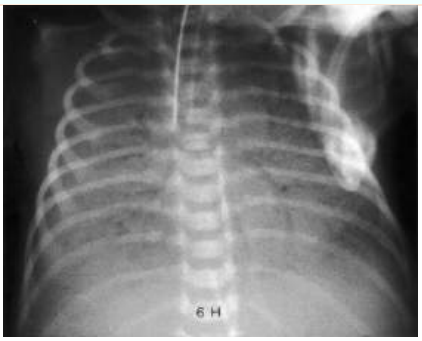


Fig. 7. Chest radiograph of an infant with GBBS pneumonia

The pretreatment and screening of mothers for GBBS has made a significant impact on the prevalence of "early" GBBS disease in the newborn, so that residents training today are much less likely to see a child with this condition than those who trained 15 years ago. Prenatal and perinatal pneumonia can also be caused by coliforms such as Escherichia coli, anerobes, and Listeria monocytogenes. Babies can present with very subtle initial symptoms including the full spectrum of respiratory distress from mild to life-threatening, temperature instability, feeding intolerance, and metabolic derangements including hypoglycemia. Often, there is little that can be done once they are delivered, so that maternal prenatal screening and treatment become the most important factors in infant survival. Since newborns are immunocompromised by definition, a number of different opportunists including Pseudomonas aeruginosa can cause infection in infants hospitalized for extended periods. Viruses including cytomegalovirus and fungi such as Candida albicans can also cause pneumonia in infants. These agents should be suspected in babies who do not respond to standard therapy. Initial therapy should include aggressive evaluation for sepsis including blood and urine cultures, and antibiotics targeting the most common causes. Typically, an aminoglycoside or third-generation cephalosporin and ampicillin are chosen as initial therapy. Newborns with pneumonia should be cared for in neonatal intensive care units where expertise in mechanical ventilation is available if needed.

CASE 2. Well-Appearing Infant with Pneumonia

A 7-week-old infant was admitted to the pediatric ward with hypoxemia and cough. The child was still eating fairly well and there was no history of fever. On examination, the child was not ill-appearing but his respiratory rate was 70–80 breaths per minute when awake. He had some scattered crackles on examination, and mild subcostal retractions. The chest radiograph showed patchy opacifications and hyperinflation (Fig. 8). Evaluation for bacterial infection was negative; however, a urine culture grew cytomegalovirus (CMV) and the serum CMV IgM was positive. The child recovered from this illness, but had recurrent episodes of wheezing and dyspnea with variable responsiveness to bronchodilators and oral corticosteroids. Stagno and his colleagues described the "afebrile pneumonia syndrome of infancy" more than two decades ago.

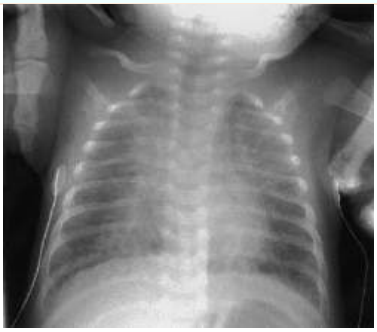


Fig. 8. Chest radiograph of a child with cytomegalovirus pneumonia.

The investigators isolated four agents from these infants with pneumonia: Chlamydia trachomatis (25%), Ureaplasma urealyticum (21%), cytomegalovirus (20%), and Pneumocystis carinii (18%). This last organism, long felt to be a protozoan, has recently been identified to be a phylogenetic fungal species and reclassified as Pneumocystis jiroveci. Pneumonia from this organism is still referred to as "PCP": Pneumocystis pneumonia.

In many cases, multiple organisms were recovered from the same infant with this clinical syndrome. Organisms were identified by culture and in the case of Pneumocystis, by counter immunoelectrophoresis and indirect immunofluorescence of serum. These studies are not available in every clinical setting today, so aside from culture for CMV, the other organisms are seldom isolated. Thus the diagnosis is often made clinically. Infants with this clinical syndrome will often require hospitalization because of hypoxemia or decreased feeding due to respiratory difficulty. If the child is to be managed as an outpatient, he or she should be followed daily until the clinical symptoms begin to improve significantly. Additionally, the parents should be given specific, concrete signs and symptoms to watch for that might herald deterioration. Treatment is usually empiric, and includes oral erythromycin for 3 weeks primarily to treat chlamydial infection. In a follow-up study, 46% of the children had recurrent episodes of wheezing and airway obstruction, requiring medical therapy.

CASE 3. Ill-Appearing Infant with Pneumonia

An 11-month old girl presented to the emergency room with a fever of 102°F (39°C), congestion, cough and a history of "grunting" respirations. The infant was not eating well. On examination the child was ill, but not septic appearing. The chest was clear to auscultation and a chest radiograph was normal. The child was discharged with a diagnosis of viral respiratory tract infection and instructions to follow-up in a pediatric clinic in the morning. The parents did not return to the doctor the next morning, but instead returned a day later, after the child developed progressive respiratory distress. A chest radiograph showed a large left-sided pneumonia. The child's blood culture grew Staphylococcus aureus, and despite heroic measures the child succumbed to overwhelming sepsis 48 hours later. It is easy to forget that pneumonia in children is potentially a life-threatening illness.

Most bacterial infections in this age group are preceded by a viral respiratory tract infection. Historically, influenza virus has been identified as a frequent preceding infection. Many of the near 25 million deaths worldwide during the 1918–1919 influenza epidemic are thought to have been from secondary bacterial pneumonia. It is likely that the viral infection alters the ability of the respiratory tract to resist infection from inhaled or aspirated bacterial pathogens. Infants with pneumonia will often be tachypneic and may have grunting respirations. They can also have other signs associated with sepsis: fever, poor feeding, and lethargy. Initial radiographs may be normal despite findings on physical examination. The diagnosis of a respiratory tract infection will often be made on the basis of clinical findings, and the decision to attempt to diagnose or treat for bacterial disease may be a subjective one.

Children with fever should be evaluated according to established protocols. Under 1 month of age, all children with fever and no identifiable source should undergo a sepsis evaluation, and receive inpatient intravenous antibiotic therapy. In older infants and children, a high index of suspicion for pneumonia should be maintained.

Any infant or young child with pneumonia should be followed closely. The child with a lower respiratory tract infection should be seen again within 24 hours of the initial visit for a reassessment, regardless of whether bacterial disease is suspected on the initial presentation. Serious, even life-threatening bacterial illness may not be apparent at first. Pneumonia in an ill-appearing infant is most often due to Streptococcus pneumoniae. Haemophilus influenzae, Type B (HIB) was seen previously but has diminished with the successful vaccination programs for this organism. Pockets of invasive HIB disease still occur in the developed world, and an immunization history is an important part of the evaluation of a child with pneumonia. Staphylococcus aureus may also cause severe pneumonia in infants and young children. Fortunately, it is not a common cause in the developed world. It should be suspected in a child who develops a rapid "white-out" pattern of consolidation radiographically. Children with staphylococcal pneumonia develop pleural disease in up to 90% of cases, and pneumatoceles develop in half of children. This agent should be suspected especially in children with pneumonia and pulmonary abscess or empyema. When bacterial pneumonia is suspected and the child appears only mildly or moderately ill, ampicillin is an acceptable initial intravenous agent to use pending culture results. Penicillin-resistant Pneumococcus, however, has been recognized with increasing frequency since 1978. Organisms produce one or more proteins with variable affinity for penicillin. Approximately 10% of Pneumococcus isolates are penicillin resistant. Resistance to ceftriaxone is uncommon, and occurs in less than 2.5% of isolates. Therefore, when the child appears ill, initial treatment should be with a second- or thirdgeneration cephalosporin (cefuroxime or ceftriaxone) for Pneumococcus or HIB. If the child is septic and Pneumococcus is suspected, treatment should begin with vancomycin. If Staphylococcus is suspected, treatment with penicillinase resistant penicillin (nafcillin or oxacillin) should be started.

CASE 4. Well-Appearing Toddler or Child with Pneumonia

A 4-year-old preschooler stayed home from his nursery school for 2 days with low-grade fever, rhinitis, and cough. His symptoms became worse and his mother brought him to your office. He had paroxysms of cough, especially at night, but was relatively well between episodes. He did not cough during the visit, and he had no previous history of severe cough with respiratory infections, or with exercise. On examination he was not tachypneic. He had mild rhinitis. Auscultation of his chest revealed diffuse heterophonous wheezing (small airway obstruction) and fine crackles. He had no hepatomegaly and no digital clubbing. A chest radiograph revealed scattered interstitial infiltrates and mild hyperinflation. Viral pneumonias are not the focus of this chapter, yet deserve mention because they are the most common cause of pneumonia in children of any age. The child in this case was well-appearing, but viruses can certainly cause severe, life-threatening infections. The most commonly isolated viruses in children with LRIs are parainfluenza (35%), RSV (22%), influenza virus (12%), adenovirus (7%) and assorted others (enterovirus, rhinovirus, 9%). Mycoplasma pneumoniae is responsible for 15% of infections. The absence of severe episodes of cough with other respiratory tract infections and exercise makes a diagnosis of asthma less likely. Most viral pneumonia begins with inhaled infectious agents, and the airways are commonly involved. Thus wheezing and hyperinflation (subcostal retractions) are frequently noted. A chest radiograph may be normal. It may also show interstitial or airspace disease. Children with LRI managed in an ambulatory setting should be followed daily until the symptoms of respiratory tract infection begin to resolve. Follow-up is critical because it is difficult to predict the course of pneumonia. In addition, viral pneumonia may become secondarily infected with a bacterial pathogen and parents may not be sophisticated enough to recognize respiratory deterioration in their children.

CASE 5. Child with Pneumonia

A 7-year-old girl with a viral respiratory tract infection awoke one night with shaking chills, worsening of cough, malaise and fever. She also complained of right-sided chest pain. On presentation to her pediatrician in the morning, she was ill-appearing and had a temperature of 104°F (40°C). Her respiratory rate was 42 breaths per minute and auscultation of her chest revealed crackles on her posterior right lung fields. A chest radiograph showed a right-sided opacification. Her white blood cell count was 21,000 WBC/hpf. A course of amoxicillin/ clavulanate PO was started, but she returned to her physician 2 days later with persistent fever, worsening cough, and increased difficulty breathing. A repeat radiograph revealed complete opacification of her right lung (Fig. 9). Room air pulse oximetry was 87%. Blood cultures obtained on her original presentation grew Streptococcus pneumoniae. She was admitted to the hospital for intravenous antibiotics, but her respiratory condition deteriorated. She was transferred to the pediatric intensive care unit where she was intubated and started on mechanical ventilation. Her hypoxemia was unresponsive to increasing levels of positive pressure on conventional ventilation so she was started on a high-frequency oscillator ventilator. She stabilized, but a pleural effusion and eventual pneumothorax on the right side necessitated chest tube placement 2 days later. She remained on high-frequency ventilation for 2 weeks, before returning to conventional ventilation and extubation after a total of more than 3 weeks of ventilator therapy. She recovered but her radiograph remained abnormal, with decreased volume on the right (Fig. 10). Pneumococcal pneumonia in childhood usually presents as a distinct, clinical syndrome characterized by an acute onset and fever. It is not rare. Laboratory studies reveal leukocytosis, and sputum Gram stain in older children will demonstrate more than 25 WBC/hpf and Grampositive diplococci. The spectrum of pneumonia from this organism can vary from a very mild course managed in an ambulatory setting, to the severe case of complicated pneumococcal pneumonia presented here. Complicated pneumonia is characterized by significant pleural effusion often requiring chest tube placement and, in some cases, pulmonary necrosis. Children with complicated pneumonia are more likely to be older (45 vs. 27 months in one series)2, are more likely to present with chest pain and to require decortication for pleural disease. In the same series, complicated pneumonia was caused by pneumococcal serotypes 1, 6, 14, and 19 in 24% of cases, as opposed to 3.6% of the children with uncomplicated pneumonia. Serotype 1, which accounted for 24% of complicated pneumonia, is not included in the currently licensed pneumococcal vaccine. Children who develop pneumococcal pneumonia are often carriers of this organism. Twenty to forty percent of children are carriers, and risk factors for the development of invasive pneumococcal disease include frequent episodes of otitis or upper respiratory tract infections (>3 in 6 months) and daycare attendance. Organisms are aspirated or inhaled, and escape the lung's extensive defense systems, including the mechanical barriers of the upper airway, the mucociliary blanket and cough, and the macrophages and humoral defenses of the distal airways. Onset of symptoms is usually abrupt with shaking chills and spiking fever. Younger children may present with febrile seizure2. Ambulatory children with suspected pneumococcal pneumonia should be treated with high-dose amoxicillin or a cephalosporin. Children ill enough to require hospitalization should receive a second- or third-generation cephalosporin or ampicillin in combination with sulbactam. Vancomycin or clindamycin should be used for severely ill children with suspected complicated pneumococcal disease.

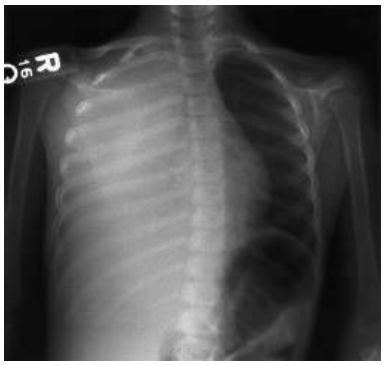


Fig. 9. Chest radiograph of a child with overwhelming *Streptococcus pneumoniae* pneumonia.

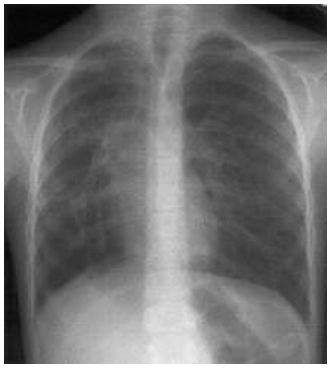


Fig. 10. Chest radiograph of resolved complicated *Streptococcus pneumoniae* pneumonia.

CASE 6. Adolescent with Pneumonia

A previously healthy 16-year-old stayed home from school with headache, abdominal pain, and sore throat. She did not have any nasal congestion, but developed paroxysms of cough. She developed a fever of 101°F (38.5°C) and generalized malaise. After 4 days of symptoms and progressive cough, her mother took her to the physician. She was uncomfortable, but not ill-appearing. She was not hypoxemic or tachypneic. Auscultation of her chest revealed crackles and heterophonous wheezing. She had a mild erythematous maculopapular exanthem. A chest radiograph revealed mild, bilateral increased interstitial infiltrates (Fig. 11). A complete blood count disclosed a mild anemia and the smear suggested hemolysis. Bedside serum cold agglutinins were positive (Figure 10-8), and serologic testing for Mycoplasma pneumoniae IgM was positive >1:32. She was treated with oral doxycycline, and recovered uneventfully within 2 weeks, although episodes of cough persisted for two additional weeks.

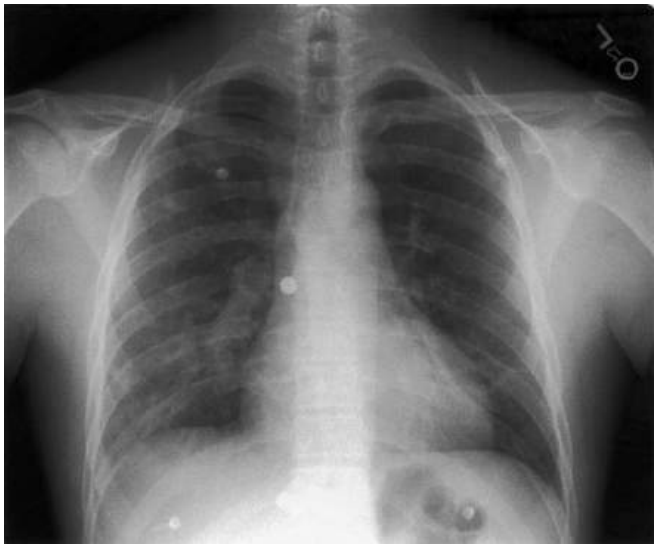


Fig. 11. Chest radiograph of an adolescent with *Mycoplasma* pneumonia.

Pneumonia due to Mycoplasma pneumoniae was called “atypical” initially because, in 1935, it did not respond to the typical pneumonia treatment, sulfonamides. It is also sometimes called “walking” pneumonia because it does not render affected children so sick that they are confined to bed. The onset of symptoms, in contrast to Pneumococcus, is usually insidious with malaise, low-grade fever and cough. Rhinitis is significant for its absence, and can help the clinician discern Mycoplasma from viral pneumonia due to adenovirus, which can have a similar clinical course. Pharyngitis is frequently noted, but may be more prominent in atypical pneumonia due to Chlamydia pneumoniae, another of the causes of this clinical syndrome. Headache and abdominal pain are also frequently seen. The physical examination will often provide no additional clues to help discern the specific cause of pneumonia. Clinical signs of pneumonia will often be present, including crackles, wheezes or coarse breath sounds. However, they may be absent early in the course of the disease. A range of different rashes may be noted from a slight erythematous eruption in mildest cases, to life-threatening Stevens–Johnson syndrome. Cardiac involvement has also been noted in some cases, including myocarditis and pericarditis leading to signs and symptoms of congestive heart failure. Rarely, hepatitis may occur and hepatomegaly will be noted on physical examination.

There is no pathognomonic pattern of the chest radiograph for children with Mycoplasma pneumonia. The radiograph can be completely normal. Bilateral interstitial infiltrates may be noted, or there may be a unilateral lobar infiltrate. Parapneumonic pleural effusion may occur in up to 20% of children with Mycoplasma pneumonia when it is carefully sought. There is usually no reason for pleurocentesis in these children. Serologically, the immunogenicity of Mycoplasma leads to production of a host of antibodies, including one to the red blood cell “I/I antigen” that causes cold agglutination of the blood cells. While this antibody may be absent in up to half of children with Mycoplasma, its presence in this clinical setting would make the diagnosis of a Mycoplasma infection all but assured.

Chlamydia pneumoniae is the other agent commonly associated with atypical or “walking” pneumonia, although the specific diagnosis is even more difficult to make. Pharyngitis and hoarseness in an adolescent or young adult with interstitial pneumonia who does not have rhinitis should prompt the clinician to consider Chlamydia in addition to Mycoplasma. While erythromycin is generally considered the first choice for therapy in this syndrome, there is some evidence that Chlamydia is more susceptible to tetracycline than to erythromycin16. Doxycycline is an excellent agent for the treatment of this syndrome in children 12 years and older. Other macrolides are also effective and the newer agent, azithromycin, shows greatest effectiveness in experimental settings.

Pediatric Pleural Effusion

The pleural space normally contains 0.3 mL per kg body weight of pleural fluid. Lymphatic vessels can cope with several hundred millilitres of extra fluid per 24 h. An imbalance between pleural fluid formation and drainage will result in a pleural effusion.

In a previously well child, pleural effusions are usually secondary to acute bacterial pneumonia and less often due to chronic infection such as pulmonary tuberculosis (TB). Other causes usually considered in adults, such as malignancies, cardiovascular diseases, or systemic inflammatory conditions, are uncommon in children.

Clinical picture

There are two usual patterns of presentation.

- In the first, the child has classic symptoms of pneumonia (fever, cough, breathlessness, abdominal pain and malaise) but they are usually more unwell than those with simple pneumonia alone, with pleuritic chest pain and even cyanosis.
- In the other clinical presentation, the child has been diagnosed with pneumonia but does not respond to 48 h of an appropriate treatment. On examination, a pleural effusion is suggested by unilateral signs of decreased chest expansion and dullness to percussion, reduced or absent breath sounds, and scoliosis.

Diagnosis

Contrary to community-acquired pneumonia (CAP), which may be diagnosed on clinical grounds only, the diagnosis of parapneumonic pleural effusion requires an imaging technique to demonstrate the presence of fluid in the pleural space. **The first imaging technique should be a posteroanterior chest radiograph**. The earliest sign of a pleural effusion is obliteration of the costophrenic angle. A rim of fluid may be seen ascending the lateral chest wall (meniscus sign). If the film is taken in a supine position, the appearance can be of a homogeneous increase in opacity over the whole lung field without blunting the costophrenic angle, or a classic pleural-based shadow. A lateral chest radiograph rarely adds anything extra and should not be routinely obtained.

Once pleural effusion has been diagnosed or suspected by a chest radiograph, **chest ultrasonography** should be obtained to confirm the diagnosis, estimate the size of the effusion, differentiate between free and loculated pleural fluid and determine its echogenicity (Fig. 12). It may also be used to guide chest drain insertion or thoracentesis.

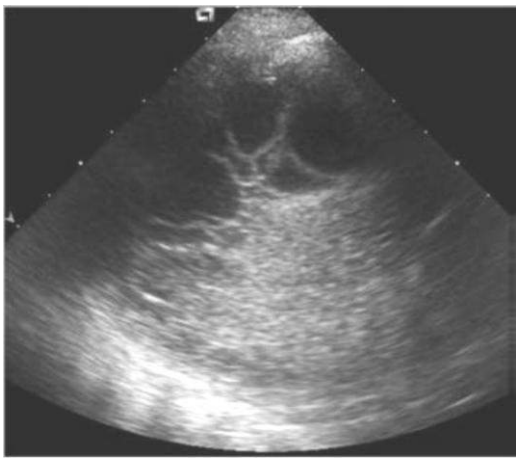


Fig. 12. Chest ultrasound showing a loculated pleural effusion.

Chest CT scans involve radiation exposure that can be equivalent to 20–400 chest radiographs depending on technical factors and should not be performed routinely. It may have a role in complicated cases, including immunocompromised children where a CT scan can detect airway or parenchymal lung abnormalities, such as endobronchial obstruction or a lung abscess, or before surgery to delineate the anatomy.

Management

All children with parapneumonic pleural effusion or empyema should be admitted to hospital and managed following local or national guidelines.

Intravenous antibiotics and careful consideration of pleural drainage procedures are the most important aspects of parapneumonic effusion/ empyema management.

Intravenous empirical antibiotic treatment should begin as soon as possible. In the most common setting of a pleural effusion arising from CAP, empirical treatment must cover Streptococcus pneumoniae, S. pyogenes and Staphylococcus aureus. In most cases, cefotaxime (150 mg/kg), coamoxiclav or cefuroxime are appropriate. Penicillin allergic patients can be treated with clindamycin alone. If pneumatoceles are evident, anti-staphylococcal cover is mandatory (cloxaciline or flucoxaciline). However, in cases of hospital-acquired pneumonia or following surgery, trauma or aspiration, broader spectrum agents should be used to cover aerobic Gram-negative rods.

An important issue is whether to insert a pleural drain or not. It is generally accepted that isolated pleural taps for diagnostic purposes are not recommended in children with a small, uncomplicated parapneumonic pleural effusion, except if there are any atypical features suggesting the presence of malignancy, such as the absence of acute fever or pneumonia and evidence of an underlying mediastinal mass or lymphadenopathy. In these uncommon situations it is important to remember that large volume aspiration and general anaesthesia pose a significant risk of sudden death in children with superior mediastinal obstruction due to malignancy, therefore, the volume of aspirated pleural fluid should be small (5 mL) and general anaesthesia should be avoided.

As a general rule, there is a good deal of evidence suggesting that a pleural drain is not always necessary and that antibiotics alone can be enough to provide excellent clinical outcomes when there is not a clear indication for chest drainage. Tube thoracostomy must be performed if the child is in respiratory distress due to lung compression by the pleural effusion, or if toxic appearance and sepsis is suspected. It also may be considered if the effusion size is large (definitions vary from 10 mm thickness in ultrasonography or radiography to one-third of the hemithorax in radiography) or is enlarging, and the child is not responding after 48 h of antibiotic treatment.

Further reading

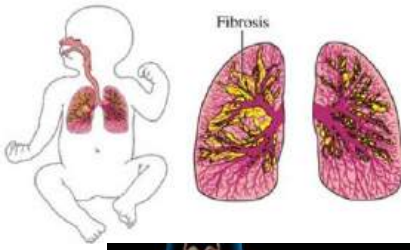
1. Hull J et al. Paediatric Respiratory Medicine, 2nd ed. Oxford University Press 2015

2. ERS Handbook: Paediatric Respiratory Medicine, 1st ed. European Respiratory Society 2013

Chronic Respiratory Diseases in Children

Chronic respiratory diseases are a group of chronic diseases affecting the airways and the other structures of the lungs.

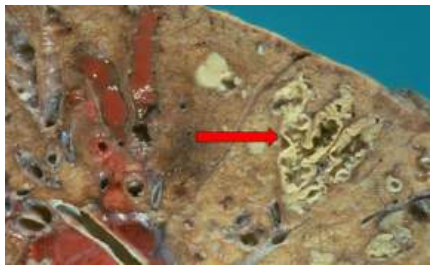
Major chronic respiratory diseases in children



Chronic lung disease (CLD) of prematurity (bronchopulmonary dysplasia)

Asthma

- Chronic bronchitis
- Chronic obstructive pulmonary disease (COPD)
- Emphysema



- Bronchiectasis

- Hypersensitivity pneumonitis (extrinsic allergic alveolitis)
- Pulmonary eosinophilia
- Pulmonary heart disease and diseases of pulmonary circulation including pulmonary embolism, pulmonary hypertension and cor pulmonale
- Interstitial lung disease (diffuse parenchymal lung diseases)
  - Sarcoidosis
  - Sleep apnea syndrome
  - Congenital thoracic malformations

ROLE OF MUCOCILIARY DYSFUNCTION IN CHRONIC AIRWAY DISEASES

Mucociliary clearance is an important primary innate defense mechanism that protects the lungs from the harmful effects of inhaled pollutants, allergens, and pathogens. Mucociliary dysfunction is a common feature of chronic airway diseases.

Normal airway mucus has two layers: outer more viscous layer, the gel phase, which is transported by ciliary beat, and inner serous layer called the sol phase, in which cilia recover from their active beat. Mucus is moved proximally by the effective coordinated beating of cilia.

Airway surface liquid (ASL) layer dehydration has a critical role in the pathogenesis of mucociliary dysfunction and chronic airway disease. ASL depletion resulted in reduced mucus clearance and histologic signs of chronic airway disease, including mucous obstruction, goblet cell hyperplasia, and chronic inflammatory cell infiltration.

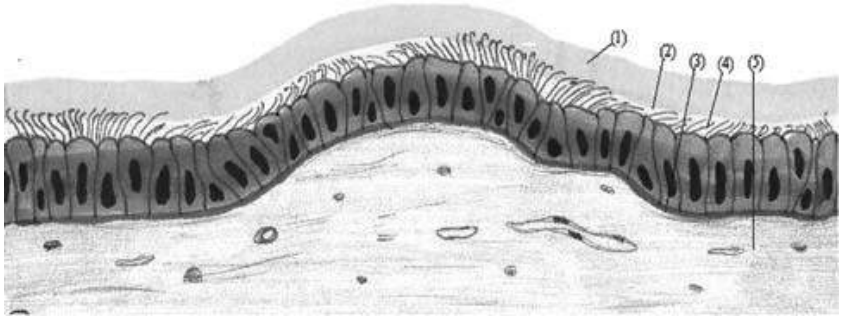


Fig. Epithelial (mucosal) layer of airway is shown (pseudostratified columnar ciliated epithelium). Goblet cells were not included for clarity and to show ciliary movement in gel and sol phases. 1 = gel phase; 2 = sol phase; 3 = basement membrane; 4 = cilia in recovery stage within sol phase; 5 = submucosal layer.

ROLE OF MATERNAL SMOKING IN CHRONIC AIRWAY DISEASES

Exposure to maternal smoking both during and after fetal development can have significant deleterious effects on lung development and subsequent susceptibility to pulmonary disorders.

Maternal smoking *during pregnancy is a risk factor for several adverse developmental outcomes, including abnormal fetal lung development. Lung development is most critical during late fetal and early postnatal life—the saccular and alveolar developmental phases. Abnormalities occurring during these stages can have long-term effects on lung function, contributing to the development of asthma in children and lung disease in adults. Maternal smoking and altered fetal pulmonary structure are related to nicotine that crosses the placenta and is expressed in breast milk. There is up-regulation of nicotinic acetylcholine receptors in the fetal lung. Animal models have demonstrated alterations in lung structure including decreased alveolarization, thickening of the alveolocapillary membrane, decreased synthesis of surfactant, decreased airway diameter, decreased vessel density, and increased airway hyperresponsiveness. Smoke exposure also changes the genetics that control lung growth and maintenance of lung structure, and accelerates lung aging. Prevention of maternal smoking during pregnancy and lactation is required and nicotine replacement therapy is not advised for these women.*
[Abbott LC, Winzer-Serhan UH 2012; Harding R, Maritz G 2012; Kajeka R 2007; Maritz GS, Harding R 2011; Wongtrakool C et al 2012.]

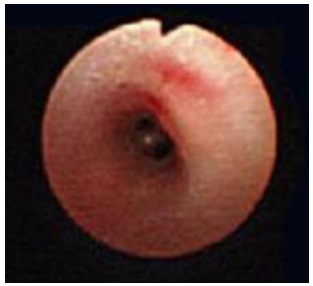
CHRONIC BRONCHITIS

Chronic bronchitis is recurring inflammation and degeneration of the bronchial tubes that may be associated with active infection. Patients with chronic bronchitis have more mucus than normal because of either increased production or decreased clearance. Coughing is the mechanism by which excess secretion is cleared.

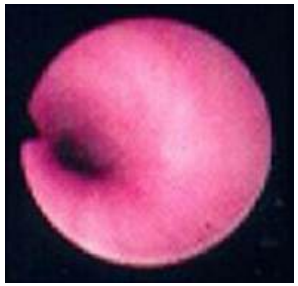
Chronic bronchitis is often associated with asthma, cystic fibrosis, dyskinetic cilia syndrome, foreign body aspiration, or exposure to an airway irritant. Recurrent tracheobronchitis may occur with tracheostomies or immunodeficiency states.

Defining chronic bronchitis and its prevalence in childhood has been complicated by the significant clinical overlap with asthma and reactive airway disease states. In adults, chronic bronchitis is defined as daily production of sputum for at least 3 months in 2 consecutive years. Some have applied this definition to childhood chronic bronchitis. Others limit the definition to a productive cough that lasts more than 2 weeks despite medical therapy.

Chronic bronchitis has also been defined as a complex of symptoms that includes cough that lasts more than 1 month or recurrent productive cough that may be associated with wheezing or crackles on auscultation. Elements of these descriptors are present in the working definitions of asthma, as well.



Normal airway color and architecture (in a child with mild tracheomalacia).



Airway of a child with chronic bronchitis shows erythema, loss of normal architecture, and swelling.

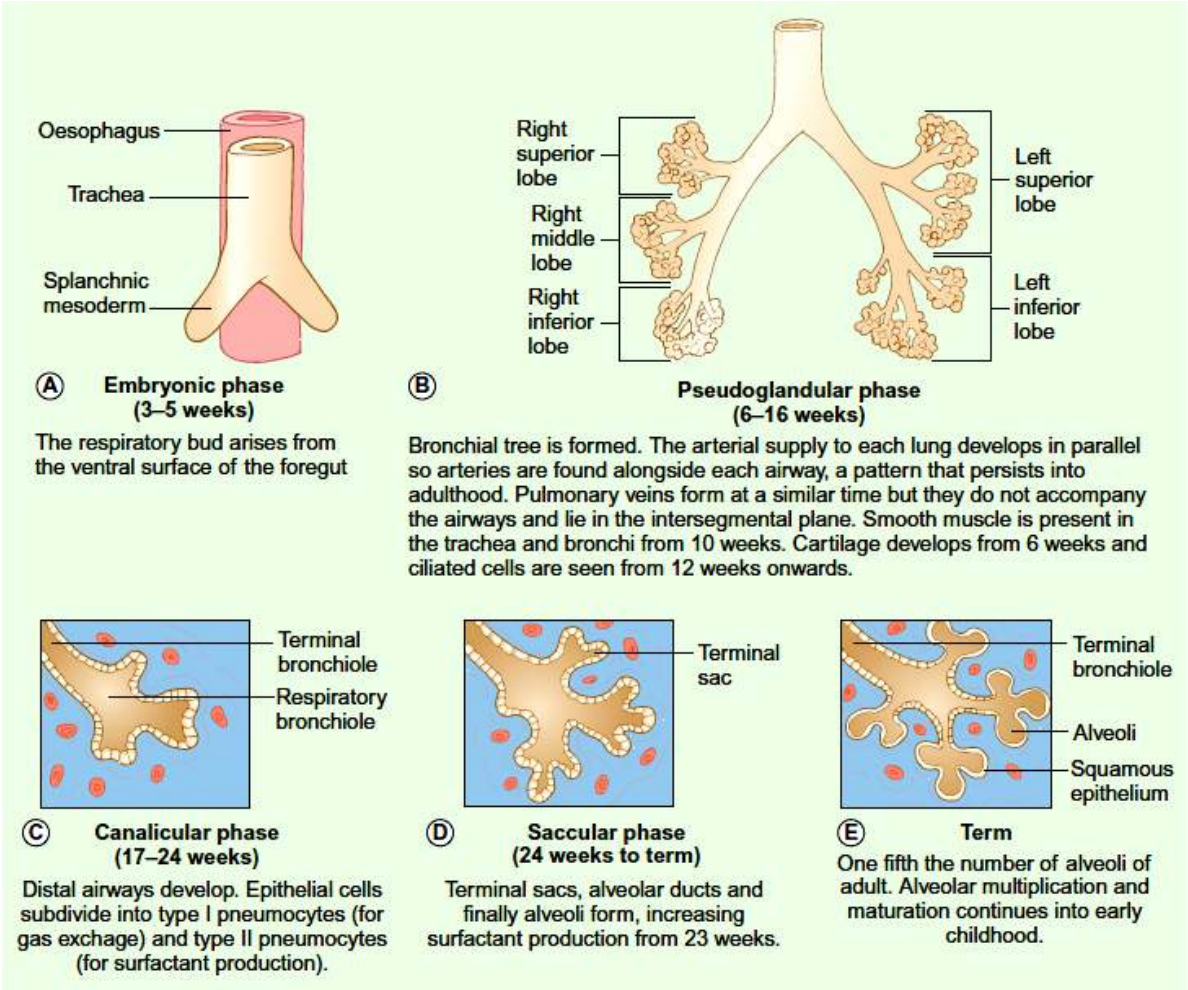
CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Chronic obstructive pulmonary disease (COPD) is conventionally thought of as a disease of adult smokers, related to airway inflammation and structural airway changes (remodeling). However, there is important epidemiological evidence, from a series of studies with overlapping age groups from birth to late middle age that early life events, including antenatal influences on lung growth, program the child to be at increased risk for future COPD [Bush A, 2008].

CONGENITAL MALFORMATIONS OF THE LUNG AND THE AIRWAY

The respiratory tree arises from the ventral surface of the foregut. Abnormal embryological development may result in congenital thoracic malformations (CTMs), which include:

- Failure of complete separation of foregut and bronchial structures, leading to different types of **tracheo-oesophageal fistula**
- **Congenital pulmonary airway malformations (CPAM)**, previously known as congenital cystic adenomatoid malformations (CCAM), from abnormal development of alveolar or bronchial tissues
- **Pulmonary sequestration** from an abnormal blood supply to part of the lung (usually systemic rather than pulmonary)
- **Congenital diaphragmatic hernia** from maldevelopment of the pleuroperitoneal canal with or without associated deficiency of the diaphragm itself
- **Cysts**, bronchogenic or foregut
- **Congenital lobar emphysema** from partial obstruction of the developing airway, most commonly due to a deficiency of bronchial cartilage development
- **Lung agenesis/bronchial atresia** from maldevelopment of the tracheobronchial tree in early fetal life.



Ⓐ **Embryonic phase (3–5 weeks)**
The respiratory bud arises from the ventral surface of the foregut

Ⓑ **Pseudoglandular phase (6–16 weeks)**
Bronchial tree is formed. The arterial supply to each lung develops in parallel so arteries are found alongside each airway, a pattern that persists into adulthood. Pulmonary veins form at a similar time but they do not accompany the airways and lie in the intersegmental plane. Smooth muscle is present in the trachea and bronchi from 10 weeks. Cartilage develops from 6 weeks and ciliated cells are seen from 12 weeks onwards.

Ⓒ **Canalicular phase (17–24 weeks)**
Distal airways develop. Epithelial cells subdivide into type I pneumocytes (for gas exchage) and type II pneumocytes (for surfactant production).

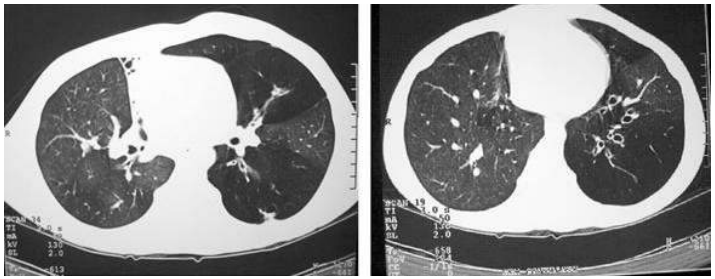
Ⓓ **Saccular phase (24 weeks to term)**
Terminal sacs, alveolar ducts and finally alveoli form, increasing surfactant production from 23 weeks.

Ⓔ **Term**
One fifth the number of alveoli of adult. Alveolar multiplication and maturation continues into early childhood.

Fig. **Phases of lung development.**

PARENCHYMAL DISEASES

Chronic obliterative bronchiolitis



Chronic obliterative bronchiolitis (COB) is a rare form of chronic obstructive lung disease that follows an insult to the lower respiratory tract. It is characterised by inflammation and fibrosis of the terminal and respiratory bronchioles that lead to narrowing and/or complete obliteration of the airway lumen.
A child with COB presents with cough, wheeze, pyrexia and tachypnoea which fail to resolve. Known causes include infection (particularly adenovirus) and chronic aspiration.

It results in characteristic changes on the high resiolution CT scan (HRCT), with patchy hyperinflation with a characteristic mosaic attenuation appearance of the lungs from adjacent lobes being either normal or hyperinflated. Lung function shows very severe irreversible obstruction. Treatment is supportive, with many children requiring oxygen therapy and, in a few cases, eventual lung transplantation.

Interstitial lung disease (diffuse parenchymal lung diseases)

Interstitial lung disease (ILD) is exceptionally rare in childhood, affecting about 1 in 100,000 children. It occurs due to a wide variety of pathological causes. In the light of more recent understanding of these etiologies, a new term – 'diffuse parenchymal lung diseases' (DPLD) – has been introduced. Approximately a third of patients present in the first two years of life and the etiology of 40–50% remains unknown. Known genetic defects which cause DPLD include abnormalities in surfactant B (SP-B), surfactant protein C (SP-C), surfactant protein ABCA3 and thyroid transcription factor-1 (TTF-1). These disorders are characterized by inflammatory and fibrotic changes that affect alveolar walls. There is usually a gradual decrease in lung compliance that results in increased work of breathing followed by a fall in arterial oxygen saturation. The diagnosis is suggested by a combination of failed response to treatment, poor growth, cough, tachypnea, reduced oxygen saturations, finger clubbing and fine crackles.

As with adults, DPLD in childhood may present as extrinsic allergic alveolitis. Care should be taken to ensure there is no exposure to potential allergens, particularly fungal spores and pigeon droppings. DPLD may complicate systemic diseases, including juvenile dermatomyositis, sarcoidosis, systemic lupus erythematosus and scleroderma. It can also occur as a reaction to drugs (azathioprine, methotrexate) or as a consequence of radiotherapy to the chest. Radiological changes tend to be non-specific, including generalized ground glass shadowing with reticular nodular infiltrates and honeycombing on CXR. HRCT provides more detail, but to establish a specific tissue diagnosis, a lung biopsy is required.
Older children may present with any number of respiratory signs. They frequently have finger clubbing and a restrictive pattern on spirometry. Two thirds of children respond to a combination of corticosteroids with or without hydroxychloroquine.

CHRONIC INFECTION

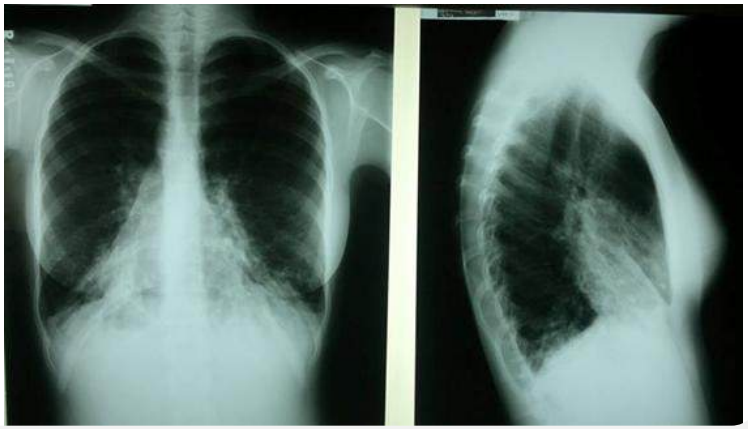
Bronchiectasis occurs when there is abnormal dilatation of the bronchi. It can be suspected on clinical grounds (persistent moist cough, clubbing and focal chest signs) but is usually diagnosed using HRCT scanning. Bronchiectasis arises from chronic airway inflammation that is driven by persistent infection. This leads to intense neutrophilic inflammation within the airways. It has been proposed that most bronchiectasis arises because a vicious cycle of infection and inflammation develops within the lung leading to impaired mucociliary clearance, followed by bacterial proliferation and more inflammation. Any condition that results in either impaired mucociliary clearance or abnormal response to infection can lead to bronchiectasis. Once bacterial growth is established within the mucus, clearance will be impaired by a combination of factors. Haemophilus influenzae, Streptococcus pneumoniae and Pseudomonas aeruginosa release mediators which directly inhibit ciliary function. They also lead to increases in local mucus production and the production of interleukin-8, which recruits neutrophils to the site of inflammation. In contrast to asthma, chronic infection is characterized by a neutrophilic inflammation.

Table. **Causes of bronchiectasis**

Post-infectious	– measles, pertussis, severe pneumonia
Immune dysfunction	– hypogammaglobulinaemia, neutrophil dysfunction, HIV infection
Impaired mucociliary clearance	– primary ciliary dyskinesia (PCD), cystic fibrosis (CF)
Systemic disorders	– rheumatic arthritis, inflammatory bowel disease
Undiagnosed foreign body or recurrent aspiration	

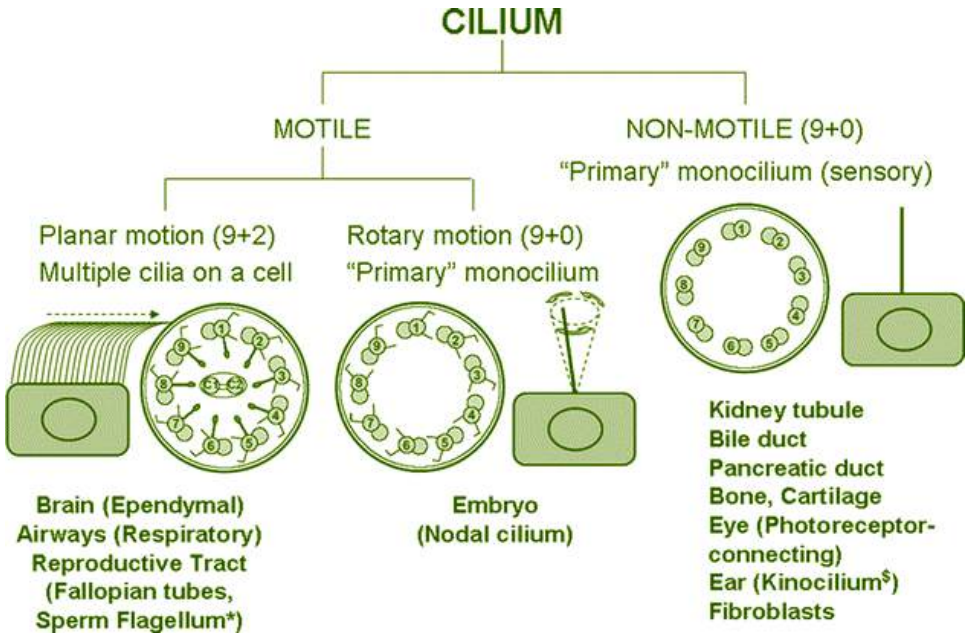
CASE STUDY

Here are chest x-rays of a 16-year-old female. Her 11y old sister has the same condition too. What condition is this?



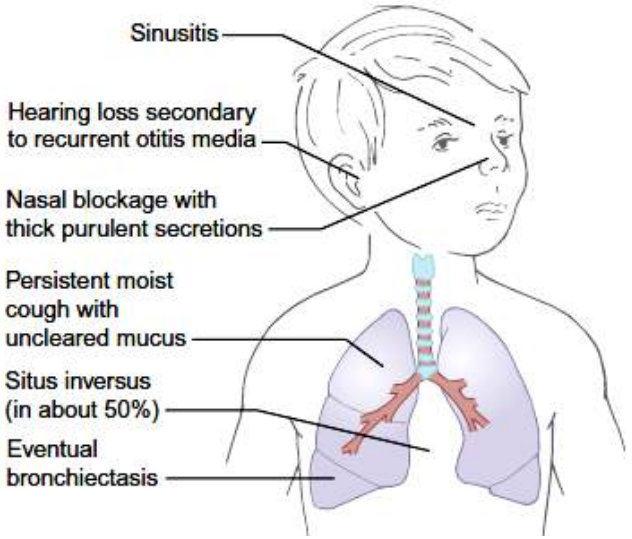
CILIARY DYSKINESIAS

Almost every cell in the body is equipped with a membrane bound, finger-like projection called a primary cilium. Cilia have been equated to cellular antennae that detect molecular signals in the environment and thus influence how cells behave. Normally functioning cilia have a fast 'upstroke' followed by a slower recovery phase in the opposite direction. The normal cilial beat frequency is between 12 and 14 times/second.
Ciliary defects, referred to as ciliopathies, are associated with a broad spectrum of human disease.



Primary ciliary dyskinesia (PCD) describes a heterogeneous group of conditions with a primary defect in the structure or function of the cilia. PCD is mainly inherited as an autosomal recessive condition. The incidence is 1 in 15,000–30,000 live births.

Children with PCD have recurrent sinopulmonary infections. Boys may have reduced fertility due either to sperm immotility or vas deferens abnormalities. Almost half of all affected children have laterality defects such as situs inversus. This is thought to occur because the functional defects seen in PCD reduce the effectiveness of nodal cilia during embryogenesis. A combination of PCD with situs inversus, chronic sinusitis, and bronchiectasis is known as **Kartagener syndrome**.



PCD is a genetic disease, but although several causative genes have been described, the mainstay of diagnosis remains the visualization of abnormal ciliary function demonstrated by electron microscopy of cilia from brush samples from inside the nose.

Treatment for respiratory infection is similar to cystic fibrosis. Optimal management requires rapid treatment and airway clearance techniques.

CYSTIC FIBROSIS

Cystic fibrosis (CF) is an inherited disease caused by a genetic mutation (defect) on chromosome 7. The defective gene results in abnormalities in the production and function of a protein called the **cystic fibrosis transmembrane conductance regulator (CFTR)**. In healthy cells CFTR acts as a chloride channel and a regulator of sodium, chloride and bicarbonate transport.

To date, over 1900 possible mutations of this gene have been described, of which 1300 are thought to be pathogenic. Specific mutation frequencies vary between different geographical locations and ethnic groups. ΔF508 (deletion of three nucleotides which code for phenylalanine at position 508 in the amino acid sequence) is the most common CFTR mutation. It accounts for nearly two thirds of the mutations in individuals with CF.

The widespread presence of CFTR throughout the body (lungs, salivary glands, pancreas, liver, kidneys, sweat ducts and reproductive tract) helps to explain why CF is a multisystem condition affecting many organs. The two major systems affected are the lungs and the gastrointestinal tract.

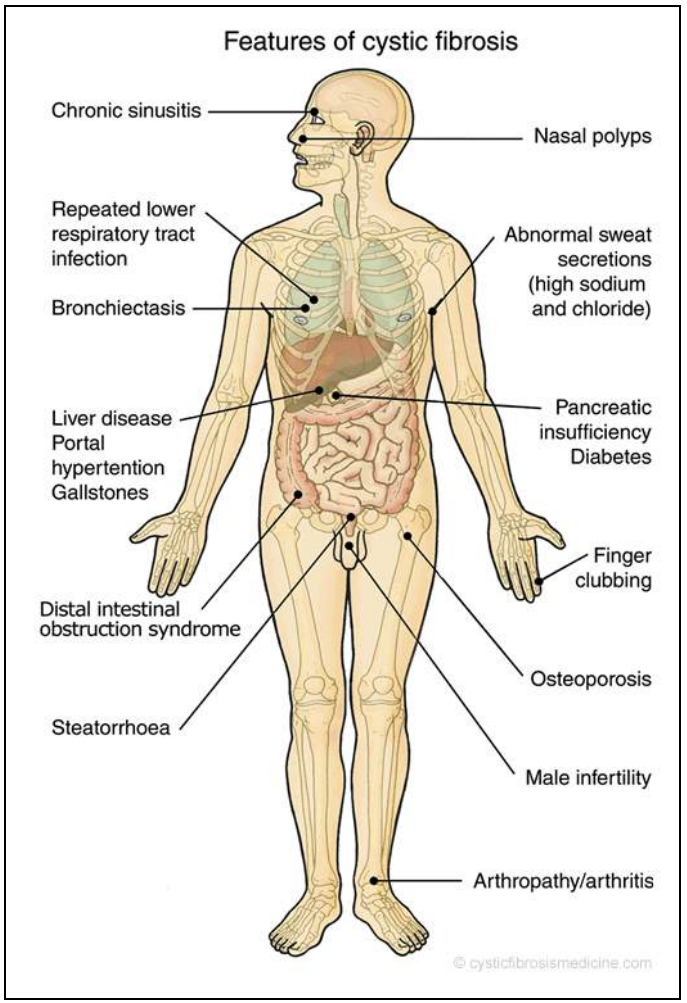
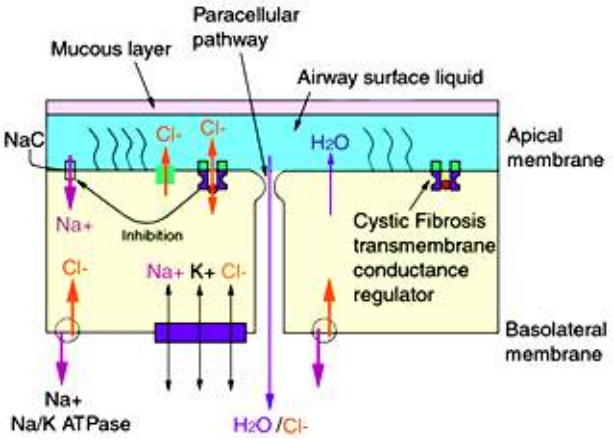
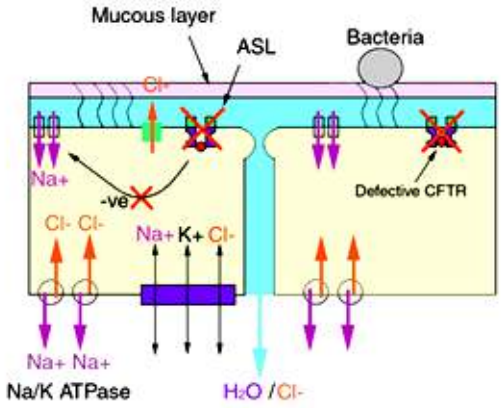


Fig. In CF, impairment of CFTR function causes reduced fluid production. Enhanced sodium absorption through epithelial Na+ channels (ENaC) and basolateral Na/K ATPase pumps results in increased fluid absorption leading to drier airways and impaired ciliary clearance.

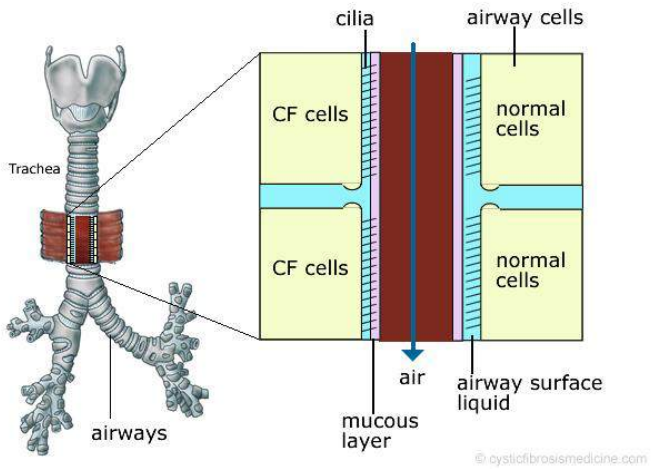


Normal airway epithelium



CF airway epithelium

In the lungs, inactive or inefficient functioning CFTR results in impaired chloride transport and enhanced sodium absorption across airway epithelial cells. This leads to a net increase in water absorption. The volume of the liquid that sits on the airway surface is reduced and the mucus in the airways becomes more viscid (sticky). In healthy lungs the cilia (small hairs on the surface of the airways) beat in a coordinated fashion so that they continually move mucus up and out of the lungs. This cleansing action of the cilia is impaired in CF because of the presence of very sticky mucus and dry airways which provide a favourable environment for bacterial infection.



Structural changes in the CFTR protein have also been linked to defective phagocytosis (ingestion and destruction of bacteria by the white blood cells) of bacteria such as *Pseudomonas aeruginosa* and to reduced clearance of infection [Di *et al*, 2006; Painter *et al*, 2006].

Overall these changes in lung physiology lead to dry airways, sticky secretions, a predisposition to chronic chest infections, bronchiectasis and scarring.

Individuals with CF may remain relatively asymptomatic despite significant decline in lung function and only develop breathlessness when a critical point is reached and lung reserve is lost. Symptoms are often a poor marker of disease severity, and other factors such as lung function, pseudomonas status and chest radiology should be taken into account.

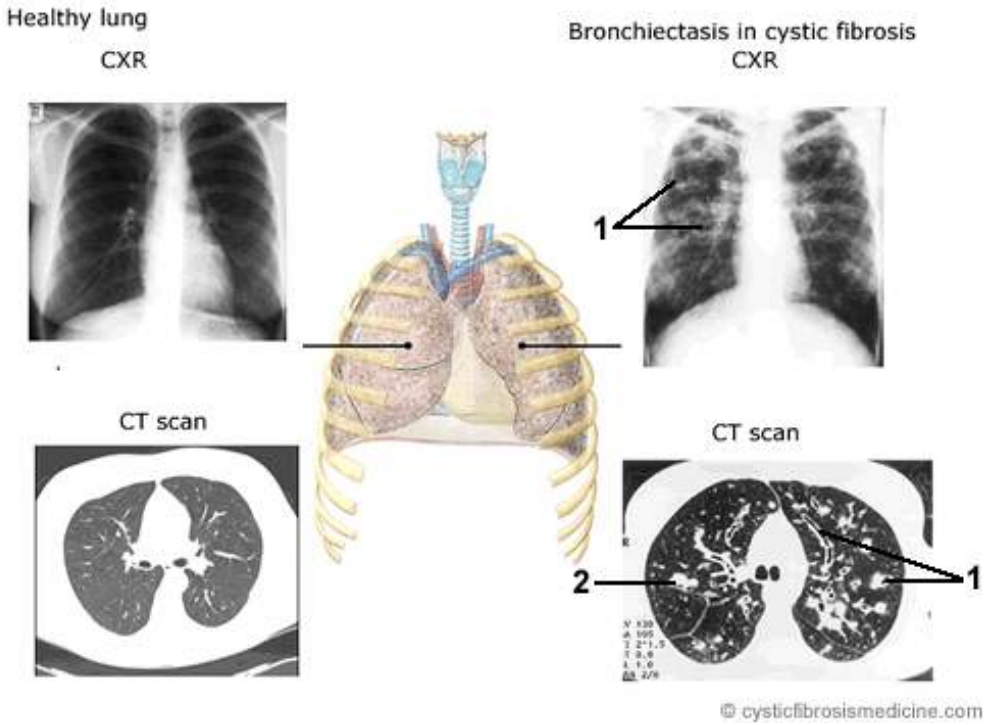


Fig. Some of chest X-ray and CT scan changes in CF:
1 -bronchiectasis, 2 - mucus plugging

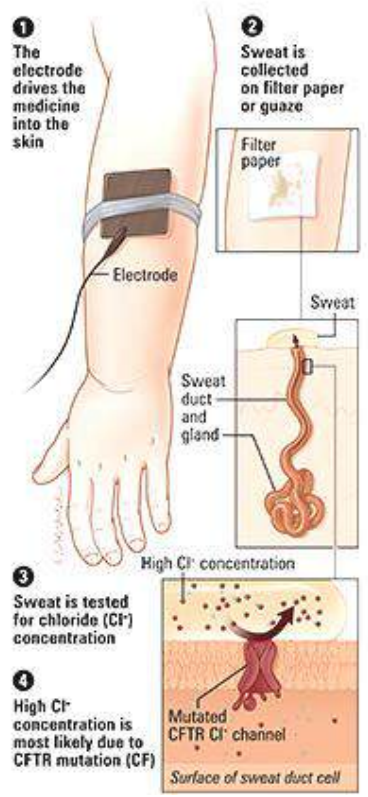
Gastrointestinal manifestations are:

• **Pancreatic disease:** Due to increased viscosity of secretions from the pancreatic duct, there is autodigestion of the pancreas from enzymes that are normally secreted into the gastrointestinal tract. Consequently, islet cells may be damaged leading to type 1 diabetes mellitus. Due to reduced pancreatic enzymes within the intestinal lumen, malabsorption of fat occurs, which clinically manifests as steatorrhoea and faltering growth. Treatment with enzyme replacement therapy (e.g. Creon) is necessary to allow the child to thrive.

• **Intestinal disease:** The chloride cotransporter (CFTR) within the small bowel that is involved in secretion of water into the gut is ineffective and may result in meconium ileus at birth (15% of children with cystic fibrosis present with intestinal obstruction within the neonatal period) or distal intestinal obstruction syndrome (DIOS) in childhood and adolescence. In DIOS there is ineffective secretion of water and chloride into the small intestine, which results in obstruction around the area of the terminal ileum, caecum and ascending colon. Gastrografin or intestinal lavage is necessary in some cases; however, severe cases require surgery and stoma formation.

Diagnosis of CF

- The diagnosis of CF is made on the basis of two positive sweat chloride tests using pilocarpine iontophoresis (60 mmol/L) along with classic clinical findings and a history of CF in an immediate family member.
  - *False-positive sweat test results are uncommon but may occur in the presence of adrenal insufficiency, nephrogenic diabetes insipidus, type I glycogen storage disease, hypothyroidism, hypoparathyroidism, familial cholestasis, and malnutrition.*
- Additional diagnostic tests include neonatal screening with increased circulating levels of immunoreactive trypsinogen, genotyping for CFTR mutations (two mutations confirm the diagnosis), nasal potential difference testing, a computed tomography scan of sinuses demonstrating pansinusitis, 24-hour fecal fat measurement looking for signs of pancreatic insufficiency, and ultrasound to assess absence of the vas deferens in males.
- CFTR-related disease include diseases that are associated with CFTR mutations but do not meet diagnostic criteria for CF including chronic pancreatitis, allergic bronchopulmonary aspergillosis (ABPA), idiopathic bronchiectasis, chronic sinusitis, and congenital bilateral absence of the vas deference.
- CFTR-related metabolic syndrome includes infants with abnormal newborn screening that subsequently show (1) intermediate sweat chloride level with one CF-causing mutation or (2) normal sweat chloride level with two CFTR mutations (one CF causing and one non CF causing).



Treatment of CF

- Treatment goals. These include to delay or prevent lung disease, to promote good nutrition and growth, and to treat complications.
- Maintenance treatment for patients with classic CF
  - *Airway clearance.* Daily airway clearance is one of the most important methods of prevention of respiratory tract infections.
    - There are many different methods, including manual chest physiotherapy, postural drainage, autogenic drainage, high-frequency chest oscillation vests, and manual percussion therapy.
    - Adjunctive therapies include the Flutter valve and Acapella device.
    - The use of a specific method is mostly dependent on patient preferences; no studies demonstrate superiority of one method over another.
    - Dornase alfa promotes airway clearance by cleaving DNA released by degenerating neutrophils, thus decreasing mucus viscosity. Its use has been shown to improve pulmonary function. It should be considered in children 6 years and older as a daily inhalation (2.5 mg).
    - Hypertonic saline (7%) promotes airway clearance by hydrating inspissated airway mucus. It has shown to reduce frequency of pulmonary exacerbations. It should be considered in children 6 years and older who have a chronic cough and reduction in pulmonary function testing.
  - *Optimization of nutrition.* Nutritional failure has been proven to be closely related to increased morbidity and frequency of pulmonary exacerbations. Therefore, it is important to maintain adequate nutrition via encouragement of a high-calorie and high-protein diet.
    - For patients who are not able to achieve appropriate oral caloric intake, a feeding gastrostomy tube may be an option.
  - *Pancreatic enzyme supplementation.* Patients with the pancreatic-insufficient form of CF manifest signs of malabsorption. Pancreatic enzyme supplementation is essential for these patients.
    - Usual dose ranges from 1,500 to 2,500 U of lipase per kilogram of patient's weight per meal.
    - Dosing is usually started at the lowest level and titrated up as needed, and it should not exceed 2,500 lipase units/kg/meal because high doses have been associated with chronic intestinal strictures.
  - *Lipid-soluble vitamin supplementation (vitamins A, D, E, and K).* Lipid-soluble vitamins are not well absorbed in patients with pancreatic insufficiency.
  - *Antimicrobials.* Chronic antimicrobial therapy is frequently used in patients with increased morbidity from colonizing microorganisms to attempt prevention of pulmonary exacerbation. These are commonly used against methicillin-resistant S. aureus, methicillin-sensitive S. aureus (Panton-Valentine leukocidin positive), Pseudomonas, and Aspergillus. In addition, chronic azithromycin therapy has proven beneficial in terms of its immunomodulatory effects; it interferes with Pseudomonas biofilm formation in the CF airways.
  - *Anti-inflammatory agents*
    - Oral glucocorticoid therapy and nonsteroidal anti-inflammatory drugs such as high-dose ibuprofen have proven benefits for some patients; however, the side effects of long-term therapy should be weighed against the benefits.
    - Azithromycin has been shown to improve respiratory function and reduce frequency of exacerbation, and its use is recommended for children 6 years and older. Its mechanism of action remains unclear.
  - *CFTR modulators*
    - Ivacaftor (VX-770) has shown to be effective at potentiating chloride channel function in cells with expressing the following mutations: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or R117H. Its use is recommended with patients who carry an approved mutation and are 6 years and older (dose 150 mg q12h).

- **Therapy for a pulmonary exacerbation**

  - This should always include intensive chest physiotherapy 3-4 times a day along with good nutritional support. Outpatient antibiotic therapy should always be attempted first if there are no signs of respiratory distress or decompensation. Choice of therapy should be based on previous sputum cultures.
  - The duration of therapy depends on clinical improvement but is generally between 2 and 3 weeks.
    - If there is failure to improve clinically while on outpatient therapy, the patient should be admitted to initiate IV antibiotic therapy for a total of 2-4 weeks.
    - All patients should be hospitalized in separate rooms with strict isolation measures as needed for resistant organisms.
    - The duration of admission depends on the severity of the patient's illness and clinical judgment (clinical improvement, improvement in spirometry, easiness of completing IV treatment at home).
    -

- **Special considerations**

  - **Allergic bronchopulmonary aspergillosis (ABPA)**
    - ABPA is an exaggerated immunologic response in the lungs against Aspergillus that results in signs of airway obstruction. It occurs in 6%-25% of patients with CF. Unlike in adults where asthma with ABPA is common, ABPA is rarely seen in children other than complicating CF.
    - Criteria for diagnosis include positive skin prick testing against Aspergillus, along with detection of specific Aspergillus anti-IgG and anti-IgE in serum. Radiographic evidence of central bronchiectasis is suggestive of the diagnosis.
    - Treatment includes oral corticosteroids and antifungals such as itraconazole.

  - **Cystic fibrosis-related diabetes mellitus (CFRD)**
    - CFRD is caused by destruction of pancreatic islet cells and resultant insulin deficiency. Patients with CF should undergo frequent (annual) oral glucose tolerance tests to screen for evidence of CFRD.
    - Treatment is generally managed by a pediatric endocrinologist. It frequently involves administration of insulin and carbohydrate counting without compromising lipid intake and high caloric necessities.

  - **Lung transplantation**
    - The most common cause of death related to CF is advanced lung disease, and for these patients, lung transplantation may be the only alternative to prolong survival.
    - The most commonly used model for CF survival was published by Kerem et al. and describes high mortality risk for patients with an FEV_1 < 30% of predicted, hypercarbia (>50 mm Hg), hypoxemia (<55 mm Hg), young age, female gender, and nutritional failure. These patients should be referred for evaluation of lung transplantation.

Table. Differential diagnoses, presenting symptoms, and findings

*[Leigh et al. Clinical and genetic aspects of primary ciliary dyskinesia/Kartagener syndrome. Genetics in Medicine (2009) **11**, 473–487]*

Symptoms	PCD	CF	Asthma	Allergic rhinitis	GERD	ILD
Cough	+++	+++	++	++	++	++
Frequency	Chronic, daily	Chronic	Intermittent	Intermittent	Intermittent	Intermittent
Character	Wet	Wet	Dry	Dry or wet	Dry or wet	Dry or wet
Time of year	Year-round	Year-round	Often seasonal	Often seasonal	Year-round	Year-round
Nasal congestion	+++	++	w/allergic rhinitis	++	−	−
Frequency	Chronic, daily	Intermittent		Intermittent		
Time of year	Year-round	Year-round		Often seasonal		
Otitis media	+++	−	−	−	+	++
Sinus disease	+++	+++	−	++	−	−
Neonatal respiratory distress	+++	−	−	−	−	+++
Findings						
Chest imaging	Hyperinflation, infiltrates, atelectasis, peribronchial thickening, bronchiectasis	Hyperinflation, infiltrates, atelectasis, peribronchial thickening, bronchiectasis	Hyperinflation, infiltrates, rare atelectasis	Normal	Normal, or infiltrates with aspiration, rare bronchiectasis	Ground-glass opacities, hyperlucency, consolidation, septal thickening, cysts, nodules
Pulmonary function testing	Obstructive, later mixed	Obstructive, later mixed	Obstructive	Normal	Normal	Restrictive

+++, occurs in over 75% of patients with classic disease; ++ occurs in many patients with classic disease; +, occurs in some patients with classic disease; −, occurs at same frequency as in general population.
PCD, primary ciliary dyskinesia; CF, cystic fibrosis; GERD, gastroesophageal reflux disease; ILD, interstitial lung disease (examples of ILD presenting in neonatal period include surfactant protein C deficiency and neuroendocrine cell hyperplasia).

REFERENCE

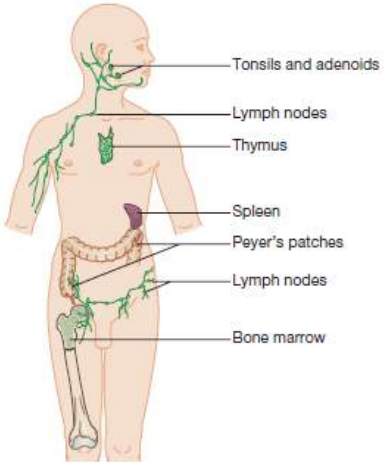
1. Hull J et al. Paediatric Respiratory Medicine, 2nd ed. Oxford University Press 2015
2. ERS Handbook: Paediatric Respiratory Medicine, 1st ed. European Respiratory Society 2013

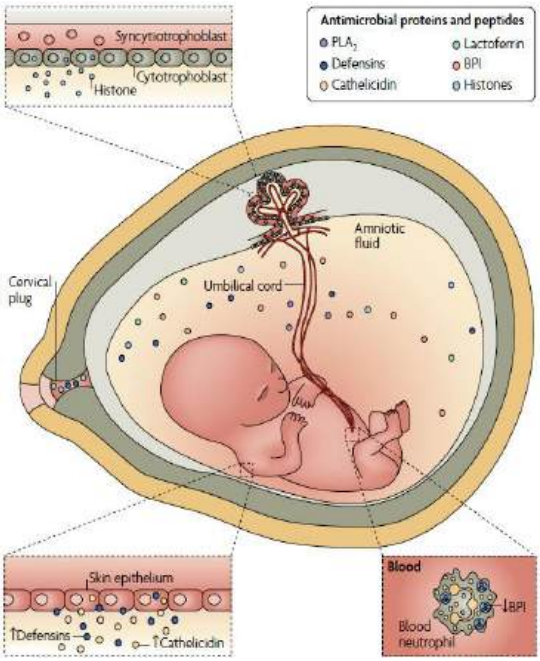
INTRODUCTION TO PEDIATRIC ALLERGY AND IMMUNOLOGY

Characteristics of the immune system in childhood

The immune system is made up of organs and tissues that are connected by the blood and lymph systems. The organs and tissues where immature (or naïve) lymphocytes are produced are described as the **primary (or central) lymphoid organs**, and where they come into contact with harmful organisms as mature lymphocytes as the **secondary (or peripheral) lymphoid organs** (Nairn and Helbert, 2007).

The primary lymphoid tissues consist of the bone marrow and the thymus, while the secondary lymphoid tissues consist of the lymph nodes, spleen and mucosal-associated lymphoid tissue (MALT).





The fetal immune system develops in a sterile and protected environment, and therefore lacks antigenic experience. It must also be modulated in order to co-exist with the mother's immune system. Soon after birth, the newborn is exposed to the "hostile world" of bacteria, viruses, fungi, and parasites, and must immediately defend itself.

During this period, the neonate mainly depends upon components of the innate or antigen-independent immune system, including phagocytes, natural killer cells, antigen presenting cells, humoral mediators of inflammation, and complement. Also, during the initial postpartum phase, the infant relies on **maternal antibodies** and the **mother's breast milk**, which is rich with immunoglobulins and WBCs.

The overall performance of the immune system in the neonatal period is diminished in several important respects. As a result, **infants in the first three months of life are more susceptible than older infants to serious bacterial infection, as well as some viral and fungal infections.** Specifically, organisms that can cause significant morbidity in neonates include: group B streptococci, Escherichia coli, herpes simplex virus (HSV), cytomegalovirus (CMV), varicella-zoster virus (VZV), respiratory syncytial virus (RSV), and Candida species.

What makes a neonate's immune system immature?

The immunological function of the neonate undergoes maturation in both the cellular and humoral components with the child's development.

Neutrophils (polymorphonuclear leukocytes)

Neonatal neutrophils are deficient in their ability to adhere to vessel walls at site of infection. Further release of neutrophils depletes a neonatal storage pool because the bone marrow storage of a neonate is only 20-30% of the pool in an adult. Neonatal neutrophils have a decreased ability to "deform" & migrate into tissues. Neonatal neutrophils have decreased chemotaxis due to decreased chemoattractant production. Bacterial killing by polymorphonuclear leukocytes, which depends on the generation of oxygen-derived free radicals, is intact in healthy-term and most premature newborns.

Monocytes

Neonates have a sufficient amount of monocytes and full capability to kill organisms, but because of a neonates deficiencies previously discussed very few monocytes get to the site of infection.

Lymphocytes

T cell-mediated immunity is not transferred from mother to fetus, in contrast to humoral immunity. Thus, young infants rely exclusively on their own T cells plus elements of the innate immune system to fight infections caused by intracellular pathogens, respond to vaccination, and reject foreign tissue.

The neonate's T-cells are unable to produce certain cytokines, which affects the interaction between T-cells and B-cells. In addition, there is a greater reactivity of T-suppressor cells relative to T-helper cells compared with those of the normal adult.

Activated T cells may be subdivided into distinct functional categories depending upon the profile of cytokines they secrete. The Th1 response promotes production of opsonizing antibodies (eg, IgG1), induction of cellular cytotoxicity, and macrophage activation. This T cell response provides defense against pathogens that replicate intracellularly, particularly mycobacteria and viruses, and also some bacteria and parasites. In comparison, Th2 responses promote the production of IgE and IgG4, and stimulate eosinophil development.

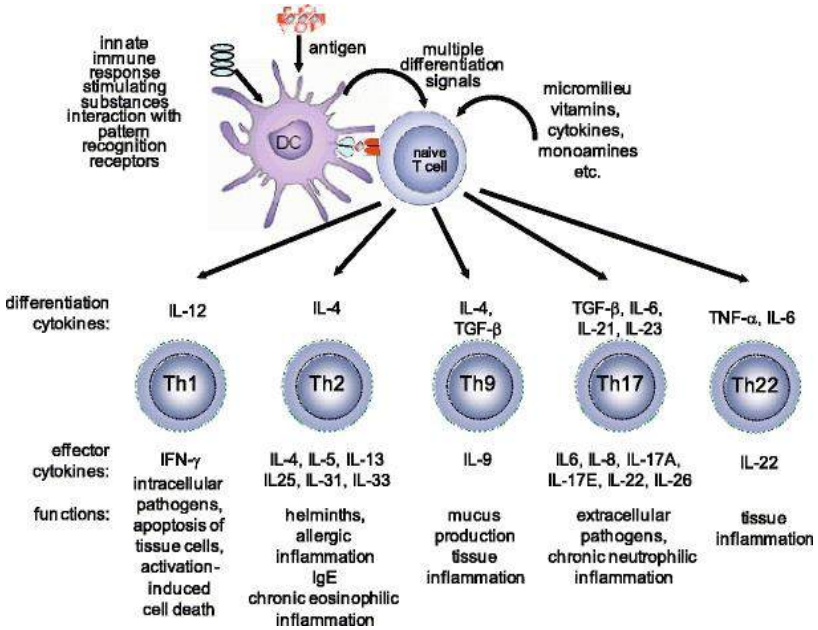


Fig. **The differentiation of naïve T cells.**

Depending on the adjuvanticity of the substances co-exposed with the antigen and status of the cells and cytokines in the microenvironment, naïve T cells can differentiate into T-helper (Th)1, Th2, Th9, Th17, and Th22 types of T cells. Based on their respective cytokine profiles, responses to chemokines, and interactions with other cells, these T-cell subsets can promote different types of inflammatory responses.

IFN interferon, **IL** interleukin, **TGF** transforming growth factor, **TNF** tumor necrosis factor

Complement system

Premature and full-term infants are deficient in all of the measurable products of complement activation.

Decreased Complement
(50%-75% of concentration in adult)

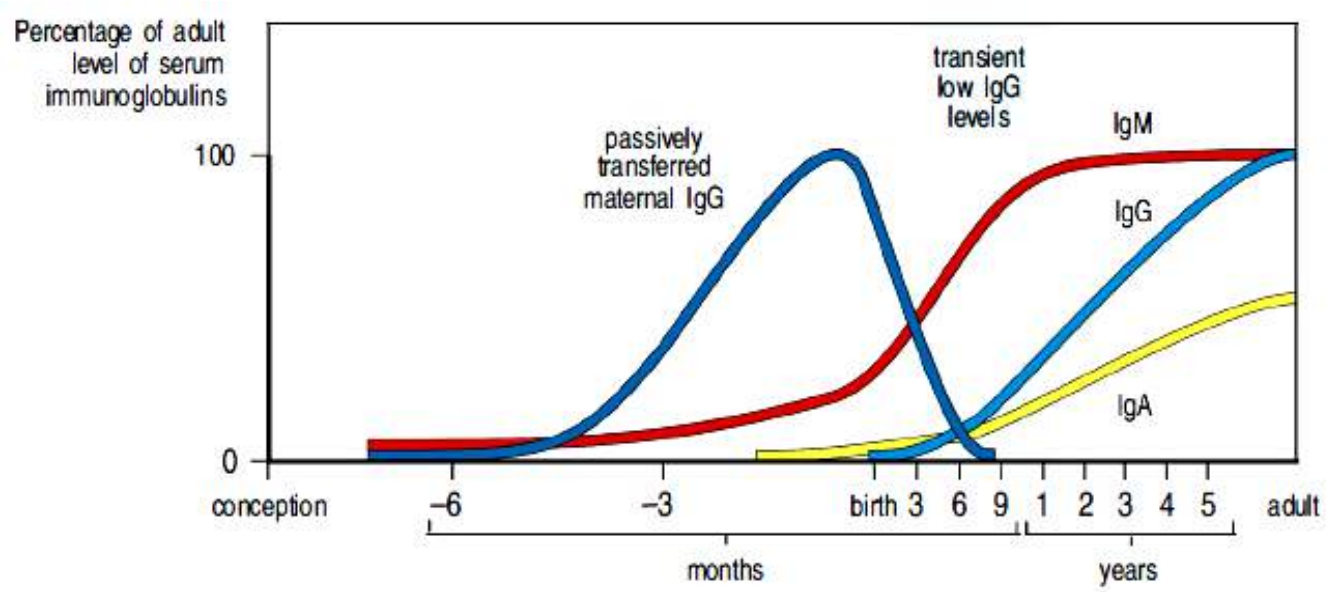
- ↓ Chemotaxins
- ↓ Lysis
- ↓ Opsonization

Complement levels increase after birth and reach adult levels between 6 to 18 months of age.

Immunoglobulin (Ig) production in the foetus and newborn

- The developmental pattern of immunoglobulins (Igs) is as follows: **IgG** transfer across the placenta occurs as early as 8 weeks gestational age. Its level is directly proportional to gestational age, but is still less than 50% of term levels at 28 weeks gestation. The IgG levels fall during the first four months of extrauterine life reaching adult levels by 4 – 6 years of age.
- By the 10th week of gestation, the fetus is capable of producing **IgM** and may make large quantities in the presence of a congenital infection. IgM production by the non-infected newborn does not reach adult levels until 1–2 years of life.
  IgA is not measurable until late in gestational life and is very limited in the infant, failing to reach adult values until puberty.
  Secretory IgA appears later than serum IgA (already limited in the infant). Diseases whose defense depends primarily upon secretory IgA, such as some of the viral respiratory agents (e.g., respiratory syncytial virus) and infectious diarrheas, remain prevalent throughout infancy. The infant is at risk for encapsulated organisms and cannot localize infections well.

Fig. **Immunoglobulin levels in newborn infants fall to low levels at about 6 months of age.**



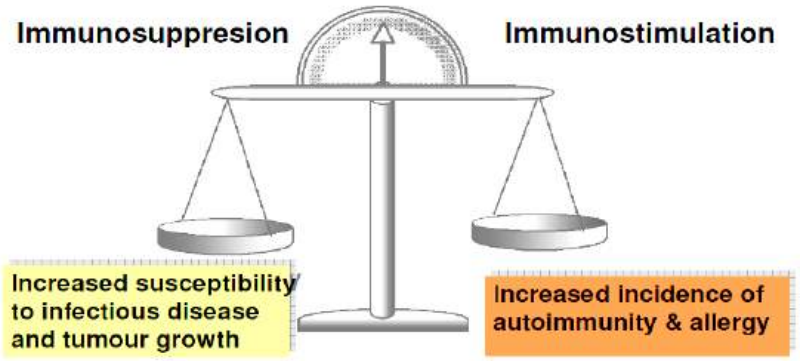
Differences in Immune Responses in Full and Preterm Infants

Immune System Component		*Full Term Infant*	*Preterm Infant*
IgG	It provides immunity against both bacterial and viral pathogens. It starts to cross the placenta and enter into fetal circulation around 30 weeks' gestation and continues until the 40th week.	Complete placental transfer, concentrations comparable to mother	Incomplete placental transfer, concentrations decreased ! *Research has shown that there are also decreased levels of IgG in post-term and small for gestation age infants*
IgM	- does not cross the placenta thus, little or no IgM is transferred to the fetus. This lack of IgM increases the infant's susceptibility to gram negative infections. The infant does however begin synthesis of this immunoglobulin very early in their fetal life. Levels of IgM have been detected around 30 weeks' gestation with higher levels detected when there is an intrauterine infection present.		
IgA	- is the most common immunoglobulin found in the gastrointestinal tract, respiratory tract, human colostrum, and breast milk. IgA does not cross the placenta, and intrauterine synthesis is minimal. Levels of IgA are usually not detected until the infant is around 2 to 3 weeks old.		
Complement		50%-75% of concentration in adult	Decreased concentration
Lymphocytes		Concentrations of T and B cells comparable to those in adults with normal response to antigens	Concentrations of T and B cells comparable to those in adults with normal response to antigens
Neutrophils		Elevated numbers at birth, with impaired functional ability	Elevated numbers at birth, with impaired functional ability
Monocytes		Normal number at birth but have impaired chemotaxis	Normal number at birth but have impaired chemotaxis
Macrophages		Normal number at birth but decreased function	Normal number at birth but decreased function
Natural Killer Cells		Concentration similar to adult level, but have diminished cytotoxic effects	Concentration similar to adult level, but have diminished cytotoxic effects

DEVELOPMENT OF CHILDREN'S IMMUNOCOMPETENCE BALANCE: LESSONS LEARNED FROM EARLY INFECTIONS

Decreased postnatal microbial stimulation results in an increased possibility of ongoing **postnatal Th2 reactions**. Modern lifestyle resulting in decreased bacterial stimulation (improvements in public health, reduction in family size with fewer infectious contacts and the early use of antibiotics) can more easily lead to this situation. This is the so-called **'hygiene hypothesis'** which is the subject of much current interest.

IMMUNOCOMPETENCE BALANCE



Immune response is dependent on the interaction of genetic and environmental factors.

GENETIC FACTORS

IMMUNE RESPONSE

ENVIRONMENTAL FACTORS

- Stress
- Microorganisms
- Radiation
- Chemicals
  - *Pharmaceutical*
  - *Environmental contaminants*

According to the hygiene hypothesis, an increased incidence of allergic pathology in westernized societies may be explained in part by a reduced microbial load early in infancy.

Allergic diseases are caused by inappropriate immunological responses to innocuous antigens driven by a Th2-mediated immune response. Many bacteria and viruses elicit a Th1-mediated immune response, which down-regulates Th2 responses. Observations of this down-regulation led to the development of the first proposed mechanism of action of the hygiene hypothesis, which stated that insufficient stimulation of the Th1 arm of the immune system lead to an overactive Th2 arm, which in turn led to allergic disease.

More pets = less asthma risk

Some data support the hypothesis that exposure to dogs and farm animals during the first year of life reduces the risk of asthma in children at age 6 years*. This information might be helpful in decision making for families and physicians on the appropriateness and timing of early animal exposure.

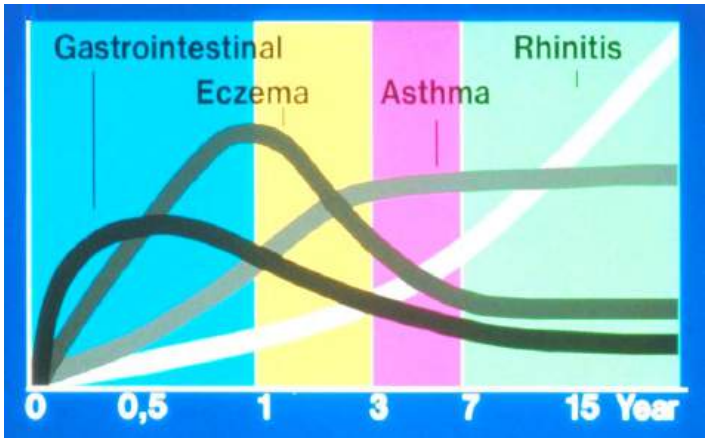
Jhun I, Phipatanakul W. Early exposure to dogs and farm animals reduces risk of childhood asthma. Evidence-based medicine. 2016;21(2):80.

ATOPY. ATOPIC MARCH

Atopy is a result of a complex interaction between multiple genes and environmental factors. It implies **specific IgE-mediated diseases**, including allergic rhinitis, asthma, and atopic dermatitis. An **allergen** is an antigen that triggers an IgE response in genetically predisposed individuals.

The term "Allergic March" (also called "Atopic March") refers to the natural history of atopic manifestations, which is characterized by a typical sequence of immunoglobulin E (IgE) antibody responses and clinical symptoms which may appear early in life, persist over years or decades and often remit spontaneously with age.

Fig. **Allergic children develop individual allergic disorders at different ages**



[Weinberg EG. The atopic march. Curr Allergy Clin Immunol. 2005;18:4Y5]

- Eczema and food allergy usually develop in infancy; both are often present
- Allergic rhinitis and conjunctivitis and asthma occur most often in preschool and primary school years
- Rhinitis and conjunctivitis often preceede the development of asthma, and in children with asthma, up to 80% have coexistent rhinitis.

"Allergic March" is frequently misunderstood as the development from minor symptoms over a mild disease expression towards more severe chronic manifestations. It also has been misinterpreted as the exclusive development from atopic dermatitis in infancy to airway disease, particularly asthma in school-age. These interpretations have been shown to underestimate the variations and heterogeneity of atopy development during the first decade of life.

INITIAL DIAGNOSTIC EVALUATION

Screening Tests

Atopy is characterized by **elevated levels of IgE** (Table 1) and **eosinophilia** (3% to 10% of white blood cells or an absolute eosinophil count of >250 eosinophils/mm3) with a predominance of Th2 cytokines, including interleukin (IL)-4, IL-5, and IL-13. Extreme eosinophilia suggests a nonallergic disorder such as infections with tissue-invasive parasites, drug reactions, or malignancies (Table 2).

Table 1. Disorders Associated with Elevated Serum Immunoglobulin E

Allergic disease	Wiskott-Aldrich syndrome
Atopic dermatitis (eczema)	Bone marrow transplantation
Tissue-invasive helminthic infections	Hodgkin disease
Hyperimmunoglobulin-E syndromes	Bullous pemphigoid
Allergic bronchopulmonary aspergillosis	Idiopathic nephrotic syndrome

Table 2. Disorders Associated with Eosinophilia	
ALLERGIC DISEASE	RESPIRATORY
Allergic rhinitis	Eosinophilic pneumonia
Atopic dermatitis	Allergic bronchopulmonary aspergillosis
Asthma	SYSTEMIC
GASTROINTESTINAL	Idiopathic hypereosinophilic syndrome
Eosinophilic gastroenteritis	Adrenal insufficiency
Allergic colitis	Mastocytosis
Inflammatory bowel disease	IATROGENIC
INFECTIOUS	Drug-induced
Tissue-invasive helminthic infections	
NEOPLASTIC	
Eosinophilic leukemia	
Hodgkin disease	

There are two methods for identifying **allergen-specific IgE**: in vivo skin testing and in vitro serum testing (Table 3).

In vivo skin testing introduces allergen into the skin via a prick/puncture or intradermal injection. The allergen diffuses through the skin to interact with IgE that is bound to mast cells. Cross-linking of IgE causes mast cell degranulation, which results in a histamine release; this prompts the development of a **central wheal and erythematous flare.** The wheal and flare are measured 15 to 20 minutes after the allergen has been placed. Properly performed skin tests are the best available method for detecting the presence of allergen-specific IgE.

In vitro serum testing, such as immunoassays like the **radioallergosorbent test** (also known as **RAST**) and enzymelinked immunosorbent assay (also known as **ELISA**), measures levels of antigen-specific IgE. Many allergists and laboratories regard the ImmunoCAP System as the method of choice. This method uses a solid phase and shows higher sensitivity, specificity, and reproducibility. The assay uses a quantitative fluorescent immunoassay (FEIA); FEIA is more sensitive than other assays. These tests are indicated for patients who have dermatographism or extensive dermatitis; who cannot discontinue medications, such as antihistamines, that interfere with skin test results; who are very allergic by history, where anaphylaxis is a possible risk; or who are noncompliant for skin testing. The presence of specific IgE antibodies alone is not sufficient for the diagnosis of allergic diseases. Diagnosis must be based on the physician's assessment of the entire clinical picture, including the history and physical examination, the presence of specific IgE antibodies, and the correlation of symptoms to IgE-mediated inflammation.

Table 3. Comparison of In Vivo Skin Tests and In Vitro Serum IgE Antibody Immunoassay in Allergic Diagnosis	
IN VIVO SKIN TEST	IN VITRO SERUM IMMUNOASSAY
Less expensive	No patient risk
Greater sensitivity	Patient/physician convenience
Wide allergen selection	Not suppressed by antihistamines
Results available immediately	Preferable to skin testing for dermatographism
	Widespread dermatitis
	Uncooperative children

From *Skoner DP: Allergic rhinitis: definition, epidemiology, pathophysiology,detection, and diagnosis, J Allergy Clin Immunol 108:S2–S8, 2001.*

PEDIATRIC ASTHMA

A 5-year-old girl with a past medical history of multiple episodes of RSV-induced bronchiolitis presents with a cough for 6 months that is exacerbated by exercise, cold air, and seasonal allergies. A chest x-ray taken during an episode of coughing reveals hyperinflation. What is the cause of the patient's cough?

Asthma is a disease of chronic airway inflammation, bronchial hyper-reactivity, and reversible airway obstruction. It affects 10% of the population and can develop at any age, but about 50% of childhood asthma develops before the age of 3 years, and nearly all has developed by the age of 7 years.

The signs and symptoms of asthma, including chronic cough, may be evident much earlier than the actual diagnosis but may be erroneously attributed to recurrent pneumonia [*American Lung Association: www.lungusa.org. Accessed on Jan. 13, 2015*].

Although about one-third of children will have an episode of wheezing before they are 1 year old, most (80%) do not develop persistent wheezing after age 3 years.

Risks factors for persistence include the following:

- Positive family history of asthma (especially maternal)
- Increased IgE levels
- Atopic dermatitis
- Rhinitis not associated with colds
- Secondhand smoke exposure

If both parents are asthmatic, the risk that their child will have asthma is 60%. For a child with only one parent with asthma, the risk is estimated to be about 20%. If neither parent has asthma, the risk is 6% to 7%.

Asthma is an atopic condition and other atopic conditions are often coexistent, e.g. eczema and allergic rhinitis.

The airways in asthma undergo significant structural remodeling:

- Increase in smooth muscle mass
- Mucus gland hyperplasia
- Persistent chronic inflammatory infiltrates
- Release of fibrogenic growth factors
- Collagen deposition
- Elastocytosis

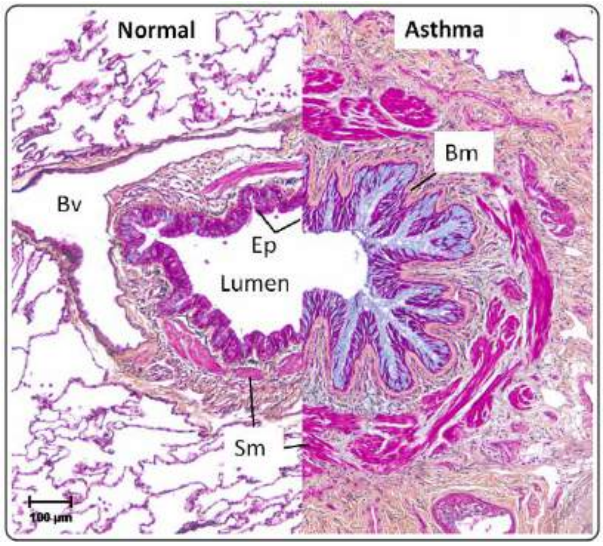


Fig. Medium-sized airways from a normal and severe asthmatic patient were sectioned and stained using Movat's pentachrome stain. The epithelium (Ep) in asthma shows mucous hyperplasia and hyper secretion (blue), and significant basement membrane (Bm) thickening. Smooth muscle (Sm) volume is also increased in asthma. Bv = blood vessel.

ASTHMA TRIGGERS

Historical points suggestive of an allergic basis for asthma

- Seasonal nature with concurrent rhinitis (suggesting pollen)
- Symptoms worsen when visiting a family with pets (suggesting animal dander)
- Wheezing occurs when carpets are vacuumed or bed is made (suggesting mites)
- Symptoms develop in damp basements or barns (suggesting molds)

- Cold air
- Emotional extremes (stress, fear, crying, laughing)
- Environmental (pollutants, cigarette smoke)
- Exercise
- Foods, food additives
- Gastroesophageal reflux disease
- Hormonal (menstrual, premenstrual)
- Irritants (strong odors, paint fumes, chlorine)
- Medications (nonsteroidal anti-inflammatory drugs, aspirin, β-blockers)
- Substance abuse
- Upper airway infections (rhinitis, sinusitis)
- Weather changes

Clinical features

The features can be *chronic* with frequent wheeze and cough (usually present if asthma is being undertreated), or *acute* with fast onset often associated with URTI. The disease varies from being extremely mild to very severe, with frequent and even life-threatening exacerbations, and interrupting daily life considerably.

Chronic features	Recurrent wheeze Difficulty in breathing } Both often with exercise If longstanding: • Chest hyperinflation • Harrison sulci (a permanent groove in the chest wall just above the costal margins at the insertion of the diaphragm) • Faltering growth • Nocturnal wheeze with cough
Exacerbation	Expiratory wheeze (NB: Babies have crackles with bronchiolitis, not infant wheeze) Respiratory distress (dyspnoea, tachypnoea, recession, cyanosis)
Life-threatening attack	Unable to speak or feed Central cyanosis Exhaustion/confusion/decreasing level of consciousness Silent chest on auscultation (due to minimal air entry) Peak flow < 30% of predicted Pulsus paradoxus (fall of inspiratory systolic BP greater than 10 mmHg from expiratory systolic BP)

DIAGNOSTIC CRITERIA FOR ASTHMA IN ADULTS, ADOLESCENTS, AND CHILDREN 6–11 YEARS

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.

DIAGNOSTIC FEATURE	CRITERIA FOR MAKING THE DIAGNOSIS OF ASTHMA
1. History of variable respiratory symptoms	
Wheeze, shortness of breath, chest tightness and cough Descriptors may vary between cultures and by age, e.g. children may be described as having heavy breathing	• Generally more than one type of respiratory symptom (in adults, isolated cough is seldom due to asthma) • Symptoms occur variably over time and vary in intensity • Symptoms are often worse at night or on waking • Symptoms are often triggered by exercise, laughter, allergens, cold air • Symptoms often appear or worsen with viral infections
2. Confirmed variable expiratory airflow limitation	
Documented excessive variability in lung function* (one or more of the tests below) The greater the variations, or the more occasions excess variation is seen, the more confident the diagnosis **AND** documented airflow limitation*	At least once during diagnostic process when FEV1 is low, **confirm that FEV1/FVC is reduced** (normally >0.75–0.80 in adults, >0.90 in children)
Positive bronchodilator (BD) reversibility test* (more likely to be positive if BD medication is withheld before test: SABA ≥4 hours, LABA ≥15 hours)	*Adults*: increase in FEV1 of >12% and >200 mL from baseline, 10–15 minutes after 200–400 mcg albuterol or equivalent (greater confidence if increase is >15% and >400 mL). *Children*: **increase in FEV1 of >12% predicted**
Excessive variability in twice-daily PEF over 2 weeks*	*Adults*: average daily diurnal PEF variability >10%** *Children*: **average daily diurnal PEF variability >13%****
Significant increase in lung function after 4 weeks of anti-inflammatory treatment	*Adults*: increase in FEV1 by >12% and >200 mL (or PEF† by >20%) from baseline after 4 weeks of treatment, outside respiratory infections
Positive exercise challenge test*	*Adults*: fall in FEV1 of >10% and >200 mL from baseline *Children*: **fall in FEV1 of >12% predicted, or PEF >15%**
Positive bronchial challenge test (usually only performed in adults)	**Fall in FEV1 from baseline of ≥20% with standard doses of methacholine or histamine**, or ≥15% with standardized hyperventilation, hypertonic saline or mannitol challenge
Excessive variation in lung function between visits* (less reliable)	*Adults*: variation in FEV1 of >12% and >200 mL between visits, outside of respiratory infections *Children*: **variation in FEV1 of >12% in FEV1 or >15% in PEF† between visits** (may include respiratory infections)

BD: bronchodilator (short-acting SABA or rapid-acting LABA); FEV1: forced expiratory volume in 1 second; LABA: long-acting beta2-agonist; PEF: peak expiratory flow (highest of three readings); SABA: short-acting beta2-agonist.
*These tests can be repeated during symptoms or in the early morning.
**Daily diurnal PEF variability is calculated from twice daily PEF as ([day's highest minus day's lowest] / mean of day's highest and lowest), and averaged over one week. †For PEF, use the same meter each time, as PEF may vary by up to 20% between different meters. BD reversibility may be lost during severe exacerbations or viral infections.11 If bronchodilator reversibility is not present at initial presentation, the next step depends on the availability of other tests and the urgency of the need for treatment. In a situation of clinical urgency, asthma treatment may be commenced and diagnostic testing arranged within the next few weeks, but other conditions that can mimic asthma (Box 1-3) should be considered, and the diagnosis of asthma confirmed as soon as possible.

CLINICAL DIAGNOSIS OF ASTHMA IN CHILDREN 5 YEARS AND YOUNGER

It may be difficult to make a confident diagnosis of asthma in children 5 years and younger, because episodic respiratory symptoms such as wheezing and cough are also common in children without asthma, particularly in those 0–2 years old.

Furthermore, it is not possible to routinely assess airflow limitation in this age group. A probability-based approach, based on the pattern of symptoms during and between viral respiratory infections, may be helpful for discussion with parents/carers. This approach allows individual decisions to be made about whether to give a trial of controller treatment. It is important to make decisions for each child individually, to avoid either over- or under-treatment.

Probability of asthma diagnosis or response to asthma treatment in children 5 years and younger

Peak expiratory flow (PEF)

- Peak flow measurements can be used in most children from about 5–7 years and are helpful in diagnosing and monitoring the severity of asthma. The child takes a deep breath, and then breathes out quickly through the mouthpiece of the peak flow meter, ensuring a good seal. The best of three measurements is taken.
- Performed much less nowadays due to relative lack of reproductibility.

Peak flow chart

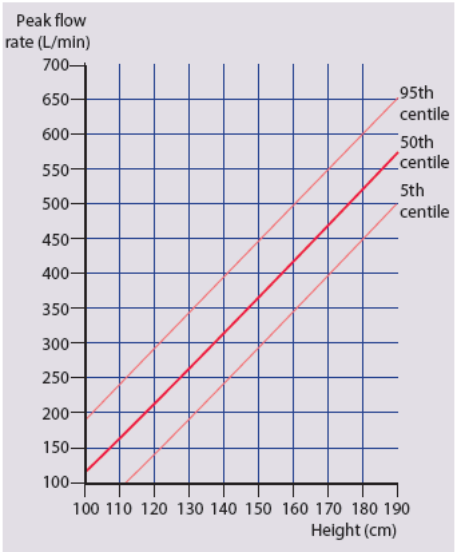


Fig. **The normal range of peak flow measurements according to height** (Godfrey S, Kamburoff PL, Nairn JR. 1970)

Important questions to ask in an asthma history

- What triggers the asthma?
- How often and how severe are the attacks?
- Does the asthma affect daily living, e.g. sport, school, sleep?
- Can they measure their peak flow properly to monitor their asthma?
- Can they use their device properly (get them to demonstrate this)?
- Do they understand the difference between quick relief and preventative medications?
- Do they recognize a deterioration, and have a good management plan for this?
- Do they recognize a severe attack and know to seek prompt medical attention?

Management

Acute attack	○ Oxygen ○ β2-agonist, e.g. salbutamol: either 10 puffs from a metered dose inhaler (MDI) via spacer device or nebulized as frequently as necessary (initially every 15 min) ○ Ipatropium bromide 6 hourly can be helpful, more in younger children ○ Systemic steroids (oral prednisolone 1–2 mg/kg [max. dose 40 mg] or IV hydrocortisone) If severe attack, then may need: ● IV infusion or bolus of salbutamol or aminophylline infusion (if on oral theophylline, no loading dose) ● Intubation and ventilation if deterioration in general condition, i.e. peak flow, blood gases, drowsiness, tiring, despite above measures
Long term	Essentially divided into: ○ **Immediate relief** medications, e.g. salbutamol inhaler (to take whenever necessary [prn]) ○ **Long term preventative** medications, e.g. beclomethasone inhaler (to take regularly each day)

Asthma medications

IMMEDIATE RELIEF BRONCHODILATORS (= Reliever (rescue) medications)	Example
◆ ***β-2 agonists:*** – Bronchodilators acting directly on the β-2 receptors in the bronchi: – Side effects due to stimulation of b-receptors: tachycardia and arrhythmias, peripheral vasodilatation, headache, fine tremor, excitement, hypokalaemia if used frequently	○ *Short acting*, e.g. salbutamol, terbutaline – used as acute relievers of symptoms ○ *Longer acting*, e.g. salmeterol, formoterol – used to prevent daily symptoms, e.g. exercise induced wheeze
◆ ***Anticholinergics:*** – Antimuscarinic bronchodilators – Slower onset (30–60 min), last up to 6 h – Rarely used in children unless < 1 year old – Sometimes used in acute attacks	e.g. ipratropium bromide, oxitropin

LONG TERM PREVENTATIVE MEDICATIONS (= Controller medications)	Example
◆ ***Inhaled corticosteroids (ICS):*** – Anti-inflammatory effect on airways – Steroid side effects minimal unless high-dose inhaled or oral steroids given regularly	e.g. beclomethasone, budesonide, fluticasone
◆ ***Methylxanthines:*** – Bronchodilators, smooth muscle relaxer – Narrow margin between toxicity (arrhythmias, convulsions) and therapeutic dose **! Due to its high toxicity, theophylline is not recommended for use in children, unless ICS are not available.**	e.g. aminophylline, theophylline
◆ ***Leukotriene receptor antagonists (LTRA):*** – Selectively block the action of cysteinyl leukotrienes preventing bronchoconstriction, mucus secretion and oedema	e.g. montelukast
◆ ***Anti-immunoglobulin E (anti-IgE):*** – is a treatment option for patients aged ≥6 years with severe persistent allergic asthma and elevated serum IgE whose asthma is uncontrolled on treatment with corticosteroids (inhaled and/or oral) and LABA, or who require high dose treatment to maintain good asthma control	e.g. omalizumab
◆ ***Anti-interleukin 5 (anti-IL5):*** – is a neutralizing antibody targeting IL-5, which is required for eosinophil maturation and survival. It is a treatment option for patients aged ≥12 years with severe eosinophilic asthma whose asthma is uncontrolled on treatment with corticosteroids (inhaled and/or oral) and LABA, or who require high dose corticosteroid treatment to maintain good asthma control.	e.g. mepolizumab, reslizumab

Delivery devices. Inhaler therapy

Inhaled drugs may be administered via a variety of devices, chosen according to the child's age and preference:

• ***Pressurised metered dose inhaler (pMDI) and spacer***

– Appropriate for all age groups: 0–2 years, spacer and facemask; >2 years, spacer alone

– A spacer is recommended for all children as it increases drug deposition to the lungs

– Useful for acute asthma attacks when poor inspiratory effort may impair the use of inhalers direct to the mouth

• *Breath-actuated metered dose inhalers* (e.g. *Autohaler*, *Easibreath*): 6+ years. Less coordination needed than a pMDI without spacer. Useful for delivering β-agonists when 'out and about' in older children

• ***Dry powder inhaler***: 4+ years

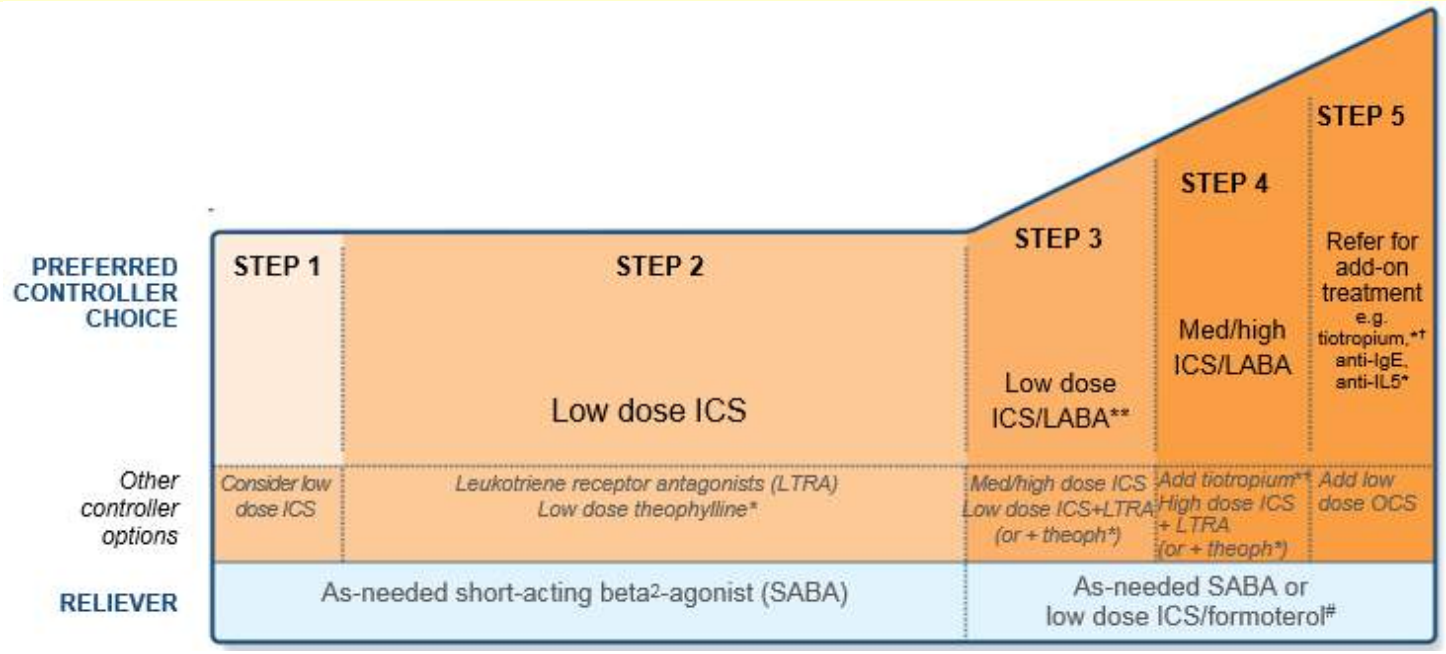
Needs a good inspiratory flow, therefore less good in severe asthma and during an asthma attack. Also easy to use when 'out and about' in older children

• ***Nebuliser***: any age

Only used in acute asthma where oxygen is needed in addition to inhaled drugs; occasionally used at home as part of an acute management plan in those with rapidonset severe asthma (brittle asthma).

Many children fail to gain the benefit of their treatment because they cannot use the inhaler correctly. This must be demonstrated and the child's ability to use it checked. In young children, parents need to be skilled in assisting their child to use the inhaler correctly. Assessing and reassessing inhaler technique is vital to good management and should be a routine part of any review.

STEPWISE APPROACH TO LONG-TERM MANAGEMENT OF ASTHMA IN CHILDREN ≥6 YEARS AND ADULTS



ICS: inhaled corticosteroids; LABA: long-acting beta$_2$-agonist; med: medium dose; OCS: oral corticosteroids; anti-IgE: anti-immunoglobulin E therapy.
*Not for children <12 years
**For children 6-11 years, the preferred Step 3 treatment is medium dose ICS
#For patients prescribed BDP/formoterol or BUD/ formoterol maintenance and reliever therapy
† Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations

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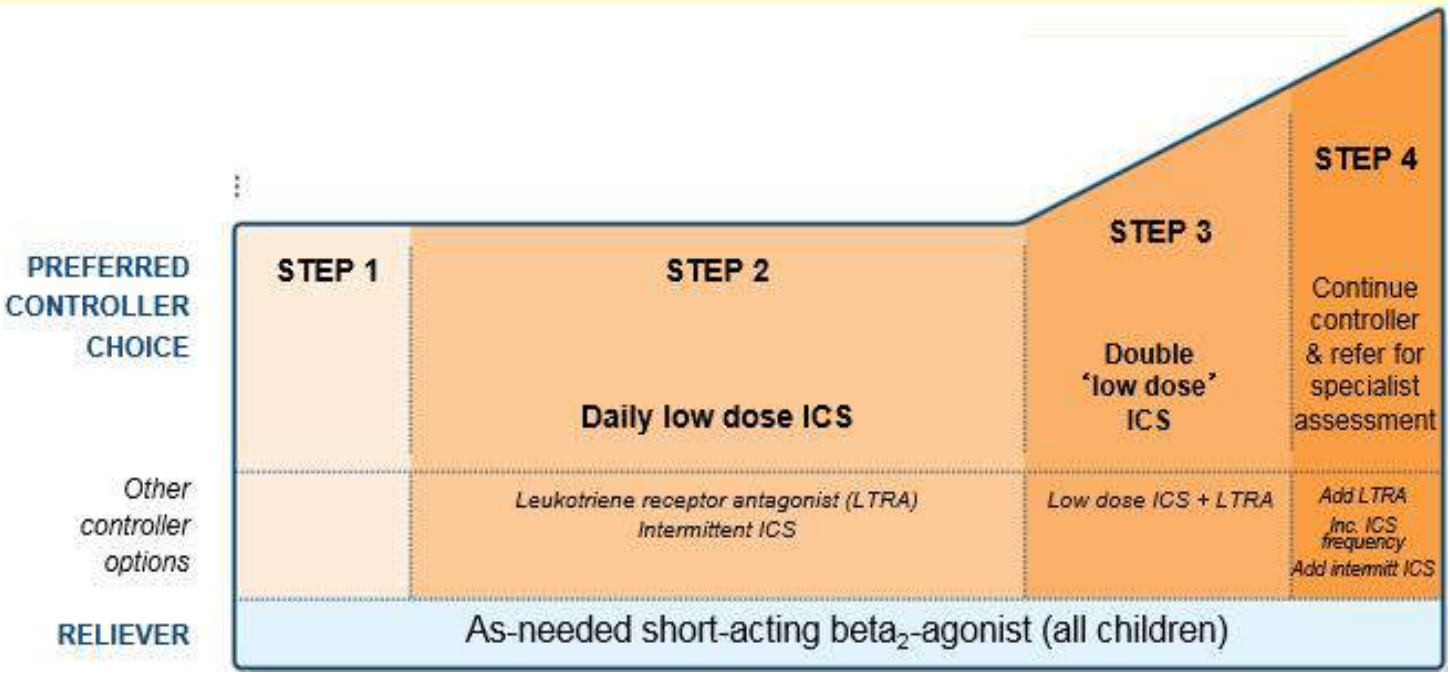
STEPWISE APPROACH TO LONG -TERM MANAGEMENT OF ASTHMA IN CHILDREN 5 YEARS AND YOUNGER



KEY ISSUES

- Assess symptom control, future risk, comorbidities
- Self-management: education, inhaler skills, written asthma action plan, adherence
- Regular review: assess response, adverse events, establish minimal effective treatment
- (Where relevant): environmental control for smoke, allergens, indoor/outdoor air pollution

Low, Medium & High Daily Doses of Inhaled Corticosteroids

Drug	Low Daily Dose			Medium Daily Dose			High Daily Dose		
	Child 0–4 Years of Age	Child 5–11 Years of Age	≥12 Years of Age and Adults	Child 0–4 Years of Age	Child 5–11 Years of Age	≥12 Years of Age and Adults	Child 0–4 Years of Age	Child 5–11 Years of Age	≥12 Years of Age and Adults
Beclomethasone HFA 40 or 80 µg/puff	NA	80–160 µg	80–240 µg	NA	>160–320 µg	>240–480 µg	NA	>320 µg	>480 µg
Budesonide DPI 90, 180, or 200 µg/inhalation	NA	180–400 µg	180–600 µg	NA	>400–800 µg	>600–1,200 µg	NA	>800 µg	>1,200 µg
Budesonide Inhaled Inhalation suspension for nebulization	0.25–0.5 mg	0.5 mg	NA	>0.5–1.0 mg	1.0 mg	NA	>1.0 mg	2.0 mg	NA
Flunisolide 250 µg/puff	NA	500–750 µg	500–1,000 µg	NA	1,000–1,250 µg	>1,000–2,000 µg	NA	>1,250 µg	>2,000 µg
Flunisolide HFA 80 µg/puff	NA	160 µg	320 µg	NA	320 µg	>320–640 µg	NA	≥640 µg	>640 µg
Fluticasone **HFA/MDI:** 44, 110, or 220 µg/puff	176 µg	88–176 µg	88–264 µg	>176–352 µg	>176–352 µg	>264–440 µg	>352 µg	>352 µg	>440 µg
DPI: 50, 100, or 250 µg/inhalation	NA	100–200 µg	100–300 µg	NA	>200–400 µg	>300–500 µg	NA	>400 µg	>500 µg
Mometasone DPI 200 µg/inhalation	NA	NA	200 µg	NA	NA	400 µg	NA	NA	>400 µg
Triamcinolone acetonide 75 µg/puff	NA	300–600 µg	300–750 µg	NA	>600–900 µg	>750–1,500 µg	NA	>900 µg	>1,500 µg

Key: *DPI*, Dry power inhaler; *HFA*, hydrofluoroalkane; *MDI*, metered-dose inhaler; *NA*, not available (either not approved, no data available, or safety and efficacy not established for this age group)

- At present, Step 1 treatment is with as-needed short-acting beta2-agonist (SABA) alone. However, chronic airway inflammation is found even in patients with infrequent or recent-onset asthma symptoms, and there is a striking lack of studies of inhaled corticosteroids (ICS) in such populations.
- Treatment with regular daily low dose ICS is highly effective in reducing asthma symptoms and reducing the risk of asthma-related exacerbations, hospitalization and death.
- For patients with persistent symptoms and/or exacerbations despite low dose ICS, consider **step up** but first check for common problems such as inhaler technique, adherence, persistent allergen exposure and comorbidities.
  - *For adults and adolescents, the preferred step-up treatment is combination ICS/long-acting beta2-agonist (LABA).*
  - *For adults and adolescents with exacerbations despite other therapies, the risk of exacerbations is reduced with combination low dose ICS/formoterol (with beclometasone or budesonide) as both maintenance and reliever, compared with maintenance controller treatment plus as-needed SABA.*
  - *For children 6–11 years, increasing the ICS dose is preferred over combination ICS/LABA.*
- Consider **step down** once good asthma control has been achieved and maintained for about 3 months, to find the patient's lowest treatment that controls both symptoms and exacerbations.
  - *Provide the patient with a written asthma action plan, monitor closely, and schedule a follow-up visit.*
  - *Do not completely withdraw ICS unless this is needed temporarily to confirm the diagnosis of asthma.*

GINA assessment of asthma control in adults, adolescents and children 6–11 years

A. Symptom control		Level of asthma symptom control		
In the past 4 weeks, has the patient had:		**Well-controlled**	**Partly controlled**	**Uncontrolled**
• Daytime asthma symptoms more than twice a week?	Yes❑ No❑	None of these	1-2 of these	3-4 of these
• Any night waking due to asthma?	Yes❑ No❑			
• Reliever needed for symptoms* more than twice a week?	Yes❑ No❑			
• Any activity limitation due to asthma?	Yes❑ No❑			

*Excludes reliever taken before exercise, because many people take this routinely

Example

A 6-year-old boy with well-controlled asthma: he has

- *daytime asthma symptoms no more than twice a week*
- *no night waking due to asthma*
- *reliever needed for symptoms no more than twice a week*
- *no activity limitation due to asthma*

GINA assessment of asthma control in children 5 years and younger

A. Symptom control		Level of asthma symptom control		
In the past 4 weeks, has the child had:		**Well-controlled**	**Partly controlled**	**Uncontrolled**
• Daytime asthma symptoms for more than few minutes, more than once/week?	Yes❑ No❑	None of these	1-2 of these	3-4 of these
• Any activity limitation due to asthma? (runs/plays less than other children, tires easily during walks/playing)	Yes❑ No❑			
• Reliever needed* more than once a week?	Yes❑ No❑			
• Any night waking or night coughing due to asthma?	Yes❑ No❑			

Example

A 5-year-old boy with well-controlled asthma: he has

- *daytime asthma symptoms for few minutes no more than once a week*
- *no night waking due to asthma*
- *reliever needed for symptoms no more than once a week*
- *no activity limitation due to asthma*

Example of patient management plan for asthma

Green zone – GO

Your asthma is under control if:
- your breathing feels good
- you do not have a cough or wheeze
- you can take part in normal activities and play games / sport.
- your are sleeping through the night
- you are not missing school because of your asthma

Peak Flows are between:
.....
.....

Green zone action –
Your normal medicines are:
Preventer
.....
.....

Other Medicines
.....
.....

Reliever
.....
as required.
Remember: If necessary take this before exercise or if you have cold-like symptoms. Take 2–4 puffs every 4 hours if you need it.
If there is no improvement, move to the Amber zone.

Amber zone – WARNING

Your asthma is getting worse if you:
- wake at night with asthma symptoms
- have a cough, wheeze or 'tight' chest
- need to use the reliever inhaler once a day, more than usual or it is not lasting for four hours.

Peak Flows are between:
.....
.....

Amber zone action –
Take all medicines as normal.

Take 4–10 puffs of reliever – one puff at a time as taught. Use a spacer if you have one and shake the MDI in between puffs. Take every four hours if needed.

- If no improvement – make an appointment to see your doctor for that day.
- If you have a Symptom/Peak Flow Diary – start filling it in and take it with you to the doctor.

Or
Start your home prednisolone .....mgs daily, if you have it. See your doctor if you are not better after 12 hours.

Remember: If no better after 10 puffs of reliever, move to Red zone.

Red zone – DANGER

Your asthma is severe if after taking 10 puffs of reliever you:
- are still breathing hard and fast
- can't talk or feed easily
- are exhausted
- are frightened and look anxious
- are very pale/grey/blue in colour

Peak Flow reading (if able) below:
.....
.....

Red zone action –
Call an ambulance now

- Keep taking one puff of reliever every 20–30 seconds or 4 slow breaths or, if you have one, nebulized reliever with oxygen until the ambulance arrives.
- Take a dose of oral steroids if not already taken.
- Don't move about
- Keep calm

ALLERGIC RHINITIS (AR)

AR is a chronic inflammatory disorder of the upper airway caused by IgE sensitization to airborne allergens in genetically susceptible individuals.

> *The upper and lower airways exist as a continuum and show similar histopathologic changes when inflamed, including epithelial damage, thickening of the basement membrane, and a predominantly eosinophilic cellular infiltrate. Epidemiologic studies support a strong association between allergic rhinitis and asthma.*

Diagnosis

- **History**

  *The clinical presentation is associated with frequent sneezing, nasal congestion, and nasal discharge. The majority of patients with AR also display or complain of ocular symptoms (itchy or watery eyes). Thus, it is termed allergic rhinoconjunctivitis (ARC). AR has been subdivided into **seasonal and perennial types** based on the time and duration of symptom occurrence. **Seasonal symptoms** occur in the fall and spring whereas **perennial AR** is caused by an allergic response to allergens that are present throughout the year, such as dust mites and pet dander.*

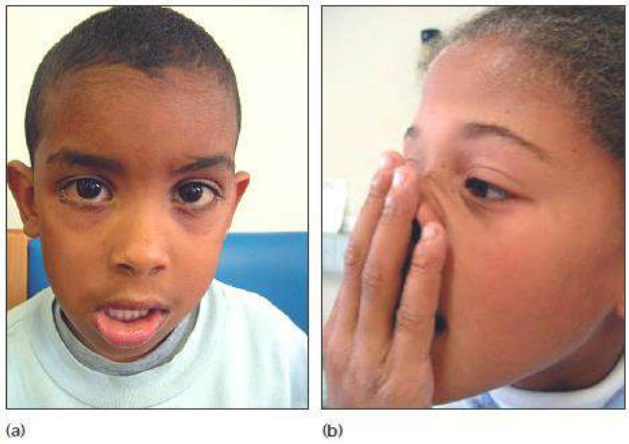


Fig. **Allergic facies. (a) There is a habitually open mouth due to mouth breathing. (b) An allergic salute, from rubbing an itchy nose. (Courtesy Dr George Du Toit.)**

- **Physical exam findings on nasal exam** - *pale, enlarged nasal turbinates and clear rhinorrhea are usually a sign of AR.*

- **Investigation**

  • Skin tests for specific antigens

  • Specific serum IgE measurements

- **Differential diagnosis**
  - ***Chronic sinusitis*** *- often has other clinical features including headache, facial pain, and purulent or green rhinorrhea.*
  - ***Viral upper respiratory infections*** *- can cause sneezing, nasal congestion, and rhinorrhea, but they are not usually associated with ocular pruritus. The duration of a viral upper respiratory infection is also brief and would not be expected to be present consistently year round.*
  - ***Adenoid hypertrophy*** *- can produce nasal airway obstruction and can lead to significant pediatric morbidity including chronic sinusitis, recurrent otitis media with effusion, and chronic serous otitis media. Ocular pruritus would not be expected with adenoid hypertrophy.*

Treatment	Symptom relief
Allergen avoidance	• Antihistamines
• Dust covers on bedding	• Montelukast
• Avoid stuffed toys	• Intranasal steroids

Antihistamines block the histamine receptors.

> *Histamine is a primary amine produced by mast cells and basophils that orchestrates many aspects of the allergic response by binding to specific receptors present on the surface of its target cells. The 4 types of histamine receptors are H1, H2, H3, and H4. Signals induced via the H1 receptor (and to a lesser extent the H2 receptor) mediate many of the acute symptoms and signs of allergic disease. Histamine receptor antagonists are widely used for the treatment of allergic disorders and many antihistamines are acceptable for use in children.*

Pretreatment with oral H1 antihistamines reduces early response to allergen and administering the medication during the course of an allergic response curbs the symptoms triggered by acute allergic inflammation. *First-generation H1 blockers* (diphenhydramine, brompheniramine, cyproheptadine, chlorpheniramine, hydroxyzine, promethazine) are lipophilic and readily penetrate the CNS causing sedation, and in some patients a paradoxical excitation.
Second-generation H1 antihistamines (loratadine, cetirizine, fexofenadine, and levocetirizine) penetrate the CNS poorly and therefore are less likely to cause sedation.

Montelukast is approved for the treatment of asthma and for relief of symptoms of perennial allergic rhinitis. Its mechanism of action is as a **Leukotriene Receptor Antagonist (LTRA)**. As a single agent, it is less effective than nasal corticosteroids, yet the safety profile of LTRAs make them a suitable alternative for patients who cannot receive steroids or who are wary of their side effects.

There are now medications such as **zileuton** that are able to partially block the synthesis of leukotrienes, and can be used in allergic conditions such as asthma.

Allergen specific subcutaneous immunotherapy (SCIT) is an effective therapy for AR. It is currently the only treatment that modifies the course of AR by redirecting the immune system toward a tolerant state. Its clinical benefits may be sustained for years after discontinuation of treatment. SCIT is a time-consuming therapy that requires long-term commitment (minimum of 2 years). The subcutaneous administration is an added drawback for children who are fearful of injections.

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1. *Donald Y. M. et al. Pediatric Allergy: Principles and Practice, 3rd ed. © 2016, Elsevier Inc.*
2. *ERS Handbook: Paediatric Respiratory Medicine, 1st ed. European Respiratory Society 2013.*
3. *Global Strategy for Asthma Management and Prevention (GINA 2017).*
4. *Janeway's Immunobiology, 9th edition - By Kenneth Murphy, Casey Weaver. Garland Science 2016.*

NEONATOLOGY

COMPETENCIES

You must…

Know	Be able to	Appreciate
• The difference between prematurity and growth restriction • The basics of neonatal resuscitation • The key congenital and perinatal conditions that present in the newborn • When a jaundiced baby requires investigation	• Examine a newborn baby • Recognize a baby in need of resuscitation • Recognize when a 'septic workup' is needed	• The newborn is susceptible to infection but may not show classic signs • A small baby may be either premature or growth retarded or a combination of the two

The neonatal period is a highly vulnerable time for infants as they are completing many of the physiologic adjustments required for extrauterine existence. The high neonatal morbidity and mortality rates attest to the fragility of life during this period; of all deaths occurring in the 1st yr of life, two-thirds are in the neonatal period.

Basic terms and classification of newborn infants

Basic terminology

➢ LIVE BIRTH

A live birth is defined as the complete expulsion or extraction from the mother of a product of human conception, irrespective of the duration of pregnancy, which, after such expulsion or extraction, shows **evidence of life**, such as breathing, beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles, regardless of whether the umbilical cord has been cut or the placenta is attached. Heartbeats are to be distinguished from transient cardiac contractions; respirations are to be distinguished from fleeting respiratory efforts or gasps.

➢ PRETERM BIRTH (PTB)

Preterm birth (PTB) occurs between fetal viability and 37 completed weeks of gestation.

➢ LIMIT OF VIABILITY

The limit of viability is defined as the stage of fetal maturity that ensures a reasonable chance of extrauterine survival. Determining the limit of viability is desirable so that interventions that are costly and painful can be avoided in the infant who does not have a chance of survival. However, deciding upon a **threshold of viability** is challenging because of the increasing frequency of survival at progressively lower gestational ages.

Factors that affect survival rates in extremely premature infants (gestational age [GA] <26 weeks) include GA, birth weight, gender, plurality, and the use of antenatal corticosteroid therapy.

The major factor in determining viability is GA. **Most countries define it as a lower limit of 20 to 22 weeks**, but this varies, preventing straightforward comparison of reported rates of neonatal mortality and morbidity.

> *A recent influential report has suggested that a less arbitrary definition of preterm birth would include all births (including live births, stillbirths, and pregnancy terminations) occurring from* ***16 weeks 0 days to 38 weeks 6 days*** *(i.e., 112 to 272 days). The rationale for the latter limit is that births between 37 and 39 weeks are associated with greater short- and long-term morbidity than those after 39 weeks, whereas the rationale for the early limit is that the pathologies inducing spontaneous abortion between 16 and 20 weeks are similar to those inducing PTB at a later gestation.*

Where accurate recording of gestational age is not possible — for example, in resourcepoor countries **— a birth weight of 500 g has historically been used to define the lower limit of viability. However, this approach leads to inaccuracies, because viable neonates born after 24 weeks may be affected by intrauterine growth restriction (IUGR), and some pre-viable infants may weigh more than 500 g.**

➢ FETAL DEATH

A fetus is defined from 8 weeks after conception until term while in the uterus. **Fetal death** is defined as death before the complete expulsion or extraction from the mother of a product of human conception, irrespective of the duration of pregnancy that is not an induced termination of pregnancy. The death is indicated by the fact that, after such expulsion or extraction, the fetus does not breathe or show any other evidence of life such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles. Heartbeats are to be distinguished from transient cardiac contractions; respirations are to be distinguished from fleeting respiratory efforts or gasps. For statistical purposes, fetal deaths are further subdivided as “early” (20–27 weeks’ gestation) or “late” (≥28 weeks’ gestation).

The term “**stillbirth**” is also used to describe fetal deaths at 20 weeks’ gestation or more. Stillbirth is not specifically divided into early and late gestations, but for international comparisons the World Health Organization defines stillbirth as at or after 28 weeks’ gestation. Fetuses that die in utero before 20 weeks’ gestation are categorized specifically as **miscarriages**. A live birth that results in death within the first year (<365 days) is defined as an infant death.

➢ INFANT DEATH

Infant deaths are characterized as neonatal (<28 days) and further subdivided into early neonatal (<7 days), late neonatal (7–27 days), or postneonatal (28–364 days).

Assessement of the live born child

- Classification of the vitality of the newborn immediately after birth
- Assessment of the newborn by the Apgar score at 1 and 5 minutes after birth
- Classification of newborn infant by weight and gestation
- Physical maturity signs

The Apgar score

Developed by Dr. Virginia Apgar, an anesthesiologist, in 1953 for the purpose of providing a simple, clear classification or grading of newborn infants which can be used as a basis for discussion and comparison of the results of obstetric practices, types of maternal pain relief and the effects of resuscitation.

A newborn infant at birth is noted to have acrocyanosis, a heart rate of 140, grimaces to stimulation, and is active and with a lusty cry. What is her Apgar score?

Apgar Newborn Scoring System

Assess	0	1	2	1 min	5 min
HEART RATE	Absent	Below 100	Above 100		
RESPIRATION	Absent	Slow	Good crying		
MUSCLE TONE	Flaccid	Some flexion	Active motion		
REACTION TO IRRITATION	No Response	Grimace	Vigorous cry		
COLOR	Blue all over	Body pink extremities blue	Pink all over		
Total Score					

The scoring system comprises 5 signs: heart rate, respiratory effort, muscle tone, reflex irritability and color, each of which is given zero, one or two points. The total score ranges from zero to ten points.

The baby is scored at 1 and 5 minutes after birth, and every 5 minutes thereafter as long as resuscitation is continuing.

- *The 1-minute score gives an idea of what was going on during labor and delivery.*
- *The 5-minute score gives an idea of response to therapy (resuscitation).*

A score of 7 – 10 is considered normal, 4 – 7 intermediate, 0 – 3 poor; the infant requires immediate resuscitation

The Apgar score significance

Rapid standardized assessement of the clinical status of the newborn infant and the need for prompt **resuscitation**. A change in score is a useful index of the response to resuscitation. On the other hand the Apgar score has limitations. It is affected by gestational age, maternal medication, resuscitation, congenital anomalies, infections and trauma.

Apgar score in preterm infants

Signs as tone, color or reflex irritability paritally depend on the physiologic maturity of the infant. The healthy preterm infants may receive a low score only because of immaturity.

Apgar score and asphyxia

In is innapropriate to use an Apgar score alone to establish the diagnosis of asphyxia. Other factors such as abnormalities in umbilical arterial blood gases, clinical cerebral function, placental pathology and multisystem organ dysfunction need to be considered.

Apgar score and prediction of neurological outcome in the term infant

A low 1-minute Apgar score alone does not correlate with the infants future outcome. An Apgar score of 0 to 3 at 5 minutes may correlate with neonatal mortality but alone does not predict later neurologic dysfunction. (75% of children with cerebral palsy have normal scores at 5 minutes). The risk of poor neurological outcome increases when the Apgar is 3 or less in 10, 15 and 20 minutes.

Classification of newborn infants by weight and gestation

✓ ***Newborn classification based on gestational age***

- *Preterm (premature)* — born at 37 weeks' gestation or less
- *Term — born between the beginning of week 38 and the end of week 41 of gestation*
- *Post-term (postmature) — born at 42 weeks' gestation or more*

✓ ***Newborn classification based on birth weight***

- *Low birth weight (LBW) — less than 2500 g*
- *Very low birth weight (VLBW) — less than 1500 g*
- *Extremely low birth weight (ELBW) — less than 1000 g*

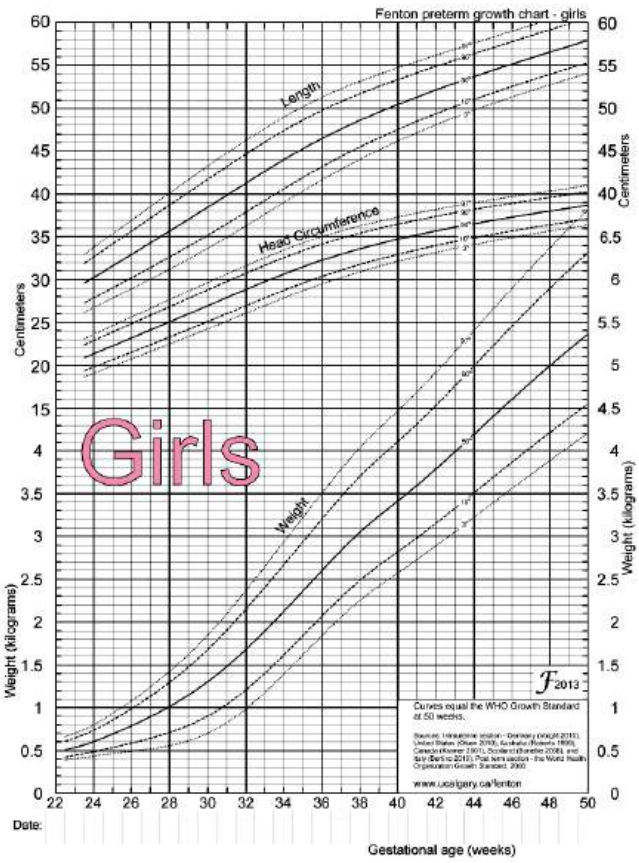
Normal weight for a term infant is 2500-4000 g.

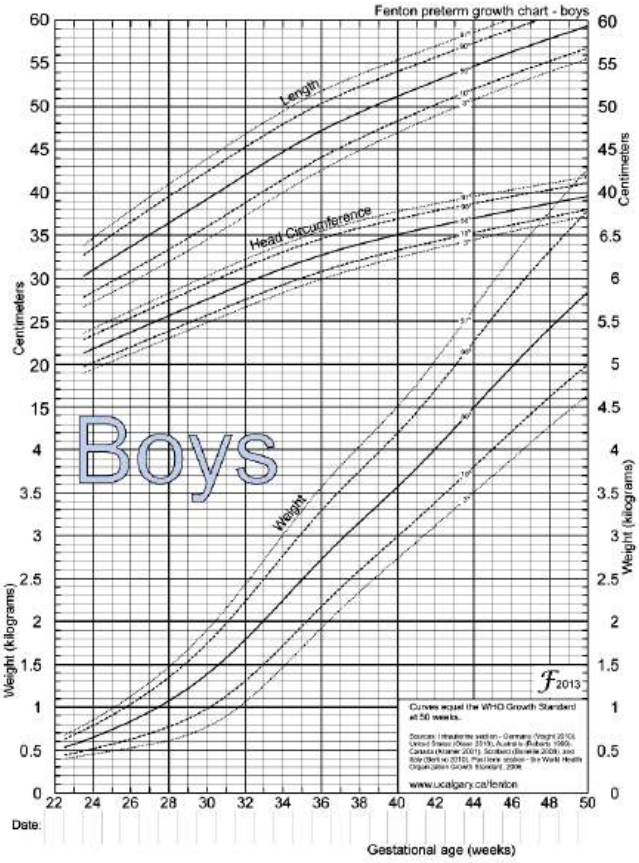
✓ ***Newborn classification based on birth weight and gestation*** is valuable in predicting the outcome. At any gestation the poorest outcome is seen in infants with marked intrauterine growth retardation.

- *Appropriate for gestational age (AGA)*— infant is one that falls anywhere between the 10th and the 90th percentile for his or her given age
- *Small for gestational age (SGA)*— infant falls below the 10th percentile for his or her gestational age
- *Large for gestational age (LGA)*— infant weighs more than the 90th percentile at any given gestational age

Evaluation of newborns enables to predict complications which may occur during fetal to neonatal transition period. Premature infants are at main risk of organ system immaturity espacially respiratory. Hyperbilirubinemia and hypothermia is a frequent problem, there is an increased risk of infection and sepsis. SGA infants are at high risk of birth asphyxia, there is often transient hypoglycemia and hypothermia even in term hypotrophic infants and increased incidence of cogenital anomalies and intrauterine infections as the underlying condition of growth failure.

Fig. **Gender-specific intrauterine growth curves**

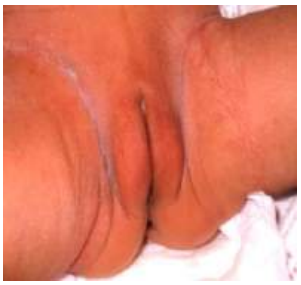




Physical maturity

Physiological term newborn

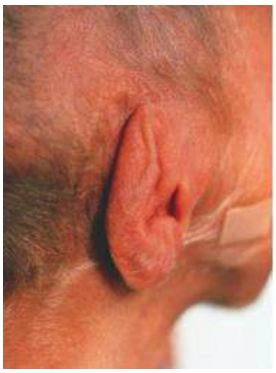
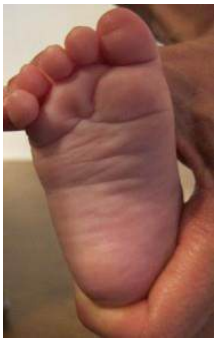
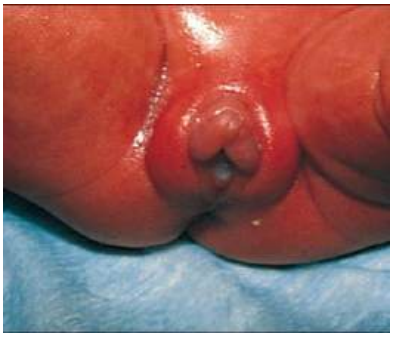
- average birth weight 3500 g, birth lenght 50 cm
- skin — pink, few visible veins, covered with vernix caseosa, subcutaneous fat is present, nails reach the fingertips
- lanugo — thinning of lanugo, balding areas
- plantar creases — covering at least the anterior 2/3 of foot
- breast — raised areola with 3 – 4 mm breast bud
- ear — cartilage present within pinna with ability for natural recoil when folded
- genitalia male — pendulous scrotum with rugae, descended testes
- genitalia female — large labia majora covering labia minora
- posture — flexed position with good muscle tone



Pathology of gestation length

Prematurity

Gross appearance of premature infant

- *Posture* — hypotonic with extension of extremities
- *Skin* — very thin, red, wrinkled and translucent with easily visible veins. There is little subcutaneous fat.
- *Lanugo* — none or abundant
- *Plantar creases* — smooth feet with few creases
- *Breast buds* — flat areola, little or no breast bud
- *Ear* — little cartilage, stays folded
- *Genitalia male* — smooth scrotum, undescended testes
- *Genitalia female* — prominent clitoris, labia minora not covered by labia majora

Etiology:

- chorioamnionitis — the major cause of premature labor
- multiple gestation pregnancy — often due to assisted reproductive technology, 40% are delivered prematurely
- maternal age: adolescents or mother older than 40 years
- diabetes mellitus
- polyhydramnios
- abruptio placentae
- low socioeconomic status
- tobacco abuse

Spontaneous preterm birth

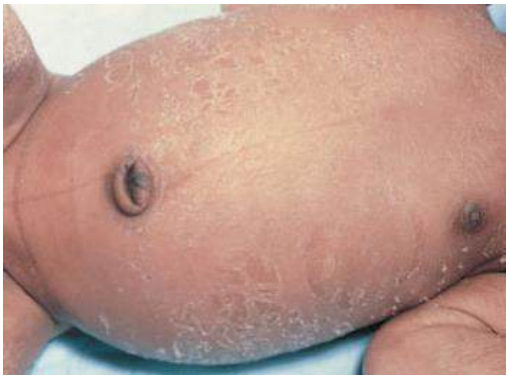
- Partus prematurus in cursu with uterine contractions
- Preterm rupture of membranes (PROM) — spontaneous rupture of membranes before the onset of labor prior to 37 weeks. PPROM is most likely due to chorioamnionitis.

Elective preterm delivery because of problems with the pregnancy.

- The most common reason is preeclampsia, eclamptic convulsions or HELLP syndrome, placental abruption, intrauterine growth retardation or certain fetal anomalies (hydrops).

Postmaturity

Gross appearance of newborn in case of true postmaturity



- skin — wrinkled, dry and peeling. Fingernails are long. Little vernix remains.
- lanugo — almost absent
- meconium staining is frequently seen
- there is often little subcutaneous fat but some infants are obviously macrosomic (LGA)

Etiology:

- the causes of prolonged gestation are unknown
- certain fetal anomalies (anencephaly) predispose to prolonged gestation but these cases are rare

Possible complications

- meconium aspiration syndrome
- birth asphyxia
- oligohydramnios, cord accidents
- macrosomia increases risk of birth trauma
- hypoglycemia, hypothermia in the early postnatal period
- increased perinatal mortality compared to term gravidity

Fetal growth disorders

I. Intrauterine growth retardation (IUGR), small for gestational age infant (SGA)

Type	Symmetric	Asymmetric (head sparing)
Reason	Early, in utero insult that affects growth of most organs	Relatively late onset after fetal organ development; abnormal delivery of nutritional substances and oxygen to the fetus
Main Etiologies	Genetic syndromes, chromosomal abnormalities, congenital infections, teratogens, toxins	Uteroplacental insufficiency secondary to maternal diseases (malnutrition, cardiac, renal, anemia) and/or placental dysfunction (hypertension, autoimmune disease, abruption)
Complications	Etiology dependent; delivery of oxygen and nutrients to vital organs usually normal	Neurologic (asphyxia) if significant decreased delivery of oxygen to brain

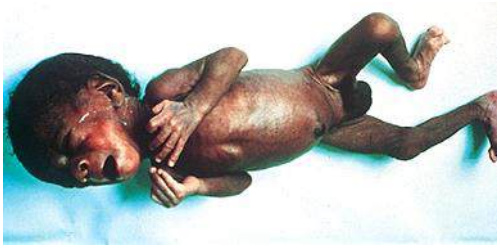
II. Large for gestational age infant (LGA)

Etiology:

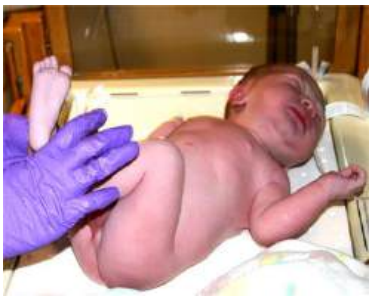
- habitus (tall and heavier women have larger babies)
- maternal obesity
- maternal diabetes
- rare macrosomic syndromes (Beckwidth — Wiedemann syndrome etc.)

Potential complications

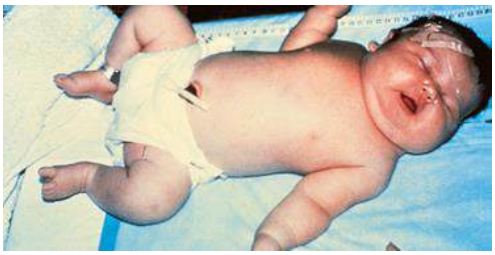
- cephalopelvic disproportion and shoulder dystocia in vaginal delivery
- increased incidence of birth injuries (skeletal system, peripheral nerves) and birth asphyxia as a result of difficult extraction
- cesarean delivery may be necessary
- diabetic fetopathy — problems of macrosomia and relative organ immaturity



SGA: 1700 g at 40 weeks



AGA: 3500 g at 40 weeks



LGA: 5000 g at 40 weeks

When it comes to evaluating multiples, comparison of size between individuals is also important. ***Discordance between siblings may indicate placental inequalities, twin-twin transfusion syndrome, or other problems.*** *These twins differ in weight by about 1 pound (0.5kg); the smaller twin, on the bottom in this photo, weighed 5 pounds and the larger one was over 6 pounds. Hematocrits were checked on both (a routine in our nursery for twins of any size) and were normal. The infants were otherwise healthy and did well.*

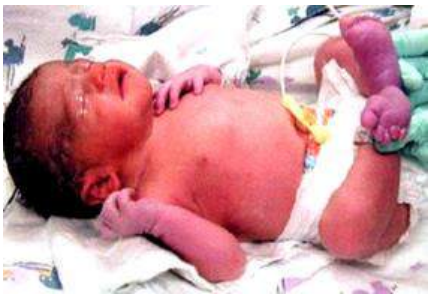
Why are monozygotic twins considered higher risk than dizygotic twins?

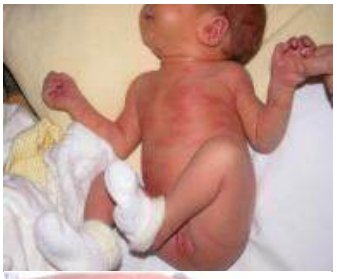
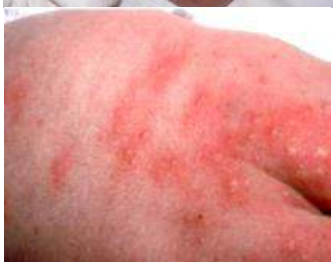
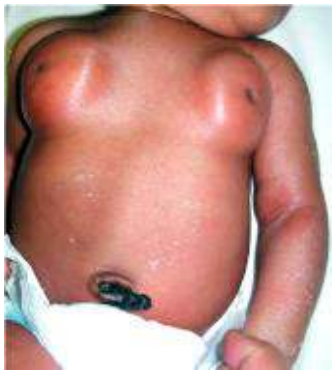
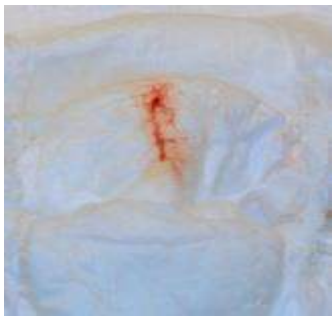
- **Monozygotic twins (identical twins)** arise from the division of a single fertilized egg. Depending on the timing of the division of the single ovum into separate embryos, the amnionic and chorionic membranes can either be shared (if division occurs >8 days after fertilization), separate (if division occurs <72 hours after fertilization), or mixed (separate amnion, shared chorion if division occurs 4 to 8 days after fertilization). Sharing of the chorion and/or amnion is associated with potential problems of vascular anastomoses (and possible twin-twin transfusions), cord entanglements, and congenital anomalies. These problems increase the risk for IUGR and perinatal death.
- **Dizygotic twins**, however, result from two separately fertilized ova and, as such, usually have a separate amnion and chorion.

Transitional events in newborn infants

Normal transitional events at birth begin with initial lung expansion, generally requiring large, negative intrathoracic pressures, followed by a cry (expiration against a partially closed glottis). Umbilical cord clamping is accompanied by a rise in blood pressure and massive stimulation of the sympathetic nervous system. With onset of respiration and lung expansion, pulmonary vascular resistance decreases, followed by a gradual transition (over minutes to hours) from fetal to adult circulation, with closure of the foramen ovale and ductus arteriosus.

Some transitional changes manifest as pathological features, and do not require any specific therapy.

COMMON EVENTS	DESCRIPTION
- ***Physiological weight loss 3-9%.***	Immediate adaptation processes after birth affect the metabolism of water and electrolytes as a result of discontinuation of placental exchange and the onset of considerable insensible water loss and thermoregulation. Subsequent adaptation includes the onset of autonomic renal regulation of fluids and electrolytes, and intake of fluids and other nutrients. The time course of adaptation may be divided into three major phases: **Phase I:** transition. The immediate postnatal phase is characterised by a relative oliguria followed by a diuretic phase, during which body fluid compartments are rearranged by isotonic or hypertonic (i.e. hypernatremic and hyperchloremic) contraction (duration hours to days). These changes are caused by considerable evaporative water loss via the immature skin as well as by continuing natriuresis (as present during foetal life). Phase I usually ends when maximum weight loss has occurred. The generally accepted water loss is up to 10% of body weight. **Phase II:** the intermediate phase is characterized by diminished insensible water loss along with increasing cornification of the epidermis, a fall in urine volume to less than 1–2 ml/kg per hour, and a low sodium excretion. **Phase III:** stable growth is characterized by continuous weight gain with a positive net balance for water and sodium. Within 10 days to two weeks, the baby should have regained enough weight so that he weighs at least what he did at birth.
- ***Acrocyanosis***	Peripheral cyanosis of the hands and feet is a common clinical finding in normal infants in the first 24 hours of life, but may be a nonspecific sign of illness. This finding is the result of a combination of high fetal hemoglobin concentrations and relatively sluggish peripheral circulation from arteriolar vasoconstriction. 
- ***Physiological jaundice***	Physiological jaundice appears between the 2nd and 5th days of life in most newborns, and disappears by 1 to 2 weeks of age. It should be differentiated from pathological jaundice.

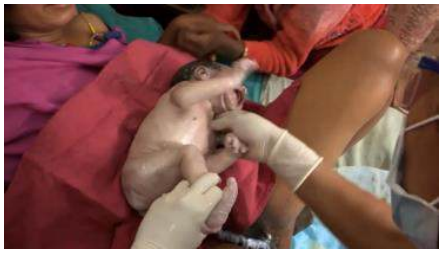
- *Toxic erythema (erythema toxicum)*	It appears as small (1–3 mm), firm, yellow or white raised bumps filled with pus on top of a red area of skin. There may be a few to many lesions, and they may be found on any area of the body, with the exception of palms and soles. Although it most frequently appears during the first 3–4 days of life, toxic erythema can be seen at birth and may not be present until 10 days of life. Erythema toxicum is an extremely common rash that does not require any treatment, as it will spontaneously go away in 5–7 days.	 
- *Unstable body temperature*	Normal newborn body temperature is defined by the World Health Organization as within the range of 36.5^{0}C to 37.5^{0}C. Thermoregulatory abilities of the newborn are limited and, without external support, newborns can readily lose heat (hypothermia) or undergo overheating (hyperthermia).	
- *Neonatal breast enlargement & galactorrhea*	It occurs in about 5% of neonates and in both sexes. Galactorrhea is the result of the influence of the mother's hormones on the baby before birth. The mother's hormones can persist in the neonate's body for weeks. The condition usually resolves spontaneously within a few months. No treatment is necessary unless the area becomes red or tender. Discourage massage or manipulation of the breast tissue because it may force bacteria into the milk glands, which can lead to mastitis.	
- *Vaginal withdrawal bleeding*	This occurs in some female infants on the third day after birth. ***Signs of normal vaginal bleeding*** in infants include a few drops of blood per day, for less than 3 days. ***Signs of abnormal vaginal bleeding*** in infants include bleeding for more than 2 days, bleeding that starts after 1 week of age, fever, fussiness, vomiting, or weight loss.	
- *Occasional misalignment of one eye*	Occasional misalignment of one eye may be normal until 3 months of age. After 3 months, refer to an ophthalmologist to prevent *amblyopia.* **! CONSISTENT EYE DEVIATION (STRABISMUS) IS NOT NORMAL AT ANY AGE.**	

You have been asked to see a 12 hour old term European baby girl who looks jaundiced. What should you do next?

NEWBORN CARE

IMMEDIATE POST-BIRTH CARE

- Approximately 85% to 90% of infants make the transition from intrauterine to extrauterine life with no assistance necessary. However, for the remaining few newborns, some assistance may be required, ranging from simple stimulation to complete resuscitation.
- In neonates born through clear amniotic fluid who start breathing on their own after birth, *suctioning of the mouth and nose should not be performed*. Suctioning should be done only if the mouth or nose is full of secretions.



Newborn is placed on mother's abdomen.

Because newborns are wet when they are born, they can suffer rapid heat loss if a warm environment is not maintained. Therefore, it is critical to maintain a warm, or thermoneutral, environment for the infant throughout the first hours and days of life. This can be accomplished by placing the infant on the mother's abdomen, with warm blankets placed over them both to maintain body heat.

The newborn is placed on the mother's chest.

Newborns without complications should be kept in skin-to-skin contact with their mothers during the first hour after birth to prevent hypothermia and promote breastfeeding.

Umbilical cord care

In newly-born term or preterm babies who do not require positive-pressure ventilation, the cord should not be clamped earlier than one minute after birth. When newly-born term or preterm babies require positive-pressure ventilation, the cord should be clamped and cut to allow effective ventilation to be performed.

RESUSCITATION

- All nurses should be familiar with the **ABCs of resuscitation**: airway, breathing, and circulation.
- Rapid assessment and action is needed for any baby who does not breathe within the 1st min of birth, or who exhibits slow or irregular gasping. Bradycardia indicates hypoxia.

- Avoid hypothermia by drying, and use the radiant heater. If needed, clear secretions from the mouth and then the nose with a soft suction catheter. In the correct position, the neck is extended, allowing for the infants large occiput. If hypoxia is not far advanced, breathing can usually be started by stimulation: gentle rubbing with towel dries and stimulates! Some asphyxated infants are pale, limp, apnoeic and bradycardic, and intermittent positive pressure ventilation is begun by either bag and mask or tracheal tube.
  Infants who recover rapidly should be given to their mothers as soon as possible. Some babies with severe asphyxia need to be admitted to the neonatal unit.

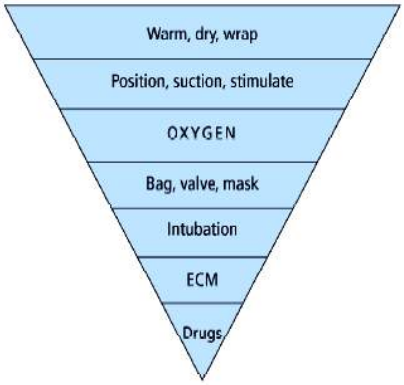


Fig. Resuscitation triangle of the newborn. If you are at a delivery, rapidly assess pulse, respiration and color. All babies are cleaned, dried and wrapped. If assessment is not satisfactory, move down the steps of the triangle, re-assess frequently, and go back up the triangle as the baby improves. External cardiac massage (ECM) and drugs are not used very often.

Fig. The resuscitaire comprises a heater, source of oxygen and suction, and an equipped platform for neonatal resuscitation.

ROUTINE CARE OF THE NORMAL BABY

- **Labelling**

- **Antibiotic eye ointment for the prophylaxis of ophthalmia neonatorum** is highly recommended in all newborns. Ophthalmia neonatorum is the inflammation of the eyes resulting from exposure to gonorrhea or chlamydia as the infant passes through the birth canal and can lead to blindness.

- **Umbilical cord care.** The cord is clamped about 1 cm fron the skin surface and cut close to the clamp. The cord stump should be observed carefully for signs of infection.

- **Administration of 1mg of vitamin K intramuscularly** is also recommended to prevent hemorrhagic disorders. Coagulation alteration is seen predominately in infants in the second or third day of life, specifically because factors II, VII, IX, and X are dependent on the synthesis of vitamin K.

- **Newborn immunization:** HepB (and BCG in many countries).

- **Bathing.** Bathing should be delayed until after 24 hours of birth. If this is not possible due to cultural reasons, bathing should be delayed for at least six hours. Appropriate clothing of the baby for ambient temperature is recommended. This means one to two layers of clothes more than adults, and use of hats/caps. The mother and baby should not be separated and should stay in the same room 24 hours a day.

- **Passage of meconium and urine.** It is important to note the time of first passing meconium and urine, and often this occurs at or soon after delivery. Both are usually passed within 24 h of birth, and delay should prompt a search for underlying pathology.

- **Feeding.** All newborns, including low-birth-weight (LBW) babies who are able to breastfeed, should be put to the breast as soon as possible after birth when they are clinically stable, and the mother and baby are ready.

- **Newborn screening tests**
  - *Hearing screening*
  - *Pulse oxymetry screening to detect critical congenital heart defect (CHD)*
  - *Screening for Developmental Dysplasia of the Hip*
  - *Screenings for genetic, metabolic, or endocrine disorders*

NEWBORN SCREENING

Hearing screening

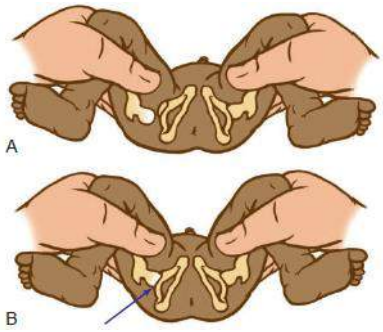
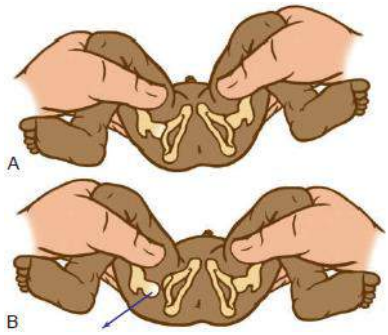
- **Family questionnaires** – parents or other caregivers may be asked about the response of their neonate or infant to sounds and their use of language, including early indicators of language such as babbling and other vocalizations.

- **Behavioural measures** – the responses of babies to behavioural measuring devices (ranging from simple noisemakers to more sophisticated audiological equipment and procedures) can also be used to identify hearing loss.

- **Physiological measures** – measures of otoacoustic emissions (OAE) or auditory brainstem response (ABR) have been shown to be effective methods of screening for hearing loss in neonates and infants. OAE measures are obtained from the ear canal by using a sensitive microphone within a probe assembly that records cochlear responses to acoustic stimuli. OAEs measure the status of the peripheral auditory system extending to the cochlear outer hair cells. ABR measurements are obtained from surface electrodes that record neural activity generated in the auditory nerve and brainstem in response to acoustic stimuli delivered via an earphone. Screening ABR measurements are usually automated (AABR) and reflect the status of the peripheral auditory system, the eighth nerve, and the brainstem auditory pathway.

Examination of the hips

Examination of the hips often causes a baby to cry, and it is therefore best left until last. The examination aims to determine whether the baby has developmental dysplasia of the hip (DDH), in which the acetabulum is too shallow and the hip can be dislocated. There are two tests, the Ortolani test and the Barlow test.

The Ortolani test	The Barlow test
	
The Ortolani maneuver is the sign of the ball of the femoral head moving in and out of the acetabulum. A, The examiner holds the patient's thigh and gently abducts the hip while lifting the greater trochanter with 2 fingers. B, When the test is positive, the dislocated femoral head falls back into the acetabulum with a palpable clunk as the hip is abducted.	**The Barlow provocative test is performed with the patient's knees and hips flexed. A, Holding the patient's limbs gently, with the thigh in adduction, the examiner applies a posteriorly directed force. B, This test is positive in a dislocatable hip.**

Ultrasonography

Because it is superior to radiographs for evaluating cartilaginous structures, ultrasonography is the diagnostic modality of choice for DDH before the appearance of the femoral head ossific nucleus (4-6 mo). During the early newborn period (0-4 wk), however, physical examination is preferred over ultrasonography because there is a high incidence of false-positive sonograms in this age group.

Newborn metabolic screening

• Every newborn before discharge or day 4 of life
• More reliable if done after 48 hours of oral feedings (substrates for metabolic diseases)
• Total diseases screened are determined by individual states. Some examples:

– Phenylketonuria	– Galactosemia	**– Hypothyroidism**
– Tyrosinemia	– Hb SS	– Cystic fibrosis
– 21-hydroxylase deficiency	– Hb C	

A 1-month-old fair-haired, fair-skinned baby presents with projectile vomiting of 4 days' duration. Physical exam reveals a baby with eczema and a musty odor. Which screening test would most likely be abnormal?

THE BABY CHECK (NEONATAL EXAMINATION)

Every newborn infant should undergo a routine examination in the first few days of life. This is a screening process to look for congenital conditions and to ensure normal adaptation from fetal life. The baby check is also called the *neonatal examination*.

The 6-week check

The examination is usually repeated between 6 and 8 weeks of age to ensure that there are no new problems and that the child is growing and feeding well. In addition, there are some important problems that may not have been apparent in the first few days of life for physiological reasons, such as the murmur of a left-to-right shunt due to a ventricular septal defect.
The structure described here allows for a complete assessment of any congenital or adaptive problems and will also identify infants at particular risk of some important neonatal problems, such as sepsis.

Maternal history

Check for all maternal factors which can cause illness in the neonate.

Condition in the mother	Effects on the baby
Diabetes mellitus	Macrosomia, hypoglycaemia, polycythaemia
Hyperthyroidism	Hypothyroidism or hyperthyroidism
Systemic lupus erythematosus	Congenital heart block
Congenital infections	Microcephaly, deafness
Teratogenic medications	Spina bifida, phocomelia
Pre-eclampsia	Intrauterine growth restriction
Smoking	Decreased birth weight
Excess alcohol intake	Fetal alcohol syndrome

History relating to the fetus

Fetal health

— Any concerns relating to the health of the fetus, such as threatened miscarriage, poor growth or breech position
— Reports of the antenatal scans – were any abnormalities identified?

Labour and delivery

— Check whether the delivery was normal vaginal, instrumental or Caesarean
— Check whether any resuscitation of the newborn was required following birth
— Look at the Apgar score.
— See if there are any **risk factors for sepsis** in the baby.

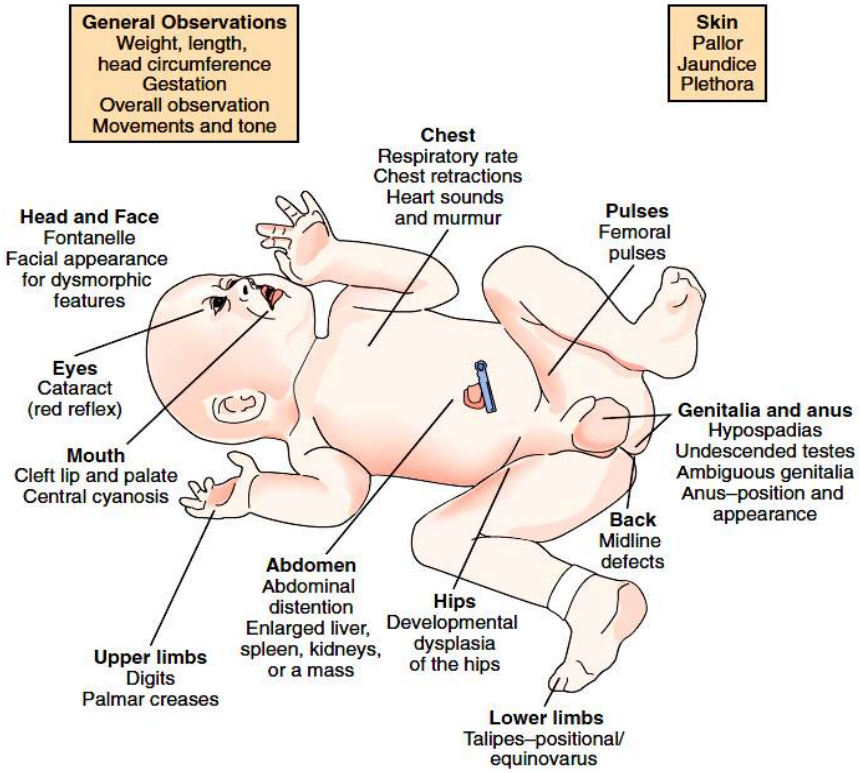
Risk factors for sepsis in newborn babies include:
- **premature labour (earlier than 37 weeks' gestation)**
- **prolonged rupture of membranes (>24 hours)**
- **maternal group B Streptococcus colonisation (on vaginal swab)**
- **maternal fever during labour**

PHYSICAL EXAMINATION

General appearance	Vital signs (VS) and body measurements	Examination of individual body parts and organs
* Conciousness/awakeness Behavior (calm, irritable) Crying (loudly, weak) * Respiratory effort * Posture at rest * Movements * Deformations and malformations * Assessment of color	* *VS:* temperature (T); respiratory rate (RR); heart rate (HR); capillary refill time (CRT); blood pressure (BP); oxygen saturation (SpO2) * *Anthropometry:* weight; length; head circumference (HC); chest circumference	• skin • skull; fontanelles; sutures • ears, eyes, nose and mouth • shoulders, arms and hands • chest and heart sounds • abdomen • groin • genitalia • femoral pulses • legs and feet • spine • **reflexes** • **hips**

Examination of the reflexes, together with the hip examination, are best left until the end of the baby check.

Main features of routine examination of the newborn



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BIRTH (PERINATAL) ASPHYXIA

There are few moments in life when humans are as vulnerable and as dependent on the help of others as at birth. In a few seconds the newborn must adapt from life in the warm, moist, sterile environment of the mother's womb to wholly different extrauterine surroundings. Every organ must adjust to this change over a few minutes or a few days; but the key to immediate survival of the newborn is a smooth cardiopulmonary transition. The neonate must successfully inflate his or her lungs and rearrange the fetal circulation.
The asphyxiated newborn undergoes an abnormal transition.

CAUSES OF NEWBORN DEPRESSION (delayed onset of regular respiration)

• Perinatal asphyxia
• Excessive suctioning (vagal stimulation causes bradycardia and apnea)
• Trauma, especially to central nervous system (tentorial tears) or cervical cord
• Drugs which depress breathing (anesthetic, narcotic, alcohol, magnesium sulfate, tranquilizers)
• Severe immaturity (surfactant-deficient lung, inadequate respiratory effort)
• Perinatally acquired sepsis: group B streptococci, *Listeria monocytogenes*
• Primary neuromuscular disease (Werdnig-Hoffmann disease, congenital myopathies, myotonic dystrophy, congenital muscular dystrophy)
• Congenital malformation obstructing the airway or preventing lung expansion (choanal atresia, Pierre-Robin syndrome, laryngeal atresia, diaphragmatic hernia, pulmonary hypoplasia)

Intrapartum asphyxia cannot be easily differentiated clinically from neonatal depression. Initial resuscitative measures are, nevertheless, similar in all situations and should be initiated without delay.

DEFINITION OF PERINATAL ASPHYXIA

The American College of Obstetricians and Gynecologists' (ACOG) Committee have defined certain criteria that must be met if neurologic deficits are to be attributed to perinatal asphyxia. All of the characteristics must be present, including evidence of at least one organ dysfunction. If such evidence is lacking, it is difficult to conclude that perinatal asphyxia is the cause of later developmental disability.

Essential characteristics of perinatal asphyxia

1) Presence of metabolic or mixed acidosis with a pH < 7.00 in the umbilical artery.
2) An Apgar score of 3 or less for longer than 5 minutes.
3) The presence of neurologic sequelae such as seizures, coma or hypotonia in the immediate neonatal period.
4) Multisystem organ dysfunction in one or more of the following systems: cardiovascular, gastrointestinal, hematologic, pulmonary, or renal.

There are numerous ***risk factors*** that allow a health care worker to anticipate the possibility of the delivery of an asphyxiated or depressed newborn.

Some of the **major antepartum factors** associated with this risk include: maternal age > 35 yrs, maternal diabetes, pregnancy-induced hypertension, fetal anemia, bleeding in the 2nd or 3rd trimester, polyhydramnios, oligohydramnios, premature rupture of membranes, intra-uterine infection, post-dates gestation, multiple gestation, small for gestational age or intrauterine growth restriction, maternal substance abuse, fetal malformations, decreased fetal activity and no prenatal care.

Some of the **major intrapartum factors** associated with this risk include: emergency cesarean section, breech presentation, premature labor, prolonged rupture of membranes > 24 hrs, intrauterine infection, precipitous labor, prolonged labor > 24 hrs, prolonged 2nd stage of labor >2 hrs, nonreassuring fetal heart rate patterns, general anesthesia, maternal analgesia with narcotics within 4 hrs of delivery, meconium stained amniotic fluid, prolapsed cord, placenta previa and abruptio placentae.

PATHOPHYSIOLOGY OF ASPHYXIA

In order to undertake the necessary and appropriate measures for resuscitation of the newborn, a firm understanding of pathophysiologic events that occur during asphyxia is vital.

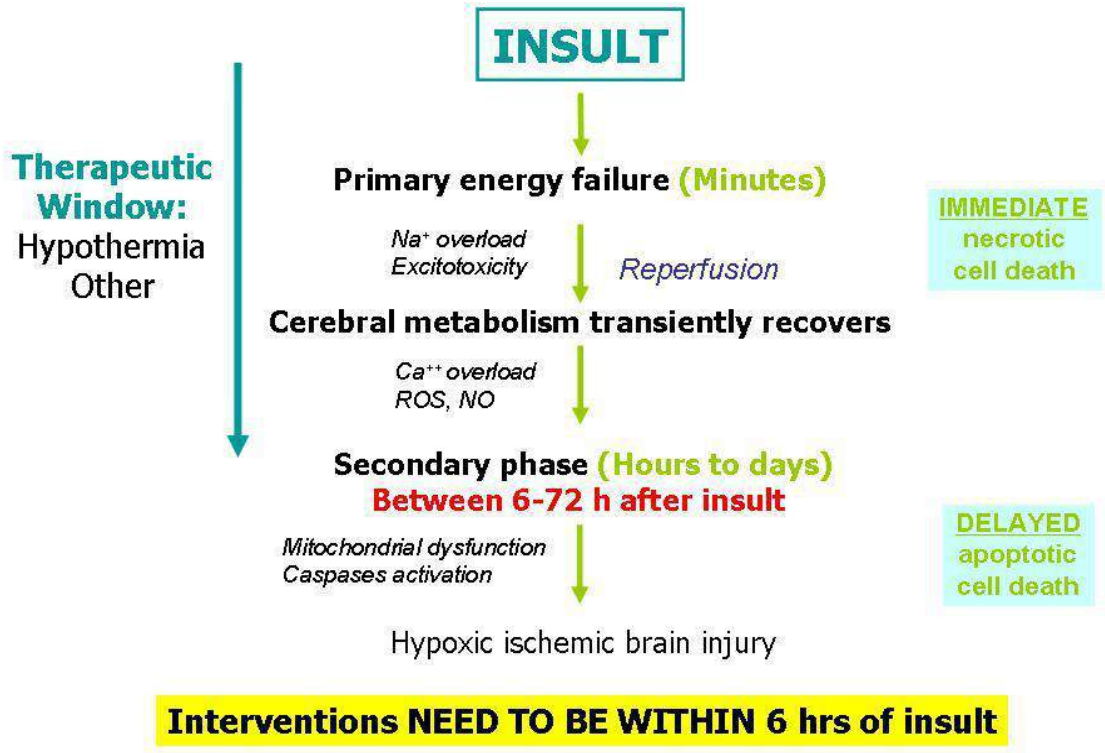
Five principal mechanisms of asphyxia have been described in the human infant during labor, delivery, and the immediate postpartum period:

1) interruption of umbilical blood flow (cord compression, prolapse);
2) failure of gas exchange across the placenta (placental insufficiency, abruption, or previa);
3) inadequate perfusion of the maternal side of the placenta (severe maternal hypotension, hypertension from any cause, or excess uterine contractility);
4) impaired maternal oxygenation (cardiopulmonary disease, anemia);
5) failure of adequate cardiopulmonary adaptation after birth (insufficient lung inflation and faulty rearrangement of the fetal circulation).

The neonatal brain is highly resistant to hypoxia-ischaemia compared with that of an adult. The degree of hypoxia-ischaemia necessary to damage the neonatal brain usually leads to impairment of other organs.

Multisystem organ dysfunction occurs from the lack of blood flow to the kidneys, liver and gastrointestinal tract in an initial attempt to preserve cerebral and cardiac blood flow. As this “dive reflex” begins to fail the cerebral and cardiac systems soon become affected. Organ failure ensues from the lack of oxygen delivery to the tissues as a consequence of hypoxemia—not enough oxygen in the blood or from ischemia—inadequate delivery of oxygenated blood to the tissues from low cardiac output or anemia. Multiple organ systems are affected by perinatal asphyxia with 82% of neonates incurring injury to one or more organs. These include the brain (72%), kidneys (42%), lungs (26%), heart (29%), bone marrow (<20%), bowel (29%), and liver (<20%).

Fig. Pathophysiology of hypoxic-ischemic brain injury in the developing brain. During the initial phase of energy failure, glutamate mediated excitotoxicity and Na+/K+ ATPase failure lead to necrotic cell death. After transient recovery of cerebral energy metabolism, a secondary phase of apoptotic neuronal death occurs. ROS = Reactive oxygen species.



Brain—Hypoxic Ischemic Encephalopathy (HIE)

Hypoxic ischemic encephalopathy is the neurologic injury that results from the lack of oxygen delivery to the brain. Evaluating the severity of the neurologic insult from hypoxic ischemic encephalopathy with the criteria from Sarnat is a very useful tool for prognosis. In the Sarnat Stages, a poor outcome is defined as mental retardation, cerebral palsy, chronic seizures, or death.

Sarnat Stages of HIE *(Arch Neurol 33:696, 1976)*

	STAGE- 1	STAGE-2	STAGE-3
Level of Consciousness	**Hyper alert**	**Lethargic or obtunded**	**Stuporous**
Neuromuscular Control			
Muscle tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebration
Stretch reflexes	Overactive	Overactive	Decreased or absent
Segmental myoclonus	Present	Present	Absent
Complex Reflexes			
Suck	Weak	Weak or absent	Absent
Moro	Strong; low threshold	Weak; incomplete; high threshold	Absent
Oculovestibular	Normal	Overactive	Weak or absent
Tonic neck	Slight	Strong	Absent
Autonomic Function	Generalised sympathetic	Generalised parasympathetic	Both systems depressed
Pupils	Mydriasis	Miosis	Variable; often unequal; poor light reflex
Heart Rate	Tachycardia	Bradycardia	Variable
GI Motility	Normal or decreased	Increased; diarrhoea	Variable
Seizures	None	Common; focal or multi-focal	Uncommon (excluding decerebration)
EEG Findings	Normal (awake)	Early: low-voltage continuous delta and theta Later: periodic pattern (awake) Seizures: focal 1-Hz spike-and-wave	Early: periodic pattern with Isopotential phases Later: totally isopotential
Duration	1–3 days	2–14 days	Hours to weeks

The initial stabilization of an infant with HIE from perinatal asphyxia includes the following steps.

1. Maintain normal ventilation. It is important to avoid low PaCO2 secondary to further risk of cerebral ischemia from decreased cerebral blood flow.
2. Diagnose and treat seizures. An EEG can help to guide diagnosis, therapy and prognosis. Ativan, phenobarbital and phenytoin should be considered for treatment of seizures, always watching closely for apnea as a side effect of therapy.
3. Maintain normal glucose levels. Hypoglycemia can cause neurologic injury and hyperglycemia can worsen neurologic outcomes after HIE.
4. Maintain normal blood pressure to ensure adequate cerebral blood flow.
5. Obtain head imagining studies (head ultrasound, CT scan or MRI) to rule out intracranial hemorrhage, to detect cerebral edema or ischemia and to establish a baseline for long-term follow-up.

EXTRACEREBRAL COMPLICATIONS ASSOCIATED WITH PERINATAL ASPHYXIA

COMPLICATIONS		MANAGEMENT
Renal	Acute kidney injury (AKI) from acute tubular necrosis (ATN)	• Strict monitoring of fluid intake, urine output, serum levels of electrolytes, pH
Pulmonary	Persistent pulmonary hypertension (also known as persistent fetal circulation -PFC) → right to left shunt → severe cyanosis and life-threatening hypoxic respiratory failure	• Maintaining of adequate oxygenation and ventilation • Antibiotics • Surfactant replacement therapy • Chest x-ray
Cardiac	• Cardiac dysfunction → hypotension • Cardiogenic shock or heart failure → pulmonary edema • Rhythm abnormalities	• Volume resuscitation with normal saline • Inotropic agents: dopamine, dobutamine • Hydrocortisone
Hematologic	• Thrombocytopenia and clotting abnormalities → diffuse intravascular coagulation (DIC); severe bleeding complications: pulmonary hemorrhage, intracranial hemorrhage, hematuria, hematochezia • Anemia	• Use of blood products (fresh frozen plasma, cryoprecipitate or even activated Factor VII for severe cases of DIC) • Platelet transfusions if platelet count < 50,000 • In an emergency it may be necessary to give uncrossmatched O negative blood to prevent cardiovascular collapse from an acute hemorrhage.
Gastrointestinal	• Liver injury (elevated ALT, AST, bilirubin) • Necrotizing enterocolitis (NEC)	• Phototherapy, vitamin K • Parenteral feeding
Metabolic	• Lactic acidosis • Hypoglycemia • Hypothermia • Hypocalcemia • Hyponatremia	• Strict monitoring of body temperature, serum levels of electrolytes, pH and glucose

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PATHOLOGY OF PREMATURITY

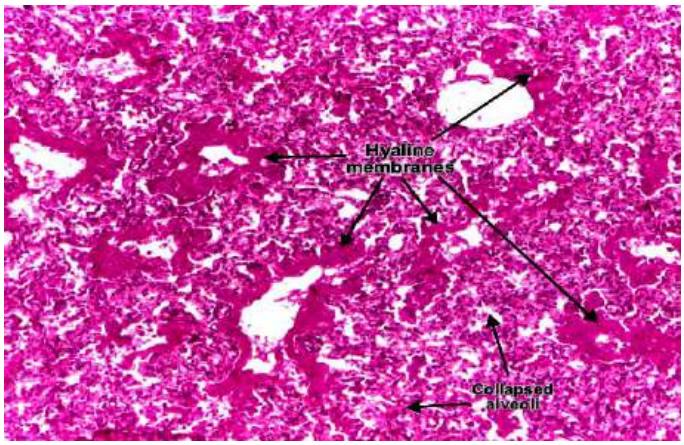
A preterm infant has difficulties with fetal to neonatal transition and maintaining homeostasis i.e. temperature control, euglycemia, fluid and electrolyte balance. Preterm infants usually exhibit significant jaundice and profound anemia. Full enteral nutrition is a problem even in healthy a near-term infant.

Internal organs immaturity

- **Lung**
  - hyaline membrane disease (HMD)
- **Intestine**
  - necrotizing enterocolitis (NEC)
- **Brain**
  - intraventricular hemorrhage (IVH)
  - periventricular leukomalacia (PVL) - infarction of the periventricular white matter
- **Cardiovascular**
  - patent ductus arteriosus (PDA)
- **Iatrogenic damage**
  - barotrauma
  - pneumothorax
  - interstitial lung emphysema
  - bronchopulmonary dysplasia (BPD)
  - retinopathy of prematurity (ROP) - *unmonitored high oxygen supplementation contributes to ROP*

Hyaline membrane disease (HMD)

Also known as **neonatal respiratory distress syndrome (NRDS)**. The incidence is inversely proportional to gestational age.



Neonatal Respiratory Distress Syndrome - NRDS (Hyaline membrane disease) is characterized by collapsed alveoli alternating with hyperaerated alveoli, vascular congestion and hyaline membranes (resulted from fibrin, cellular debris, red blood cells). Hyaline membranes appear like an eosinophilic, amorphous material, lining or filling the alveolar spaces and blocking the gases exchange.

Etiology:

Deficiency of pulmonary surfactant.

Vicious cycle: Decreased alveolar surfactant — lungs collapse at end expiration with each breath — increasing difficulty in breathing — exhaustion — atelectases (airless areas) — hypoxemia — endothelial and epitethelial damage: hyaline membrane formation — profound hypoxemia, hypercarbia and acidosis — progressive atelectases, abundant hyaline membranes.

Surfactant

- synthesized by type II pneumocytes
- consists of lecithin, sfingomyelin and surfactant associated proteins
- reduces surface tension at the air-liquid barrier in the alveoli
- produced by 20 to 24 weeks of gestation and is secreted into the fetal airways by 30 weeks

  - produced in considerable amounts after 35 weeks of gestation but modulation by variety of stimuli is possible (hormones, intrauterine stress including natural labor)

Clinical signs:

- *Signs of respiratory distress:* tachypnea, cyanosis, intercostal and subcostal recession, nasal flaring, grunting, rapid increase in oxygen requirement

Prevention of HMD

- administration of surfactant (prophylactic or treatment of symptoms)
- the incidence of HMD has been reduced by 50% with the use of **antenatal corticosteroids** to promote lung maturity. The corticosteroids are administered to pregnant women with threatened premature delivery at 24 – 34 weeks of gestation

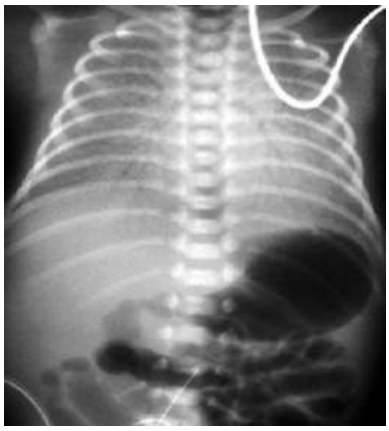


Fig. The classic radiographic findings of RDS include diffuse symmetric reticulogranular densities, prominent central air bronchograms and generalized hypoventilation. Neonatal pneumonia can have a similar appearance. The classic findings may not be present because of the early intervention with surfactant and ventilatory support with intubation.

Bronchopulmonary dysplasia (BPD)

BPD is a chronic lung disease that occurs in infants who received respiratory support with mechanical ventilation and prolonged oxygenation. It is seen in babies recovering form respiratory distress syndrome, sepsis or prolonged apnea and most babies who develop BPD nowadays have birthweights below 1000 g.

Etiology:

- extreme lung immaturity
- hyperoxia injury
- barotrauma
- patent ductus arteriosus
- fluid overload
- fetal inflammatory response — antenatal exposure to proinflammatory cytokines as found in choriamnionitis or funisitis effects pulmonary developement and contributes to the developement of BPD. There is also strong association of BPD and postnatal sepsis.

Classic BPD

Originally described in 1967 as severe lung injury caused by oxygen toxicity and barotrauma with prolonged aggresive ventilation in the treatment of RDS. Its etiopathogenesis was abnormal reparative process in response to injury and inflammation. There was a progress from an acute exsudative phase of acinar injury to reparative and chronic fibroproliferative phase. The histopathologic findings originally reported were airway epithelial lesions, smooth muscular hyperplasia, extensive peribronchiolar and instersticial fibrosis, focal hemorrhage, areas of overdistension and atelectasis and hypertensive vascular disease.

New BPD

In recent years with gentler ventilation techniques, antental glucocoricoid therapy and surfactant therapy the histologic changes seen in infants differ. New BPD is characterised by decrease in alveolar number (enlarged simplified alveoli), abnormal microvasculature and interstitium with less prominent celularity and fibroproliferation. The current view is that new BPD is caused by interruption of normal developemental pathways for terminal maturation and alveolarization of lungs of very preterm infants. The maximum rate of accretion of alveoli is seen in a period from 25 weeks to 4 months after birth.

Clinical signs:

- there is delayed resolution of NRDS
- classified as mild, moderate or severe depending on the need for supplemental oxygen and positive pressure ventilation
- most patients with BPD survive
- increased risk for repated and serious pulmonary infections and asthma during childhood
- poor growth and psychomotoric delay is a frequent problem
- severe BPD is complicated by cor pulmonale and secondary pulmonary hypertension

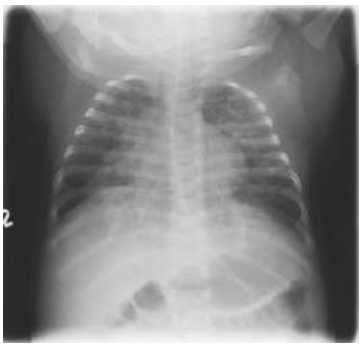


Fig. Chest X-ray of bronchopulmonary dysp.lasia (BPD) showing fibrosis and lung collapse, cystic changes and overdistension of the lungs

NEONATAL INFECTIONS

CONGENITAL INFECTIONS (TORCH)

The most common congenital infections are described by the acronym TORCH:

T	Toxoplasmosis
O	***Other:*** syphilis, hepatitis B, varicella zoster virus (VZV), human immunodeficiency virus (HIV), listeria monocytogenes, parvovirus B19, enteroviruses, lymphocytic choriomeningitic virus, zika virus …
R	Rubella
C	Cytomegalovirus (CMV)
H	Herpes simplex virus (HSV)

The infection can be transmitted during intrauterine life via the placenta or by contamination of amniotic fluid via the cervix or during delivery via the birth canal.

> *Infections acquired in the first two trimesters of pregnancy generally result in **malformations**, while infections occurring during the third trimester cause **destructive lesions**. However, because the infection can persist over time, it is possible to observe a heterogeneous spectrum of abnormalities, which include both malformations and destructive lesions.*

Common Features

While each of the congenital infections possesses distinct clinical manifestations and sequelae, some of these infections share characteristics.

It is important to think of one or more of these infections when a neonate presents with:

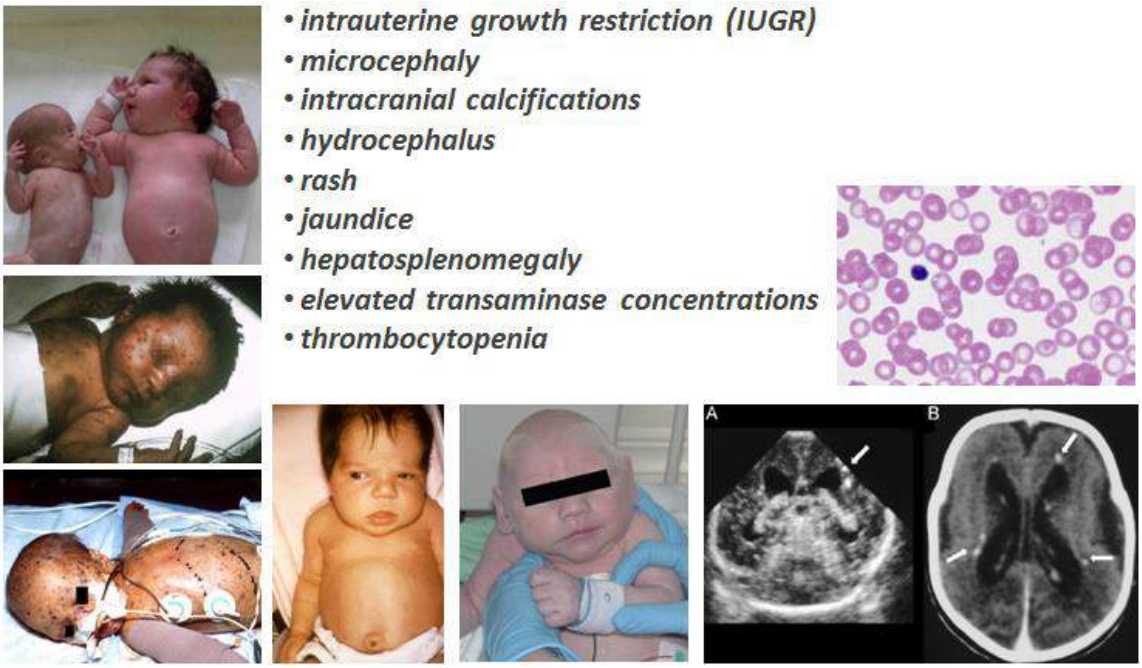


Fig. One-day-old term infant who exhibits cholestatic jaundice and "blueberry muffin" spots consistent with extramedullary (dermal) hematopoiesis after congenital human cytomegalovirus infection

Table. Clinical Manifestations of Common Congenital Infections

Sign	Cytomegalovirus	*Toxoplasma*	Rubella	Herpes Simplex Virus
Hepatosplenomegaly	++	+	+	+
Jaundice	+	+	+	+
Exanthem	−	+	−	++
Petechiae/purpura	++	+	+	−
Hydrocephalus	+	++	−	+
Microcephalus	++	+	−	+
Intracerebral calcifications	++	++	−	+
Heart defects	−	−	++	−
Bone lesions	−	−	++	−
Glaucoma	−	−	+	−
Intrauterine growth restriction	+	+	+	+
Chorioretinitis	++	++	−	+
Cataracts	−	−	++	+
Adenopathy	−	+	+	+
Dental defects	+	−	−	−

−=never or rare, +=occurs, ++=diagnostic importance
Modified after C.J. Baker, MD, personal communication.

However, many congenital infections may be **silent at birth** (asymptomatic), with symptoms manifesting years later (e.g. *hearing loss, chorioretinitis and visual impairment, or diminished mental and motor capabilities*).

Prenatal imaging is a valuable tool for the assessment of **brain damage** in cases of diagnosed fetal infection or it may lead to the suspicion of an infection in those cases with suggestive findings in the absence of infection history. Apart from CNS involvement, different unspecific signs of a fetal infection can be detected by fetal MR. They usually are diffuse plancental thickening, oligohydramnios, fetal ascites or hydrops, hepatomegaly or cardiomegaly, and pericardial or peritoneal effusion.

TREATMRNT

CMV	Gancyclovir; Foscarnet
Congenital Toxoplasmosis	A combination treatment with pyrimethamine-sulfadiazine and folinic acid for about 1 year
Congenital Rubella Syndrome	There is no specific treatment for congenital rubella infection. Care involves supportive treatment. Heart defects often can be corrected surgically, but damage to the nervous system is permanent.
HSV	Acyclovir

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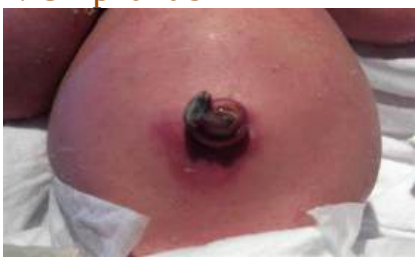
LOCALIZED BACTERIAL INFECTIONS IN NEWBORNS

1. Omphalitis



The umbilical cord may become colonized by a variety of potentially pathogenic bacteria mainly Staph, Streptococci and E. coli. Occasionally infection of the umbilical cord becomes disseminated, either by blood stream or by direct spread via the umbilical vessels to the peritoneal cavity. Tetanus, diphtheria and necrotizing fasciitis may also occur as complications of umbilical infection.
Such infections are still responsible for a high proportion of deaths in the neonatal period in developing countries.

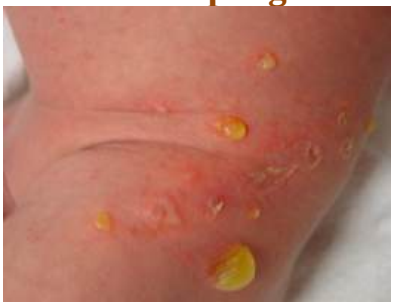
CLINICAL FEATURES
The skin lesion presents with cellulitis where the skin around the umbilical area becomes indurated.
Bullae may appear in the center of the indurated area followed by necrosis.
Purpura: Purpuric reactions are common manifestations of omphalitis and may be related to bacterial toxins.

TREATMENT
The most important aspect of treatment is early surgical excision of necrotic tissue.
The use of Hexachlorophene as an antiseptic was popular until it became apparent that this could lead to serious neurotoxicity, particularly in the preterm infant. The best substitute may be Chlorhexidine that can be applied as a dusting powder rather than as an alcoholic solution. Antibiotics are of limited value.

2. Staphylococcal pustulosis

Staphylococcal pustulosis manifests on any area of skin as a papulopustular rash that may coalesce and form bullae. Physicians should obtain a Gram stain and culture of any pustular lesions in a newborn.

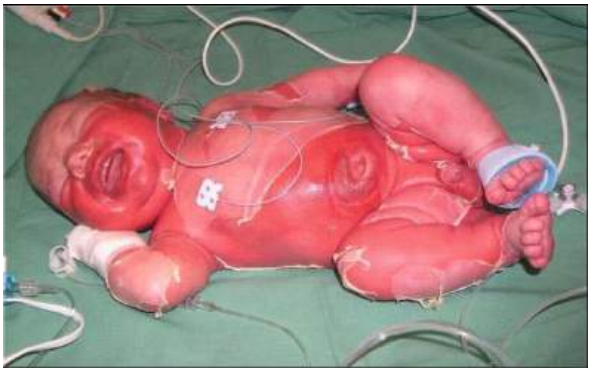
3. Bullous impetigo



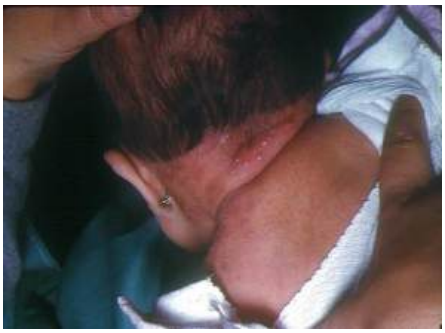
Bullous Impetigo is a cutaneous condition that characteristically occurs in the newborn, and is caused by a bacterial infection, presenting with bullae. It can be caused by Exfoliative toxin A. The pyogenic superficial infection can be divided into two other subdivisions; Impetigo, and non-bullous impetigo. Bullous impetigo is caused by *Staphylococcus aureus*, which produces exfoliative toxins, whereas non-bullous impetigo is caused by either *Staphylococcus aureus*, or *Streptococcus pyogenes*. Bullous Impetigo can cause deaths in fewer than 3% of infected children, but up to a 60% death rate in adults. 30% of all Impetigo cases are related to Bullous impetigo.

4. Staphylococcal scalded skin syndrome (SSSS) or Ritter disease

SSSS is a generalized form of bullous impetigo. Children are more at risk because of lack of immunity and immature renal clearance capability (exfoliative toxins are renally excreted).

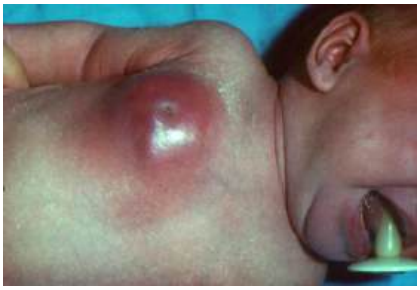


5. Periporitis or pseudofurunculosis (sweat gland abscesses)



Periporitis is the term applied to pustular lesions appearing in the neonatal skin as a result of secondary infection of sweat glands by staphylococcus aureus.
The commonest sites involved are the buttocks, upper part of the trunk and the scalp. The lesion affects mainly malnourished infants and young children. Skin lesions may progress to sweat gland abscesses.

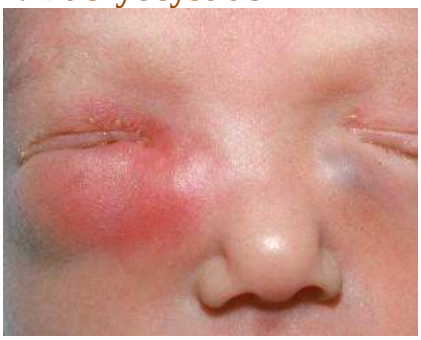
6. Neonatal mastitis



Influx of maternal hormones through the placenta into the fetal circulation often causes the newborn's breasts to be enlarged. In addition, some secretion (ie, witch's milk) may be evident. These changes disappear with time.

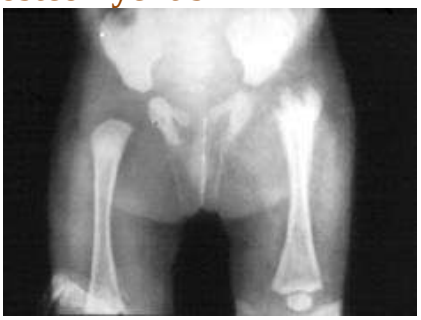
Mastitis neonatorum or infections of the breast tissue may also occur during the newborn period. Treatment includes antibiotics. If an abscess occurs, needle aspiration should be performed. Surgical drainage should be considered only when needle aspiration is unsuccessful, because an operation may damage the breast bud and result in reduction of adult breast size.

7. Dacryocystitis



Neonatal dacryocystitis is a special type of dacryocystitis that occurs in less than 1% of all newborns. The onset is usually acute, and the neonate has a swollen mass in the inferior medial canthal area. Often, there is tearing and a mucopurulent discharge. Significant morbidity and even mortality can be associated with this condition. However, the usual course is more indolent with chronic tearing, mattering, failure to thrive, and even amblyopia. Due to anatomic differences, blacks are less likely to develop the condition. Although incomplete canalization of the nasolacrimal duct is often the basis for this condition, neonatal infection can also be causative.
Untreated lacrimal sac infection may result in orbital cellulitis. In addition to antibiotics, probing and irrigation are required.

8. Neonatal acute osteomyelitis



In both neonates and older children, osteomyelitis due to bacteremia is much more common than that due to spread from contiguous infections; in the neonate, almost all cases arise following bacteremic spread of infection. Accordingly, factors that predispose to bacteremia have also been identified as risk factors for osteomyelitis. In preterm neonates, umbilical catheterization is associated with a higher incidence of bone infection. The hips, knees, and neighboring bones are most commonly involved. Urinary tract infection, periumbilical skin infections, and venous cut-downs for intravenous access have also been identified as risk factors in various retrospective studies.
Most bone infections in neonates are localized to the metaphysis of long bones. The femur and tibia are the most frequently involved bones, accounting for about 50% of all cases. The humerus and the fibula are the next most commonly infected long bones. The predilection for infection in the metaphysis is explained by the developing circulatory patterns near the ends of the bones.
DIAGNOSIS:
1) XRAY (Bone changes usually not present until > 1 week)
2) Bone scans
3) MRI
4) Aspiration

NEONATAL SEPSIS

The Third International Consensus Definitions for Sepsis (2016)

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.
In lay terms, sepsis is a life-threatening condition that arises when the bodys' response to an infection injures its own tissues and organs.

Newborn infants are at much higher risk for developing sepsis than children and adults. Prematurely born neonates experience the highest incidence and mortality of sepsis among all age groups.

The overall incidence of neonatal sepsis ranges from one to five cases per 1000 live births. The estimated incidence is lower in term infants, with a reported rate of one to two cases per 1000 live births.

Neonates are more susceptible for developing sepsis for 3 reasons:

- **Potential risk factors of transition period**
- **Immature immune response**
- **Genetic predisposition**

Risk Factors for Neonatal Sepsis

Prenatal/maternal	Intrapartum	Neonatal
Poor prenatal care Poor nutrition Substance abuse	▪ **Prolonged rupture of membranes (>12 to 18 hours)** ▪ **Maternal fever** ▪ **Prolonged labor** ▪ **Colonization with Group B Streptococcus (GBS)** ▪ **Maternal infections, eg. maternal UTI**	Low birth weight Prematurity Birth asphyxia Meconium staining Resuscitation *endotracheal tubes or indwelling catheters*

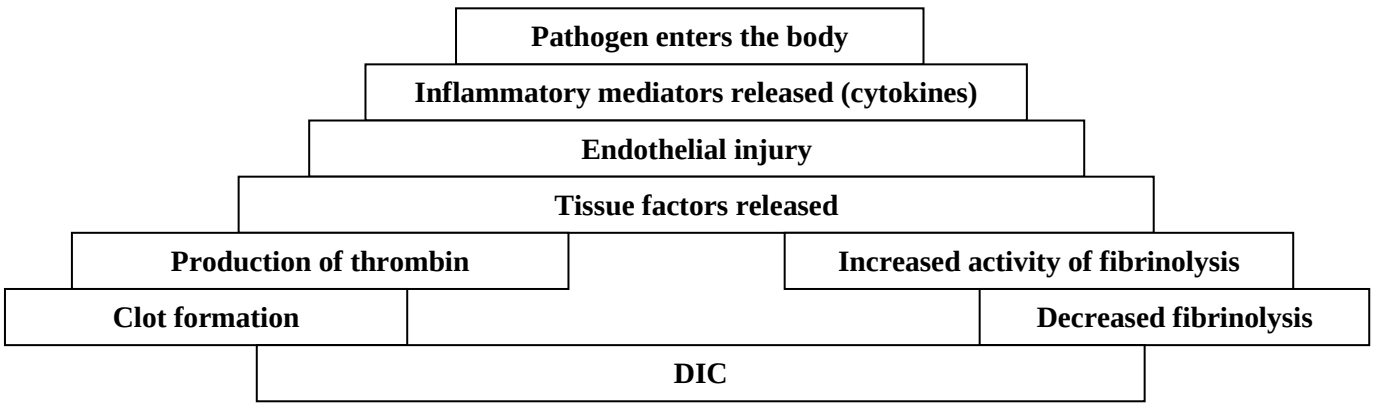
Genetic Predisposition to Sepsis

The body's first response to infection requires recognition of the presence of a pathogen. After recognition has occurred the body responds appropriately to resolve the problem. Many polymorphisms have been recognized within both of these phases and they have been implicated in influencing the susceptibility to and/or outcome from sepsis.

Let's look further into these two phases to see the effect polymorphisms have on neonatal sepsis:

Recognition Phase	**Response Phase**
The body's initial response to infection requires **recognition** of the presence of a pathogen. **Polymorphisms** in genes coding for proteins involved in the recognition of pathogens can influence the susceptibility to and/or outcome of neonatal sepsis. ***Let's look into two of these:*** **Lipopolysaccharide (LPS)** — **Mannose-Binding Lectine (MBL)** ***LPS***, a major component of bacteria, is a powerful stimulator of the innate immune response. LPS elicits it's response by binding to a cell surface receptor that is compromised of 3 proteins. One of these proteins is TLR4. **TLR4 is required for LPS to respond.** When there are polymorphisms in TLR4 there is a reduced response to LPS and that enhances the susceptibility to infection! ***MBL*** has two primary immunodefensive roles: - involved with opsonization - leads to activation of complement system, independent of antibodies. Polymorphisms cause deficiencies in MBL level. This results in decreased levels of MBL. This deficiency is associated with increased susceptibility to infections!	After the initial recognition of a pathogen occurs the body responds by releasing elevated levels of proinflammatory cytokines followed by a release of anti-inflammatory cytokines. This dual release of opposite cytokines helps the cytokines return to a baseline level and that enables the start of tissue repair to start. It is generally accepted that an imbalance between proinflammatory and anti-inflammatory cytokines result in clinical manifestations of sepsis. This Imbalance is due to polymorphisms in various proteins involved in the response to pathogens. **Let's look into two of these :** **Tumor Necrosis Factor (TNF)** — **Interleukin 10 (IL-10)** ***TNF*** is a proinflammatory cytokine that is responsible for the initial activation of the inflammatory response. There are several polymorphisms associated with an increased secretion of TNF resulting in the susceptibility to sepsis. **IL-10** is an anti-inflammatory cytokine produced by primarily monocytes. IL-10 helps regulate the over expression of proinflammatory cytokines. There are three polymorphisms noted that result in an over expression of IL-10. This over expression is proposed to induce immunosuppression in bacterial sepsis and therefore increasing mortality by inhibiting bacterial clearance.

Disseminated intravascular coagulation (DIC) development in sepsis



Early versus Late Onset Neonatal Sepsis

Characteristics	EOS	LOS
Routes of acquisition	Typically acquired during the intrapartum period, often from organisms in the maternal genital tract	Postnatal environment (nosocomial or community-acquired infections)
Onset	Occurs within the first few days of life: 85% of newborns with early onset sepsis begin to show symptoms within the first 24 hours of life, 5% have symptoms between 24 and 48 hours, a very small percentage of infants show symptoms between 48 hours and 6 days of life. Premature infants have the most rapid onset.	Similar to early-onset sepsis, there is variability in its definition ranging from an onset at >72 hours or ≥7 days of age
Presentation	A sudden onset and rapid progression to septic shock often characterize these infections. The main clinical feature of a newborn with early onset sepsis is **respiratory distress**, which often presents as mild nasal flaring and tachypnea. The respiratory distress can quickly progress to **multisystem failure** and **shock** if not caught early. *Sepsis and septic shock may manifest as respiratory distress by causing acute respiratory distress syndrome [ARDS], hypovolemic stimulation of baroreceptors, stimulation of respiratory centers by cytokines, and lactic acidosis.*	The clinical manifestations may be acute physiological deterioration or manifestations of a more localized infection that has progressed to sepsis.
Mortality Rate	up to 50%	10% to20%
Common causative organisms	GBS E. coli	**Gram-positive bacteria:** Coagulase-negative Staphylococci (CoNS) Methicillin-resistant Staphylococcus aureus (MRSA) **Gram-negative bacteria:** E. coli, Klebsiella, Pseudomonas, Enterobacter **Fungal organisms:** Candida
Initial Empirical Therapy	Ampicillin (or amoxycillin) + gentamicin Rare – third-gen. cephalosporins	Vancomycin Aminoglycosides Aminopenicillins Third-gen. cephalosporins (should be discouraged outside of suspected meningitis)

How is Neonatal Sepsis Diagnosed?

There is no definite marker in neonatal sepsis, but there are determinants of organ dysfunction, infection and SIRS (systemic inflammatory response syndrome).

Septic work-up:
**** Complete Blood Count (CBC)***
**** Blood & Urine cultures***
**** Lumbar Puncture (LP)***
**** Chest X-Ray***
**** Line cultures***

- **INFECTION** - a suspected or proven (by positive culture, tissue stain, or polymerase chain reaction test) infection caused by any pathogen OR a clinical syndrome associated with a high probability of infection. Evidence of infection includes positive findings on clinical exam, imaging, or laboratory tests (e.g., white blood cells in a normally sterile body fluid, perforated viscus, chest radiograph consistent with pneumonia, petechial or purpuric rash, or purpura fulminans).
  Infection can be associated with SIRS.

  SIRS *was proposed by the American College of Chest Physicians and Society of Critical Care Medicine to describe the nonspecific inflammatory process occurring in adults after trauma, infection, burns, pancreatitis, and other diseases.* ***The SIRS criteria*** *were developed for use in adults and therefore contain a number of clinical signs and laboratory values specific to adults. A number of modifications of these criteria for a pediatric population can be found in the literature.*
  The major difference in the definition of SIRS between adults and children is that the diagnosis of pediatric SIRS requires that ***temperature or leukocyte abnormalities be present*** *(i.e., SIRS should not be diagnosed if a pediatric patient exhibits only elevated heart and respiratory rates). In addition, numeric values for each criterion need to be modified to account for the different physiology of children. Finally,* ***bradycardia may be a sign of SIRS in the newborn age group but not in older children*** *(in whom it is a near terminal event).*

  SIRS CRITERIA
  The presence of at least two of the following four criteria, **one of which must be abnormal temperature or leukocyte count:**
  ● Core temperature of > 38.5°C or < 36°C.
  ● Tachycardia, defined as a mean heart rate > 2 SD above normal for age in the absence of external stimulus, chronic drugs, or painful stimuli; or otherwise unexplained persistent elevation over a 0.5- to 4-hr time period **OR for children <1 yr old: bradycardia, defined as a mean heart rate <10th percentile for age in the absence of external vagal stimulus, β-blocker drugs, or congenital heart disease; or otherwise unexplained persistent depression over a 0.5-hr time period.**
  ● Mean respiratory rate > 2 SD above normal for age or mechanical ventilation for an acute process not related to underlying neuromuscular disease or the receipt of general anesthesia.
  ● Leukocyte count elevated or depressed for age (not secondary to chemotherapy-induced leukopenia) or >10% immature neutrophils.

- **SEPSIS is now defined as life-threatening organ dysfunction associated with a dysregulated host response to infection.**

  • *The original conceptualization of sepsis as infection with at least 2 of the 4 SIRS criteria focused solely on inflammatory excess. However, the validity of SIRS as a descriptor of sepsis pathobiology has been challenged. Sepsis is now recognized to involve early activation of both pro- and anti-inflammatory responses, along with major modifications in nonimmunologic pathways such as cardiovascular, neuronal, autonomic, hormonal, bioenergetic, metabolic, and coagulation, all of which have prognostic significance. In addition, 1 in 8 patients admitted to critical care units in Australia and New Zealand with infection and new organ failure did not have the requisite minimum of 2 SIRS criteria to fulfill the definition of sepsis (poor concurrent validity) yet had protracted courses with significant morbidity and mortality.*

  • *Nonspecific SIRS criteria such as pyrexia or neutrophilia will continue to aid in the general diagnosis of infection. These findings complement features of specific infections (eg, rash, lung consolidation, dysuria, peritonitis) that focus attention toward the likely anatomical source and infecting organism. However, SIRS may simply reflect an appropriate host response that is frequently adaptive. Sepsis involves organ dysfunction, indicating a pathobiology more complex than infection plus an accompanying inflammatory response alone.*

  • *Sepsis-induced organ dysfunction may be occult; therefore, its presence should be considered in any patient presenting with infection. Conversely, unrecognized infection may be the cause of new-onset organ dysfunction. Any unexplained organ dysfunction should thus raise the possibility of underlying infection.*

  • *Specific infections may result in local organ dysfunction without generating a dysregulated systemic host response.*

- **SEPTIC SHOCK**
  Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality. Patients with septic shock can be identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors and having hyperlactatemia despite adequate volume resuscitation.

Organ Dysfunction Criteria in Children

Cardiovascular dysfunction

Despite administration of isotonic intravenous fluid bolus ≥40 mL/kg in 1 hr

- Decrease in BP (hypotension) <5th percentile for age or systolic BP <2 SD below normal for age OR
- Need for vasoactive drug to maintain BP in normal range (dopamine >5 mcg/kg/min or dobutamine, epinephrine, or norepinephrine at any dose) OR
- Two of the following

Unexplained metabolic acidosis: base deficit > 5.0 mEq/L
Increased arterial lactate >2 times upper limit of normal
Oliguria: urine output <0.5 mL/kg/hr
Prolonged capillary refill: >5 secs
Core to peripheral temperature gap >3°C

Respiratory

- PaO2/FIO2 <300 in absence of cyanotic heart disease or preexisting lung disease OR
- PaCO2 >65 torr or 20 mm Hg over baseline PaCO2 OR
- Proven need or >50% FIO2 to maintain saturation ≥92% OR
- Need for nonelective invasive or noninvasive mechanical ventilation*d*

Neurologic

- Glasgow Coma Score ≤11 OR
- Acute change in mental status with a decrease in Glasgow Coma Score ≥3 points from abnormal baseline

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Hematologic

- Platelet count <80,000/mm3 or a decline of 50% in platelet count from highest value recorded over the past 3 days (for chronic hematology/oncology patients) OR
- International normalized ratio >2

Renal

- Serum creatinine ≥2 times upper limit of normal for age or 2-fold increase in baseline creatinine

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Hepatic

- Total bilirubin ≥4 mg/dL (not applicable for newborn) OR
- ALT 2 times upper limit of normal for age

Age-specific Vital Signs and Laboratory Variables

Age Group	Heart Rate, Beats/Min		Respiratory Rate, Breaths/Min	Leukocyte Count, Leukocytes × 10^3/mm	Systolic Blood Pressure, mm Hg
	Tachycardia	Bradycardia			
0 days to 1 wk	>180	<100	>50	>34	<65
1 wk to 1 mo	>180	<100	>40	>19.5 or <5	<75
1 mo to 1 yr	>180	<90	>34	>17.5 or <5	<100
2–5 yrs	>140	NA	>22	>15.5 or <6	<94
6–12 yrs	>130	NA	>18	>13.5 or <4.5	<105
13 to <18 yrs	>110	NA	>14	>11 or <4.5	<117

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NEONATAL PNEUMONIA

Pneumonia is an important cause of neonatal infection and accounts for significant morbidity and mortality, especially in developing countries.

Neonatal pneumonia can have early or late onset.

Characteristics	Early-onset pneumonia	Late-onset pneumonia
Routes of acquisition	• Intrauterine aspiration of infected amniotic fluid • Transplacental transmission of organisms from the mother to the fetus through the placental circulation • Aspiration during or after birth of infected amniotic fluid.	Postnatal environment (nosocomial or community-acquired infections)
Onset	Within the first 3 or 7 days of life, mostly within 48 hours *Congenital or intrauterine pneumonia can be considered a variant of early onset pneumonia*	Usually occurs after 7 days of age
Presentation	Clinical signs are unspecific and present as respiratory distress of various degree, suspicious appearing tracheal aspirates, cough, apnea, high or low temperature, poor feeding, abdominal distension, and lethargy.	
Chest x-ray	The radiographical appearance may also vary, showing reticulogranular-nodular infiltrates, and bilateral streaky or hazy lungs. *As small bronchioli tend to collapse there may be compensatory hyperaeration in areas free of pneumonial infiltration. In addition there may be pleural effusions and/or pneumatocele formation in more complicated cases. Alveolar patterns with coarse, patchy parenchymal infiltrates, consolidation, and diffuse granularity are more typical for bacterial infections while parahilar streakiness, diffuse hazy lungs or reticulo-nodularity are more common in viral disease.*	
Common causative organisms	• Bacterial infections *Group B Streptococcus (g +)* *Escherichea coli (g-)* *Staphylococcus aureus (g+)* *Listeria monocytogenes (g+)* *Enterococcus (g +)* *Ureaplasma urealyticum (g+)* • Herpes simplex virus (HSV) • Fungal infections	• Predominance of gram positive bacteria including S. pyogenes, S. aureus, and S. pneumoniae • Citrobacter diversus (assoc. with brain and lung abscesses) • Bacillus cereus (assoc. with necrotizing pneumonia in preterm infants) • Chlamydia trachomatis has a long incubation period and typically is associated with pneumonia occurring between two and four weeks of age • Viral infections (adenovirus, parainfluenza, rhinovirus, enteroviruses, influenza, respiratory syncytial virus [RSV]) • Fungal infections
Initial Empirical Therapy	As pneumonia is often associated with or non distinguishable from bacterial sepsis initial therapy at the NICU includes broad spectrum intravenous antibiotics according to local protocols.	

REFERENCE

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2. *Nissen MD. Congenital and neonatal pneumonia. Pediatrics Resp. Reviews 2007; 8:195- 203*
3. *Duke T. Neonatal pneumonia in developing countries. Arch Dis Child Fetal Neonatal Ed.2005; 90: F2011-F219*

NOSOCOMIAL INFECTIONS

Nosocomial infection is defined as an infection acquired in the hospital that was neither present nor incubating at the time of hospital admission.

For most bacterial nosocomial infections, this means that the infection usually becomes evident 48 hours (i.e., the typical incubation period) or more after admission. However, because the incubation period varies with the type of pathogen and to some extent with the patient's underlying condition, each infection must be assessed individually for evidence that links it to the hospitalization.

Neonates, especially those requiring NICU care, are more susceptible to nosocomial infections. Multiple factors contribute to this population's high risk for infection, including prematurity and the related relative immunodeficiency, use of central venous catheters, ventilator support, use of urinary catheters, receipt of parenteral nutrition and lipids, and exposure to broadspectrum antimicrobials.

There are two special situations in which an infection is considered nosocomial:
(a) infection that is acquired in the hospital but does not become evidence until after hospital discharge and
(b) infection in a neonate that results from passage through the birth canal.

Some would argue that neonatal infections acquired during vaginal delivery are inevitable and, therefore, should not be counted as nosocomial. However, these neonatal infections (e.g., group B streptococcal bacteremias with early onset) are considered nosocomial, they can be identified as maternally acquired, and the analysis of their incidence can be disseminated to obstetricians for interventional strategies.

Table. Nosocomial Bacterial Infections in Patients in the Neonatal Intensive Care Unit (NICU)

Site of Infection	Common Pathogens	
Bloodstream/sepsis	**CONS** **S. aureus**	**Pseudomonas aeruginosa** **Candida sp**
Pneumonia	**CONS** **S. aureus**	**P. aeruginosa** **Respiratory syncytial virus**
Skin/soft tissue/surgical site	**CONS**	**S. aureus**
Conjunctivitis/Ocular	**CONS**	**P. aeruginosa**
Urinary tract	**Gram-negative bacilli**	**Enterococci**
Endocarditis	**CONS**	**S. aureus**
Central nervous system	**CONS**	**S. aureus**
Osteoarthritis	**S. aureus**	**Group B streptococci**

Infection control practices in the NICU

1. Hand Hygiene Practices

- Removal of all rings; no nail polish or false nails
- Initial 3-minute scrub to the elbow
- A 10-second scrub before and after handling each infant
- Use of alcohol-based hand gels before and after handling infant

2. Personal Protective Equipment and Universal Gloving

3. Antisepsis for Central Catheter Insertion

4. Health-care Worker Vaccination (influenza immunization, a tetanus, diphtheria, and acellular pertussis vaccine)

REFERENCE

1. *Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM: CDC definitions for nosocomial infections, 1988, Am J Infect Control 16:28-40, 1988.*
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3. *Polin, R. A., & Saiman, L. (2003). Nosocomial infections in the neonatal intensive care unit. NeoReviews, 4(3), e81-e89.*
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NEONATAL JAUNDICE

Case Scenario. A 2-day-old infant is noticed to be jaundiced. He is nursing and stooling well. Indirect bilirubin is 11.2 mg/dL; direct is 0.4 mg/dL. Physical exam is unremarkable except for visible jaundice.

Jaundice is quite common in neonatal period

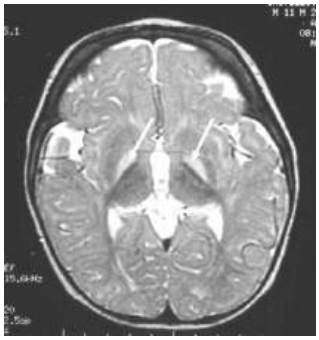
- 60% of term infants and 80% of preterm infants
- Visible jaundice from sclera, mucosa and skin

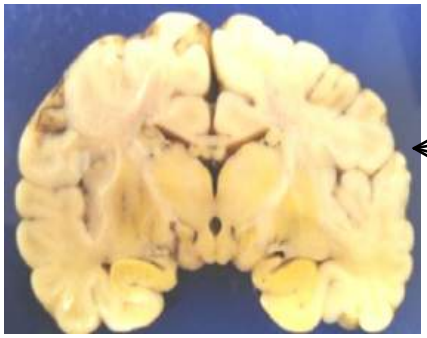
Can cause serious consequences:

[1] *Actue phase*

- respiratory failure
- bilirubin encephalopathy
- neonatal death

[2] *Lifelong neurologic sequelae* — ***kernicterus***





- cerebral palsy
- epilepsy
- mental retardation
- auditory and visual disfunctions

Why jaundice is so prevalent in neonatal period ???

Bilirubin metabolism in neonates

Bilirubin is produced in the reticuloendothelial system as the end product of heme catabolism and is formed through oxidation-reduction reactions. Approximately 75% of bilirubin is derived from hemoglobin, but degradation of myoglobin, cytochromes, and catalase also contributes.

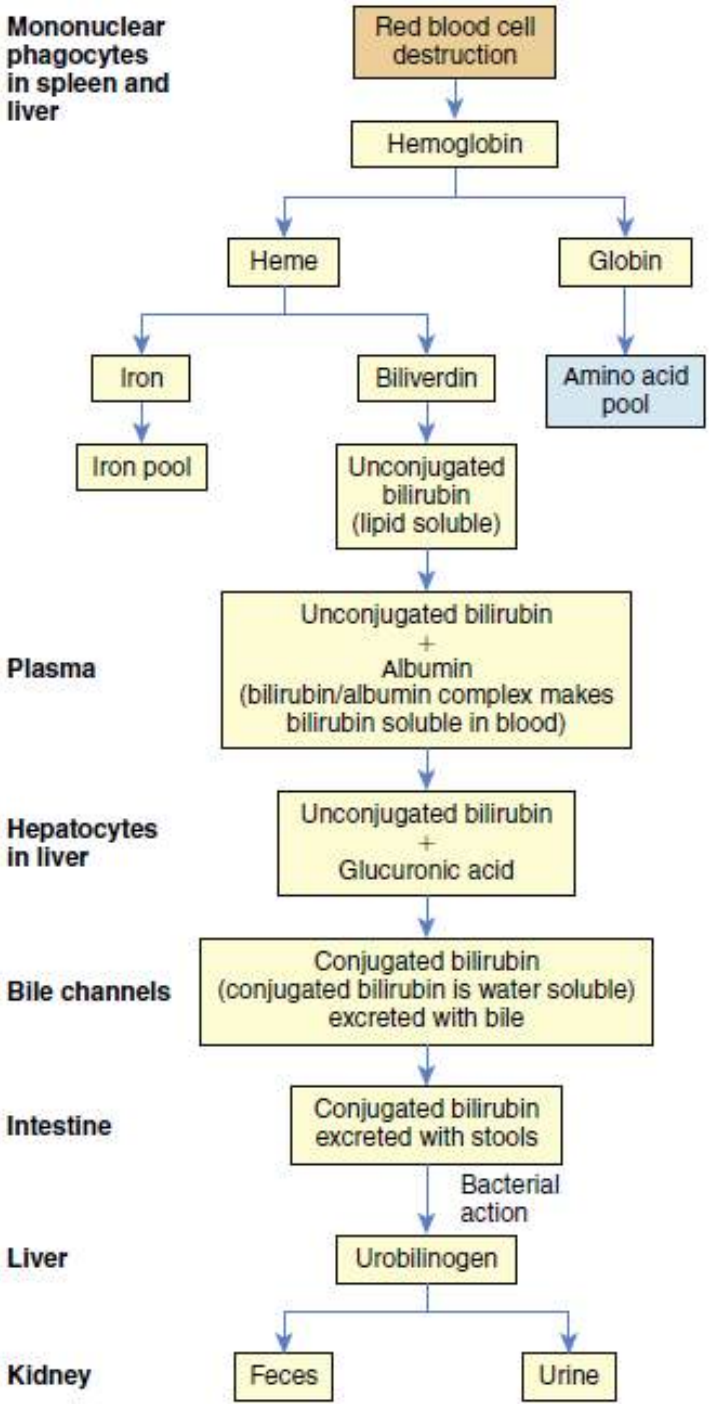
- In the first oxidation step, **biliverdin** is formed from heme through the action of heme oxygenase, the rate-limiting step in the process, releasing iron and carbon monoxide. The iron is conserved for reuse, whereas carbon monoxide is excreted through the lungs and can be measured in the patient's breath to quantify bilirubin production.
- Next, water-soluble biliverdin is reduced to **bilirubin**, which, because of the intramolecular hydrogen bonds, is almost insoluble in water in its most common isomeric form (bilirubin IXα Z,Z).
- Because of its hydrophobic nature, unconjugated bilirubin is transported in the plasma tightly **bound to albumin**. Binding to other proteins and erythrocytes also occurs, but the physiologic role is probably limited. Binding of bilirubin to albumin increases postnatally with age and is reduced in infants who are ill. The presence of endogenous and exogenous binding competitors, such as certain drugs, also decreases the binding affinity of albumin for bilirubin. A minute fraction of unconjugated bilirubin in serum is not bound to albumin. This free bilirubin is able to cross lipid-containing membranes, including the blood-brain barrier, leading to **neurotoxicity**. In fetal life, free bilirubin crosses the placenta, apparently by passive diffusion, and excretion of bilirubin from the fetus occurs primarily through the maternal organism.
- When it reaches the liver, bilirubin is transported into liver cells, where it binds to ligandin. **Uptake of bilirubin into hepatocytes** increases with increasing ligandin concentrations. Ligandin concentrations are low at birth but rapidly increase over the first few weeks of life. Ligandin concentrations may be increased by the administration of pharmacologic agents such as phenobarbital.
- Bilirubin is **bound to glucuronic acid (conjugated)** in the hepatocyte endoplasmic reticulum in a reaction catalyzed by uridine diphosphoglucuronyltransferase (UDPGT). Monoconjugates are formed first and predominate in the newborn. Diconjugates appear to be formed at the cell membrane and may require the presence of the UDPGT tetramer.

  Bilirubin conjugation is biologically critical because it transforms a water-insoluble bilirubin molecule into a water-soluble molecule. Water-solubility allows conjugated bilirubin to be excreted into bile. UDPGT activity is low at birth but increases to adult values by age 4-8 weeks. In addition, certain drugs (phenobarbital, dexamethasone, clofibrate) can be administered to increase UDPGT activity.
- At birth, the gut is sterile, and normal gut flora takes time to establish. The bacteria in the adult gut convert conjugated bilirubin to urobilinogen (stercobilinogen) which is then oxidized to stercobilin and excreted in the stool. In the absence of sufficient bacteria, the bilirubin is de-conjugated by brush border β-glucuronidase and reabsorbed. This process of re-absorption is called **enterohepatic circulation**. It has been suggested that bilirubin uptake in the gut (enterohepatic circulation) is increased in breast fed babies, possibly as the result of increased levels of epidermal growth factor (EGF) in breast milk.

Unconjugated (indirect) bilirubin	Conjugated (direct) bilirubin
– Fat-soluble – Is not easily excreted – Neurotoxic	– Water soluble – It is mostly excreted in stool and some in the urine – Nontoxic

Table. Bilirubin metabolism in neonates.

BILIRUBIN METABOLISM	The Metabolic Characteristics of Bilirubin in Newborns



1. Increased bilirubin production:

[1] Life span of RBC:
- Preterm: < 70 days
- Term: 80 days
- Adult: 120 days

[2] Turnover rate of neonatal hemoglobin:
2 times faster than that of adults

2. Insufficient binding between bilirubin and albumin:

[1] **low content of serum albumin** —> bilirubin-albumin complex↓

[2] **different degree of acidosis at birth** —> binding affinity↓

3. Deficient bilirubin conjugation in the hepatocyte:

[1] **Low uptake of bilirubin into hepatocytes**

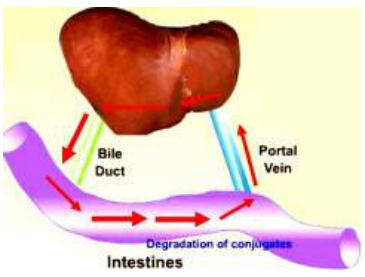
[2] **Low UDPGT activity at birth**

4. Increased enterohepatic circulation of bilirubin

[1] **intestinal flora is not fully developed** to convert bilirubin to urobilinogen

[2] **abundant β-glucuronidase** —> deconjugation of conjugated bilirubin

[3] **Low intestinal motility** —> increased absorption of bilirubin



NONPATHOLOGIC JAUNDICE

I. *Physiologic jaundice*

Physiologic jaundice is an exaggerated normal process seen in 60% of term infants, and 80% of *premature* infants. It is characterized by unconjugated hyperbilirubinemia that peaks by the third or fourth day of life in full-term newborns and then steadily declines by 1 week of age. Asian newborns tend to have higher peak bilirubin concentrations and more prolonged jaundice. Premature infants are more likely to develop jaundice than full-term babies.

Neonatal physiologic jaundice results from simultaneous occurrence of the following two major phenomena:

- *Bilirubin production is elevated because of increased breakdown of fetal erythrocytes. This is the result of the shortened lifespan of fetal erythrocytes and the higher erythrocyte mass in neonates.*
- *Hepatic excretory capacity is low both because of low concentrations of the binding protein ligandin in the hepatocytes and because of low activity of glucuronyl transferase (UDPGT), the enzyme responsible for binding bilirubin to glucuronic acid, thus making bilirubin water soluble (conjugation).*

II. «*Breastfeeding failure jaundice*» vs «*Breast milk jaundice*»

Breast-feeding failure jaundice is caused by insufficient breast milk intake, resulting in inadequate quantities of bowel movements to remove bilirubin from the body. This can usually be ameliorated by frequent breastfeeding sessions of sufficient duration to stimulate adequate milk production. Passage of the baby through the vagina during birth helps stimulate milk production in the mother's body, so infants born by cesarean section are at higher risk for this condition.

Breast milk jaundice

Whereas breast *feeding failure* jaundice is a mechanical problem, breast *milk* jaundice is more of a biochemical problem. The term applies to jaundice in a newborn baby.

First, at birth, the gut is sterile, and normal gut flora takes time to establish. The bacteria in the adult gut convert conjugated bilirubin to stercobilinogen which is then oxidized to stercobilin and excreted in the stool. In the absence of sufficient bacteria, the bilirubin is de-conjugated by brush border β-glucuronidase and reabsorbed. This process of re-absorption is called enterohepatic circulation. It has been suggested that bilirubin uptake in the gut (enterohepatic circulation) is increased in breast fed babies, possibly as the result of increased levels of epidermal growth factor (EGF) in breast milk.

Second, the breast-milk of some women contains a metabolite of progesterone called 3-alpha-20-beta pregnanediol. This substance inhibits the action of the enzyme UDPGT responsible for conjugation and subsequent excretion of bilirubin. In the newborn liver, activity of glucuronyl transferase is only at 0.1-1% of adult levels, so conjugation of bilirubin is already reduced. Further inhibition of bilirubin conjugation leads to increased levels of bilirubin in the blood . However, these results have not been supported by subsequent studies.

Third, an enzyme in breast milk called lipoprotein lipase produces increased concentration of nonesterified free fatty acids that inhibit hepatic glucuronyl transferase, which again leads to decreased conjugation and subsequent excretion of bilirubin.

Despite the advantages of breast feeding, there is a strong association of breast feeding with neonatal hyperbilirubinemia and thus risk of kernicterus, though this is uncommon. Serum bilirubin levels may reach as high as 30 mg/dL. Jaundice should be managed either with phototherapy or with exchange blood transfusion as is needed. Breast feeds however need not be discontinued. The child should be kept well hydrated and extra feeds given.

PATHOLOGIC JAUNDICE

Pathologic jaundice usually appears within the first 24 hours after birth and is characterized by a rapidly rising serum bilirubin concentration (>5 mg/dL per day), prolonged jaundice (>7 to 10 days in a full-term infant), or an elevated direct bilirubin concentration(>2mg/dL). Conjugated hyperbilirubinemia never has a physiologic cause and must always be investigated.

PHYSIOLOGIC JAUNDICE VERSUS PATHOLOGIC JAUNDICE

Physiologic Jaundice	Pathologic Jaundice
Appears on second to third day of life (term)	May appear in first 24 hours of life
Disappears by fifth day of life (term) — 7th	Variable
Peaks at second to third day of life	Variable
Peak bilirubin <13 mg/dL (term)	Unlimited
Rate of bilirubin rise <5 mg/dL/d	Usually >5 mg/dL/d

CAUSES OF PATHOLOGIC JAUNDICE

I. UNCONJUGATED HYPERBILIRUBINEMIA

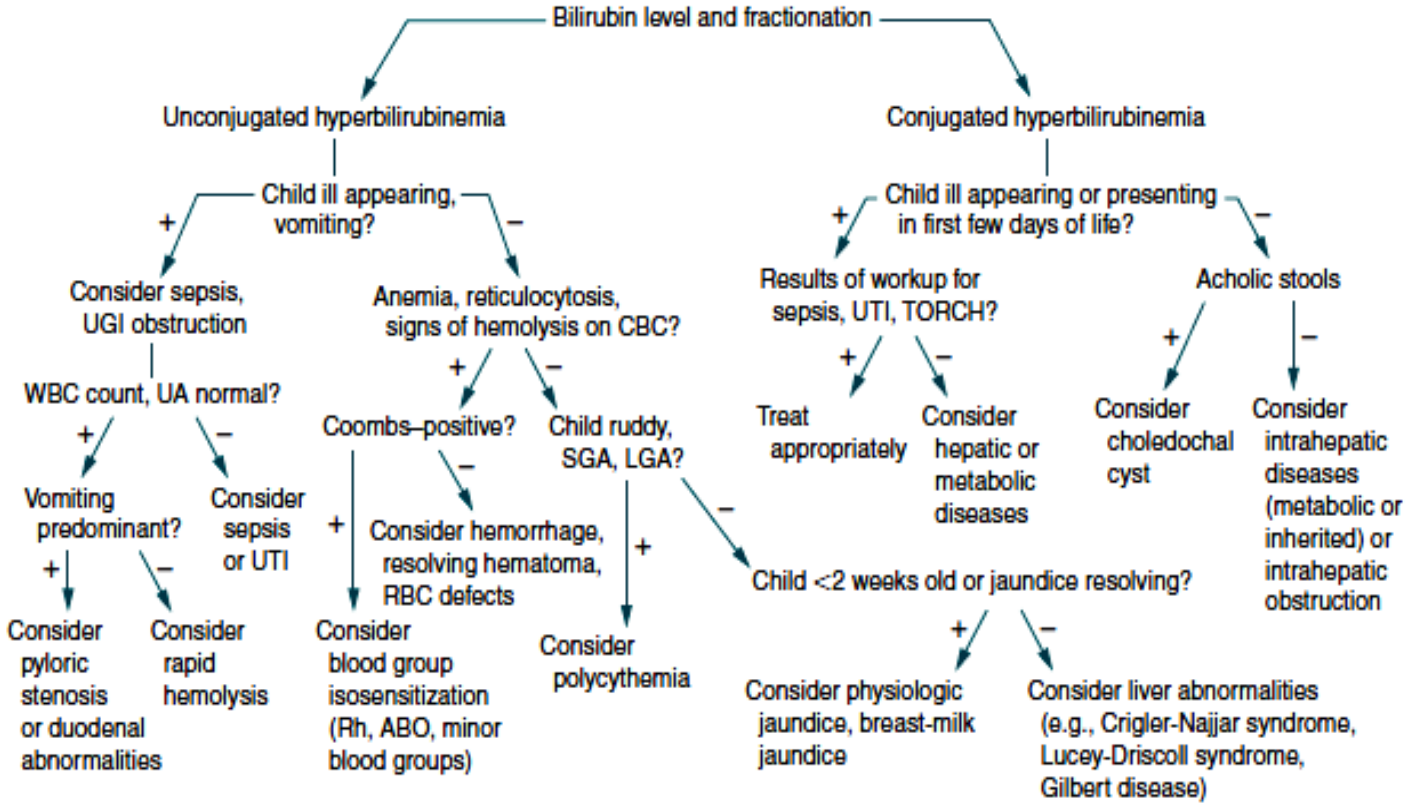
Increased Bilirubin Production	Decreased Bilirubin Conjugation	Increased Enterohepatic Circulation
• **Blood group incompatibility** — Rh, ABO, and minor blood group • **Red blood cell (RBC) enzyme abnormalities** — glucose-6-phosphate dehydrogenase (G6PD), pyruvate kinase, and hexokinase deficiency • **RBC membrane defects** — hereditary spherocytosis, elliptocytosis, and pyknocytosis • **Hemoglobinopathies** — α-thalassemia, and sickle cell disease • **Increased RBC load** — cephalohematoma, polycythemia, and ecchymosis • **Infants of diabetic mothers**	• **Hormonal deficiency** — hypothyroidism and panhypopituitarism • **Bilirubin metabolism disorders** — Gilbert syndrome, Crigler–Najjar (types 1 and 2), and Lucey-Driscoll syndrome • **Sepsis** — bacterial, viral, and fungal • **Urinary tract infection (UTI)**	• **Bowel obstruction or ileus** • **Pyloric stenosis**

II. CONJUGATED HYPERBILIRUBINEMIA

Conjugated hyperbilirubinemia is defined as a level ≥ 1 mg/dL (≥17.1 μmol/L) if the total bilirubin is < 5 mg/dL (<85.5 μmol/L), or a conjugated fraction that accounts for > 20% of the total bilirubin if the total bilirubin is > 5 mg/dL (>85.5 μmol/L).

Bile Duct Abnormalities	Infection	Metabolic/Genetic Disorders	Miscellaneous
• Biliary atresia • Choledochal cyst	• TORCH infections • Sepsis • Urinary tract infection	• Galactosemia • Tyrosinemia • α 1 -Antitrypsin deficiency • Alagille syndrome	• Total parenteral nutrition (TPN)-related cholestasis • Neonatal hemochromatosis • Idiopathic neonatal hepatitis

EVALUATION OF A NEWBORN WITH JAUNDICE



CBC, complete blood count; *LGA,* large for gestational age; *SGA,* small for gestational age; *TORCH,* toxoplasmosis, other infections, rubella, cytomegalovirus, herpes simplex; *UA,* urinalysis; *UTI,* urinary tract infection; *WBC,* white blood cell; *UGI,* upper gastrointestinal

DIAGNOSIS

1. Bilirubin Level - In term infants a normal total serum bilirubin (TSB) level is between 1.0 - 10.0 mg/dL (17.1-171 μmol/L)

- There is NO safe bilirubin level identified (*see* page 9)

2. Complete Blood Count

- This test will determine if the infant has increased red blood cells in the *circulatory system* (polycythemia)
- If an infant has a *hematocrit* greater than 65% this places that infant at risk for hyperbilirubinemia

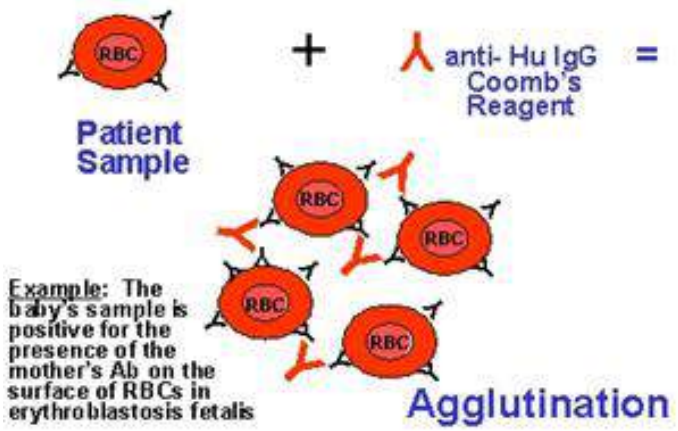
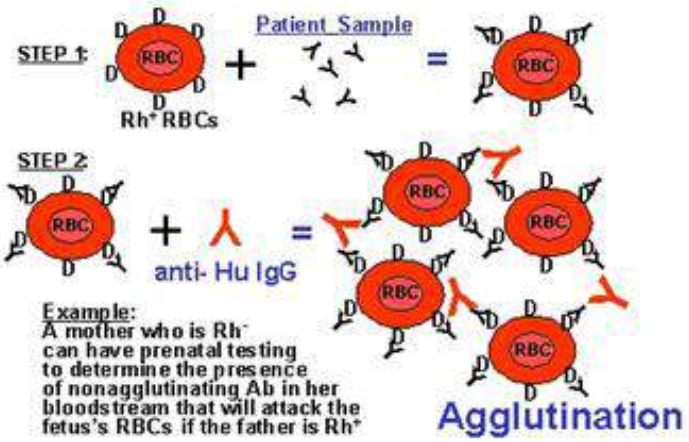
3. Reticulocyte Count

- This test measures young non-nucleated red blood cells
- If the reticulocyte count is greater than 5% in the first week of life, this identifies the infant as trying to replace destroyed red blood cells

4. Blood Groups & Types

ABO grouping and Rh types are confirmed by examining RBCs for presence of blood group *antigens* and RBCs and *antibodies* against these antigens

5. Coombs Test

Direct Coombs Test	Indirect Coombs Test
	

- The direct coombs test is a direct measure of the amount of maternal antibody coating the infant's red blood cell. If the antibody is present, the test is positive.

- The indirect coombs test measures the effect of a sample of the infant's serum (which is thought to contain maternal antibodies) on unrelated adult RBCs. If the infant's serum contains antibodies, they will interact with and coat these adult RBCs (positive test).

6. G6PD Level

- it can be false-positive in patients who are actively *hemolysing*. It can therefore only be done several weeks after a hemolytic episode

7. Albumin Level

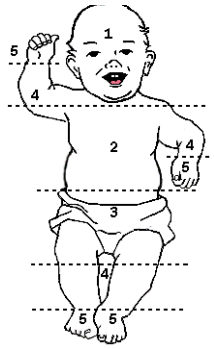
- This test indicates the reserve amount of serum *albumin* available for binding indirect bilirubin
- A normal albumin level in a term infant is between 2.6 - 3.6 g/dL

8. Visual Assessment

- "Visual assessment of jaundice is most accurate when the infant's skin is blanched with light digital pressure in a well-lit room"
- "As bilirubin levels rise, the accuracy of visual assessment decreases"

Kramer Zones Showing Progression of Jaundice

- Jaundice proceeds in a cephalopedal progression, meaning jaundice progresses from the head down to the toes
- This diagram demonstrates what level the bilirubin is at depending on what areas of the infant's body is jaundiced
- For example, if the infant was noted to be jaundiced from the head to the neck that would be zone 1 and the bilirubin level would be between 4 – 6 mg/dL



ZONE	1	2	3	4	5
SBR (mcmol/L)	100	150	200	250	>250
SBR (mg/dL)	4-6	6-8	8-14	14-19	>19

9. Tests for

- Blood chemistry
- UTI
- sepsis
- thyroid functions
- metabolic diseases
…….

Transcutaneous Bilirubin Measurement

Transcutaneous bilirubinometry (TcB) is a noninvasive method of measuring total bilirubin levels. Some concerns have been raised regarding the accuracy of these readings at levels >15 mg/dL and in African American and Hispanic populations. However, this technique has gained widespread use as a screening tool to help detect early hyperbilirubinemia in the newborn nursery.

The AAP has recently advocated the use of TcB to assist screening for hyperbilirubinemia in healthy newborn infants ≥35 weeks' gestation prior to discharge from the newborn nursery. However, elevated levels must be confirmed with serum measurements if the TcB value is at 70% of the TSB level recommended for the use of phototherapy or in the high-intermediate zone on the **Bhutani risk nomogram**.

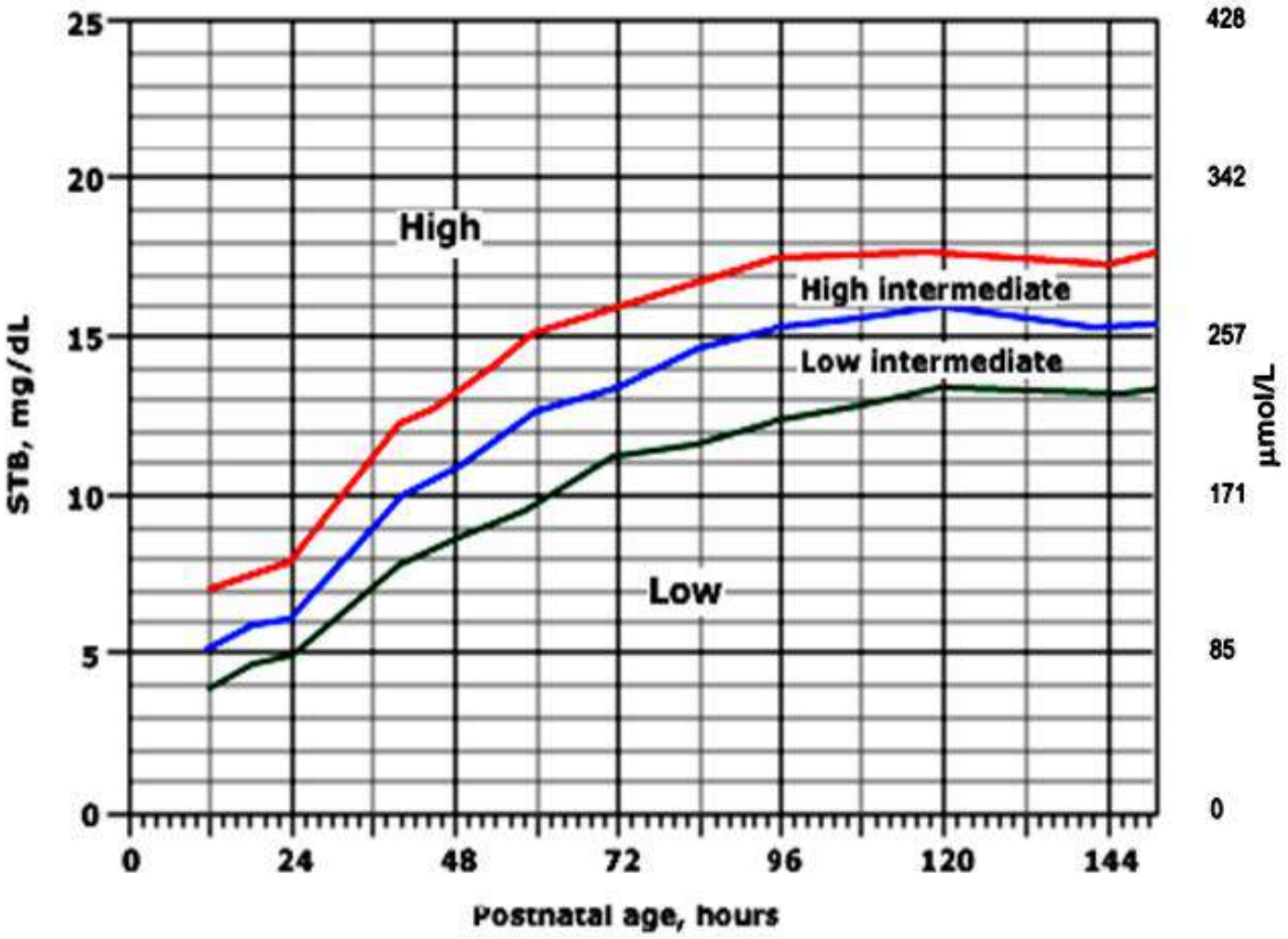


Fig. Bhutani risk nomogram [Bhutani VK, Johnson L, Sivieri EM. Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term neonates. *Pediatrics.* 1999;103:6–14.]

Hemolytic Disease of the Fetus and Newborn (HDFN)

Once called *red cell isoimmunization* in pregnancy, the formation of antibodies to red cell antigens is now termed *red cell alloimmunization*. The perinatal consequence of this process is hemolysis and anemia in the fetus and newborn, or hemolytic disease of the fetus and newborn (HDFN).

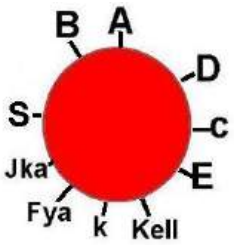
Hemolytic disease of the fetus and newborn (HDFN) due to red cell alloimmunization has been a fascinating clinical picture for many centuries. The first report of a condition called ***hydrops fetalis*** *dates back to 1609, when a French midwife described the delivery of twins. The first twin was hydropic and stillborn and the second suffered from jaundice and subsequently died of kernicterus. These two conditions were not linked until 1932, when Diamond et al. described that hydrops and kernicterus were manifestations of the same disease, which they called* ***erythroblastosis fetalis****. However, the exact cause was still unknown. Since 1940, the analyses of Landsteiner and Wiener contributed largely to a better understanding of the pathogenesis of HDFN. In their studies with rhesus monkeys Landsteiner and Wiener observed that agglutination of human red blood cells occurred in the presence of rhesus monkey red cell antiserum, whereas subjects who lacked the antigen on their red cells did not show agglutination.4,7 The authors called this antigen 'Rhesus' (Rh) and consequently the Rh-blood group system was born. Since then it has become clear that the most common cause of severe HDFN is 'Rhesus disease', resulting from maternal immunization to the Rhesus D (Rh D) antigen.*

EPIDEMIOLOGY

The widespread adoption of guidelines for the administration of antenatal and postpartum rhesus immune globulin (RhIG) has resulted in a marked decline in the prevalence of red cell alloimmunization caused by the RhD antigen. Cases, however, continue to occur because of maternal sensitization in the first two trimesters of pregnancy, inadvertent omission of RhIG, and inadequate dosing after delivery when there has been an excessive fetomaternal hemorrhage.

PATHOGENESIS

It is well established that the fetal-maternal interface is not an absolute barrier, and there is evidence that considerable trafficking of many types of cells occurs between the fetus and the mother throughout gestation.



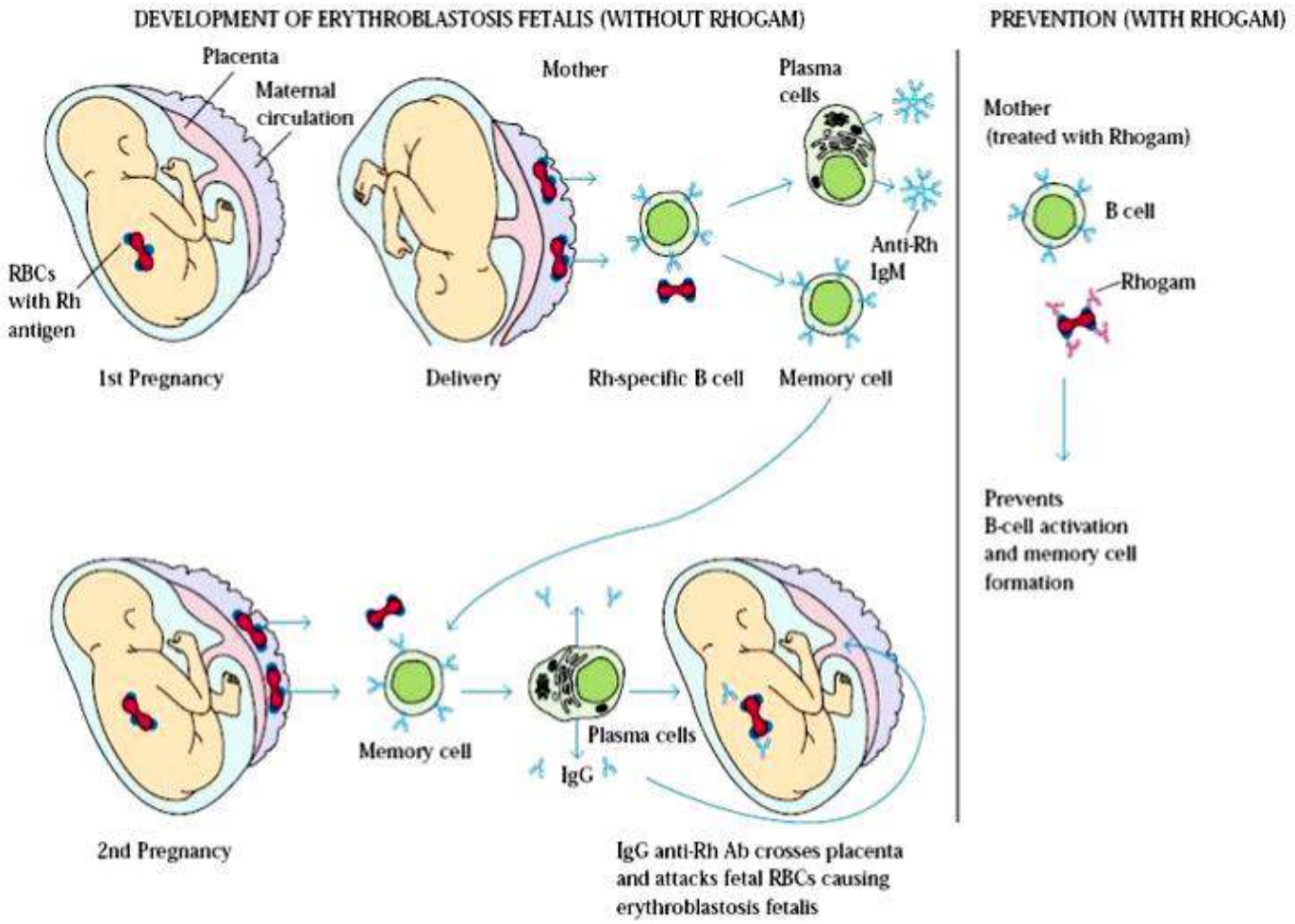
More than 60 different anti–red cell antibodies have been associated with HDFN.

In most cases, the antigenic load of a putative antigen on the fetal erythrocytes and erythrocytic precursors is insufficient to stimulate the maternal immune system. However, in the case of a large fetomaternal hemorrhage before birth or at delivery, B lymphocyte clones that recognize the foreign red cell antigen are established. The initial maternal production of IgM is short-lived and is followed by a rapid change to an IgG response. A human antiglobulin titer can usually be detected by 5 to 16 weeks after the sensitizing event.

After the initial antigenic exposure, memory B lymphocytes await the appearance of red cells containing the putative antigen in a subsequent pregnancy. If stimulated by fetal erythrocytes, these B lymphocytes differentiate into plasma cells that can rapidly proliferate and produce IgG antibodies and an increase in the maternal titer. Maternal IgG crosses the placenta and attaches to fetal erythrocytes that have expressed the paternal antigen. These cells are then sequestered by macrophages in the fetal spleen, where they undergo extravascular hemolysis, producing fetal anemia.

Rh Incompatibility

Rh incompatibility occurs when an Rh-negative mother carries an Rh-positive fetus. The mother must have had previous sensitization to the Rh antigen, usually via a prior pregnancy, which results in the production of antibodies directed against the Rh antigen. Rh-positive infants born to Rh-negative mothers display a wide spectrum of disease, ranging from unaffected (15% to 20%) to severe disease, including erythroblastosis fetalis, and fetal death (25%).



PREVENTION

All current rhesus immune globulin (RhIG) products (**RhoGAM; HyperRHO S/D; Rhophlac; WinRho-SDF**) are polyclonal antibody products derived from human plasma. The latter two products are purified by ion-exchange chromatography and can therefore be administered by either the intravenous or the intramuscular route. All current products undergo micropore filtration to eliminate viral transmission.
A novel polyclonal recombinant antibody known as **rozrolimupab** has been used in phase one and two clinical trials and has demonstrated no serious or adverse effects.

- *All pregnant patients should undergo an **antibody screen at the first prenatal visit**. If there is no evidence of anti-D alloimmunization in the RhD-negative woman, patients should receive RhIG at 28 weeks' gestation.*
  The American Association of Blood Banks (AABB) recommends that a repeat antibody screen be obtained before antenatal RhIG administration, even though the incidence of alloimmunization before 28 weeks is very low. Severe maternal sensitization does occasionally occur before 28 weeks, and by not performing the antibody screen, the clinician loses the opportunity to detect a potentially salvageable anemic fetus. It is therefore prudent to repeat the antibody screen.
- *The RhD antigen is expressed on the fetal red blood cell as early as 38 days after conception. This has led to the recommendation to administer RhIG for early pregnancy events such as spontaneous abortion, elective abortion, threatened abortion, and ectopic pregnancy, where the background rate of subsequent sensitization is 2% to 3%.*
- *RhIG should also be administered for such events as hydatidiform mole, genetic amniocentesis and chorion villus biopsy, fetal death in the second or third trimester, blunt trauma to the abdomen, late amniocentesis, and external cephalic version. In ongoing pregnancies when RhIG is administered in the first or second trimester for one of these indications, a repeat dose should still be given at 28 weeks' gestation. Alternatively, if the antenatal dose was given in the late second trimester (e.g., at 22 weeks for suspected placental abruption), the dose should be repeated 12 weeks later (i.e., at 34 weeks' gestation in that example).*
- *RhIG should be administered within 72 hours of delivery if umbilical cord blood typing reveals an RhD-positive infant.*

ABO Incompatibility

ABO incompatibility occurs when a mother with type O blood carries a fetus with type A or B blood. This condition is confined to mothers with type O blood because these women carry anti-A and anti-B IgG antibodies that cross the placenta. Mothers with type A or type B blood produce mostly IgM antibodies against their respective antigens, and these IgM antibodies fail to cross the placenta. Because A and B antigens are common in nature, group O mothers are previously sensitized to these antigens and hemolysis may occur in the first pregnancy.

Although ABO incompatibility occurs in 15% of all pregnancies, ABO hemolytic disease occurs in less than 5% of ABO-incompatible mother–infant pairs. Hemolysis tends to be less severe than with Rh incompatibility. The classic presentation is anemia, reticulocytosis, and hyperbilirubinemia occurring in the first 24 to 72 hours of life.

TREATMENT

- Phototherapy is treatment of choice
- Encourage frequent feedings
- Intravenous hydration
- Exchange transfusion

1. Phototherapy

- In the mid-1950s, Sister Jean at Rochford General Hospital in England noted that infants exposed to sunlight were less jaundiced in the uncovered skin areas than their nonexposed counterparts.
- Phototherapy works by converting indirect bilirubin to lumirubin, a water-soluble compound that is a more excretable form of bilirubin.
- Only certain wavelengths (colors) of light are absorbed by bilirubin; as bilirubin is a yellow pigment, blue is absorbed more effectively, however, green light is more deeply absorbed into the skin.
- The only true contraindication to phototherapy is congenital porphyria or a family history of porphyria. Phototherapy in these patients could result in severe blistering and photosensitivity.

2. Frequent Feedings

Encouraging frequent feedings at least eight times per day helps to stimulate intestinal motility and removal of *meconium*, thus reducing reabsorption of direct bilirubin into the system.

3. Intravenous Hydration

Intravenous hydration of infants with hyperbilirubinemia was thought to decrease bilirubin levels, however, unless an infant is dehydrated intravenous hydration is not indicated.

4. Exchange Transfusion

- An exchange transfusion is used only in extreme cases when phototherapy has failed
- The process for an exchange transfusion involves small amounts of blood being removed from the infant and then replaced with the same amount of donor RBCs and plasma
- The process continues until twice the circulating volume has been replaced
- The exchange replaces ≈87% of the circulating blood volume and decreases the bilirubin level by ≈55%

Jaundiced infant under phototherapy (with eye proctection)

Jaundiced infant receiving exchange transfusion (through umbilical lines)

OBSTRUCTIVE JAUNDICE

- A high conjugated bilirubin, pale stools (lack of stercobilinogen) and dark urine (presence of bilirubin) indicates an obstructive cause which may be either intrahepatic (e.g. hepatitis) or extrahepatic (e.g. biliary atresia).
- The conjugated component of total bilirubin should always be checked in any baby with jaundice at more than 2 weeks of age. A delay in the diagnosis of biliary atresia beyond 6 weeks of age reduces the likelihood of successful surgery for that condition (biliary drainage by a Kasai portoenterostomy).
- It can be difficult to distinguish clinically between neonatal hepatitis and biliary atresia, and a radionucleotide scan (or occasionally a liver biopsy) is usually indicated. Urgent referral to a specialist paediatric hepatology service is advised.

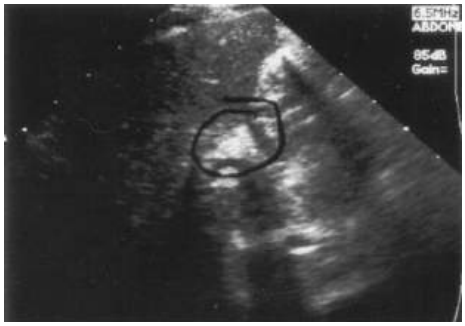


Fig. Biliary atresia (Triangular cord sign= Echogenic area anterior to right portal vein)

HEPATITIS

Neonatal hepatitis can occur in a wide range of disease processes including congenital infections (e.g. toxoplasmosis, cytomegalovirus [CMV]) and metabolic diseases (e.g. α-1-antitrypsin deficiency).

What advice should be given to a mother who is breastfeeding her jaundiced baby?

- Continue breastfeeding. Evaluate for adequate latching and audible swallowing of milk by the baby, and assess whether the infant seems to be consoled after feeding.
- Use an electric breast pump to facilitate "let-down of milk" and to collect expressed breast milk for extra supplementation.
- Avoid maternal use of opioid analgesics (e.g., Percocet, Tylenol III, and other codeine preparations) that could have an impact on the newborn's feeding and stooling.
- Identify ways to reduce maternal stress and anxiety to promote lactation.

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PEDIATRIC EMERGENCIES

Triage

Triage is the process of rapidly screening sick children soon after their arrival in hospital, in order to identify:

*– those with **emergency signs**, who require immediate emergency treatment*

*– those with **priority signs**, who should be given priority in the queue so that they can be assessed and treated without delay*

*– **non-urgent cases**, who have neither emergency nor priority signs*

Emergency signs include:

- obstructed or absent breathing
- severe respiratory distress
- central cyanosis
- signs of shock (cold hands, capillary refill time longer than 3 s, high heart rate with weak pulse, and low or unmeasurable blood pressure)
- coma (or seriously reduced level of consciousness)
- convulsions
- signs of severe dehydration in a child with diarrhoea (lethargy, sunken eyes, very slow return after pinching the skin or any two of these)

Children with these signs require **immediate** emergency treatment to avert death.

Priority signs include:

- **T**iny infant: any sick child aged < 2 months
- **T**emperature: child is very hot
- **T**rauma or other urgent surgical condition
- **P**allor (severe)
- **P**oisoning (history of)
- **P**ain (severe)
- **R**espiratory distress
- **R**estless, continuously irritable or lethargic
- **R**eferral (urgent)
- **M**alnutrition: visible severe wasting
- **O**edema of both feet
- **B**urns (major)

The **priority signs** identify children who are at higher risk of dying. These children should be **assessed without unnecessary delay**.
If a child has one or more emergency signs, don't spend time looking for priority signs.

FIRST CHECK FOR EMERGENCY SIGNS IN THREE STEPS:

• Step 1. Check whether there is any airway or breathing problem; start immediate treatment to restore breathing. Manage the airway and give oxygen.

• Step 2. Quickly check whether the child is in shock or has diarrhoea with severe dehydration. Give oxygen and start IV fluid resuscitation. In trauma, if there is external bleeding, compress the wound to stop further blood loss.

• Step 3. Quickly determine whether the child is unconscious or convulsing. Give IV glucose for hypoglycaemia and/or an anti-convulsant for convulsing.

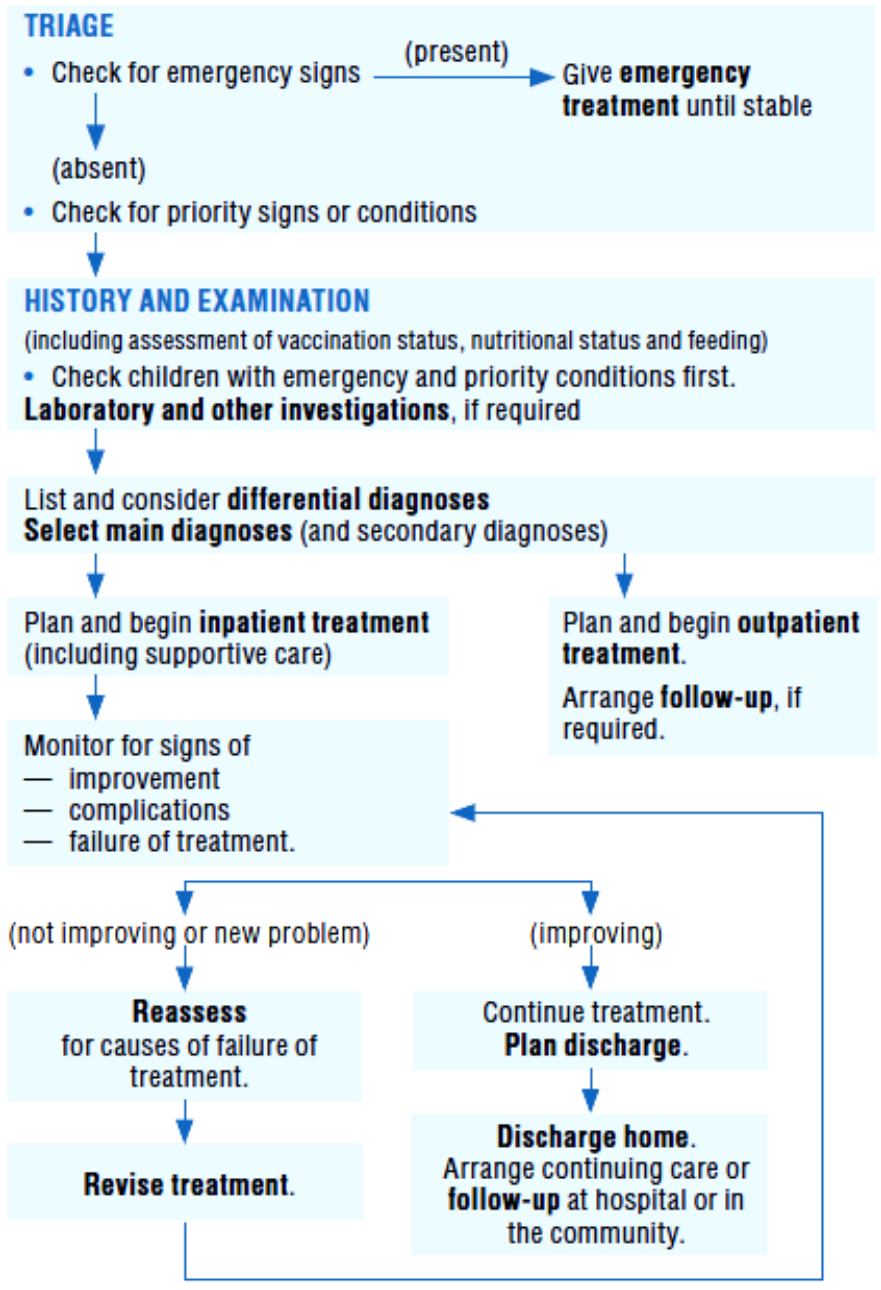
IF EMERGENCY SIGNS ARE FOUND:

• Call for help from an experienced health professional if available, but do not delay starting treatment. Stay calm and work with other health workers who may be required to give the treatment, because a very sick child may need several treatments at once. The most experienced health professional should continue assessing the child, to identify all underlying problems and prepare a treatment plan.

• Carry out emergency investigations (blood glucose, blood smear, haemoglobin [Hb]). Send blood for typing and cross-matching if the child is in shock, appears to be severely anaemic or is bleeding significantly.

• After giving emergency treatment, proceed immediately to assessing, diagnosing and treating the underlying problem.

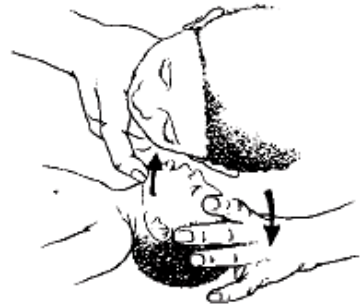
Chart. Stages in the management of a sick child admitted to hospital: key elements



Assessment of emergency signs

■ **Assess the airway and breathing (A, B)**

- *Does the child's breathing appear to be obstructed?* Look at the chest wall movement, and listen to breath sounds to determine whether there is poor air movement during breathing. Stridor indicates obstruction.
- *Is there central cyanosis?* Determine whether there is bluish or purplish discoloration of the tongue and the inside of the mouth.
- *Is the child breathing?* Look and listen to determine whether the child is breathing.
- *Is there severe respiratory distress?* The breathing is very laboured, fast or gasping, with chest indrawing, nasal flaring, grunting or the use of auxiliary muscles for breathing (head nodding). Child is unable to feed because of respiratory distress and tires easily.



Look, listen and feel for breathing

■ **Assess circulation (for shock) (C)**

Children in shock who require bolus fluid resuscitation are lethargic and have cold skin, prolonged capillary refill, fast weak pulse and hypotension.

- *Check whether the child's hand is cold*. If so, determine whether the child is in shock.
- *Check whether the capillary refill time is longer than 3 s*. Apply pressure to whiten the nail of the thumb or the big toe for 5 s. Determine the time from the moment of release until total recovery of the pink colour.
- *If capillary refill is longer than 3 s, check the pulse*. Is it weak and fast? If the radial pulse is strong and not obviously fast, the child is **not** in shock. If you cannot feel the radial pulse of an infant (< 1 year old), feel the brachial pulse or, if the infant is lying down, the femoral pulse. If you cannot feel the radialpulse of a child, feel the carotid. If the room is very cold, rely on the pulse to determine whether the child is in shock.
- *Check whether the systolic blood pressure is low for the child's age*. Shock may be present with normal blood pressure, but very low blood pressure means the child is in shock.

Normal blood pressure ranges in infants and children

Age	Systolic blood pressure
Premature	55–75
0–3 months	65–85
3–6 months	70–90
6–12 months	80–100
1–3 years	90–105
3–6 years	95–110

■ **Assess for coma or convulsions or other abnormal mental status (D)**

- *Is the child in coma?* Check the level of consciousness on the 'AVPU' scale:
  A alert,
  V responds to **v**oice,
  P responds to **p**ain,
  U unconscious.
- *Is the child convulsing?* Are there spasmodic repeated movements in an unresponsive child?

If the child is not awake and alert, try to rouse the child by talking or shaking the arm. If the child is not alert but responds to voice, he or she is lethargic. If there is no response, ask the mother whether the child has been abnormally sleepy or difficult to wake. Determine whether the child responds to pain or is unresponsive to a painful stimulus. If this is the case, the child is in coma (unconscious) and needs emergency treatment.

Common Acute and Emergent Problems in Pediatrics

Common complaints leading to acute care visits for potential emergencies include:

- ***fever***
- ***altered mental status***
- ***seizures***
- ***respiratory distress*** *(see "The Respiratory System")*
- ***vomiting****, and* ***abdominal pain*** *(see "The Digestive System")*

CASE STUDY

An 8-month-old girl is brought to the emergency department with a 2-day history of fever and increased fussiness. She is irritable but consolable by parents. Her parents believe that her immunizations are up-to-date, but they do not have the immunization record with them. On examination, she has a rectal temperature of 39.5°C (103.1°F). The rest of the physical examination is within normal limits, and no source for the fever is apparent.

Questions

1. What are the serious bacterial infections in febrile newborns and infants?
2. What has been the effect of conjugated vaccines against Haemophilus influenzae and Streptococcus pneumoniae on the incidence of bacteremia and meningitis in febrile newborns and infants?
3. What are the challenges in differentiating between serious and benign febrile illnesses in young children?
4. What diagnostic studies are recommended in the evaluation of febrile newborns, infants, and children?
5. When are empiric antibiotics indicated and when should febrile newborns and infants be hospitalized?

FEVER is the most common reason for a sick child visit. Most fevers are the result of self-limited viral infections. However, pediatricians need to be aware of the age-dependent potential for **serious bacterial infections** (e.g., urinary tract infections, sepsis, meningitis, pneumonia, dysentery, osteoarticular infection). During the first 2-3 mo of life, the neonate is at risk for **sepsis** caused by pathogens that are uncommon in older children. These organisms include group B streptococcus, Escherichia coli, Listeria monocytogenes, and herpes simplex virus. In neonates, the history must include maternal obstetric information and the patient's birth history. Risk factors for sepsis include maternal group B streptococcus colonization, prematurity, chorioamnionitis, and prolonged rupture of membranes. If there is a maternal history of sexually transmitted infections during the pregnancy, the differential diagnosis must be expanded to include those pathogens. Septic infants can present with lethargy, poor feeding, grunting respirations, and cool or mottled extremities, in addition to fever (or hypothermia). Infants with fever, irritability, and a bulging fontanel should be evaluated for **meningitis**. As the infant matures beyond 3 mo of age, the bacterial pathogens that usually cause bacteremia, sepsis, and meningitis are Streptococcus pneumoniae, Haemophilus influenzae type b, and Neisseria meningitidis. Urosepsis secondary to an E. coli urinary tract infection also needs to be considered. Immunization against some serotypes of S. pneumoniae has markedly reduced the occurrence of occult bacteremia and serious infections caused by that organism, as has immunization against H. influenzae type b. These remain potential concerns in those children not fully immunized against these pathogens. Other ailments that manifest with fever include **septic arthritis and osteomyelitis, juvenile idiopathic arthritis,** and **Kawasaki disease**. Children with a septic joint generally present with only 1 joint that is painful and often have pseudoparalysis of that joint. In contrast, patients with juvenile rheumatoid arthritis may present with pain, stiffness, swelling, and warmth of several joints. The diagnosis of Kawasaki disease should be considered if the patient meets the diagnostic criteria for this illness although some patients may have an atypical or incomplete presentation.

For patients presenting with ALTERED MENTAL STATUS, the pediatrician should inquire about the presence of other symptoms, such as fever or headache. Screening questions should be asked regarding feeding changes, medications in the household, or the possibility of trauma. Parents will often describe a febrile child as "lethargic," but further questioning will reveal a tired-appearing child who interacts appropriately when the child has defervesced. Febrile patients need to be differentiated from the lethargic patient who presents with sepsis or meningitis. Infants with meningitis or sepsis may have a history of irritability, inconsolability, poor feeding, grunting respirations, seizures, decreased urine output, and/or color changes such as pallor, mottling, or cyanosis. Patients with poisonings or inborn errors of metabolism can also present with lethargy, poor feeding, unusual odors, seizures, and/or vomiting. Nonaccidental trauma should always be considered in a lethargic infant. Older children may present with altered mental status as a result of meningitis/encephalitis, trauma, or ingestions. Children with meningitis may have a history of fever and complaints of neck pain; other associated symptoms can include rash, headache, photophobia and/or vomiting. Children with ingestions can present with other abnormal neurologic symptoms such as ataxia, slurred speech, seizures, or characteristic constellations of vital sign changes and other physical findings (toxidromes).

SEIZURES IN CHILDHOOD

A seizure is an episode of neurologic dysfunction caused by abnormal neuronal activity that results in a sudden change in behavior, sensory perception, or motor activity.

Seizure disorder is a general term that is usually used to include any one of several disorders including epilepsy, febrile seizures, and possibly single seizures and seizures secondary to metabolic, infectious, or other etiologies (e.g., hypocalcemia, meningitis).

> *The term "**epilepsy**" refers to recurrent, unprovoked seizures from known or unknown causes. The term "ictus" describes the period in which the seizure occurs, and the term "**postictal**" refers to the period after the seizure has ended but before the patient has returned to his or her baseline mental status.*
>
> *A **focal or partial seizure** consists of abnormal neuronal firing that is limited to 1 hemisphere or area of the brain and that manifests itself as seizure activity on 1 side of the body or one extremity. These seizures are classified as simple partial if there is no change in mental status or complex partial if there is some degree of impaired consciousness.*
>
> *A **generalized seizure** consists of abnormal electrical activity involving both cerebral hemispheres that causes an alteration in mental status. Traditionally, the patient with 30 minutes of continuous seizure activity or a series of seizures without a return to full consciousness is defined as being in **status epilepticus (SE).** Newer definitions suggest that SE is defined by duration of 5 continuous minutes of generalized seizure activity or 2 or more separate seizure episodes without return to baseline.*

Clinical Presentation

1. *Motor Changes*
   - Repetitive non-purposeful movements
   - Staring
   - Lip-smacking
   - Falling down without cause
   - Stiffening of any or all extremities
   - Rhythmic shaking of any or all extremities

. If these motor behaviors can be interrupted by verbal or physical stimulation, they are not considered seizure activity.

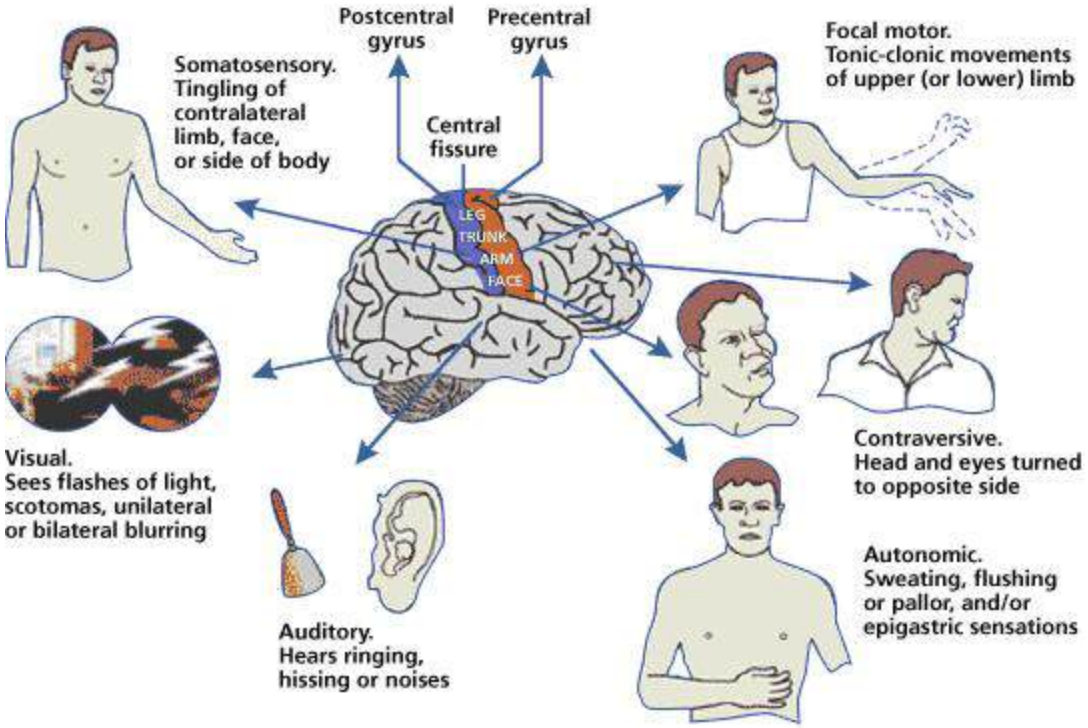
Seizure activity *cannot* be interrupted with verbal or physical stimulation

2. *Sensory and Autonomic*

Common sensory symptoms described by a parent or caregiver may include: feeling nauseous, odd or peculiar; losing bowel or bladder control; or feeling numb or tingling anywhere on the body. Also, experiencing odd smells or sounds may be noted.

3. *Consciousness*

- Consciousness is the usual alertness or responsiveness the child demonstrates.
- Parents/caregivers may report or you may observe the child to have:
  - Baseline alertness
  - Diminished level of consciousness
  - Unresponsive and unconscious



Events That Mimic Seizures

A careful history from a reliable witness is essential in evaluating a child who presents with a reported seizure. Since witnessing a seizure can create a highly charged emotional environment, it is important to identify characteristics of seizures and consider conditions which may mimic seizures in order to make an accurate diagnosis. **Breath holding, apnea, syncope, and dizziness** should be considered as alternative diagnoses. **Tics, myoclonus, rigors, and shuddering** can be misinterpreted as changes in motor control. Psychogenic and pseudoseizures are clinically similar to epileptic seizures, but do not result from an abnormal electrical discharge from the brain.

PEDIATRIC SEIZURES

- *Febrile seizure (SFS)*
- *Acute symptomatic seizures (eg. in meningitis, electrolyte imbalance, hypoglicemia)*
- *Unprovoked seizures (UnS)*
- *Status epilepticus (SE)*

➢ FEBRILE SEIZURE

Febrile seizures are the most common seizure disorder in childhood, affecting less than five percent of children between the ages of six months and five years.

- Caused by the increase in the core body temperature greater than 100.4F or 38C
- Threshold of temperature which may trigger seizures is unique to each individual
- Can occur within the first 24 hours of an illness
- Can be the first sign of illness in 25 - 50% of patients

Febrile seizures are a benign condition. For a febrile seizure diagnosis to be established, the child must have no other history of seizures, metabolic diseases, or signs of central nervous system infections, such as meningitis.

Febrile Seizure: Two Types

Simple Febrile	Complex Febrile
▪ 6 months – 5 years of age ▪ Febrile before, during or after seizure ▪ Generalized seizure lasting less than 15 minutes, and ▪ Occurs once in a 24-hour period	▪ 6 months – 5 years of age ▪ Febrile before, during or after seizure ▪ Prolonged (lasting more than 15 minutes), ▪ Focal seizure, or ▪ Occurs more than once in 24 hours

Febrile Seizure: Prehospital Assessment	Febrile Seizure: Prehospital Management

▪ Assess A,B,C's
▪ Assess neurological status (D = Disability using AVPU)
▪ Obtain seizure history from a dependable witness:
  ▪ How long was the seizure?
  ▪ What did it look like (movements, eye deviation)?
  ▪ History of previous seizures (child and family)?
  ▪ Does the child have a current illness/fever?
  ▪ Any indications of trauma or abuse?
  ▪ Length of postictal phase?
▪ List current medications
  ▪ Include any antipyretics given (time and dose)
	▪ Monitor A, B, C, D's
	▪ Position with C-Spine protection (if trauma)
	▪ Follow seizure and aspiration precautions (per protocol)
	▪ Physical exam
	▪ Check blood glucose
	▪ If blood glucose ≤ 60 mg/dL, treat as appropriate

Simple Febrile Seizure: Diagnostic Testing
(Evidence-based recommendations from the 2011 AAP Subcommittee on Febrile Seizures)

Lumbar Puncture	EEG	CT/MRI
• A lumbar puncture should be performed in any child who presents with a (simple febrile) seizure and a fever and has meningeal signs and symptoms (e.g., neck stiffness, Kernig and/or Brudzinski signs) or in any child whose history or examination suggests the presence of meningitis or intracranial infection. • In any infant between 6 and 12 months of age who presents with a (simple febrile) seizure and fever, a lumbar puncture is an option when: - *the child is considered deficient in Haemophilus influenza type b or Streptococcus pneumoniae immunizations (i.e., has not received scheduled immunizations as recommended) or* - *when the immunization status cannot be determined because of an increased risk of bacterial meningitis.* • A lumbar puncture is an option in the child who presents with a (simple febrile) seizure and fever and is pretreated with antibiotics, because antibiotic treatment can mask the signs and symptoms of meningitis.	Should *not* be performed in a neurologically healthy child. Results are *not* predictive of recurrence or development of epilepsy	Not indicated

FEBRILE SEIZURE: TREATMENT

In general, antiepileptic therapy, continuous or intermittent, is not recommended for children with one or more simple febrile seizures. Parents should be counseled about the relative risks of recurrence of febrile seizures and recurrence of epilepsy, educated on how to handle a seizure acutely, and given emotional support. If the seizure lasts for >5 min, then acute treatment with **diazepam, lorazepam, or midazolam** is needed. Rectal diazepam is often prescribed to be given at the time of recurrence of febrile seizure lasting >5 min. Alternatively, buccal or intranasal midazolam may be used and is often preferred by parents. Intravenous benzodiazepines, phenobarbital, phenytoin, or valproate may be needed in the case of febrile status epilepticus. If the parents are very anxious concerning their child's seizures, intermittent oral diazepam can be given during febrile illnesses (0.33 mg/kg every 8 hr during fever) to help reduce the risk of seizures in children known to have had febrile seizures with previous illnesses. Intermittent oral nitrazepam, clobazam, and clonazepam (0.1 mg/kg/day) have also been used. Other therapies have included intermittent **diazepam** prophylaxis (0.5 mg/kg administered as a rectal suppository every 8 hr), **phenobarbital** (4-5 mg/kg/day in 1 or 2 divided doses), and valproate (20-30 mg/kg/day in 2 or 3 divided doses). In the vast majority of cases it is not justified to use these medications owing to the risk of side effects and lack of demonstrated long-term benefits, even if the recurrence rate of febrile seizures is expected to be decreased by these drugs. Other antiepileptic drugs (AEDs) have not been shown to be effective. Antipyretics can decrease the discomfort of the child but do not reduce the risk of having a recurrent febrile seizure, probably because the seizure often occurs as the temperature is rising or falling.

SIMPLE FEBRILE SEIZURE: FAMILY EDUCATION

Here are some frequently asked questions parents/ caregivers may have prior to discharge:

- *Is my child brain damaged?*
  - There is no evidence of impact on learning abilities after seizure from SFS.
- *Will this happen again?*
  - If child is under 12 months of age at time of first seizure, recurrence rate is 50%
  - If child is greater than 12 months of age at time of first seizure, recurrence rate is 30%
  - Most recurrences occur within 6-12 months of the initial febrile seizure
- *Will my child get epilepsy?*
  - For simple febrile seizures, there is *no* increased risk of epilepsy
- *Why not treat for possible seizures or fever?*
  - Anticonvulsants can reduce recurrence. However potential side effects of medications outweigh the minor risk of recurrence
  - Prophylactic use of antipyretics does not have impact on recurrence

For complex febrile seizures, there is a *slight* increase in the risk of epilepsy.

- **Instruct parent/caregivers to prevent injury during a seizure:**
  - Position child while seizing in a side-lying position
  - Protect head from injury
  - Loosen tight clothing about the neck
  - Prevent injury from falls
  - Reassure child during event
  - *Do not* place anything in the child's mouth

Prior to discharge home…

- Educate regarding use of:
  - Thermometer
  - Antipyretics for fever management
  - When to contact 9-1-1 or ambulance
  - Identify Primary Care Provider for follow-up appointment and stress importance of follow-up

➢ FIRST UNPROVOKED SEIZURE

A first unprovoked seizure is a seizure that occurs without an immediate precipitating event in the absence of fever. Occurrence suggests a potential underlying neurological condition that predisposes the child to recurrent seizures. An unprovoked seizure may be due to a yet undiagnosed brain abnormality, genetic or cryptogenic. Predictors of recurrence include having an abnormal EEG, an abnormal neurologic exam, and a prolonged first seizure.

Presentation may be consistent with partial seizure, generalized tonic-clonic or tonic seizure. To be classified as first unprovoked, **there must be no history of previous seizures and no immediate precipitating cause such as fever, trauma or infection.**

Lumbar puncture is only indicated if there are other symptoms that suggest a diagnosis of meningitis.

If neuroimaging is recommended, MRI is the modality of choice. Due to the potential need for sedation with MRI, this study is usually done on an outpatient basis. Children in whom an MRI may be indicated include those under the age of one year, children with significant cognitive or motor impairment, or those with unexplained abnormalities on their neurological exam. Also, consider an MRI if the seizure is focal in nature and in those with an abnormal EEG.

An emergent CT scan should be considered as part of the Emergency Department management if the child has significant cognitive or motor impairment, exhibits a focal deficit not resolving or has not returned to baseline, or if the MRI is not available.

An EEG should be obtained on all children who have had a nonfebrile seizure. This can be arranged as an outpatient and should be done in coordination with a neurologist, preferably a pediatric neurologist, who will then read the EEG. The EEG results will help predict the risk of recurrence, classify the seizure type, and influence decisions about further imaging studies.

Here are some frequently asked questions parents may have prior to discharge:

- *How likely is it that my child will have seizures again?*
  The risk of recurrence relates to the underlying etiology and EEG results (normal or abnormal). The majority of children who experience an unprovoked seizure will have few or no recurrences. Approximately 10% will go on to have additional seizures regardless of therapy.
- *Is there a risk of dying from the seizure if we don't start medication today?*
  Sudden unexpected death is very uncommon (usually related to an underlying neurologic handicap rather than seizure activity). There are no studies showing treatment after a first seizure alters the small risk of sudden death.

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YEREVAN STATE MEDICAL UNIVERSITY AFTER MKHITAR HERATSI
DEPARTMENT OF PEDIATRICS №1

The

Pediatric Cardiovascular System

Grigoryan M E

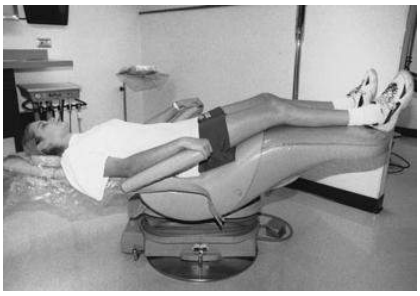
2017

Contents

COMPETENCIES

You must…

Know	Be able to	Appreciate
• How children with cardiovascular diseases present • The normal and abnormal development of CVS	• Carry out a good cardiac examination • Differentiate clinically between innocent and pathological murmurs • Take a good history to differentiate syncope from other fits, faints and funny turns	• That finding a murmur may induce parental anxiety



A 14-year-old girl has a sudden loss of consciousness during dental treatment. What to do?

You are evaluating a 16-year-old boy for preparticipation sports screening. What are the most common causes of sudden death during competitive exercise?

A 15-year-old boy presents with a 10-year history of uncontrolled DM type 1, hypertension, dyspnea, generalized edema, normal ejection fraction, and low-grade proteinuria. Does he have heart failure?

A 12-year-old patient presents with premature atrial contractions on an ECG. There is no significant murmur and a normal examination. Doppler velocity by echo is 2 m/s.Would you let him participate in all sports?

1. Cardiovascular Health and Risk in Children and Adolescents

Types of Heart Disease Observed in Children and Adolescents

➢ **All heart diseases, known in adults, may occur in children, but the structure of childhood cardiovascular morbidity is different. For example, congenital heart disease is more common in childhood versus myocardial infarction commonly seen in adults.**

Most cardiac disease in childhood is congenital. **Congenital heart disease (CHD)** is the type of heart disease that a baby is born with. In reality, it is a defect, or abnormality of the heart or blood vessels near the heart, and not a disease, so the term "congenital heart defect" is often used.
Cardiovascular defects occur in 0.8% of live births. However, this estimate does not include:

- affected fetuses who die *in utero*. In autopsy studies, the incidence of congenital heart disease in the fetus approaches 30/1,000. In patients with diagnosed intrauterine cardiac malformations, 17.5% do not survive to birth. Of those who do survive to delivery, 30% die before 1 year of life.
- relatively "silent" abnormalities, such as a bicuspid aortic valve, small atrial septal defects, or subtly abnormal mitral valves, which may present as heart disease in adults or may be noted as incidental findings on postmortem examination.

Two major types of acquired heart disease in children are rheumatic heart disease and Kawasaki disease.

- **Rheumatic heart disease** is the most common acquired heart disease in many countries of the world, especially in developing countries. It is responsible for about 233,000 deaths annually. The worst affected areas are sub-Saharan Africa, south-central Asia, the Pacific and indigenous populations of Australia and New Zealand.
- **Kawasaki disease** is a systemic vasculitis, with a predilection for coronary arteries. It is the leading cause of acquired heart disease among children in developed countries. It predominantly affects children under the age of 5 years.

➢ **Ideal cardiovascular (CV) health* in childhood is related to lower prevalence of cardiovascular disease (CVD) factors in adulthood** (*Laitinen TT et al, 2012*).

** Ideal CV health was defined as the simultaneous presence of four beneficial health measures that included never having tried smoking, body mass index <85 percentile, physical activity at goal levels, and diet consistent with current dietary recommendations.*

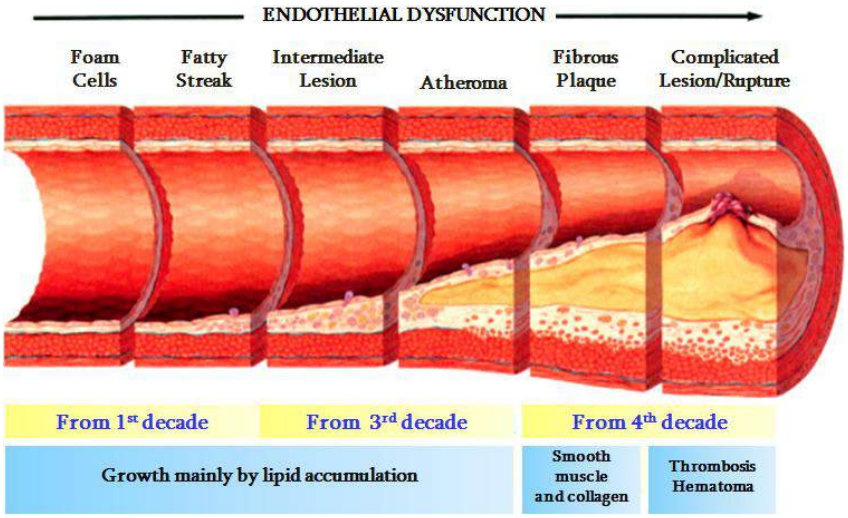
In adults, the increased cardiovascular risk associated with factors such as high blood pressure, elevated lipid levels, smoking, a sedentary lifestyle, and being overweight is well known; however, it is important to recognize that these risk factors often develop and begin to detrimentally affect health in childhood (table 1).

Table 1 Known risk factors for CVD

(From *Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. Summary Report, 2012*)

Family history	**Blood pressure**	**Metabolic syndrome**
Age	**Lipids**	**Inflammatory markers**
Gender	**Overweight (BMI 85th-95th)/Obesity (BMI ≥ 95th)**	**Perinatal factors**
Nutrition/Diet	**Diabetes mellitus and other predisposing conditions**	**(eg. prematurity, maternal smoking)**
Physical inactivity	**(eg. Kawasaki disease, chronic inflammatory diseases,**	
Tobacco exposure	**HIV)**	

Unhealthy behavioral habits begin at a very early age. lack of exercise and a poor diet lead to excess weight and obesity, which in turn contribute to raised blood pressure, glucose intolerance, hyperlipidemia, atherosclerosis.



- More than 42 million children under the age of 5 years are ***overweight***, predisposing them to the early onset of cardiovascular conditions. Close to 31 million of these are living in developing countries (*WHO, 2013*).
- More than 10% of adolescents currently use ***tobacco products***, with almost 25% of these children lighting their first cigarette before the age of 10 (*The Global Youth Tobacco Survey*).
- Pathological changes in the cardiovascular system, such as the development of fatty streaks and ***early atherosclerotic lesions***, occur in children as young as 5 years of age and that these changes are correlated with the presence of risk factors (*The Korean War study by Enos; The Bogalusa Heart Study; The Pathological Determinants of Atherosclerosis in Youth Study*).

For most children, atherosclerotic vascular changes are minor and can be minimized or even prevented with adherence to a healthy lifestyle. However, in some children, the atherosclerotic process is accelerated because of the presence of identifiable risk factors (eg, obesity and hypertension) and/or specific diseases that are associated with premature CVD (eg, diabetes mellitus and Kawasaki disease).

The co-occurrence of the risk factors that increase a patient's chance of developing heart disease and type 2 diabetes is called ***metabolic syndrome.*** Among the variety of diagnostic criteria, the most used are that from WHO and that of NCEP-ATP III (US National Cholesterol Education Program - Adult Treatment Panel III) (table 2).

Table 2 Definition of metabolic syndrome (MS) in children and adolescents

(From *Silveira LS et al. Metabolic Syndrome: Criteria for Diagnosing in Children and Adolescents. Endocrinol Metab Synd 2: 118, 2013*)

		WHO	NCEP-ATP III
AGE			12-19
MS DIAGNOSIS		3 or more risk factors	3 or more risk factors
RISK FACTORS	**Obesity**	BMI >95th percentile	Waist circumference ≥ 90th percentile
	Glycemic homeostasis	• Hyperinsulinemia *prepubertal (stage 1 Tanner) > 15 mU/L* *pubertal (stages 2-4 Tanner) > 30 mU/L* *post-pubertal (stage 5 Tanner) ≥ 20 mU/L* • Fasting glucose ≥ 6.1 mM/L • Glucose intolerance (at 120 min ≥ 7.8 mM/L)	Fasting glucose ≥ 110 mg/dL
	Elevated Arterial Pressure	SBP >95th percentile for age, sex and stature	SBP/DBP ≥90th percentile for age and sex and stature
	Dyslipidemia	• TG > 105 mg/dL for < 10 years > 136 mg/dL for ≥ 10 years • HDL < 35 mg/dL • Total cholesterol > 95th percentile	• TG ≥ 110 mg/dL • HDL ≤ 40 mg/dL

Pediatric and Young Adult Sudden Cardiac Arrest (SCA)

There are many cardiac disorders predisposing to pediatric and young adult SCA (table 3). Excluding the Sudden Infant Death Syndrome (SIDS), which has an incidence around 1–1.5/1000 infants, sudden death in a young person is a rare event. The incidence of SCA in the young is widely debated, ranging from 0.5 to 20 per 100,000 person-years. In comparison, adults experience SCA at a rate of 135 per 100,000 person-years.

Approximately 20–25% of the deaths occur during sports [Gajewski, Saul, 2010]. SCA ranges from 1:160,000 to 1:300,000 deaths per year in competitive athletes 12 to 35 years of age [Meyer et al, 2012]. High risk groups include males, black athletes, and basketball athletes. The most common finding in this cohort at autopsy after sudden cardiac death is **autopsy negative sudden unexplained death** - AN–SUD [(Harmon et al, 2015].

A number of **risk markers** are used to assess the magnitude of risk for sudden death: *family history of premature sudden death; extreme LV hypertrophy (>30 mm); nonsustained ventricular tachycardia on Holter electrocardiographic recording; unexplained (not neurally mediated) syncope; and blood pressure decrease or inadequate increase during upright exercise [European Heart Journal (2010) 31, 3084–3093].*

Table 3 Cardiac disorders predisposing to pediatric and young adult SCA

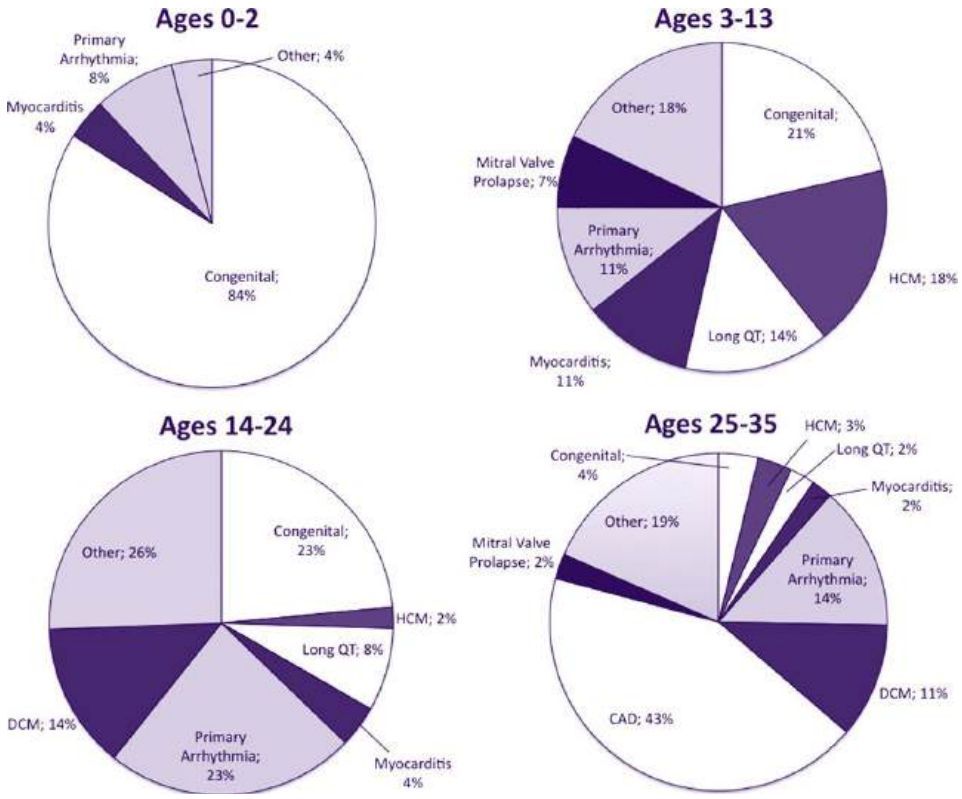
*[*From *American Academy of Pediatrics policy statement on sudden cardiac arrest in children. Pediatrics 2012;129;e1094]*

Structural/functional	Electrical	Other
1. Hypertrophic cardiomyopathy* 2. Coronary artery anomalies 3. Aortic rupture/Marfan syndrome* 4. Dilated cardiomyopathy or restrictive cardiomyopathy* 5. Myocarditis 6. Left ventricular outflow tract obstruction 7. Mitral valve prolapse 8. Coronary artery atherosclerotic disease 9. Arrhythmogenic right ventricular cardiomyopathy* 10. Postoperative congenital heart disease	11. Wolff-Parkinson-White (WPW) syndrome 12. LQTS* 13. Brugada syndrome* 14. Catecholaminergic polymorphic ventricular tachycardia* 15. Short QT syndrome* 16. Complete heart block	17. Drugs and stimulants; some prescription medications 18. Primary pulmonary hypertension* 19. Commotio cordis

* Familial/genetic

Fig. Detailed causes of cardiac arrest by age group [Meyer et al, 2012]

HCM – hypertrophic cardiomyopathy
DCM – dilated cardiomyopathy
CAD – coronary artery disease



2. Developmental Anatomy & Physiology of the Cardiovascular System

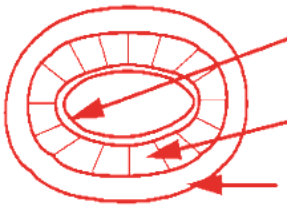
The cardiovascular system (CVS) is the first organ system to form and function in the developing embryo, at around the third week of gestation.
Congenital heart and vascular anomalies are borne from embryonic derangements that occur early in the developmental cycle. Several genetic derangements, drugs, alcohol, radiation, viruses, environmental factors, chemicals, folic acid deficiency, and others play a major role in the generation of cardiovascular anomalies.

Heart Development (Cardiogenesis)

Cardiac progenitor cells arise in the mesodermal layer and have the potential to form the major cell types of the heart (cardiomyocytes, smooth muscle, and endothelium/endocardium).

I. Formation of Tubular Heart

Heart development begins with the formation of two endocardial tubes which merge to form **the tubular heart**, through which blood eventually flows in a cranial direction.



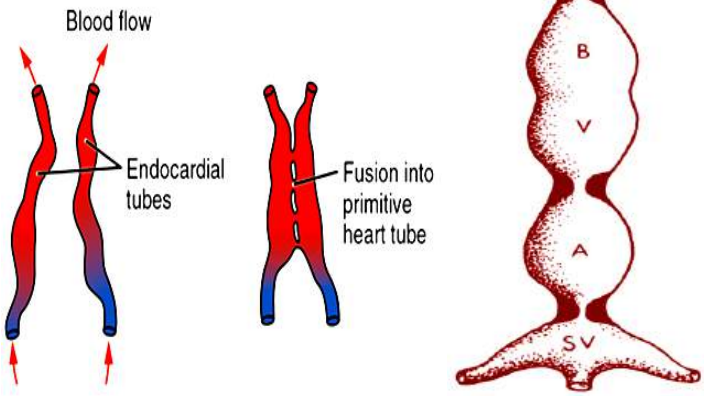
Endothelial tube

Cardiac jelly

Myoepicardial mantle

The mesenchyme surrounding the tube condenses to form the myoepicardial mantle (the future myocardium). Gelatinous extracellular matrix called **cardiac jelly** separates this mantle from the endothelial heart tube (the future endocardium).
In addition, a series of constrictions (sulci) divide the heart tube into sections: *sinus venosus; primitive common atrium; primitive ventricle; bulbus cordis; and truncus arteriosus.*

Primary hert tube



20 days 21 days 22 days

Truncus arteriosus → *will form the roots and proximal portion of the aorta and pulmonary artery*

Bulbus cordis → ***distal portion (conus cordis)*** *— will form the outflow tracts of both ventricles*

Bulbus cordis → ***proximal portion*** *— will form the RV*

Primitive ventricle → *will form the LV*

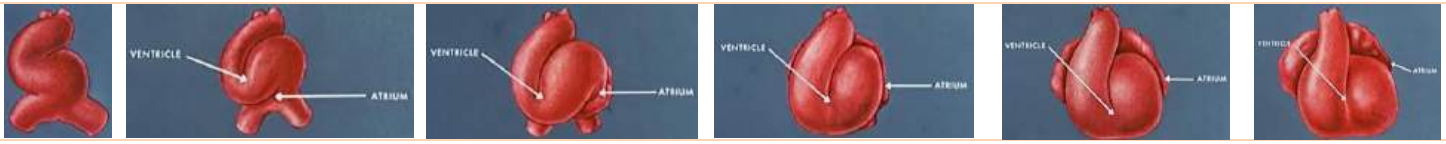
Primitive atrium → *will become the front parts of the left and right atria and their appendages*

Sinus venosus → *will develop into the posterior part of the right atrium, the sinoatrial node and the coronary sinus*

The heart is beating at Day 22. Contractions are of myocardic origin and are likened to peristalsis.

II. Looping of Heart Tube

The heart tube continues stretching and by day 23 **cardiac looping** begins. Under normal circumstances the tube **loops to the right (D-loop).**The cephalic portion curves in a frontal clockwise direction. The atrial portion starts moving in a cephalic ally and then moves to the left from its original position. This curved shape approaches the heart and finishes its growth on day 28.

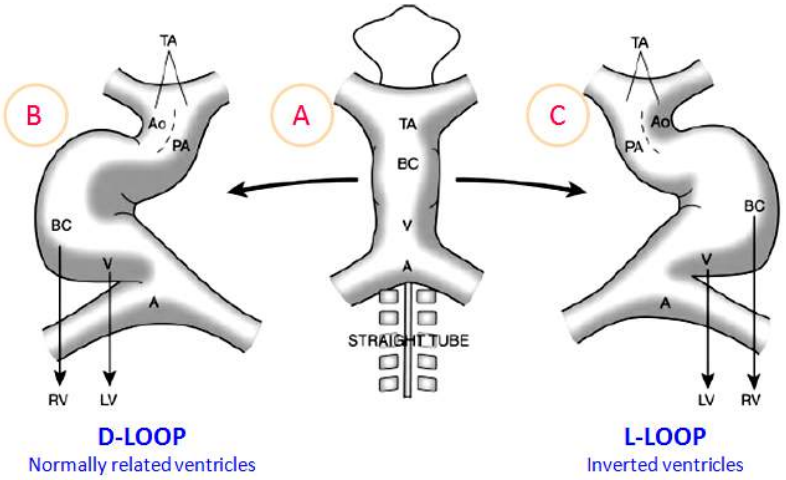


Cardiac looping represents the first visible sign of left-right asymmetry.
When cardiac looping is abnormal, **the ventricles are inverted (L-loop):** morphological right ventricle is on the left, and morphological left ventricle is on the right (situs inversus, heterotaxy).

Fig. Cardiac loop formation.

(A) Straight heart tube or preloop stage
(B) D -loop, with normally related ventricles
(C) L -loop, with inverted (mirror image) ventricles

A, atrium
Ao, aorta
BC, bulbus cordis
LV, morphological left ventricle
RV, morphologic right ventricle
PA, main pulmonary artery
TA, truncus arteriosus



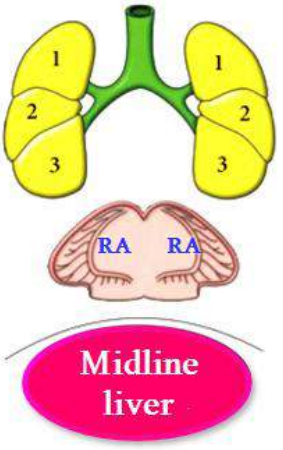
In **situs inversus**, the position of the visceral organs is reversed. The arrangement is a mirror image of the normal situs. The left lung is trilobed, and the right has two lobes. Pulmonary venous return is again to the left atrium but the left atrium is on the right side of the heart.

The majority of patients with ventricular inversion has **visceroatrial heterotaxy (also known as atrial isomerism):** lack of differentiation of right-sided and left-sided organs during fetal development.

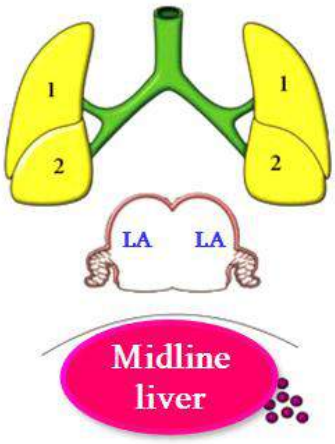
There are two subtypes:

- **Right atrial isomerism (bilateral right-sidedness)** is associated with absence of a spleen (asplenia), two right atria (RA), two right lungs, midline liver.
- **Left atrial isomerism (bilateral left-sidedness)** is associated with multiple splenic tissues (polysplenia) which may or may not be functional, two left atria (LA), two left lungs, midline liver.

In both cases the ventricles have either concordant or discordant position.

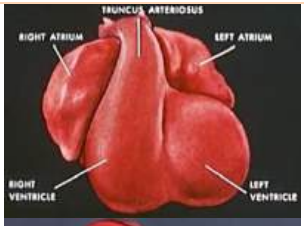


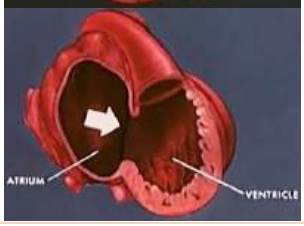
RIGHT ISOMERISM



LEFT ISOMERISM

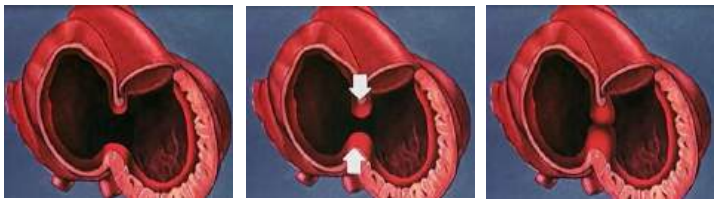
III. Development of Chambered Hearts (Cardiac Septation)





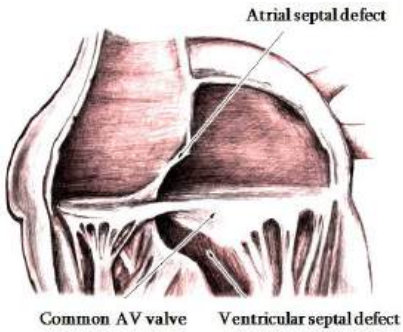
When looping is complete, the external appearance of the heart is similar to that of a mature heart; internally, the structure resembles a single tube, although it now has several bulges resulting in the appearance of primitive chambers.

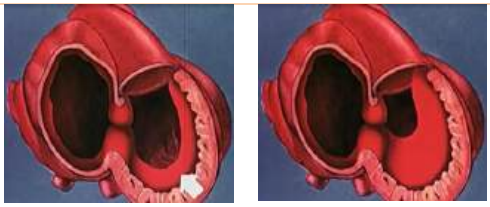
The common atrium (comprising both the right and left atria) is connected to the primitive ventricle (future left ventricle) via the **atrioventricular canal**. The primitive ventricle is connected to the bulbus cordis (future right ventricle) via the **bulboventricular foramen**. The distal portion of the bulbus cordis is connected to the truncus arteriosus via an outlet segment (the conus).



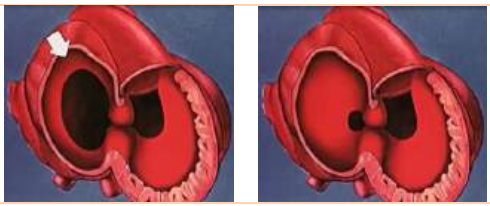
As the linear heart tube loops rightward, the **endocardial cushions** of the inflow and outflow tracts become adjacent to one another. These cushions consist of protrusions of cardiac jelly. Complete septation of the atrioventricular canal occurs with fusion of the endocardial cushions.

Failure of fusion of the superior and inferior endocardial cushions results in **complete atrioventricular canal defect** (also referred to as complete atrioventricular septal defect): the presence of both atrial and ventricular septal defects with a common AV valve.



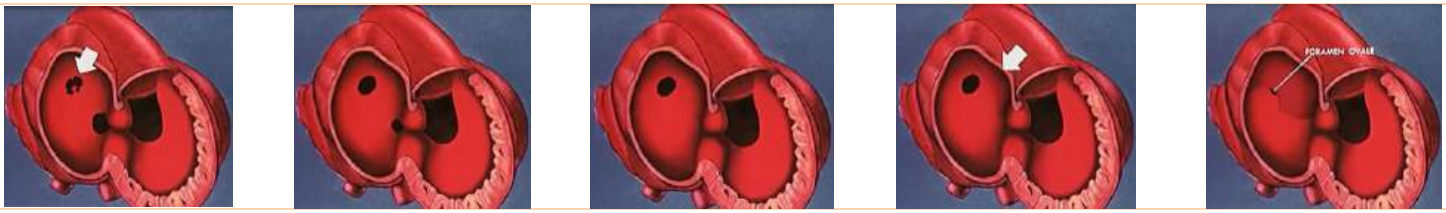


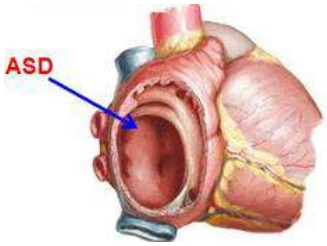
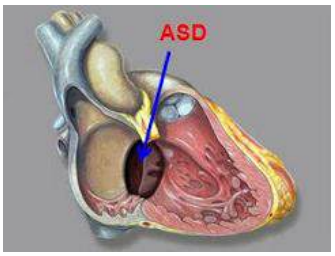
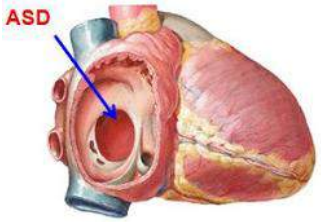
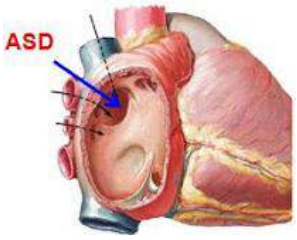
Septation of the ventricles begins at about embryonic day 25. A **muscular interventricular septum** begins to grow superiorly from the ventricular floor between the presumptive right and left ventricles. This septum stops short of the atrioventricular canal, leaving a space called the **interventricular foramen** which permits blood from both ventricles to exit via the conus cordis. **Ventricular septal defects (VSD)** can occur in any portion of the developing interventricular septum.



Septation of the atria begins at ≈30 days with growth of the septum primum downward toward the endocardial cushions. The orifice that remains is the **ostium primum**. The endocardial cushions then fuse and, together with the completed **septum primum**, divide the atrioventricular canal into right and left segments.

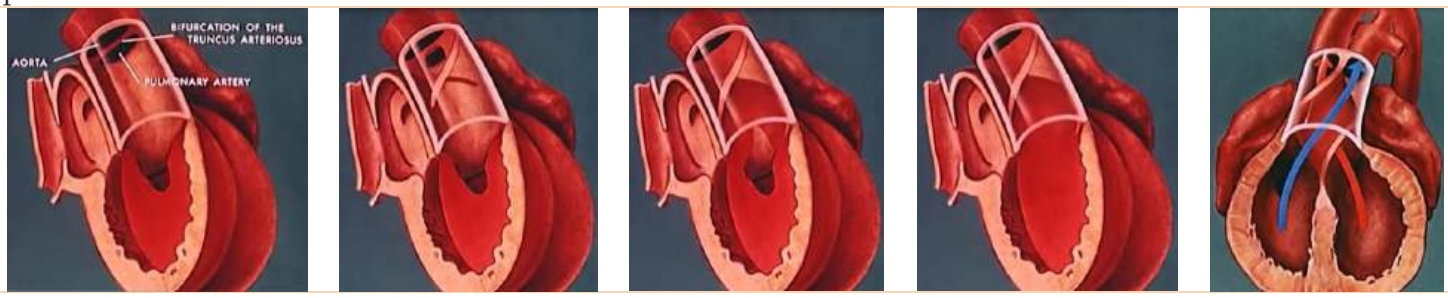
Before the foramen primum closes, a 2nd opening appears in the posterior portion of the septum primum, the **ostium secundum**, and it allows a portion of the fetal venous return to the right atrium to pass across to the left atrium. Finally, the **septum secundum** grows downward, just to the right of the septum primum. Together with a flap of the septum primum, the ostium secundum forms the **foramen ovale**, through which fetal blood passes from the inferior vena cava to the left atrium.



Failure of atrial septation results in atrial septal defects (ASD).			
Complete absence of the atrial septum results in a **common atrium**	Lack of fusion of the septum primum with the absent endocardial cushion results in **ostium primum ASD**	A combination of excessive resorption of the septum primum and large foramen ovale defects results in **ostium secundum ASD**	Defects in the sinus venosus portion of the atrial septum **results in sinus venosus ASD**
			

IV. Conotruncal septation

The cardiac outflow tract consists of the muscularized conus and the adjacent truncus arteriosus, collectively termed the **conotruncus**. The **outlet or conotruncal septum** develops from ridges of cardiac jelly, similar to the atrioventricular cushions. These ridges fuse to form **a spiral septum** that brings the future pulmonary artery into communication with the anterior and rightward right ventricle and the future aorta into communication with the posterior and leftward left ventricle.



Abnormalities in septation or incomplete spiraling of the conotruncus result in several different defects. For example:

- Failure of septation of the truncus arteriosus results in **persistent truncus arteriosus.**
- If the truncus septates, but fails to rotate, **transposition of the great arteries** (TGA) occurs (communication of the right ventricle with the aorta and left ventricle with the pulmonary artery).
- If the conotruncal septum fails to fuse with the muscular ventricular septum, **perimembranous VSD occurs.** Unlike muscular ventricular septal defects, this does not have the potential to close spontaneously after birth.
- If the conotruncal septum is deviated to the PA side, **tetralogy of Fallot** occurs. The conotruncal septum between the aorta and pulmonary artery forms in tetralogy of Fallot, but because of malalignment of the great vessels, the conotruncal septum fails to connect to the muscular ventricular septum, resulting in a ventricular septal defect.

Fig. TGA (2) with associated patent foramen ovale (1) and patent ductus arteriosus (3)

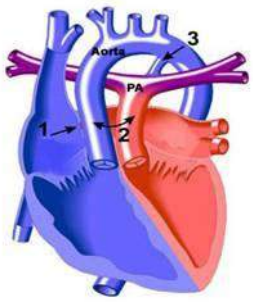
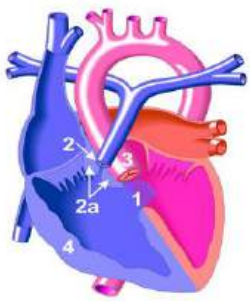


Fig. Tetralogy of Fallot (TOF)

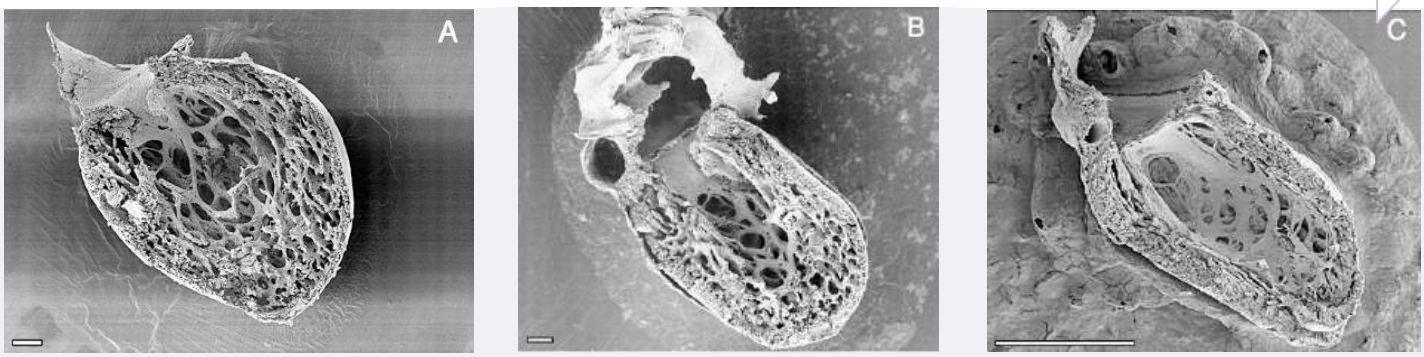
1- VSD
2- pulmonary valve stenosis
2a- stenosis of the outflow tract (infundibular stenosis) from the right ventricle into the pulmonary artery
3- overriding aorta
4- right ventricular hypertrophy



Development of Myocardium

During development, the majority of the heart muscle is a sponge-like meshwork of interwoven myocardial fibers. As normal development progresses, these trabeculated structures undergo significant compaction that transforms them from spongy to solid. The compaction process coincides with the invasion of the epicardial coronary arteries and vascularization of the myocardium. Failure of the process of compaction results in **non-compaction cardiomyopathy (NCC), also called spongiform cardiomyopathy** - a rare congenital cardiomyopathy that affects both children and adults.

Fig. The process of compaction [Sedmera et al, 2008]

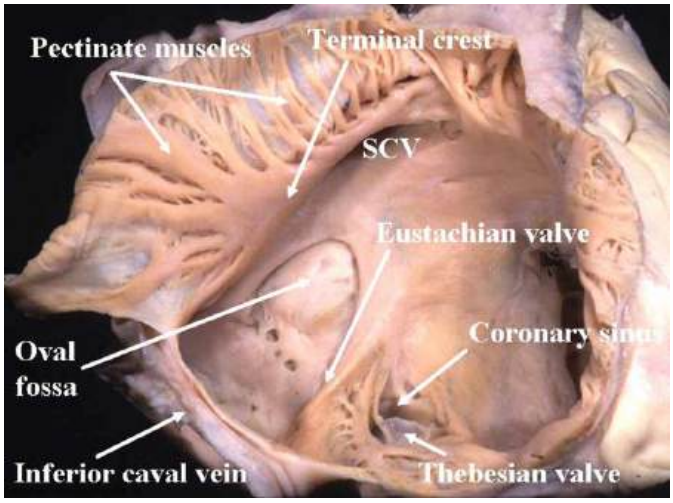
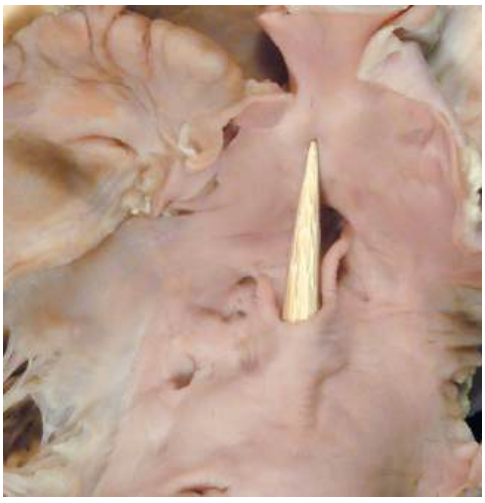


At 6 weeks
Abundant fine trabeculations

At 8 weeks
Trabeculae start to solidify

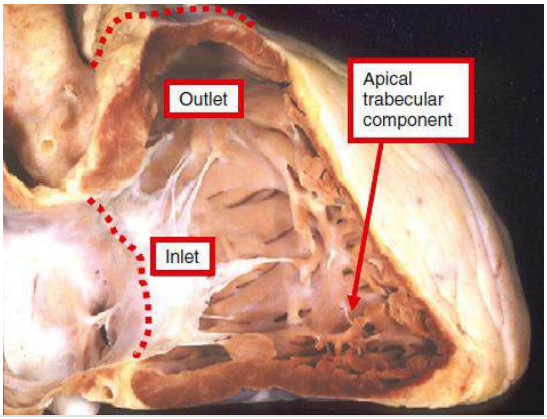
Early fetal period
Compaction almost completed

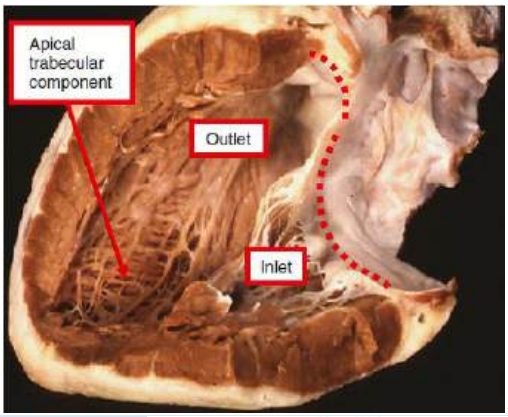
Anatomic Hallmarks of Cardiac Chambers

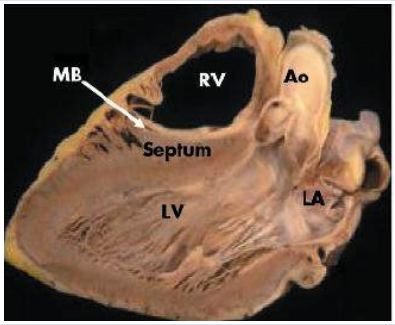
The morphologically right atrium (RA)	The morphologically left atrium (LA)
*The best hallmarks: limbus of the fossa ovalis, and ostium of the IVC**	*The best and most specific hallmark is the valve of the fossa ovalis*
	

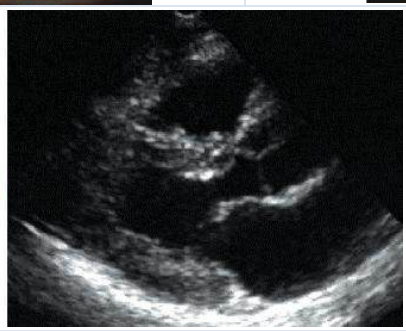
** Since some patients with congenital heart disease may have absence of the typical left atrial (**valve of the fossa ovalis**) and right atrial (**limbus of the fossa ovalis**) characteristics, the next best marker for the right atrium is the **ostium of the IVC**. The suprahepatic IVC nearly always connects directly to the right atrium. This rule is particularly useful in the evaluation of complex heterotaxy patients.*

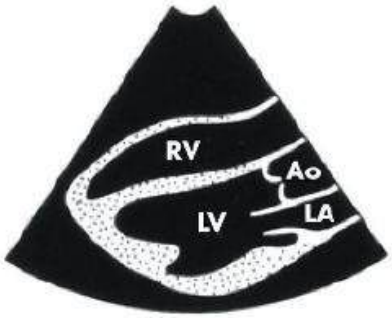
The morphologically right ventricle (RV)	The morphologically left ventricle (LV)
Inlet *Tricuspid valve* **Apical trabecular component** *Course apical trabeculations* **Outlet (right ventricular outflow tract - RVOT)** – *a muscular tube (infundibulum), which connects to the pulmonary artery*	**Inlet** *Mitral valve* **Apical trabecular component** *Fine apical trabeculations* **Outlet (left ventricular outflow tract - LVOT)** – *consists partially of muscular, partially of fibrous tissue. Dorsally it is incomplete, so that the mitral and aortic valves are connected to each other by fibrous tissue.*



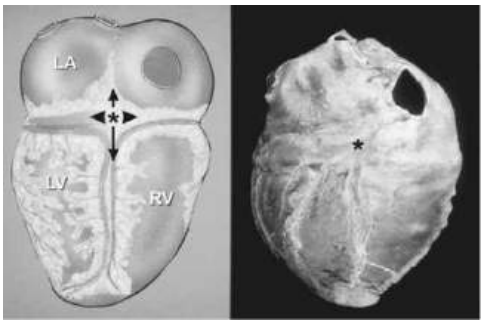






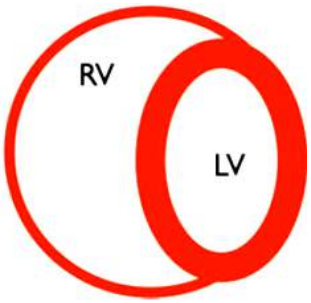


The most reliable anatomic feature that distinguishes the normal right ventricle from the left ventricle is the level of insertion of AV valve insertion at cardiac crux (*): the tricuspid valve is always lower than the mitral valve and always enters a morphological RV. *The other patterns are not reliable in many forms of congenital heart disease.*



The right and left ventricular pressures are nearly equal *in utero* (the foramen ovale allows equalization of preload of the right and left ventricles). After the 31st week of gestation until term, the right ventricle of the fetus gains myocardial mass because it pumps against the high resistance of the small muscular pulmonary arteries. The left ventricle, on the other hand, pumps against the low resistance of the placenta's blood vessels. At birth the mass difference between the right and left ventricles is a ratio of 1 to 1.3 (while, in adults the right ventricle muscle mass is approximately one-sixth that of the left ventricle because of different loading conditions).

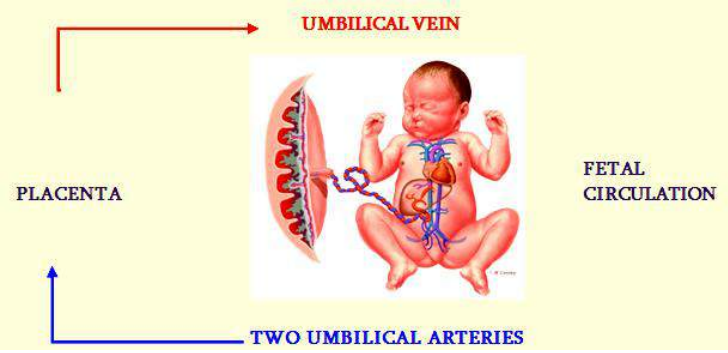
*The right ventricle, being **thin walled** and the most anterior structure, is more commonly ruptured than the other chambers in the accidents.*



Fetal Circulation

The fetal and maternal circulations are connected to the **placenta**, which provides the fetus with nutrition and oxygen and removes waste metabolites and carbon dioxide.

A single umbilical vein carries oxygenated blood from the placenta to the fetus and **two umbilical arteries** carry non-oxygenated blood from the fetus to the placenta.



- **The umbilical vein** enters the liver, where it joins with the **portal sinus**. Some of this blood is shunted directly to the inferior vena cava through the **ductus venosus**, while some enter the right and left portal veins and flow into the hepatic parenchyma.
- The inferior vena cava blood enters the right atrium, and approximately 40% is diverted to the left atrium through the **foramen ovale**. Most of the blood crossing the foramen ovale corresponds to the stream of well-oxygenated blood in the inferior vena cava coming from the ductus venosus.
- In the left atrium, this blood mixes with a relatively small quantity of pulmonary venous blood, enters the left ventricle, and then proceeds to the coronary circulation and vessels supplying the head, neck, and upper extremities.

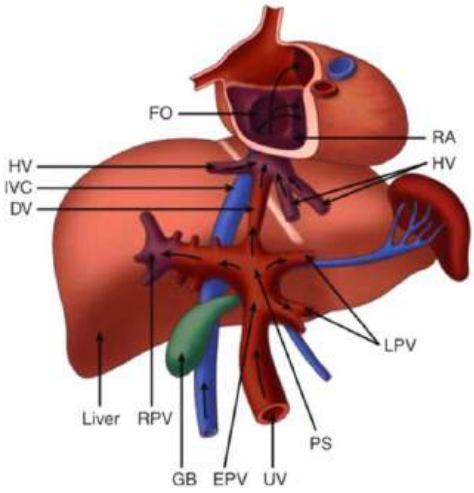


Fig. Subdiaphragmatic venous system in the fetus [Mavrides et al. 2001].

Note the constriction of the ductus venosus which

(1) acts to control the amount of blood entry into the heart and into the liver (This sphincter closes when a uterine contraction renders the venous return too high, preventing a sudden overloading of the heart.)

(2) creates a streaming effect directing oxygen-rich blood preferentially across the foramen ovale to the left atrium.

DV ductus venosus, EPV extrahepatic portal vein, GB gall bladder, FO foramen ovale, HV hepatic vein, IVC inferior vena cava, LPV left portal vein, PS portal sinus, RA right atrium, RPV right portal vein, UV umbilical vein

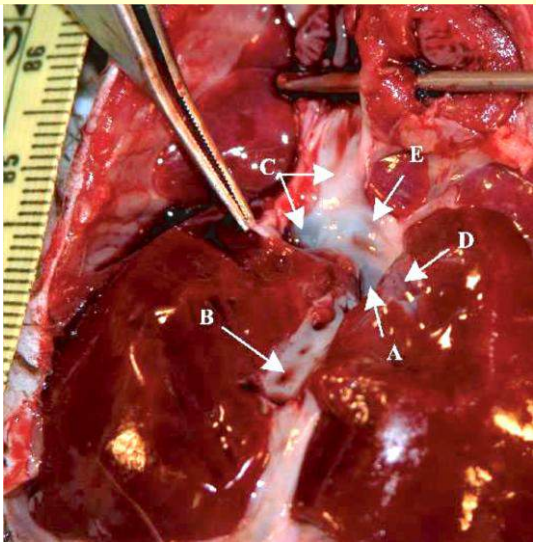


Fig. Frontal (anterior view) of the ductus venosus and central venous system in a rhesus fetus at term [Tchirikov et al. 2005].

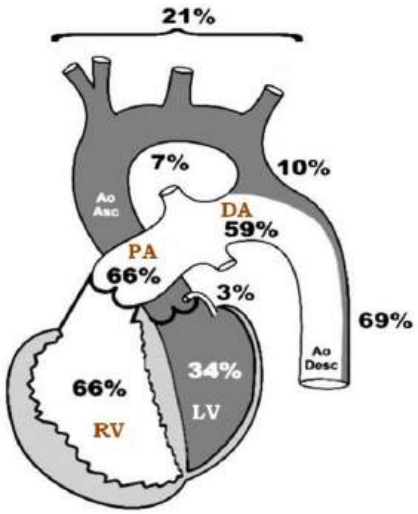
The foramen ovale is marked by metal wire with a diameter of 2 mm.

A, ductus venosus; B, umbilical vein; C, abdominal and cardiac portions of the inferior vena cava; D, left branch of the portal vein; E, collectus venosus.

In the fetus the most oxygenated blood is supplied to the liver, head and upper extremities. Thus, they grow faster than other organs!

- Blood entering the right atrium from the superior vena cava joins with the remaining (60%) blood in the inferior vena cava, which corresponds mainly to the less-oxygenated bloodstream from the distal inferior vena cava (fetal lower body). This blood enters the right ventricle[1].
- From the right ventricle, the blood is ejected into the pulmonary artery. Because the pulmonary arterial circulation is vasoconstricted, only approximately 5% of right ventricular outflow enters the lungs. The major portion of this blood bypasses the lungs and flows right-to-left through the **ductus arteriosus** (DA) into the descending aorta to perfuse the lower part of the fetal body, including providing flow to the placenta via the 2 umbilical arteries (approximately 65% of descending aortic blood flow returns to the placenta).
- **In the fetus, ≈ 60% of total fetal cardiac output is derived from the right ventricle, while 40% is being derived from the fetal left ventricle[2].**

Fig. The distribution of blood flow in the heart and major vessels of the fetal sheep[2] [Somoza, 2007]

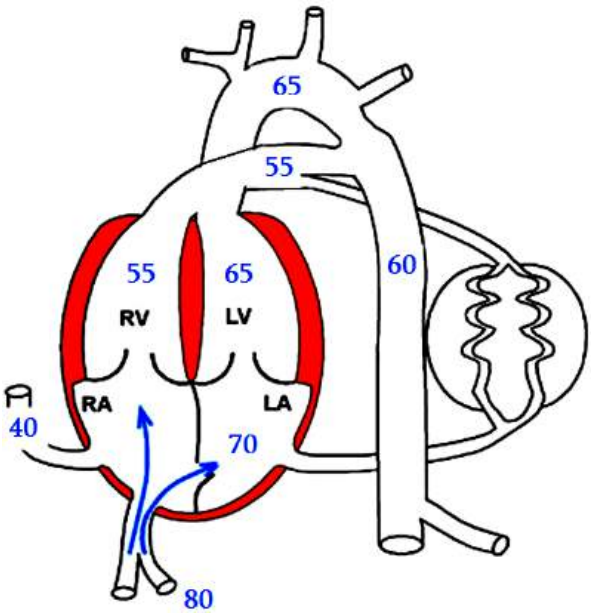


1 *There is a flap of tissue at the right atrial–inferior vena caval junction - **the Eustachian valve**. The leftward and superior position of the Eustachian valve directs 95% of blood flow caudally from the superior vena cava away from the foramen ovale and toward the tricuspid valve.*

2 ***The distribution of blood flow in the fetus*** *is generally described as a percentage of combined ventricular output (CVO), which is the combined output of left and right ventricles. The estimated cardiac output of the human fetus (553 mL/kg/min^{-1}) is higher than that of sheep (450 mL/kg/min–1). In addition, the right and left ventricular outputs are more similar in the human compared with the sheep [De Smedt et al. 1987]. The ratio of the right-to-left ventricular outputs decreases with advancing gestation, from 1.3 at 15 weeks to 1.1 at 40 weeks. These data are consistent with the fact that the larger human brain requires a higher left ventricular output than the brain of the sheep.*

- **There are 5 components of venous return in the fetus:** the upper body systemic venous return via the superior vena cava - SVC (PO_2 = 12 to 14 mm Hg, O_2 saturation = 40%); the lower body systemic venous return, via the inferior vena cava - IVC (O_2 saturation = 70%); the placental return, also via the IVC (PO_2 = 32 to 35 mm Hg, O_2 saturation = 80%); the coronary venous return, primarily via the coronary sinus (O_2 saturation ≈ 20%); and the pulmonary venous return, via the pulmonary veins (O_2 saturation = 45%).
- Despite the fact that over 90% of combined venous return drains exclusively into the right atrium, the differential streaming, in association with the foramen ovale, which shunts blood from the right atrium into the left, allow for **the left ventricle to receive a large amount of relatively highly saturated (O_2 saturation = 65%) blood and the right ventricle to receive primarily poorly oxygenated blood (O_2 saturation = 55%).** Besides, the foramen ovale allows equalization of preload of the right and left ventricles.

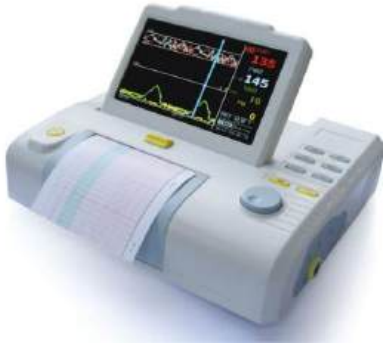
Fig. Oxygen saturation in the heart chambers and major vessels of the fetus



The least saturated blood in the fetus is in the coronary sinus and the superior vena cava, the oxygen having been used by the head and brain or the myocardium.

ASSESSMENT OF FETAL HEART RATE AND RHYTHM

The fetal heart rate (FHR) can be monitored by cardiotocography (electronic fetal monitor), and doppler ultrasonography.



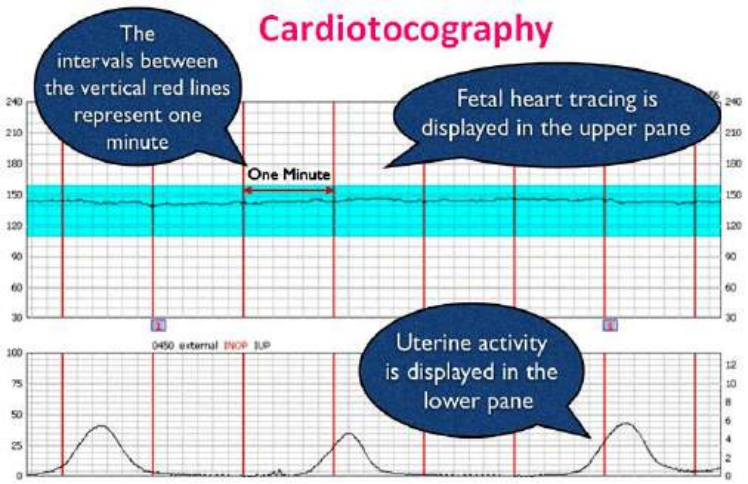
Although the myocardium begins to contract rhythmically by 3 weeks after conception (from spontaneously depolarizing myocardial pacemaker cells in the embryonic heart) it is first visible on sonography around 6 weeks of gestation. The FHR is then usually around 100 to 120 beats per minute (bpm). With further growth and maturation of the conduction system, including definition of the sinoatrial node as the primary cardiac pacemaker with its highest intrinsic rate of spontaneous depolarisation, there is a subsequent increase in the rate to 170 bpm by 9–10 weeks. The rise in heart rate is followed by a decrease to 150 bpm by 14 weeks, likely as a consequence of increasing parasympathetic control and improved myocardial contractility. By 20 weeks the average fetal heart rate is 140 bpm with a gradual decrease to 130 (110-150) bpm by term.

The normal fetal heart rate (FHR) pattern is characterized by:

- **a baseline frequency of between 110 and 150 bpm**
- **presence of periodic accelerations (increased FHR)**
- **a normal heart rate variability with a bandwidth of between 5 and 25 bpm**
- **episodic decelerations (decreased FHR) caused by a a vagal nerve reflex as a result of fetal head compression by the uterine contraction (such as during labor).**

The FHR pattern is abnormal when one or more of the following features are observed:

- a baseline frequency of below 110 or above 150 beats per minute,
- absence of accelerations for more than 45 minutes,
- decreased or absent FHR variability
- the existence of repeated variable or late decelerations.



Fetal hypoxemia can have a direct depressing effect on the function of the central nervous system and fetal myocardium, which can result in decrease or loss of fetal heart rate variability.

Doppler ultrasound provides a non-invasive method for the study of fetal hemodynamics.

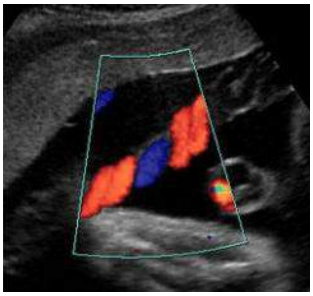


Fig. Ultrasound image with color Doppler showing the umbilical cord, red umbilical arteries and blue umbilical vein

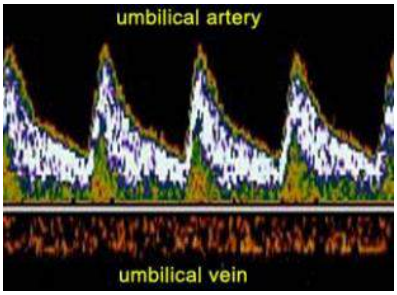


Fig. Normal flow velocity waveforms from the umbilical vein (bottom) and artery (top) at 32 weeks of gestation

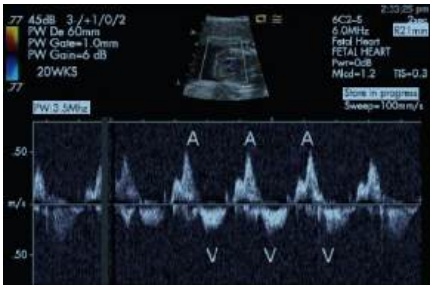


Fig. Doppler assessment of fetal rhythm with simultaneous sampling of the left ventricular inflow (A: flow during atrial systole) and outflow (V: ventricular outflow)

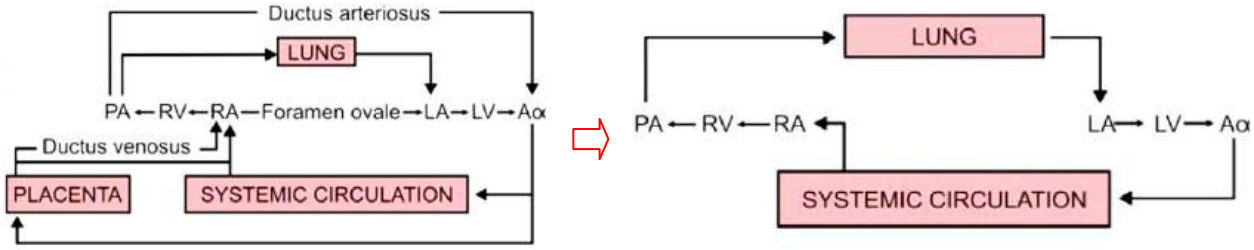
Circulatory Changes after Birth

Changes in the cardiovascular system at birth are caused by cessation of placental blood flow and the beginning of respiration.

I. Shunts at all the three levels are closed.

Closure of the ductus venosus	Closure of the ductus arteriosus	Closure of the oval foramen
- occurs shortly after that of the umbilical arteries and vein. Hence, blood from the placenta may enter the newborn for some time after birth.	*- closure by contraction of its muscular wall occurs almost immediately after birth (it is induced by oxygen). Complete anatomical obliteration by proliferation of the intima is thought to take 1 to 3 months.* *Because of closure of the ductus arteriosus, the amount of blood flowing through the lung vessels increases rapidly. This, in turn, raises pressure in the left atrium. Simultaneously, pressure in the right atrium decreases as a result of interruption of placental blood flow.*	*- is caused by an increased pressure in the left atrium, combined with a decrease in pressure on the right side: the septum primum is pressed against the septum secundum. During the first days of life, however, this closure is reversible. Crying by the baby creates a shunt from right to left, which accounts for cyanotic periods in the newborn. Constant apposition gradually leads to fusion of the two septa in about 1 year. In 20% of individuals, however, perfect anatomical closure may never be obtained (**patent foramen ovale**).*

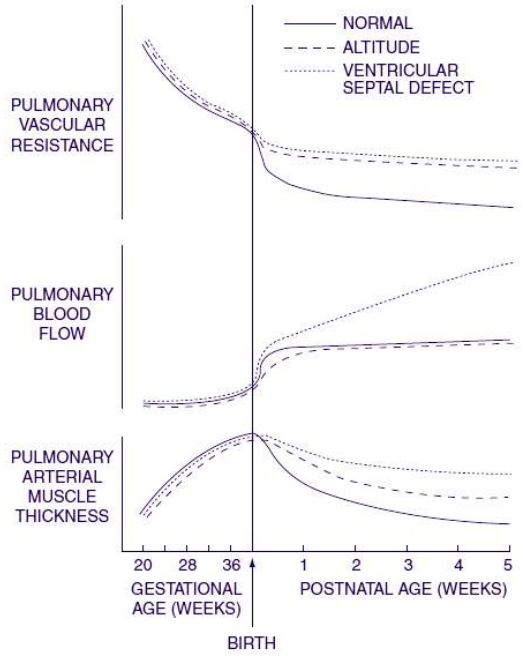
II. The circulation changes from parallel to series.
Separate ventricular output occurs (not combined).



- As pulmonary vascular resistance falls immediately at delivery and during the first few weeks of life, pulmonary blood flow increases and pulmonary arterial muscle thickness decreases.
- Systemic vascular resistance increases as there is no placental circulation. Blood vessels lengthen and thicken in response to increased pressures.

Approximately 24 hours after birth, a normal infant's mean pulmonary arterial blood pressure should decrease to about half of systemic arterial pressure. It takes anywhere from 2 to 6 weeks for the pulmonary arterial blood pressure to reach adult levels.

Children living at elevation have been shown to have higher mean pulmonary artery pressures as compared to those living at sea level. This increase in pulmonary pressure is even more exacerbated with exercise. This may have a role in explaining the relatively increased risk of persistence of the PDA in children living at altitude.



The failure of the normal circulatory transition after birth is called **P**ersistent **F**etal **C**irculation (**PFC**) or **P**ersistent **P**ulmonary **H**ypertension of the **N**ewborn (**PPHN**). This is most commonly associated with the following etiologies [Teng RJ, Wu TJ. 2013]:

- *acute pulmonary vasoconstriction in meconium aspiration syndrome, neonatal respiratory distress syndrome, pneumonia etc*
- *hypoplasia of the pulmonary vascular bed*
- *constriction, or premature closure of the ductus arteriosus in utero, which can occur after exposure to nonsteroidal anti-inflammatory drugs (NSAIDs) (eg, ibuprofen, naproxen) during the third trimester.*

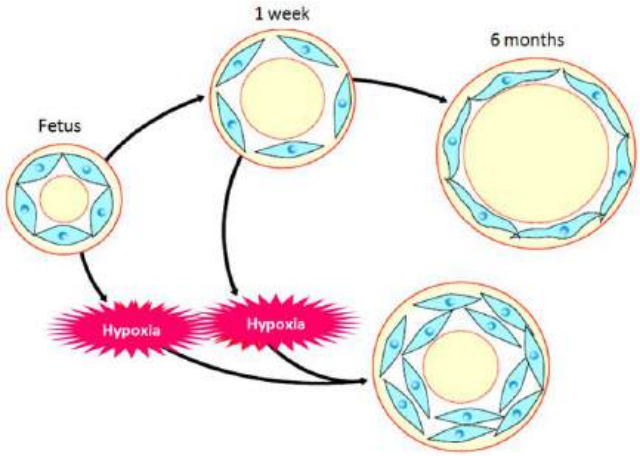


Fig. Diagram showing postnatal structural changes and the effect of chronic hypoxia on pulmonary arteries [Gao Y, Raj JU. 2011]

Failure of the ductus arteriosus to close within 48-96 hours of postnatal age results in a left to right shunt across the ductus and overloading of the pulmonary circulation.

The various factors contributing to an increased incidence of patent ductus arteriosus (PDA) in preterms include:

- Increased sensitivity of the ductus to prostaglandins as compared to term neonates
- Higher incidence of hypoxia and acidosis
- Higher incidence of *neonatal respiratory distress syndrome*
- Defective smooth muscle migration resulting in compromised anatomical closure
- Excessive fluid administration

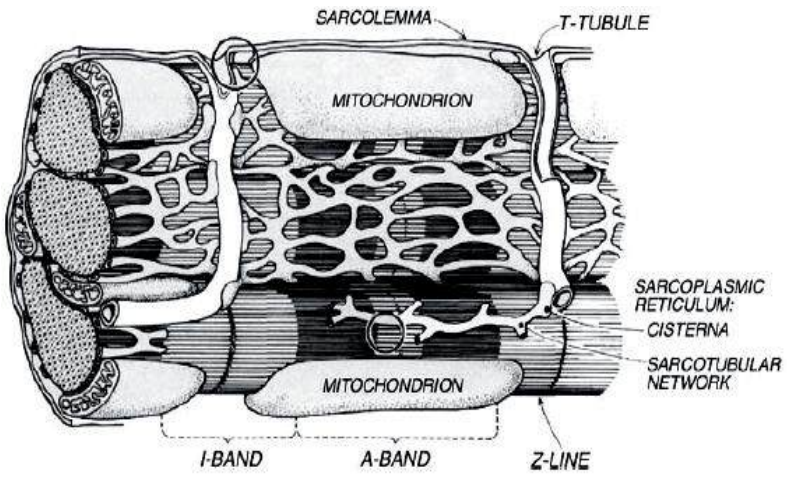
CASE

A 1-week-old neonate is brought to the emergency department by the paramedics limp and pale. His parents report that he had been doing well until the past day when he started feeding poorly. His breathing became more labored per parents. In the emergency department, the patient is intubated and given multiple normal saline boluses because of poor perfusion.

*Some forms of congenital heart disease (such as hypoplastic left heart syndrome and coarctation of the aorta) rely on blood flowing through the ductus arteriosus (**ductal-dependent lesions**) and thus will deteriorate rapidly when the ductus arteriosus closes within the first few weeks of life. These infants can present pale, have poor perfusion, and have a similar presentation to an infant with septic shock. While it would be important to work this patient up for septic shock and start antibiotics, congenital heart disease should be considered, in which case starting PGE to reopen a closed duct could be lifesaving.*

Cardiac Myocyte Structure During Development

Fig. Ultrastructure of the working mature myocardial cell [Katz, 1975]



Contractile proteins are arranged in a regular array of thick and thin filaments.

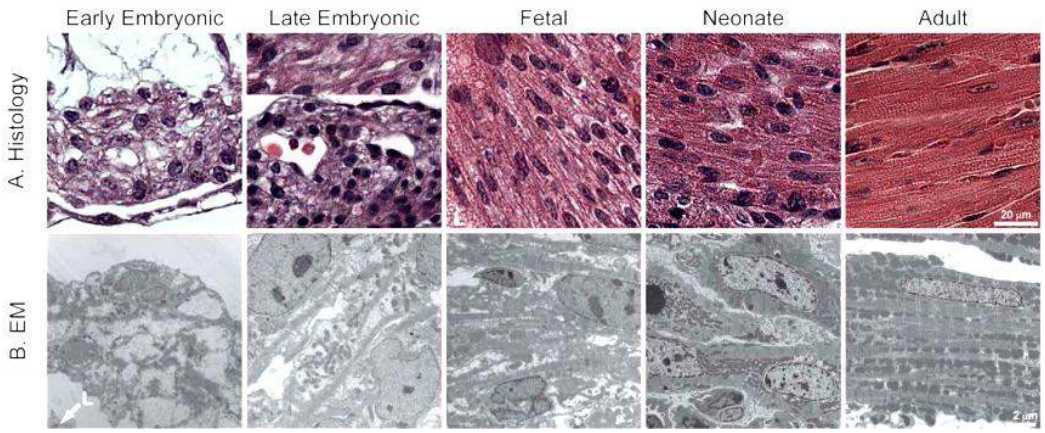
The A-band represents the region of the sarcomere occupied by the thick filaments into which thin filaments extend from either side. **The I-band** is occupied only by thin filaments that extend toward the center of the sarcomere from the Z-lines, which bisect each I-band.

The sarcomere, the functional unit of the contractile apparatus, is defined as the region between two Z-lines, and contains two half I-bands and one A-band.

The sarcoplasmic reticulum, a membrane network that surrounds the contractile proteins, consists of the sarcotubular network at the center of the sarcomere and the subsarcolemmal cisternae, which abut on the **transverse tubular system (t-tubules)** and the **sarcolemma**. The membrane surrounding the t-tubules is continuous with the sarcolemma, so that the lumen of the t-tubules carries the extracellular space toward the center of the myocardial cell.

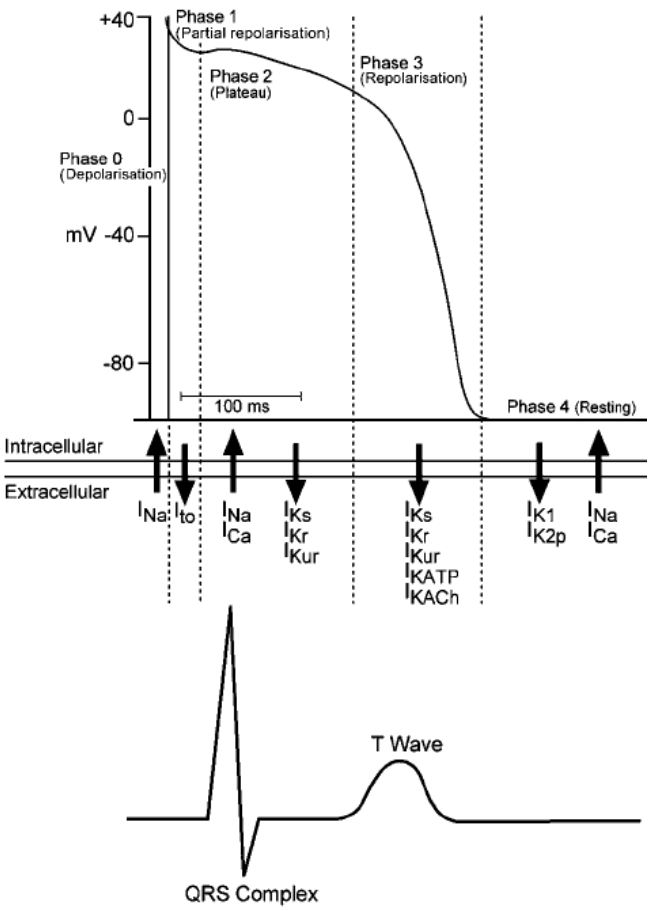
- The neonatal myocycte is quite different structurally from the mature myocyte.

Fig. Histology (A, hematoxylin and eosin stained) and electron micrographs (B, EM) of ventricular myocytes in early embryonic, late embryonic, fetal, neonatal, and adult hearts [Porter GA et al. 2011]

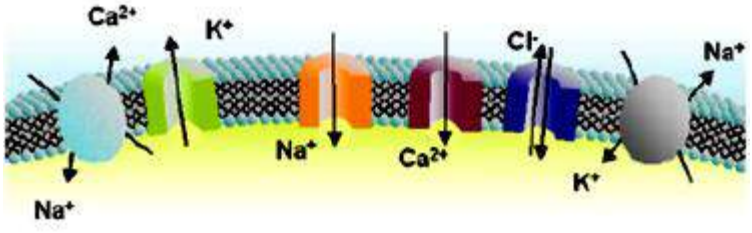


IMMATURE CARDIAC MYOCYTE	MATURE CARDIAC MYOCYTE
• Rounded, relatively short	• Slender and longer shape
• Quite disorganized intracellularly *- myofibrils are relatively less dense and are more likely to be situated along the periphery of the cell; the more central portion of the myocyte is made up of disorganized clumps of mitochondria and nuclei* *- lower number of sarcomeres with expression of fetal isoforms of contractile proteins*	• More organized ultrastructural appearance *- myofibrils are densely concentrated and are aligned in parallel with the axis of the cell, organized into alternating rows of mitochondria* *- increased number of sarcomeres with expression of different isoforms of contractile proteins (in some conditions re–expression of fetal proteins may occur)*
• Lower number and volume of mitochondria	• Increased number and volume of mitochondria with thickened cristae
• Predominant source of energy is glucose. *Neonatal cells have a higher glucose uptake than adult cells and are less sensitive to hypoxia.*	• Predominant source of energy are activated long chain fatty acids. *This is accompanied by a decrease in the amount of stored glycogen in the heart after birth.*

Cardiac Ion Channels During Development



Normal cardiac excitation and relaxation involves a delicate balance of complex dynamic interactions between ionic currents passing through a variety of membrane channels and the cellular environment.



Five major types of ion channels determine the transmembrane potential of a cell. Under physiologic conditions, calcium and sodium ions flow into the cell and depolarize the membrane potential, whereas potassium ions flow outward to repolarize the cell. Many genes are involved in maintaining this dynamic balance.

➢ **Major depolarizing currents & their corresponding genes**

I_{Na} (fast inward Na current)	*SCN5A*
$I_{Ca\text{-}L}$ (slow inward Ca current)	*CACNA1C*

➢ **Major repolarizing currents & their corresponding genes**

I_{Kr} (inward rapid rectifier)	*KCNH2/KCNE2*
I_{Ks} (inward slow rectifier)	*KCNQ1/KCNE1*

In general, the action potentials and resting potentials in cardiomyocytes are altered greatly during development. These electrophysiological changes are mainly produced by developmental changes in ion channels.

- **The fast sodium current** (mainly encoded by SCN5a and SCN1b), which is responsible for the upstroke of the AP, is markedly increased during development. There are few functional sodium channels present at the earliest stage, but the density increases progressively during development.
- The main **potassium current** in fetal ventricular myocytes is I_{Kr} (mainly encoded by KCNH2 and KCNE2), whereas I_{Ks} (encoded by KCNQ1 and KCNE1) is lacking or very small, though in the early neonate I_{Ks} becomes the dominant repolarizing current.
- In mature myocytes, the sarcoplasmic reticulum stores the most important source of calcium involved in the initiation of myocyte contraction. Calcium enters the myocyte during the action potential through L-type voltage-gated calcium channels. This calcium then activates the calcium-release channel (also called the ryanodine receptor), causing release of calcium from the sarcoplasmic reticulum. In immature cardiac myocytes, the function and organization of the sarcoplasmic reticulum is not yet to mature levels, and activation is more dependent on ***extracellular calcium influx through the L-type calcium channels***. These developmental differences further explain the extreme sensitivity of neonates to calcium channel antagonists. Indeed, some authors have suggested that calcium chloride is an effective inotrope in neonates after cardiopulmonary bypass.

Developmental Changes in Cardiac Systolic and Diastolic Functions

Two relatively simple but crucial relationships are essential to an understanding of cardiovascular physiology. These can be stated as follows:

(1) Cardiac Output = Stroke Volume × *Heart Rate*

(2) Stroke Volume ∝ *Preload, Afterload, and Contractility*

Cardiac output (CO) is an integrated indicator of overall cardiac function.

Although the cardiac output increases with increasing age and body weight, the cardiac output per kilogram falls (fig.).

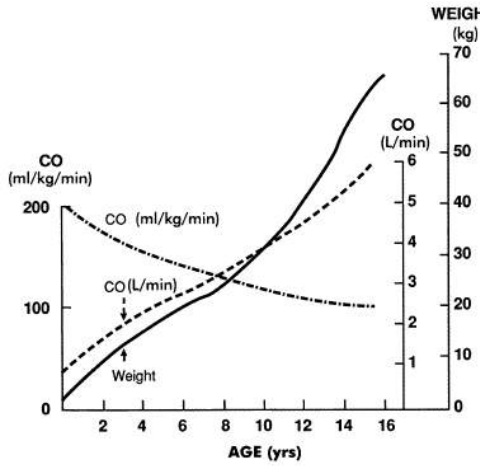


Fig. Developmental changes in cardiac output and cardiac index with regard to weight and age [Rudolph, 1974]

➢ Immature heart is characterized by **limited functional reserves:**

- *Decreased density of contractile elements results in **reduced contractility** at all cardiac muscle lengths. Additionally, at any given tension, the velocity of shortening is diminished compared to the adult.*
- *Higher percentage of noncontractile elements results in **reduced ventricular compliance** and therefore higher resting or passive tension, but lower ability to generate tension during contraction. This **limits the size of the stroke** volume. Cardiac output is therefore rate dependent, and bradycardia is associated with reduced cardiac output.*
  At all ages the right ventricle is more compliant than the left.
  Despite a relatively reduced ability to develop tension, the neonatal myocardial contractility can be augmented with inotropes.

➢ In normal infants, sympathetic cardiac control decreases with postnatal age and parasympathetic control over heart rate increases [Yiallourou SR et al, 2012].

➢ **The compensatory cardiovascular responses** of the child to states of decreased ventricular preload, impaired myocardial contractility, and alterations in vascular tone differ from those of adults. For example, in septic adults cardiac output is usually maintained despite myocardial dysfunction because of reduced systemic vascular resistance. There is a decreased ejection fraction but maintenance of cardiac output via ventricular dilatation and an increased heart rate. Hyperdynamic–low systemic vascular resistance sepsis or 'warm shock' is frequently encountered in adults. Septic children, however, most frequently present with a low cardiac output–high systemic vascular resistance or 'cold shock' picture. Children do not develop the ventricular dilatation seen in adults that maintains cardiac output and, whilst tachycardia contributes to compensatory mechanisms, the proportional increase in heart rate seen in adults is not sustainable in children. Because vasomotor regulatory mechanisms usually remain intact, the mainstay of treatment is aggressive fluid resuscitation and positive inotropes.

*Tachycardia is the child's principal means of maintaining an adequate CO in conditions of decreased ventricular preload, impaired myocardial contractility, or congenital heart disease categorized by an anatomic left-to-right shunt. **In addition to CO, the primary regulator of blood pressure is systemic vascular resistance (SVR). Children maximize SVR to maintain a normal blood pressure, even with significant decreases in their CO. Increases in SVR are due to peripheral vasoconstriction mediated by the sympathetic nervous system and angiotensin.** As a result, blood flow is redistributed from nonessential vascular beds such as the skin, skeletal muscles, kidneys, and splanchnic organs, to the brain, heart, lungs, and adrenal glands. Such regulation of vascular tone, either endogenously or exogenously via vasoactive medications, can normalize blood pressure independent of CO. **Therefore, in pediatric patients, blood pressure is a poor indicator of cardiovascular homeostasis.** The evaluation of heart rate and end-organ perfusion, including capillary re-fill, the quality of the peripheral pulses, mentation, urine output, and acid-base status, is more valuable than blood pressure in determining a child's circulatory status.*

3. Cardiovascular Assessment in Children

BASIC TOOLS IN ROUTINE EVALUATION OF PEDIATRIC CARDIAC PATIENTS

➢ HISTORY TAKING

I. Gestational and natal history

Maternal conditions	1. There is a high incidence of cardiomyopathy in infants born to mothers with diabetes. In addition, these babies have a higher incidence of structural heart defects (e.g., TGA, VSD, PDA). 2. Maternal lupus erythematosus and mixed connective tissue disease have been associated with a high incidence of congenital heart block in offspring. 3. Maternal infections - Maternal rubella infection during the first trimester of pregnancy commonly results in multiple anomalies, including cardiac defects. - Infections by cytomegalovirus, herpesvirus, and coxsackievirus B are suspected to be teratogenic if they occur in early pregnancy. Infections by these viruses later in pregnancy may cause myocarditis. - HIV infection (in illicit drug users) has been associated with infantile cardiomyopathy.
Maternal intake of medications during pregnancy	1. Several medications are suspected teratogens: amphetamines; anticonvulsants; angiotensin-converting enzyme (ACE) inhibitors (captopril, enalapril, lisinopril) and angiotensin II receptor antagonists (losartan); lithium; retinoic acid; progesterone and estrogen. 2. Excessive alcohol intake during pregnancy has been associated with CHD (fetal alcohol syndrome). 3. Although cigarette smoking has not been proved to be teratogenic, it does cause intrauterine growth retardation.
Birth weight	1. If an infant is small for gestational age, it may indicate intrauterine infections or use of chemicals or drugs by the mother. Rubella syndrome and fetal alcohol syndrome are typical examples. 2. Infants with high birth weight, often seen in offspring of mothers with diabetes, show a higher incidence of cardiac anomalies.

II. Postnatal history

Growth and development	Weight gain and general development may be delayed in infants and children with congestive heart failure (CHF) or severe cyanosis. Weight is affected more significantly than height.
Feeding pattern	Poor feeding of recent onset may be an early sign of congestive heart failure (CHF) in infants, especially if the poor feeding is the result of fatigue and dyspnea.

General medical history

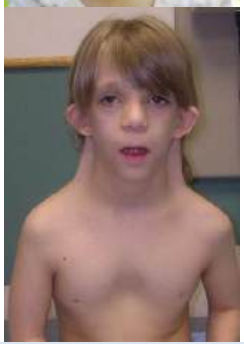
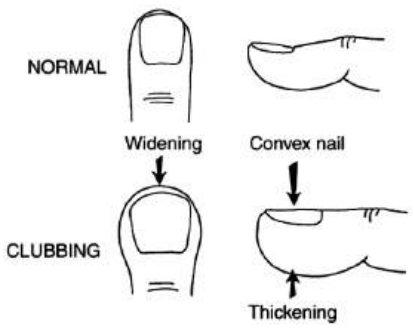
- *A history of cyanosis, "cyanotic spells" (see p. 38)*
- *Tachypnea, dyspnea, and puffy eyelids – signs of CHF (see p. 39)*
- *Frequency of respiratory infections.* Congenital heart diseases with large left-to-right shunt and increased pulmonary blood flow predispose to lower respiratory tract infections.
- *Exercise Intolerance* – may result from any significant heart disease. Obese children may be inactive and have decreased exercise tolerance in the absence of heart disease. With infants who do not walk or run, an estimate of exercise tolerance can be gained from the infant's history of feeding pattern.
- *Chest pain (see p. 39)*
- *Syncope (see p. 39)*
- *Palpitation.* Paroxysms of tachycardia (e.g., supraventricular tachycardia) or single premature beats commonly cause palpitation. Children with hyperthyroidism or mitral valve prolaps (MVP) may first be taken to a physician because of complaints of palpitation.
- *A history of recent sore throat and joint symptoms.*
- *Neurologic symptoms.*
  - ✓ A history of stroke suggests thromboembolism secondary to cyanotic CHD with polycythemia or infective endocarditis. In the absence of cyanosis, stroke can rarely be caused by paradoxical embolism of a venous thrombus through an ASD.
  - ✓ A history of headache may be a manifestation of cerebral hypoxia with cyanotic heart disease, severe polycythemia, or brain abscess in cyanotic children. Although it is claimed to occur in adults, hypertension with or without COA rarely causes headaches in children.
  - ✓ Choreic movement strongly suggests rheumatic fever.
- *Medications.* Medications may be responsible for the chief complaint of the visit or certain physical findings.
  - ✓ Tachycardia and palpitation may be caused by cold medications or antiasthmatic drugs.
  - ✓ Behavioral changes, depression, and mood swings are the most common side effects of β-blockers in children.

III. Family history

CHD	A history of CHD in close relatives increases the chance of CHD in a child. In general, when one child is affected, the risk of recurrence in siblings is about 3%, which is a threefold increase.
Hereditary diseases	Some hereditary diseases may be associated with certain forms of CHD. For example, Marfan's syndrome is frequently associated with aortic aneurysm or with aortic or mitral insufficiency. long-QT syndrome (sudden death caused by ventricular arrhythmias), and idiopathic sudden death in the family should be inquired about.
Hypertension and atherosclerosis	Essential hypertension and coronary artery disease show a strong familial pattern. The most important risk factor for atherosclerosis is a positive family history, with coronary heart disease occurring before age 55 years in one's father or grandfather and before age 65 years in one's mother or grandmother. Clustering of cardiovascular risk factors occurs frequently in the same individual (metabolic syndrome), which calls for investigation for other risk factors when one risk factor is found.

➢ PHYSICAL EXAMINATION

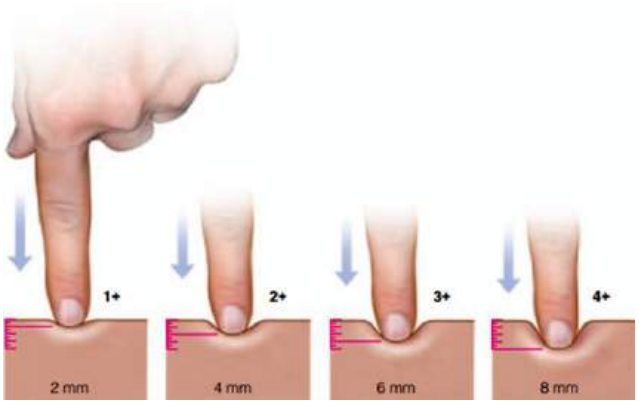
I. Inspection

General appearance and nutritional state	The physician should note whether the child is in distress, well nourished or undernourished, and happy or cranky. Obesity should also be noted; besides being associated with other cardiovascular risk factors such as dyslipidemia, hypertension, and hyperinsulinemia, obesity is also an independent risk factor for coronary artery disease.
Respiratory Rate, Dyspnea, and Retraction	Tachypnea, along with tachycardia, is the earliest sign of left-sided heart failure. If the child has dyspnea or retraction, this may be a sign of a more severe degree of left-sided heart failure or a significant lung pathology.
Dysmorphic signs	**Obvious chromosomal and other genetic abnormalities** known to be associated with certain congenital heart defects should be noted by the physician. *For example:*  *- about 40% to 50% of children with Down syndrome have a congenital heart defect; the two most common defects are atrioventricular canal defect and ventricular septal defect (VSD)*  *- about 35% of girls with Turner syndrome (X0 syndrome) has CHD: coarctation of the aorta, bicuspid aortic valve, aortic stenosis; aortic dissection later in life*  *- about 90% of people with Marfan syndrome develop changes in their heart and blood vessels: aortic aneurysm (increased risk of aortic dissection or rupture); mitral valve prolaps*
Color	The physician should note whether the child is cyanotic *(see p. 38),* pale, or jaundiced. ▪ *Pallor may be seen in infants with vasoconstriction from CHF or circulatory shock or in severely anemic infants.* ▪ *Newborns with severe CHF and those with congenital hypothyroidism may have prolonged physiologic jaundice. Patent ductus arteriosus (PDA) and pulmonary stenosis (PS) are common in newborns with congenital hypothyroidism.* ▪ *Hepatic disease with jaundice may cause arterial desaturation because of the development of pulmonary arteriovenous fistula (e.g., arteriohepatic dysplasia).*
Inspection of the chest	Precordial bulge, with or without actively visible cardiac activity, suggests chronic cardiac enlargement. Acute dilatation of the heart does not cause precordial bulge. Harrison's groove, a line of depression in the bottom of the rib cage along the attachment of the diaphragm, indicates poor lung compliance of long duration, such as that seen in large left-to-right shunt lesions.
Clubbing	Long-standing arterial desaturation (usually longer than 6 months' duration), even if too mild to be detected by an inexperienced person, results in clubbing of the fingernails and toenails. When fully developed, clubbing is characterized by a widening and thickening of the ends of the fingers and toes, as well as by convex fingernails and loss of the angle between the nail and nail bed. Reddening and shininess of the terminal phalanges are seen in the early stages of clubbing. 

Bilateral pitting edema

Pitting edema is graded on a scale of one to four. The scaling depends on both the "pit" leaves and depth and how long the pit will remain.

Grade	Definition
1+	2mm or less: slight pitting, no visible distortion, disappears rapidly.
2+	2-4mm indent: somewhat deeper pit, no readably detectable distortion, disappears in 10-25 seconds.
3+	4-6mm: pit is noticeably deep. May last more than a minute. Dependent extremity looks swollen and fuller.
4+	6-8mm: pit is very deep. Lasts for 2-5 minutes. Dependent extremity is grossly distorted.



In **slow edema**, the pitting remains for more than 1 min, and it is most likely due to congestion. If, however, the pitting disappears in less than 40 s (**fast edema**), the cause is almost certainly a low albumin level (the venous pressure presumably controls the rate of tissue fluid flow from the legs) [Henry JA, Altmann P, 1978].

II. Palpation

Peripheral pulses

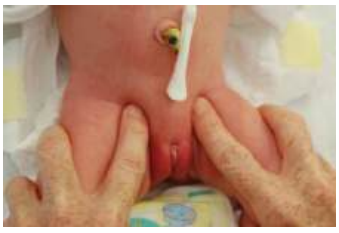
The physician should count the pulse rate and note any irregularities in the rate and volume. The normal pulse rate varies with the patient's age and status. The younger the patient, the faster the pulse rate.

- Increased pulse rate is seen in excitement, fever, heart failure, hyperthyrosis, anemia or arrhythmia.
- Bradycardia may mean heart block, effects of drugs, hypothyrosis, intracranial hypertension, hyperkalemia and so on.
- Irregularity of the pulse suggests arrhythmias, but sinus arrhythmia (an acceleration with inspiration) is normal.

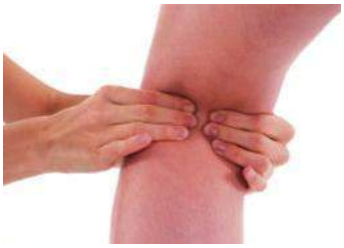
Age	Heart Rate at Rest (beats/min)
0- 12 mo	100-160
1-12 y	70-110
13-19 y	55-90

[From *Soghier L. Reference Range Values for Pediatric Care, first ed. AAP 2014*]

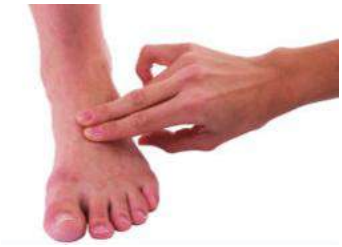
Peripheral pulses are easily palpable in all extremities, including the feet, in every normal infant. The peripheral pulses normally appear to be bounding in premature babies because of the lack of subcutaneous tissue.



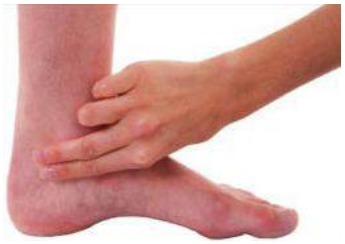
Femoral pulses



Popliteal pulse



Dorsalis pedis pulse

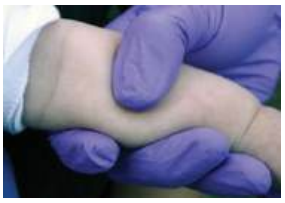
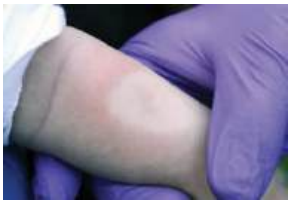
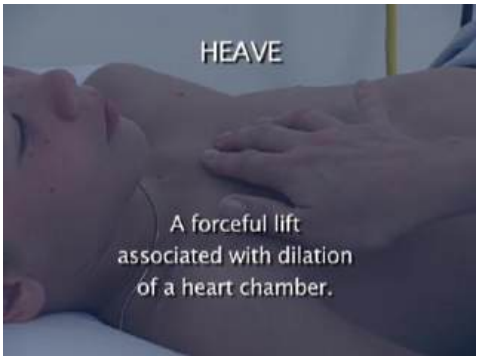
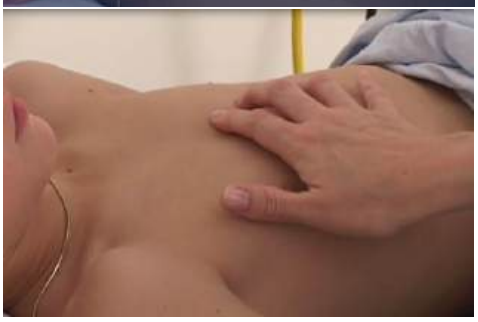


Posterior tibial pulse

Brachial pulse

The right and left arm and an arm and a leg should be compared for the volume of the pulse. Every patient should have palpable pedal pulses, of the dorsalis pedis, tibialis posterior, or both. It is often easier to feel pedal pulses than femoral pulses. Attempts at palpating a femoral pulse often wake up a sleeping infant or upset a toddler.

- If a good pedal pulse is felt, coarctation of the aorta (COA) is effectively ruled out, especially if the blood pressure (BP) in the arm is normal.
- Weak leg pulses and strong arm pulses suggest COA.

Capillary refill time (CRT)	▪ Skin perfusion may be assessed by the temperature of the skin or by CRT (the time required for color to return to the skin after pressure blanching that part of the skin is released). ▪ Normal CRT is 2 s or less; however, low environmental temperature may cause peripheral vasoconstriction and lengthening of capillary refill.  
Apical impulse	▪ Palpation of the apical impulse is usually superior to percussion in the detection of cardiomegaly. Its location and diffuseness should be noted. Percussion in infants and children is inaccurate and adds little. ▪ The apical impulse is normally at the fifth intercostal space in the midclavicular line after age 7 years. Before this age, the apical impulse is in the fourth intercostal space just to the left of the midclavicular line. An apical impulse displaced laterally or downward suggests cardiac enlargement. 
Point of maximal impulse (PMI)	▪ The PMI is helpful in determining whether the RV or LV is dominant. With RV dominance, the impulse is maximal at the lower left sternal border or over the xiphoid process; with LV dominance, the impulse is maximal at the apex. Normal newborns and infants have RV dominance and therefore more RV impulse than older children. ▪ If the impulse is more diffuse and slow rising, it is called a **heave**. If it is well localized and sharp rising, it is called a **tap**. Heaves are often associated with volume overload. Taps are associated with pressure overload. 
Hyperactive Precordium	The presence of a hyperactive precordium characterizes heart disease with volume overload, such as that seen in defects with large left-to-right shunts (e.g., PDA, VSD) or heart disease with severe valvular regurgitation (e.g., aortic or mitral regurgitation).
Thrills	Thrills are vibratory sensations that represent palpable manifestations of loud, harsh murmurs. A thrill on the chest is felt better with the palm of the hand than with the tips of the fingers. However, the fingers are used to feel a thrill in the suprasternal notch and over the carotid arteries.  ▪ Thrills in the upper left sternal border are seen in pulmonic stenosis (PS). ▪ Thrills in the upper right sternal border are seen in aortic stenosis (AS). ▪ Thrills in the lower left sternal border are characteristic of a VSD. ▪ Thrills in the intercostal spaces are found in older children with severe COA and extensive intercostal collaterals. 

III. Blood Pressure (BP) Measurement

Arterial pressure varies continuously over the cardiac cycle, but in clinical practice only systolic and diastolic pressures are routinely reported. These are invariably measured in the brachial artery using cuff sphygmomanometry.

- **Auscultatory BP measurement techniques**

The right size cuff will have a bladder width that is at least 40% of the child's midarm circumference and a bladder length that encircles 80% to 100% of the midarm circumference. When in doubt, choose a larger cuff because a cuff that is too-small may result in artificially elevated BP.

After the child has been resting for 5 minutes:

1. Locate the child's radial pulse, quickly inflate the sphygmomanometer to 60 mmHg, then slowly continue to inflate in increments of 10 mmHg until the pulse disappears.
2. Note the peak inflation level, which is the value at which the pulse disappears þ 30 mmHg.
3. Deflate the cuff, and after 30 seconds inflate the sphygmomanometer to the peak inflation level.
4. Deflate by 2 to 3 mmHg/second to a level that is 10 mmHg lower than the last Korotkoff sound (K5).

a. Systolic BP (SBP) = onset of Korotkoff sounds (K1).

b. Diastolic BP (DBP) = disappearance of Korotkoff sounds (K5).

- **Oscillometric measurements of BP** are generally easier to obtain (especially in infants and small children) and correlate well with auscultatory measurements. One caution is that not all oscillometric devices in clinical use have been validated for their accuracy.

- Averaging three BP readings makes the BP readings more reproducible.

- BP levels in children and adolescents are assessed via BP tables that are based on auscultatory measurements (http://www.nhlbi.nih.gov/files/docs/guidelines/child_tbl.pdf).

- There are also percentile values of normative oscillometric BPs for neonates and children up to 5 years [Park et al, 2005].

	Percentile						
Age	**5th**	**10th**	**25th**	**Mean**	**75th**	**90th**	**95th**
Systolic Blood Pressure							
1–3 days	52	56	58	65	71	74	77
2–3 wks	62	66	71	78	84	89	92
1–5 mo	76	79	88	94	102	106	111
6–11 mo	79	84	88	94	99	104	109
1 yr	80	84	89	94	99	104	108
2 yr	82	85	91	95	101	106	109
3 yr	84	87	92	98	103	108	112
4 yr	86	90	95	100	105	110	114
5 yr	89	93	96	102	107	113	116
Diastolic Blood Pressure							
1–3 days	31	33	37	41	45	50	52
2–3 wks	31	37	42	47	63	58	61
1–5 mo	45	48	53	59	64	71	75
6–11 mo	41	44	52	57	63	67	69
1 yr	44	48	52	57	73	67	69
2 yr	45	47	52	56	61	65	68
3 yr	44	47	52	56	61	65	69
4 yr	44	48	52	56	61	65	68
5 yr	44	48	53	57	62	66	68

• Classification of BP

	Children and adolescents [National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. 2004]	Adults (mmHg) [JNC 7 report. 2003]
Normal BP	SBP and DBP less than the 90th percentile	SBP < 120 and DBP < 80
Prehypertension	SBP or DBP ≥ the 90th percentile but < the 95th percentile or BP exceeds 120/80 mmHg	SBP 120-139 or DBP 80-89
Hypertension	SBP or DBP ≥ 95th percentile plus 5 mmHg	SBP ≥ 140 or DBP ≥ 90

• Common Causes of Hypertension by Age

Infants	1 – 7 yr	7 – 12 yr	Adolescence
Thrombosis of renal artery or vein Congenital renal malformations COA Bronchopulmonary dysplasia	Renal artery stenosis Renal parenchymal disease Wilms tumor Neuroblastoma COA	Renal parenchymal disease Renovascular abnormalities Endocrine causes Essential hypertension	Essential hypertension Renal parenchymal disease Endocrine cause

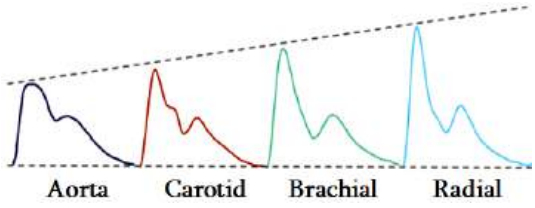
• Interpretation of arm and leg BP values

Four-extremity BP measurements are often obtained to rule out COA. The same cuff selection criterion (i.e., 40% to 50% of the circumference) applies for calf or thigh pressure determination, often requiring the use of a larger cuff for the lower extremity. The patient should be in the supine position for BP measurements in the arm and leg. When using the auscultatory method, the thigh pressure is obtained with the stethoscope placed in the popliteal fossa (over the popliteal artery) with the legs bent and in the supine or prone position. Calf BP is difficult to obtain by the auscultatory method.

How do BP levels in the arm and leg compare in normal children? Even when a considerably wider cuff is selected for the thigh, the systolic pressure in the thigh or calf is about 5 to 10 mm Hg higher than that in the arm except in the newborns in whom the arm and calf pressures are the same [Park et al, 1993]. This partly reflects the **peripheral amplification of systolic pressure**. Thus, the systolic pressure in the thigh (or calf) should be higher than or at least equal to that in the arm except in newborns (the absence of a higher systolic pressure in the leg in newborns may be related to the presence of a normally narrow aortic isthmus). If the systolic pressure is lower in the leg, COA may be present. The presence of a femoral pulse does not rule out a coarctation.

• The phenomenon of systolic pressure amplification

The shape of the pressure waveform changes continuously throughout the arterial tree.



Although diastolic and mean arterial pressures are relatively constant, systolic pressure may be up to 40 mmHg higher in the brachial artery than in the aorta *(Kroeker EJ, Wood EH, 1955; Ohte N et al, 2007)*. This **phenomenon of systolic pressure amplification** arises principally because of an increase in arterial stiffness moving away from the heart. As the pressure wave travels from the highly elastic central arteries to the stiffer brachial artery, the upper portion of the wave becomes narrower, the systolic peak becomes more prominent, and systolic pressure increases.

This phenomenon is used in new techniques for non-invasive assessment of central blood pressure.

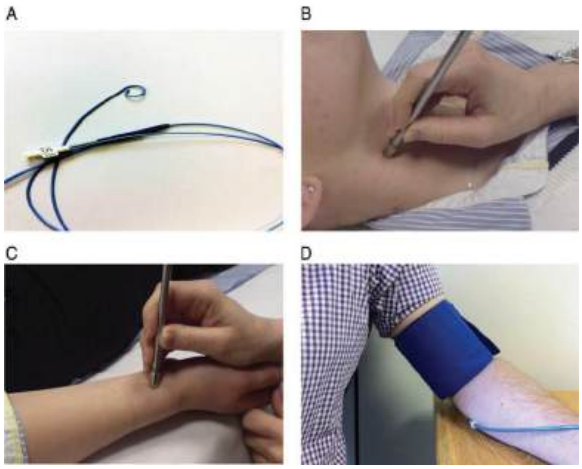
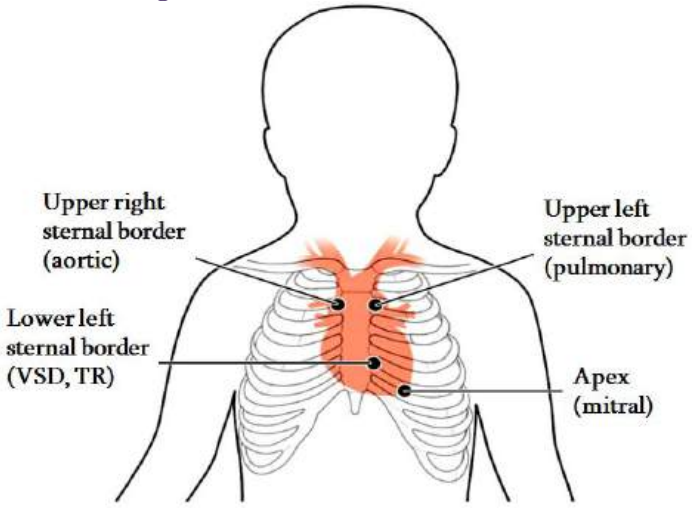


Fig. Techniques for assessing central blood pressure.

(A) invasive cardiac catheterization;
(B) direct applanation tonometry of the carotid artery;
(C) applanation tonometry of the radial artery;
(D) cuff-based oscillometry at the brachial artery.

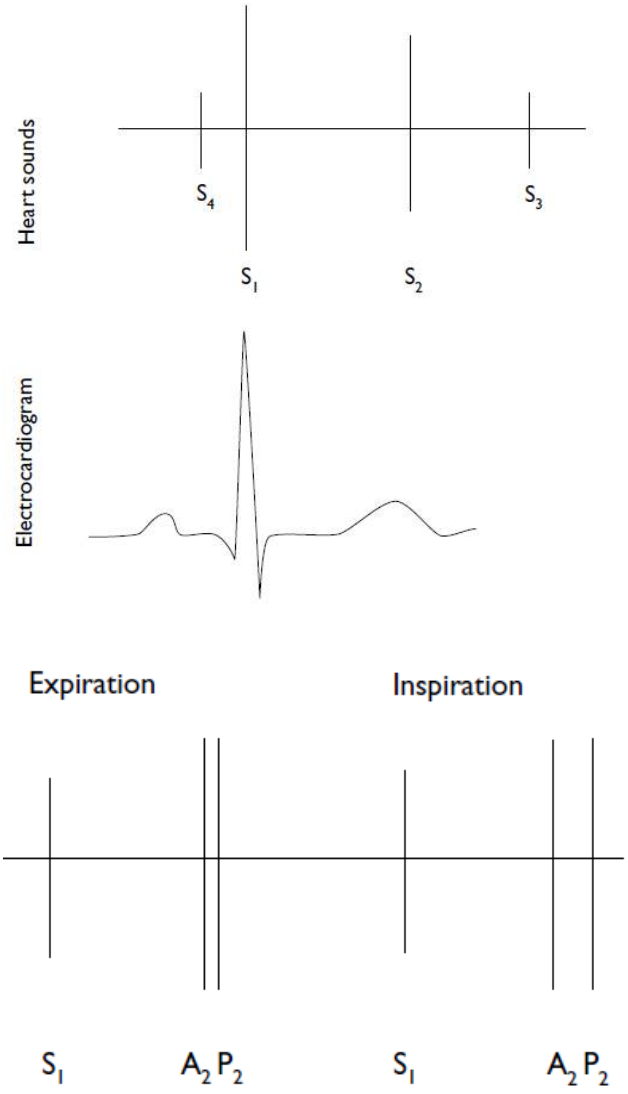
IV. Auscultation of the Heart

The listening areas used in cardiac auscultation



- The diaphragm of the stethoscope is placed firmly on the chest for high-pitched sounds; a lightly placed bell is optimal for low-pitched sounds.
- The physician should initially concentrate on the characteristics of the individual heart sounds and their variation with respirations and later concentrate on murmurs.
- The patient should be supine, lying quietly, and breathing normally.
- The 1st heart sound is best heard at the apex or lower left sternal border, whereas the 2nd heart sound should be evaluated at the upper left and right sternal borders.

Normal and abnormal heart sounds



First Heart Sound (S1)

The S1 is caused by closure of the atrioventricular valves (mitral and tricuspid).

- Splitting of the S1 may be found in normal children, but it is infrequent.
- Abnormally wide splitting of S1 may be found in right bundle branch block (RBBB) or Ebstein's anomaly.
- Splitting of S1 should be differentiated from ejection click or S4.

Second Heart Sound (S2)

The S2 is caused by closure of the semilunar valves (aortic and pulmonary). The S2 in the upper left sternal border (i.e., pulmonary valve area) is of critical importance in pediatric cardiology.

- During inspiration, the decrease in intrathoracic pressure results in increased filling of the right side of the heart, which leads to an increased right ventricular ejection time and thus delayed closure of the pulmonary valve; consequently, splitting of the 2nd heart sound increases during inspiration and decreases during expiration.
- *A widely split and fixed S2* is found in conditions that prolong the RV ejection time or that shorten the LV ejection, e.g., atrial septal defect (ASD), pulmonic stenosis (PS).
- *An accentuated pulmonic component* of the 2nd sound with narrow splitting is a sign of pulmonary hypertension.
- *A single 2nd sound* occurs in pulmonary or aortic atresia or severe stenosis, truncus arteriosus, and, often, transposition of the great arteries.

Third Heart Sound (S3)

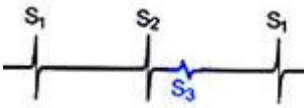
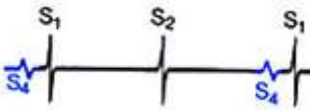
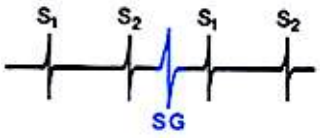
The S3 is a somewhat low-frequency sound in early diastole and is related to rapid filling of the ventricle. It is best heard at the apex or lower left sternal border. It is commonly heard in normal children and young adults (due to rapid ventricular filling).
A loud S3 is abnormal and is audible in conditions with dilated ventricles and decreased ventricular compliance (e.g., large-shunt VSD or CHF). When tachycardia is present, it forms a "Kentucky" gallop*.

Fourth Heart Sound (S4) or Atrial Sound

The S4 is a relatively low-frequency sound of late diastole (i.e., presystole) and is rare in infants and children. When present, it is always pathologic and is seen in conditions with decreased ventricular compliance or CHF. With tachycardia, it forms a "Tennessee" gallop*.

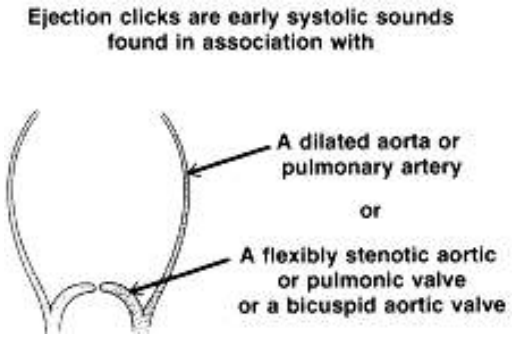
Gallop Rhythm

A gallop rhythm is a rapid triple rhythm resulting from the combination of a loud S3, with or without an S4, and tachycardia. It generally implies a pathologic condition and is commonly present in CHF.
** A common aid in distinguishing S3 and S4 is to remember that S3 has the same cadence as the word "Kentucky" ("Ken-tu-cky" = S1-S2-S3) and S4 sounds like "Tennessee" ("Ten-nes-see" = S4-S1-S2).*

KEN—TUC—KY gallop (accent on 2nd syllable)	TEN—NES—SEE gallop (accent on 1st syllable)	A summation gallop (SG) - tachycardia and a superimposed S3 and S4
		

Ejection clicks

Ejection clicks are high-pitched sounds that occur at the moment of maximal opening of the aortic or pulmonary valves. They are heard just after the first heart sound. The sounds occur in the presence of a dilated aorta or pulmonary artery or in the presence of a bicuspid or flexible stenotic aortic or pulmonary valve. They are heard so close to the 1st heart sound that they may be mistaken for a split 1st sound.



Non-ejection clicks

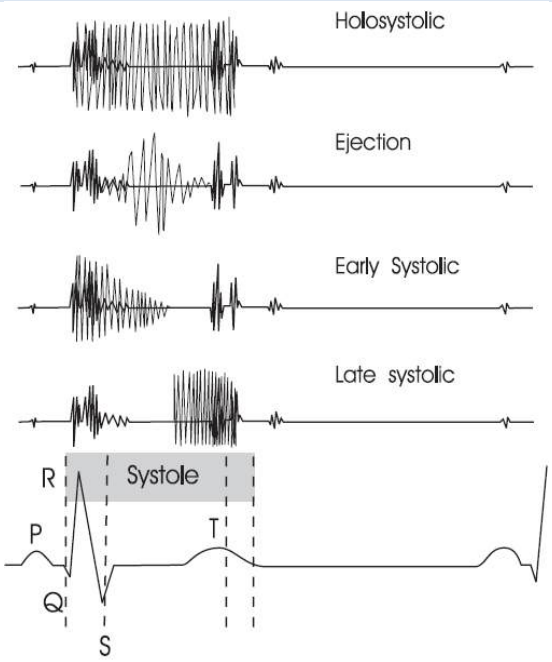
Systolic nonejection clicks are most commonly produced by the mitral or tricuspid valve apparatus. These clicks usually occur in mid to late systole and appear to be related to tensing of the chordae tendineae or valve leaflets when mitral or tricuspid valve prolapse is present.

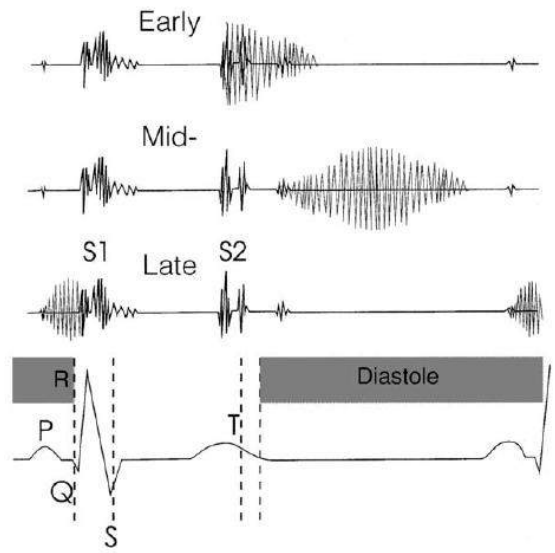
Heart murmurs

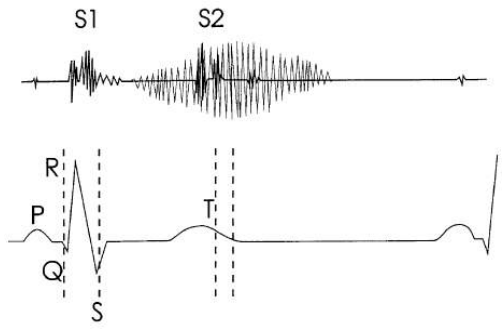
Cardiac murmurs that arise from turbulence or vibrations within the heart and vascular system may be innocent or pathologic. Each heart murmur must be analyzed in terms of intensity (grade 1 to 6), timing (systolic or diastolic), location, transmission, and quality (musical, vibratory, blowing, and so on).

Intensity of the murmur is customarily graded from 1 to 6:

Grade 1: heard only with intense concentration
Grade 2: faint, but heard immediately
Grade 3: easily heard, of intermediate intensity
Grade 4: easily heard and associated with a thrill (a palpable vibration on the chest wall)
Grade 5: audible with the stethoscope barely on the chest
Grade 6: audible with the stethoscope off the chest

Types of Systolic Murmurs	Description	Examples
	1. Holosystolic or pansystolic murmur	Mitral regurgitation Tricuspid regurgitation VSD
	2. Ejection systolic or crescendo-decrescendo murmur	Aortic stenosis Pulmonic stenosis
	3. Early systolic murmur (short regurgitant murmurs)	Tricuspid regurgitation (without pulmonary hypertension) Large VSD or very small VSD
	4. Late systolic murmur	Mitral valve prolaps

Types of Diastolic Murmurs	Description	Examples
	1. Early diastolic or decrescendo murmur	- Aortic regurgitation - Pulmonary regurgitation
	2. Mid-diastolic murmur	- Mitral stenosis - Tricuspid stenosis - Atrial myxoma
	3. Presystolic (late diastolic) murmur	- Mitral stenosis - Tricuspid stenosis - Atrial myxoma
	* *Aortic regurgitation is sometimes associated with* ***Austin Flint murmur****: mid-diastolic and presystolic murmur heard at the apex. This is caused by the aortic regurgitant jet impinging on the normal mitral inflow and augmenting mitral inflow turbulence.*	

Continuous Murmurs	Description	Examples
	*The continuous murmur begins in systole and proceeds up to and through the second heart sound (S2) proceeding through part or all of diastole.*	- Patenet ductus arteriosus (PDA) - Arteriovenous fistulae - Some types of innocent murmurs (venous hum, mammary arterial souffle´)

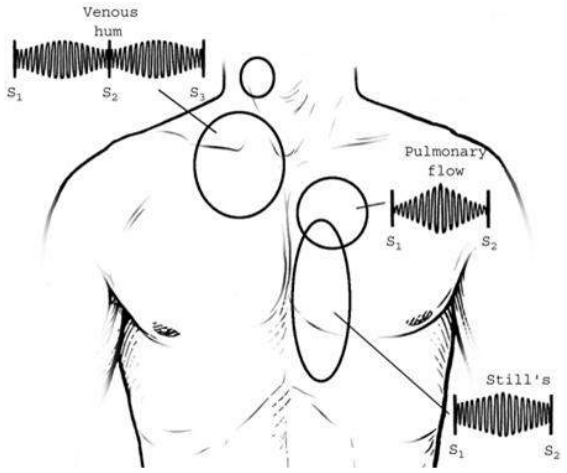
Innocent or normal murmurs of childhood

More than 80% of children have innocent murmurs of one type or another sometime during childhood.

Normal murmurs of childhood can be both systolic and continuous but are **never solely diastolic.**

The intensity or loudness of the murmur is grade 3 or less and consequently is never associated with a palpable thrill.

Most murmurs, both innocent and organic, are accentuated by fever, anemia, or increased cardiac output.



Innocent systolic murmurs	
1. The vibratory Still's murmur	▪ cause: turbulence of blood being ejected from the left ventricle ▪ most typically audible in children between ages 2 and 6 years but may be present as late as adolescence or as early as infancy ▪ maximal at the lower left sternal edge and extending to the apex ▪ generally loudest in the supine position and often changes in character, pitch, and intensity with upright positioning
2. Pulmonary flow murmur	▪ originate from the right ventricular outflow tract and radiate along the pulmonary arteries and thus may be well heard in the back and axilla bilaterally ▪ can occur at any age, but they are common particularly in adolescents or in children with pectus excavatum
3. Peripheral pulmonary arterial stenosis murmur	▪ audible in newborns and infants less than 1 year of age ▪ turbulence is caused by relative disparity between pulmonary trunk and its small branches
4. Supraclavicular or brachiocephalic systolic murmur	▪ due to normal blood flow into the aorta and into the head and neck vessels ▪ heard best high up in the chest and above the clavicles
5. Aortic systolic murmur	▪ arise from the outflow tract in older children and adults - *in children, these murmurs may arise secondarily to extreme anxiety, anemia, hyperthyroidism, fever, or any condition of increased systemic cardiac output* - *in trained athletes, slower heart rates with increased stroke volume may give rise to short crescendo-decrescendo murmurs of low to medium pitch*

Innocent continuous murmurs	
1. Venous hum	▪ commonly audible in children between the ages of 3 and 6 years ▪ originates from turbulence in the jugular venous system ▪ diastolic component is louder than the systolic component ▪ maximally audible at the right or left infraclavicular and supraclavicular areas ▪ heard only in the upright position and disappears in the supine position ▪ can be obliterated by rotating the head or by gently occluding the neck veins with the fingers
2. Mammary arterial souffle´	▪ occurs most frequently late in pregnancy and in lactating women but may rarely occur in adolescence ▪ originates from the plethoric vessels of the chest wall ▪ resolves with termination of lactation

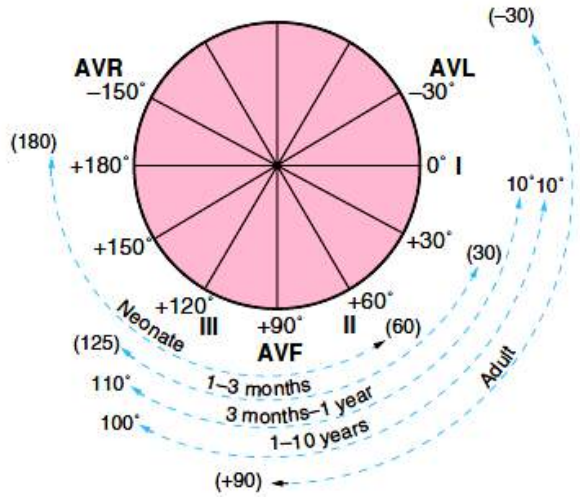
➢ ELECTROCARDIOGRAPHY (ECG, EKG)

Changes occur in the normal ECG from birth to adult life. They relate to developmental changes in cardiovascular physiology, body size, the position and size of the heart relative to the body, and variations in the size and position of the cardiac chambers relative to each other.

Attention must be paid to the **QRS complex (ventricular depolarization)** and the **T wave (ventricular repolarization)**, which change mainly during the first year of life.

Three patterns can be distinguished through the morphology of the QRS complex and the T wave:
- The neonatal pattern
- The infant pattern
- The adult pattern

Fig. Cardiac axis during childhood



The cardiac axis is the average direction of spread of the depolarization wave through the ventricles and it changes significantly during childhood, from *right and anterior* in infants, to *left and posterior* in adults.

Neonatal Pattern (the first month)	The Infant Pattern (after 1st month)	The Adult Pattern (after 2-3 years)
Prevalent electrical activity in the right ventricle	Electrical forces of the ventricles are balanced	Prevalent electrical activity in the left ventricle
▪ In the V1 lead the R wave is dominant over the S wave ▪ In the V6 lead the S wave is dominant over the R wave	▪ In the V1 lead, the R wave will still be dominant over the S wave ▪ In the V6 lead, the R wave will be dominant over the S wave ▪ A narrow Q wave (up to 10 mm) deep to appear in the II, III, aVF and V6 leads	▪ In the V1 lead the S wave will dominate over the R ▪ In the V6 lead, the R wave will dominate over the S wave

T wave:

- For the first week of life, T waves are positive throughout the precordial leads
- After the first week, the T waves become negative in V1-V2-V3 (= the "juvenile T-wave pattern")*
- This T-wave inversion usually remains until ~ age 8-10; thereafter the T waves become positive in V1-V2-V3.
- However, the juvenile T-wave pattern can persist into adolescence and early adulthood (= "persistent juvenile T waves").

* After the first week of life a positive T wave in V1–V2 indicates raised systolic pressure in the right ventricle, and can be a sign of congenital heart disease causing right ventricular pressure load (changes in the T wave in V1–V2 are correlated with systolic pressure in the right ventricle and thus correlate with changes in pulmonary vascular resistance).

Normal Parameters of Pediatric ECG

Basic parameters*	In adults	In children
PR interval	The normal duration range of the adult PR interval is between 120 ms and 220 ms.	*PR interval is generally shorter:* ▪ the first month 80 – 120 ms ▪ 2 months – 1 yr 80 – 140 ms ▪ 1 – 5 yr 100 - 160 ms ▪ 6 – 12 yr 110 – 180 ms
QRS duration	The normal adult QRS duration is 100 ms at the highest.	*Upper limit of the norm* ▪ newborn 65 ms ▪ 1 month – 1 year 80 ms ▪ > 8 yr 100 ms
QT interval	QT interval is an important parameter in pediatric ECGs because its increase is an indicator of cardiac electrical instability, and thus of fatal arrhythmia risk. It is generally measured in the II, V5 and V6 leads. The QT interval is dependent on heart rate and is corrected by using Bazett's formula: $QTc = \frac{QT}{\sqrt{RR}}$ The corrected QT interval (QTc) normal value is less than 440 ms in children and adult males, while in women the upper limit of the norm is 470 ms.	

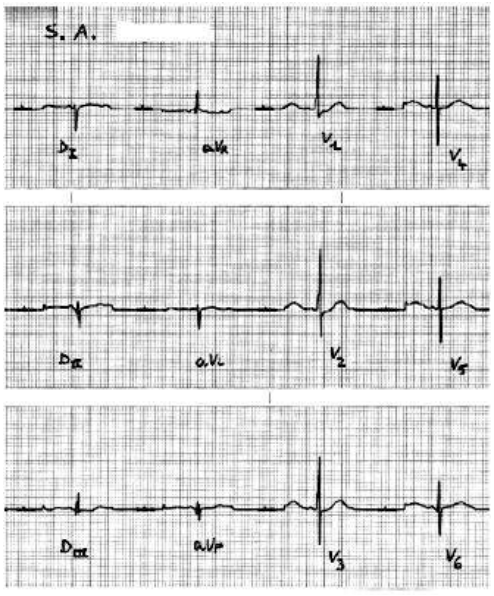
* *At the usual paper speed of the ECG at 25 mm/s, 1 mm (little square) = 40 ms and 5 mm = 200 ms.*

QUIZ

Recognize the corresponding electrocardiogram of:

- *a 2-day-old newborn* ___
- *a 5-month-old infant* ___
- *a 4-year-old child* ___

1



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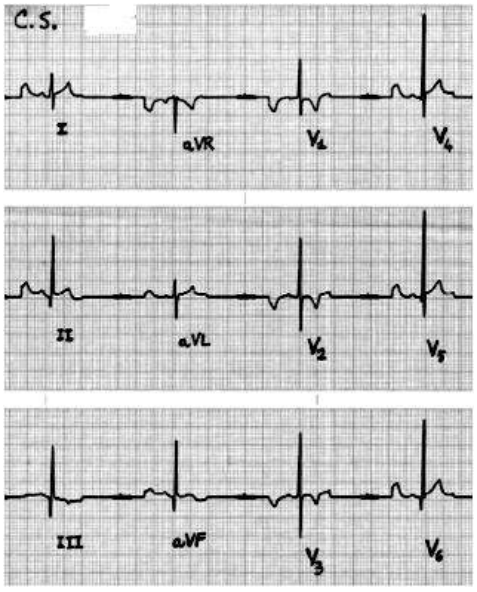

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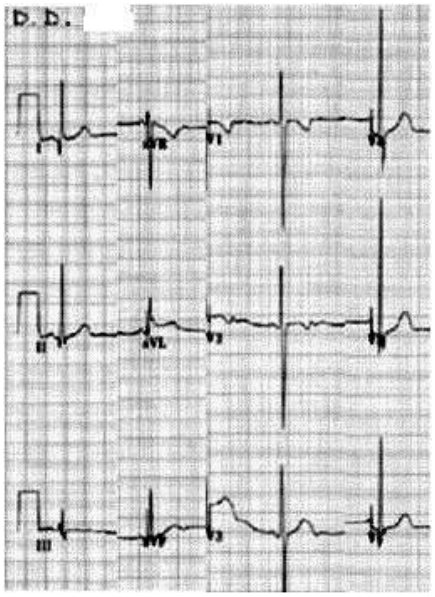


➢ CARDIAC INTERPRETATION OF CHEST RADIOGRAPHY

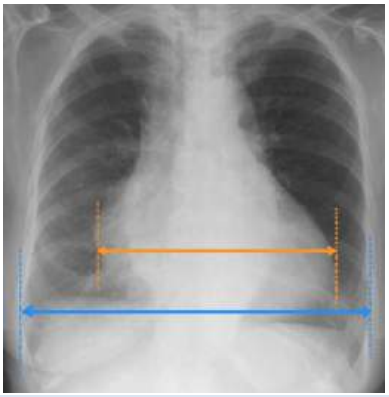
This also depends on developmental changes of cardiovascular system:

- the heart is large in relation to body size in the infant. It lies somewhat horizontally and occupies a large portion of the thoracic cavity
- growth of the lungs causes the heart to assume a lower position, and by 7 years of age the heart has assumed an adult position that is more oblique and lower

When assessing the cardiovascular system on a chest X-ray, the following must be noted:
— the size of the heart (small, normal, or large)
— the contours of the heart reflecting various cardiovascular components, which can be enlarged, absent, or displaced
— the pulmonary vascularity, which can be diminished, normal, or increased

Heart size

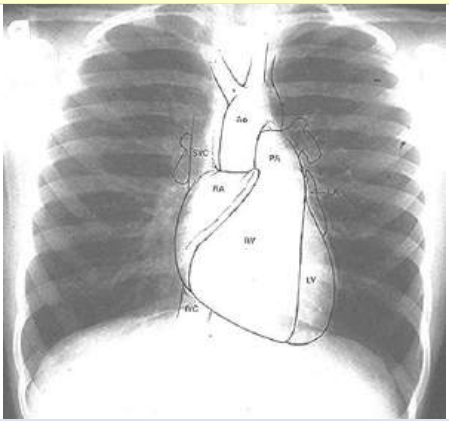
Heart size is estimated by measurement of the **cardiothoracic (CT) ratio**, which is the maximal cardiac width compared to the widest internal diameter of the rib cage (normally it is 50% or 0.5). A CT ratio of more than 0.5 indicates cardiomegaly.
Cardiac size should be evaluated only when the film is taken during inspiration with the patient in an upright position. However, the CT ratio cannot be used with accuracy in newborns and small infants, in whom a good inspiratory chest film is rarely obtained. Furthermore, the thymus may overlap not only the base of the heart but also virtually the entire mediastinum, thus obscuring the true cardiac silhouette.



Heart contours

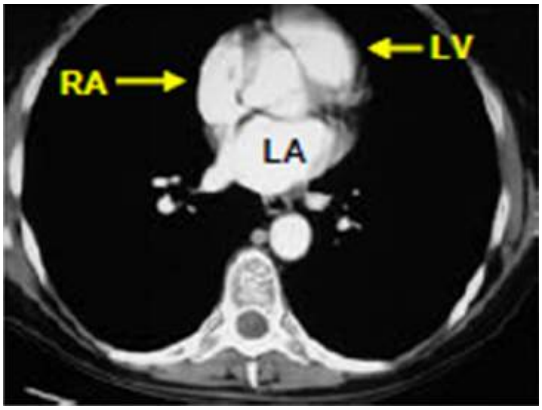
The right cardiac silhouette is formed
- superiorly by the superior vena cava (SVC)
- inferiorly by the right atrium (RA)

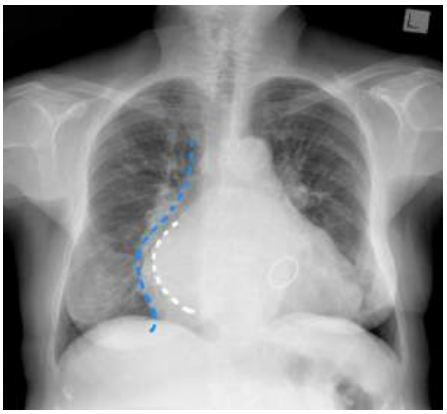
The left cardiac border is formed from the top to the bottom by
- the aortic arch
- the main pulmonary artery (PA)
- the left ventricle (LV)



Normally the right ventricle (RV) and the left atrium (LA) sit right in the middle of the heart (RV- anteriorily, LA- posteriorly) and do not form a normal border on the frontal film.

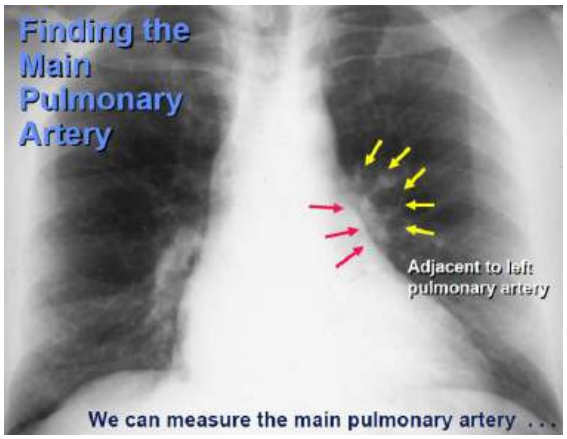
When the LA enlarges, it may produce a "double-density" on the right side of the heart.

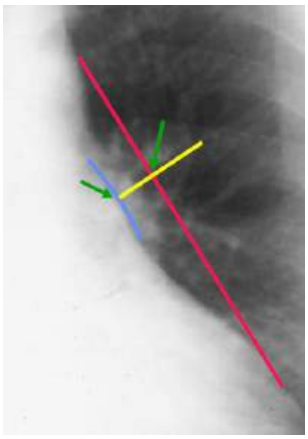


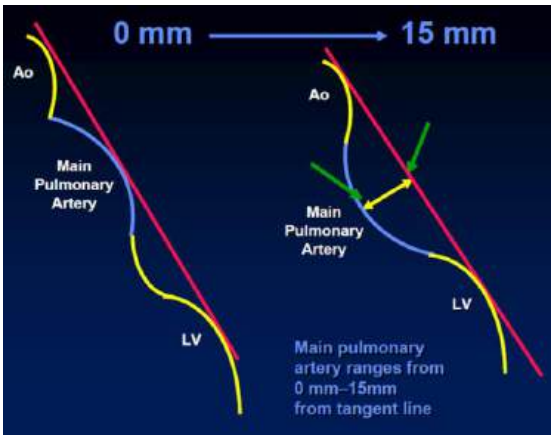


The contour of the main pulmonary artery (PA)

If we draw a tangent line from the apex of the aortic arch and measure along a perpendicular to that tangent line, the distance between the tangent and main PA falls in a range between 0 mm (touching the tangent line) to as much as 15 mm (away from the tangent line).



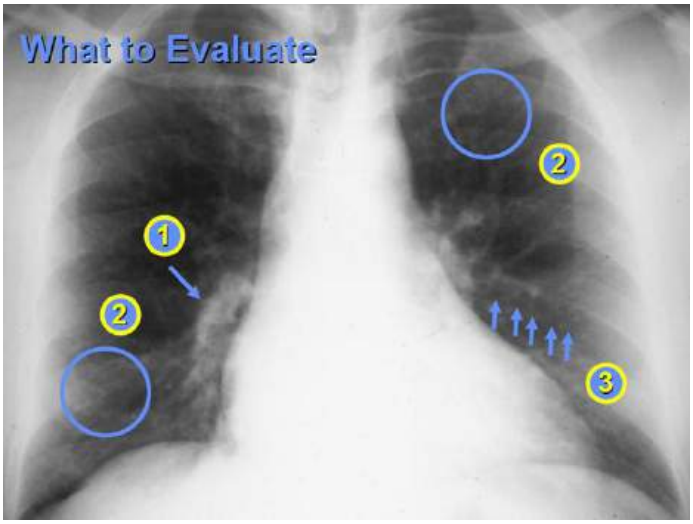




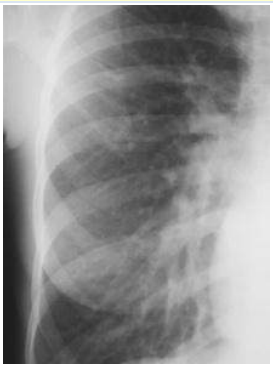
Pulmonary blood flow

We must evaluate:

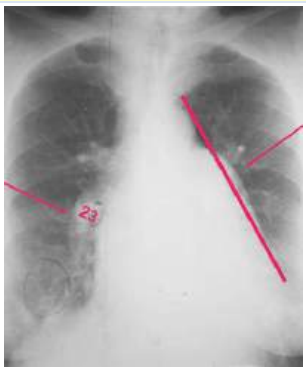
1. Right descending pulmonary artery - RDPA (normally, should not be more than 17 mm in diameter)
2. Distribution of flow in the lungs:
   - *in erect position, blood flow to bases more than to apices*
   - *size of vessels at bases is normally greater than size of vessels at apex*
   - *we cant measure size of vessels at the left base because the heart obscures them*
3. Central versus peripheral:
   - *central vessels give rise to progressively smaller peripheral vessels*



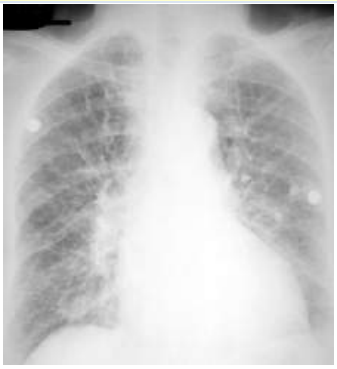
An increase in pulmonary blood flow or congestion of the pulmonary veins will cause prominence of the pulmonary blood vessels. A significant increase in pulmonary blood flow will cause dilation of peripheral pulmonary vessels, allowing their visualization in the normally dark peripheral lung fields.



Increased flow:
- all of the vessesls everywhere in the lung are bigger than normal, but distribution of flow is maintained as in normal



Pulmonary arterial hypertension:
- RDPA >17 mm
- Main PA projects beyond the tangent line



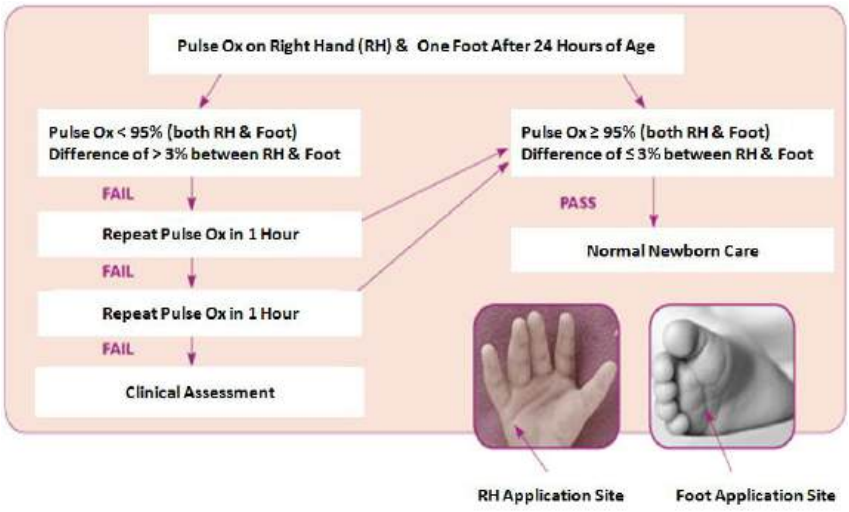
Venous hypertension:
- upper lobe vessels equal to or larger than the size of lower lobe vessels (cephalization)

SPECIAL TOOLS IN EVALUATION OF PEDIATRIC CARDIAC PATIENTS

Pulse Oxymetry Screening to Detect Critical CHD

Although there is no universally agreed on definition of critical CHD (CCHD), it usually refers to CHD that requires surgical or interventional cardiologic management in the first year after birth, typically in early infancy, to prevent mortality and/or severe morbidity.

The most common types of CCHD include transposition of the great arteries (TGA), hypoplastic left heart (HLH), total anomalous pulmonary venous drainage, and critical coarctation/interruption of the aorta.

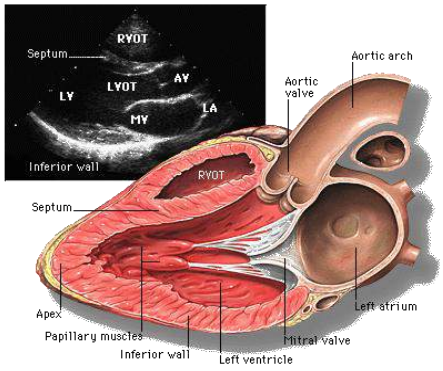


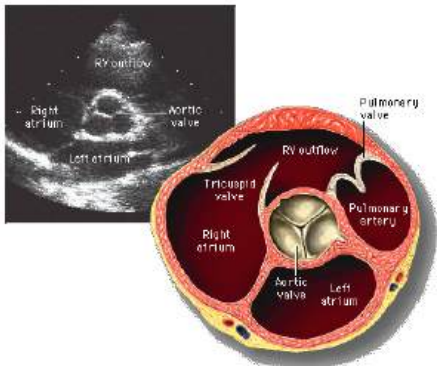
Echocardiography (EchoCG)

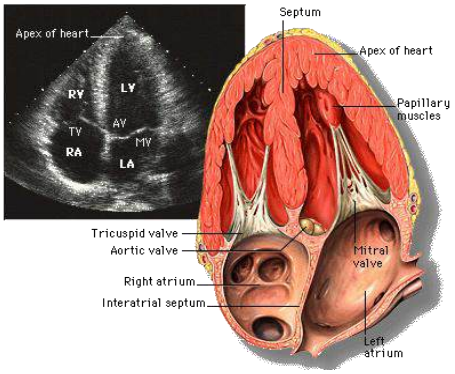
- Echocardiography has become the most important noninvasive tool in the diagnosis and management of cardiac disease, providing a full anatomic evaluation in one, two, three, or four dimensions, which are called M-mode, 2D, three-dimensional (3D), and four-dimensional (4D) echocardiography, respectively. Many congenital heart defects now are surgically repaired based on the echocardiogram without need for cardiac catheterization.
- Transesophageal echocardiography (TEE) provides better imaging when transthoracic imaging is inadequate. It is used intraoperatively to assess results and cardiac function after surgery. TEE and intracardiac echocardiography are used to guide interventional catheterization and radiofrequency ablation of dysrhythmias.

TRANSTHORACIC 2D ECHOCARDIOGRAMS

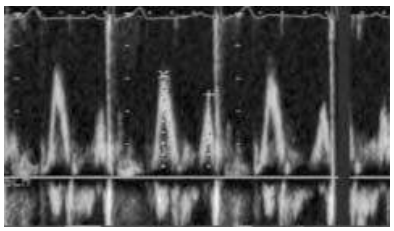
Parasternal long axis view (PLAX)	Parasternal short axis view (PSAX)	Apical 4 chamber view (A4C)







- Physiologic data on the direction and velocity of blood flow can be obtained with the use of Doppler.



When flow across the mitral and tricuspidal valves is assessed with Doppler echoCG, two waves are characteristically seen. These represent passive filling of the ventricle (early [E] wave) and active filling with atrial systole (atrial [A] wave). Classically, the E-wave velocity is slightly greater than that of the A wave. They are change with respiration.

With inspiration, there is a fall in pleural pressure and a rise in intraabdominal pressure. These changes lead to increased right-sided venous return and increased RV stroke volume. Doppler E velocity across the tricuspid valve is increased, while the Doppler E velocity across the mitral valve is slightly decreased.

MRI, MRA, CT, and Radionuclide Studies

- **Magnetic resonance imaging (MRI)** is useful in detecting the cardiac chamber morphology and evaluating areas that are less well visualized by echocardiography, such as distal branch pulmonary artery anatomy and anomalies in systemic and pulmonary venous return.
- **Magnetic resonance angiography (MRA)** displays and analyzes cardiac wall thickening, chamber volume, and valve function. Blood flow velocity and blood flow volume can be calculated.
- **Computer processing of MRA** images allows the noninvasive visualization of the cardiovascular system from inside of the heart or vessels.
- **Cardiac computed tomography (CT)** includes:
  - Coronary computed tomographic angiography (CTA)
  - Coronary artery calcium (CAC) scoring
  - Assessment of ventricular structure and systolic function
- **Radionuclide scintigraphy** is used primarily for assessing right and left ventricular function, provides valuable information for the evaluation of intra- and extracardiac shunts and assessment of myocardial perfusion.

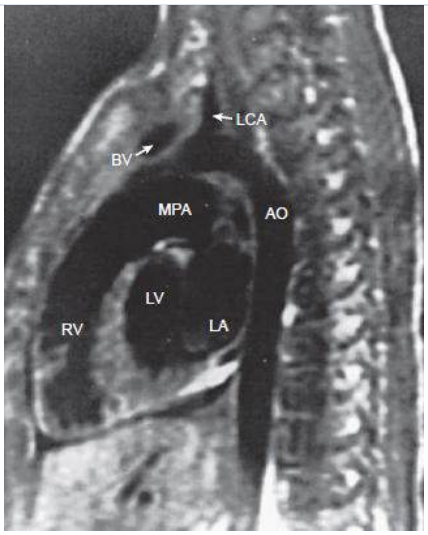


Fig. Sagittal normal MRI [Bisset GS, 1990].
AO, aorta; BV, brachiocephalic vein; LA, left atrium; LCA, left coronary artery; LV, left ventricle; MPA, main pulmonary artery; RV, right ventricle

Cardiac Catheterization

Cardiac catheterization is performed in patients who need additional anatomic information or precise hemodynamic information before operating or establishing a management plan. Pressures, oxygen saturations, and oxygen content are measured in each chamber and blood vessel entered. This information is used to calculate systemic and pulmonary blood flow and resistance.

Angiography is performed by injecting contrast material into selected sites to define anatomy and supplement noninvasive information.

An increasing percentage of cardiac catheterizations are done to perform an intervention, including balloon dilation of stenotic valves and vessels, ballooning and stenting of stenotic lesions, closure of collateral vessels by coil embolization, and device closure of PDAs, secundum ASDs, patent foramen ovales, and muscular VSDs.

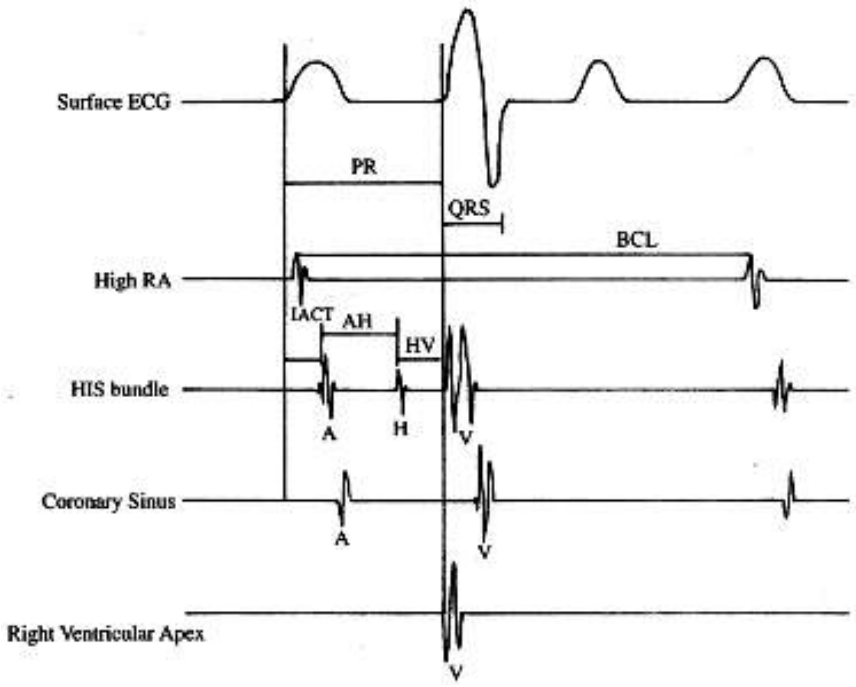
Catheterization with electrophysiologic studies allows for precise mapping of the electrical activity, can assess the risk of abnormal heart rhythms, and often is done in anticipation of radiofrequency ablation of the site of a dysrhythmia.

Intracardiac Electrophysiologic Study

Here, one surface ECG lead is shown, as well as intracardiac electrograms from the high right atrium (RA), His bundle, coronary sinus, and right ventricular apex.

Conduction intervals are as follows:

1. BCL (basic cycle length) – is the interval between successive A waves (measured from the RA catheter);
2. PR and QRS on the surface ECG;
3. IACT (intraatrial conduction time) – is the interval from the SA node to the AV node (measured from the beginning of the P wave on the surface ECG to the A deflection on the His bundle electrogram);
4. AH interval (from the atrium to the His bundle);
5. HV interval (from the His bundle to the ventricles).



4. Common Syndromes Associated with Cardiac Lesions in Children

Cardiac disease presents in a wide variety of ways, including postnatal collapse, cyanosis, heart failure, syncope or, rarely, sudden death.

CYANOSIS

- ***Cyanosis is a bluish discoloration of the skin and mucous membranes resulting from an increased concentration of deoxygenated hemoglobin in the cutaneous veins. To visualize true cyanosis, there must be at least 5 g/dL of deoxygenated hemoglobin.***

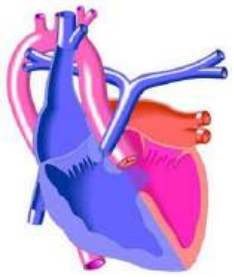
  This level of deoxygenated hemoglobin in the cutaneous vein may result from either **desaturation of arterial blood** or **increased extraction of oxygen by peripheral tissue** in the presence of normal arterial saturation.

  Cyanosis associated with desaturation of arterial blood is called **central cyanosis**; cyanosis with normal arterial oxygen saturation is called **peripheral cyanosis**.

	TWO CATEGORIES OF CYANOSIS	
	Peripheral	**Central*** **
Pathophysiology	Increased O2 extraction by the tissues	Systemic arterial oxygen desaturation
Distribution	Distal extremities +/- circumoral or perioral area* (but pink mucous membranes)	Globally cyanotic including mucous membranes
Associations	—	Clubbing, polycythemia
Causes	Congestive heart failure (CHF) Circulatory shock Hypovolemia Vasoconstriction from cold *etc.*	1. Pulmonary diseases 2. Right to left shunts (cyanotic CHD)** 3. Hemoglobin disorder (eg, methemoglobinemia) 4. Central nervous system disorders (hypoventilation)

* **Circumoral cyanosis**, cyanosis around the mouth, is found in normal children with fair skin. Isolated circumoral cyanosis is not significant. In a newborn, acrocyanosis may cause confusion. **Acrocyanosis** is a bluish or red discoloration of the fingers and toes of normal newborns in the presence of normal arterial oxygen saturation.

** The most common cyanotic heart defect is tetralogy of Fallot (TOF), which includes the following four abnormalities: a large VSD, right ventricular outflow tract (RVOT) obstruction, right ventricular hypertrophy, and overriding of the aorta. Blood is ejected from both ventricles to both pulmonary artery and aorta. Cyanosis is dependent on the severity of RVOT obstruction (in severe stenosis more deoxygenated blood from the RV flows into the aorta).



*** Unlike pulmonary and CNS diseases, cyanosis in right-to-left shunts and Hb disorders (such as methemoglobinemia) does not respond to inhalation of 100% O2.

- **Main factors affecting cyanosis detection**

1. *Hemoglobin level*
   - ✓ Cyanosis does not occur in severe anemia (Hb level is 5g/dL or less).
   - ✓ Cyanosis can be seen in polycythemic patients with normal O2 saturation.

2. *Skin pigmentation*
   - ✓ Cyanosis is more difficult to detect in children with dark pigmentation. The best indicator of cyanosis is the tongue due to the rich vascular supply and lack of pigmented cells (the color of the tongue is not affected by race or ethnic background).

HEART FAILURE (HF)

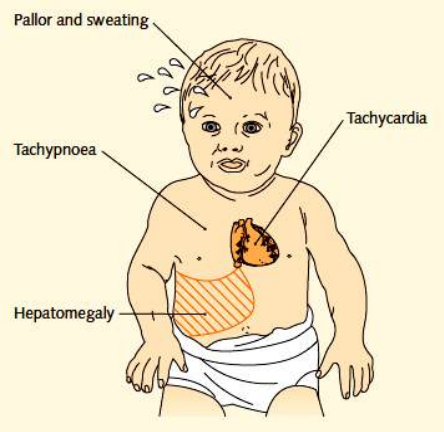
- ***Heart failure is a syndrome caused not only by compromised cardiac performance but also by the effects of compensatory mechanisms.***

Compromised heart pump → Accumulation of blood in the venous circulation

Sympathetic nervous system stimulation, activation of the renin-angiotensin system, and vasopressin secretion → Renal vasoconstriction and reduction of glomerular filtration, sodium and water retention

- **The 2013 ACC/ AHA definitions:**

· Heart failure with reduced ejection fraction (HFrEF): EF ≤40%, systolic HF
· Heart failure with preserved ejection fraction (HFpEF): EF ≥50%, diastolic HF



- HF has has **a variety of age dependent clinical presentations** *(see p.43).*

· *Infants:* respiratory distress (tachypnea, grunting, nasal flaring, chest retractions); diaphoresis; feeding difficulties due to increased respiratory efforts and fatigability, which eventually results in poor weight gain (failure to thrive).
Wheezing or persistent cough at night may be an early sign of CHF.
Physical findings: tachycardia, gallop rhythm (S3, S4); signs of systemic venous congestion: hepatomegaly, puffy eyelids and sacral edema. Ankle edema, which is commonly seen in adults, is not found in infants.
· *Older children:* dyspnea; exercise intolerance; somnolence; anorexia; cough; wheezing, or crackles (rales); gallop rhythm; hepatomegaly; peripheral edema and jugular venous distention.

CHEST PAIN

- Cardiac causes of chest pain are rare in children and adolescents.
  - ✓ The three most common noncardiac causes of chest pain in children are costochondritis, trauma to the chest wall or muscle strain, and respiratory diseases with cough (e.g., bronchitis, asthma, pneumonia, pleuritis).
  - ✓ Cardiac conditions that may cause chest pain include severe AS (usually associated with activity), pulmonary hypertension, mitral valve prolapse (MVP), severe PS, pericarditis, and Kawasaki's disease (in which stenosis or aneurysm of the coronary artery is common).
  - ✓ Chest pain of cardiac origin is not sharp; it manifests as a deep, heavy pressure or the feeling of choking or a squeezing sensation, and it is usually triggered by exercise. Pain of cardiac origin, except for pericarditis, is not affected by respiration.

SYNCOPE

- Syncope is defined as a transient loss of consciousness and muscle tone that reverses without intervention. Syncope in children is most often neurally mediated.
- **Neurocardiogenic (vasovagal) syncope** is very common in the teenage years. These patients may have a seizure when syncopal. These convulsions, triggered by a sudden reduction of oxygen to the brain, are clinically similar to and can be misdiagnosed as generalized epileptic seizures.
  Neurocardiogenic syncope is usually triggered by dehydration, heat, standing for a long time without movement, hot showers, the sight of blood, pain, swallowing, vomiting, and or sudden stress.
  History is usually the clue to distinguishing syncope from epileptic seizures: There is initially pallor and sweating followed by blurring of vision, dizziness, nausea, and then gradual collapse with loss of consciousness.
  Conservative measures should be tried before introducing pharmacotherapy. Recommending liberalization of fluid intake may be adequate.
- **Cardiac syncope** is potentially life-threatening (see p. 40) and can usually be suspected after the use of simple evaluative measures, including history, physical examination and ECG. Cardiac syncope is usually sudden without the gradual onset and the symptoms that accompany vagal syncope.

COMMON LIFE-THREATENING CARDIAC CONDITIONS IN CHILDREN AND YOUNG ADULTS

Cardiac Ion Channelopathies

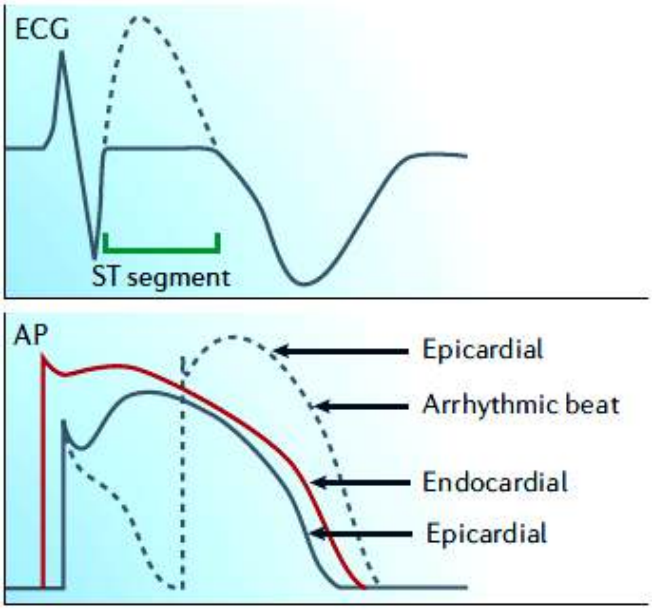
Ion channel diseases are inherited electrophysiologic abnormalities associated with mutations in genes encoding proteins that form or interact with the specialised channels that conduct sodium, potassium and/or calcium ions. This heterogeneous group includes Brugada syndrome, long QT syndrome and catecholaminergic polymorphic ventricular tachycardia.

Channelopathies have features in common: a genetic basis; a structurally normal heart; and predisposition to life-threatening cardiac arrhythmias.

Genetic testing is predominantly used to confirm diagnosis by identifying a causative mutation in a patient with overt clinical phenotype.

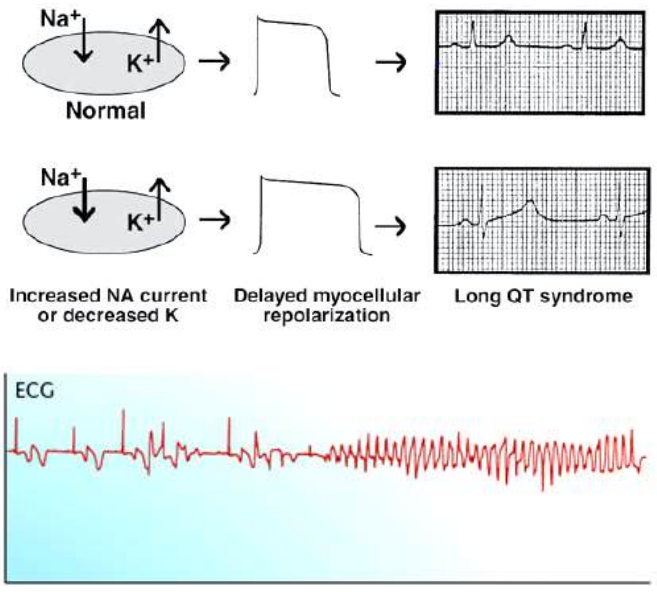
Brugada syndrome (BS) – is linked to mutations causing loss of function in a sodium channel (SCN5A). This results in very rapid repolarization in the outer (epicardial) layer of heart muscle. Electrical current flows from normally repolarizing inner-layer (endocardial) cells to the early-repolarizing epicardium. The resulting large voltage gradient produces depolarization and reactivation of the endocardial cell, causing extra beats that can initiate ventricular tachyarrhythmias.

- ✓ As in acute myocardial ischaemia, electrophysiological deterioration in the Brugada syndrome can be precipitated by Na^+–channel blocking drugs (quinidine, lidocaine, flecainide).
- ✓ Typical ECG findings, like acute myocardial ischaemia, include coved ST segment elevations in leads V1-V3 (reflecting abnormal local repolarization); death results from either ventricular fibrillation or tachycardia.
- ✓ Typically causes sudden death during sleep, after a large meal, or associated with fever and drugs.



Long QT syndrome (LQTS) - has more than 10 subtypes, but the most common types are loss-of-function mutations in KCNQ1 (encoding the I_{Ks}), loss-of-function mutations in KCNH2 (encoding the I_{Kr}), and gain–of–function mutations in SCN5A (encoding the I_{Na}).

- ✓ Long QT syndromes cause paroxysmal ventricular tachyarrhythmias of characteristic, polymorphic morphology (Torsades de Pointes) by impairing repolarization and causing arrhythmogenic early after-depolarizations (EADs) and ectopic beats.
- ✓ Sudden death typically occurs with exertion (especially swimming), excitement, but also at rest.
- ✓ All persons with QT-interval prolongation should be screened for acquired causes such as hypocalcemia, hypothyroidism, and the use of drugs that can prolong the QT interval: chloral hydrate, erythromycin, clarithromycin, terfenadine, sotalol, amiodarone etc.



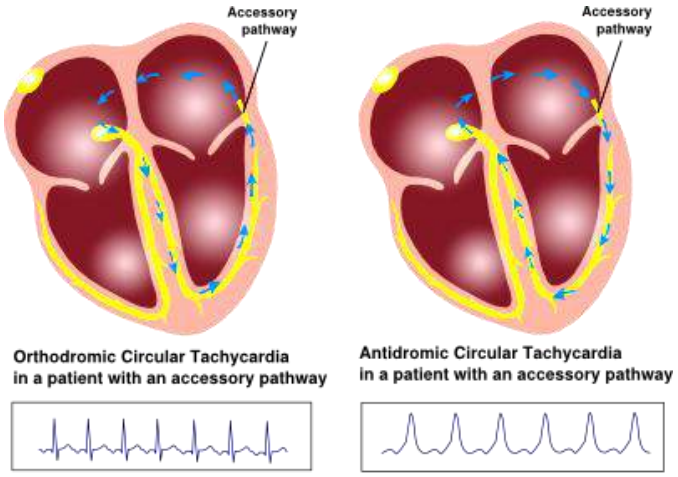
Catecholaminergic polymorphic ventricular tachycardia (CPVT) – is linked to mutations causing disturbances of intracellular calcium homeostasis and excitation–contraction coupling (eg, gene, encoding the cardiac ryanodine receptor). Calcium leakage from the sarcoplasmic reticulum is exacerbated during adrenergic stimulation, causing calcium overload and delayed afterdepolarisations.

- ✓ Sudden death occurs during exertion or excitement.

Wolff -Parkinson-White (WPW) syndrome

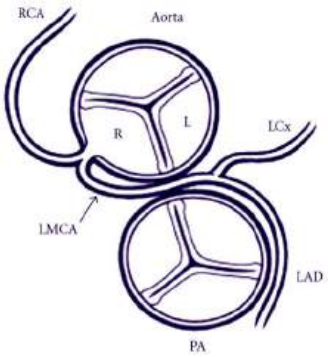
This is the most common accessory pathway syndrome affecting the heart. The classic features are a shortened PR interval and a slurring of the upstroke of the QRS complex, called the delta wave, that leads to prolongation of the QRS to greater than 100 ms. Approximately 70% of individuals with this condition have no underlying cardiac disease.

- ✓ Only 50% of patients will ever experience symptoms. Symptoms that most commonly occur are related to supraventricular tachycardias that accessory may occur due to participation of the pathway in a re-entrant circuit.
- ✓ There is a small but lifetime risk of catastrophic events (syncope, hemodynamic collapse) and/or sudden cardiac death from ventricular tachyarrhythmia and fibrillation.



- ✓ The most common tachycardias that present are **narrow complex tachycardias** where normal conduction occurs through the AV node and retrograde conduction occurs through the accessory pathway (orthodromic tachycardia).
  Wide complex tachycardias may also occur where the antegrade conduction is through the accessory pathway and retrograde conduction occurs through the AV node (antidromic tachycardia).
- ✓ Amiodarone or procainamide are the recommended treatments for wide complex tachycardias since medications that act on the AV node (beta-blockers, calcium antagonists) may enhance conduction through the accessory pathway.
- ✓ Electrophysiologic study of patients with WPW may allow for ablation of the accessory pathway and elimination of the associated arrhythmias.

Other Conditions Predisposing to Sudden Cardiac Arrest

Coronary artery anomalies	The most common coronary anomaly, accounting for one-third of all coronary anomalies is the origin of the left circumflex coronary artery from the right main coronary artery. This has no general clinical significance.Much less common (accounting for 1% to 3% of coronary anomalies) but of greater clinical significance is **the origin of the left main coronary artery (LMCA) from the right sinus of Valsalva.** When the LMCA passes between the aorta and the pulmonary artery, it is associated with sudden death. 
Myocarditis	○ Associated with atrial and ventricular tachyarrhythmias or bradyarrhythmias ○ Sudden deaths probably related to conduction system inflammation ○ Should abstain from sports for 6 months
Dilated Cardiomyopathy	Sudden death from ventricular tachyarrhythmia
Hypertrophic cardiomyopathy	Sudden death from myocardial ischemia and secondary ventricular arrhythmias
Arrhythmogenic Right Ventricular Cardiomyopathy	○ Sudden death from ventricular tachyarrhythmia ○ Can cause death yet have normal or near normal cardiac examination, before and after death
Mitral Valve Prolapse (MVP)	Not all patients with MVP are excluded from competitive sports, but some risk factors include mitral regurgitation, arrythmogenic syncope, history of ventricular arrhythmia or supraventricular tachycardia (SVT).

Heart Failure in Children

Heart failure occurs when the heart is unable to pump blood at a rate commensurate with metabolic needs (oxygen delivery). It may be due to a change in **myocardial contractility** that results in low cardiac output or to **abnormal loading** conditions being placed on the myocardium. The abnormal loading conditions may be **afterload** (pressure overload, such as with aortic stenosis, pulmonary stenosis, or coarctation of the aorta) or **preload** (volume overload, such as in ventricular septal defect [VSD], patent ductus arteriosus [PDA], or valvular insufficiency). Volume overload is the most common cause of heart failure in children.

The age of presentation is helpful in creating the differential diagnosis. In the first weeks of life, excessive afterload being placed on the myocardium is most common. Heart failure presenting around 2 months of age is usually due to increasing left-to-right shunts that become apparent as the pulmonary vascular resistance decreases. Acquired heart disease, such as myocarditis and cardiomyopathy, can present at any age.

In adults, cardiac failure usually involves failure of the left ventricle, with the most common causes in developed nations being coronary artery disease; hypertension-induced cardiac stress, arrhythmias and valvular disease. In developing nations, it has been reported that other causes are frequently implicated, including rheumatic heart disease and cardiomyopathy.

In children, the causes of cardiac failure are significantly different and many cases are due to congenital malformations, such as left-to-right shunts. In these patients the function of both the right and the left ventricles will be affected and these children suffer from high-output cardiac failure. Other significant causes of heart failure in children are cardiomyopathy and anthracycline toxicity, which lead to low-output cardiac failure. In developing nations, many cases are caused or exacerbated by anaemia, often secondary to malaria and malnutrition. It has also recently been identified that infants in ethnic minority groups in developed countries may be at risk of heart failure linked with hypocalcaemia and vitamin D deficiency.

Table **Causes of heart failure**

Volume overload	– Left-to-right shunts – Valvar regurgitation – Complex congenital cardiac lesions – Arteriovenous malformation, e.g. vein of Galen, haemangioma
Pressure overload	– Left heart obstruction, e.g. aortic stenosis, coarctation of the aorta, hypoplastic left heart – Acute hypertension, e.g. haemolytic uraemic syndrome, glomerulonephritis – Right heart obstruction, e.g. pulmonary stenosis
Cardiac arrhythmias	– Congenital complete heart block – Supraventricular tachycardia – Ventricular tachycardia
Ventricular dysfunction	– Myocarditis – Cardiomyopathy: dilated, hypertrophic, restrictive – Sepsis or anaemia – Pericardial effusion/cardiac tamponade – Ischaemia, e.g. birth asphyxia, anomalous left coronary artery

- ***Heart failure is a syndrome caused not only by compromised cardiac performance but also by the effects of compensatory mechanisms.***

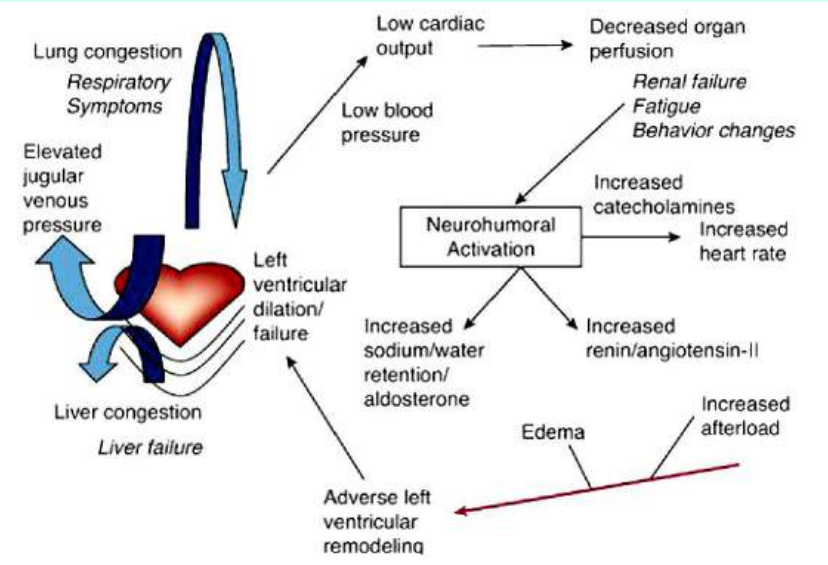


FIGURE. *Schematic representation of heart failure syndrome. Regardless of the etiology, the pathogenesis of heart failure has similar mechanisms. A decrease in cardiac output results in decreased end organ perfusion and activation of a neurohormonal cascade. Stimulation of endogenous catecholamines and activation of renin angiotensin aldosterone system causes increasing heart rate, preload and afterload. These compensatory mechanisms increase myocardial oxygen consumption and eventually lead to reverse remodeling, ventricular dilatation, increased propensity for arrhythmias, and decreased coronary reserve.*

- **The 2013 ACC/ AHA definitions:**
  - Heart failure with reduced ejection fraction (HFrEF): EF ≤40%, systolic HF
  - Heart failure with preserved ejection fraction (HFpEF): EF ≥50%, diastolic HF

- **Clinical Manifestations**

Signs of heart failure include tachycardia, tachypnea, pallor, cool extremities, hepatomegaly and peripheral edema.

- Typically presents with predominantly respiratory symptoms (tachypnea) and feeding difficulties. The history will often reveal that infant is feeding for longer periods of time than normal, and that feedings are terminated due to respiratory distress. Infants frequently become diaphoretic with feedings. Diaphoresis suggests adrenergic activation and is a major sign of CHF in infants. Ultimately, due to poor feeding and increased caloric expenditure, poor weight gain ensues (failure to thrive).
- Hepatomegaly is a reliable finding in infants with heart failure:
  - Decreased renal blood flow via activation of renin-angiotensin system leads to fluid retention, systemic venous congestion, and hepatomegaly.
- Young infants may have periorbital or facial edema. Jugular venous distension can be noted in older children.

- **Modified Ross Classification of Heart Failure for Children**

Class I	Asymptomatic
Class II	Mild tachypnea or diaphoresis with feeding in infants Dyspnea on exertion in older children
Class III	Marked tachypnea or diaphoresis with feeding in infants Marked dyspnea on exertion Prolonged feeding times with growth failure
Class IV	Symptoms such as tachypnea, retractions, grunting, or diaphoresis at rest

- **Heart Failure Staging in Pediatric Heart Disease (AHA, ACC)**

Stage	Interpretation	Clinical Examples
A	At risk for developing HF	Congenital heart defects Family history of cardiomyopathy Anthracycline exposure
B	Abnormal cardiac structure or function No symptoms of HF	Univentricular hearts Asymptomatic cardiomyopathy Repaired congenital heart disease
C	Abnormal cardiac structure or function Past or present symptoms of HF	Repaired and unrepaired congenital heart defects Cardiomyopathies
D	Abnormal cardiac structure or function Continuous infusion of intravenous inotropes or prostaglandin E1 to maintain patency of a ductus arteriosus Mechanical ventilatory and/or mechanical circulatory support	Same as stage C

- **Laboratory Studies**

• *Pulse oximetry* is helpful in identifying cyanosis in infants who have HF caused by increased pulmonary blood flow (left-to-right shunts) because recognizing cyanosis in an infant is nearly impossible by physical examination alone. Decreased percutaneous oxygen saturation never is associated with acyanotic heart disease unless poor tissue perfusion or intrapulmonary right-to-left shunting occurs.

• The *12-lead electrocardiogram* is essential to assess arrhythmiainduced HF.

• The *chest radiograph* may demonstrate cardiac enlargement, increased pulmonary blood flow, venous congestion, or pulmonary edema. However, chest radiographs generally have a high specificity but low sensitivity for detecting cardiac enlargement.

• Although not useful for the evaluation of HF, which is a **clinical diagnosis**, *echocardiography* is essential for identifying causes of HF such as structural heart disease, ventricular dysfunction (both systolic and diastolic), chamber dimensions, and effusions (both pericardial and pleural).

• Recently, a number of *HF biomarkers* have been identified that aid in assessing the severity of HF and predicting the course of the disease. BNP (brain natriuretic peptide) measurement is a readily available test that can distinguish between primary respiratory disease and cardiac-induced tachypnea. Because this peptide is released primarily in response to atrial stretching, it is a sensitive marker of cardiac filling pressure and diastolic dysfunction. C-reactive protein and TNF-alpha are both sensitive markers of systemic inflammation that correlate positively with a worse HF outcome in adult studies. C-reactive protein may augment interleukin-B, which can damage myocardium directly. TNF-alpha depresses nitric oxide endothelial relaxation acutely, an effect that can lead to ventricular remodeling and dysfunction over time.

- **Principles of Managing Heart Failure**

Recognition and Treatment of Underlying Systemic Disease	**Preload Reduction** ● Diuretics ● BNP
Timely Surgical Repair of Structural Anomalies	**Sympathetic Inhibition** ● Beta blockers ● BNP ● Digoxin
Afterload Reduction ● Angiotensin-converting enzyme inhibitors ● Angiotensin receptor blockers ● Milrinone ● Nitrates ● Brain natriuretic peptide (BNP)	**Cardiac Remodeling Prevention** ● Mineralocorticoid inhibitors ● Digoxin

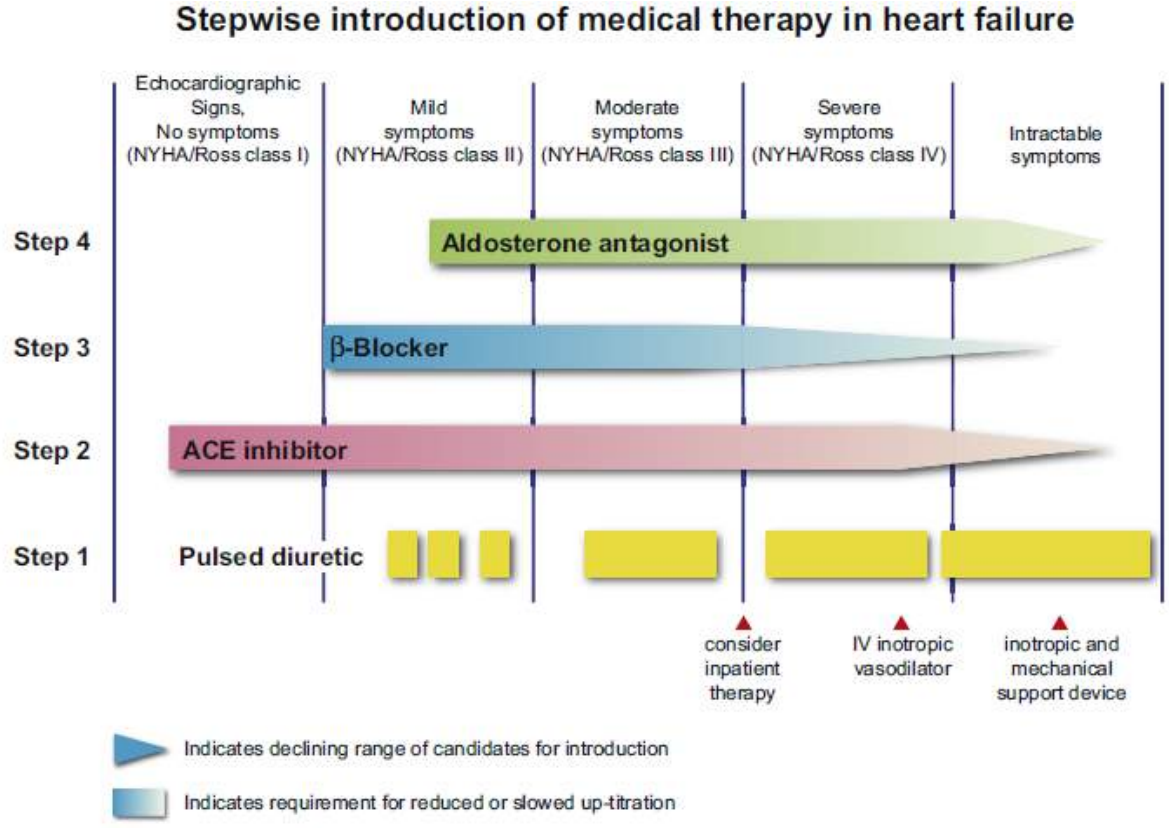
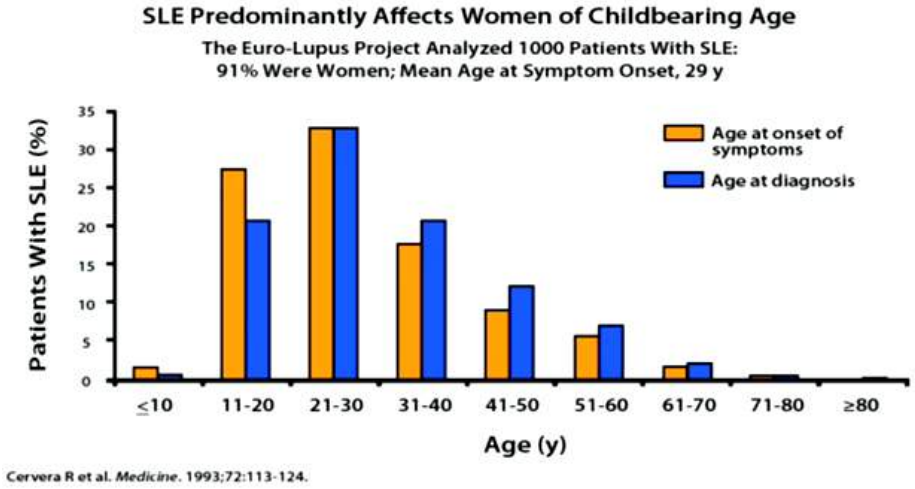


FIGURE. A symptom-based guide to the introduction of oral maintenance therapy for children with chronic heart failure (HF). The introduction of bblocker therapy might be considered in patients already taking ACE inhibitor therapy with asymptomatic persistent moderate reduction in left ventricular ejection fraction (usually ejection fraction less than 40%), especially if the etiology is considered to be ischemic heart disease. Lighter shading for each drug indicates when the possibility of a lower target dose, or slower increment than usual is needed, because of advanced HF with severely compromised systolic function. Narrowing of the bars indicates the possibility that fewer patients will tolerate the introduction of that agent at that given symptomatic stage. Note the preferred use of pulsed diuretic therapy, which becomes more frequent as symptoms advance. Red arrows indicate the point at which admission to hospital and additional support therapies might be required. ACE, angiotensin-converting enzyme; IV, intravenous; NHYA, New York Heart Association.

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

➢ Definition & Epidemiology

- Systemic lupus erythematosus (SLE) is a chronic, autoimmune disease affecting multiple organ systems.
- Can be life threatening. Pediatric patients with SLE have a more severe clinical course in comparison with their adult counterparts.
- Twenty percent of SLE cases are diagnosed during the first 2 decades of life. Pediatric SLE (pSLE) usually presents in post-pubescent females, with an average age of onset of 12 years. Before puberty, the male:female ratio is 1:3, but after puberty it increases to 1:9. Ethnicity plays an important role in the incidence of SLE. The incidence of SLE before age 19 years is between 6.0 and 18.9 cases per 100,000 in white girls but is higher in African American (20–30/100,000) and Puerto Rican girls (16.0–36.7/100,000). In addition, the incidence of SLE is higher in Hispanic, Native American, Pacific Islander, and Asian individuals than in white individuals.



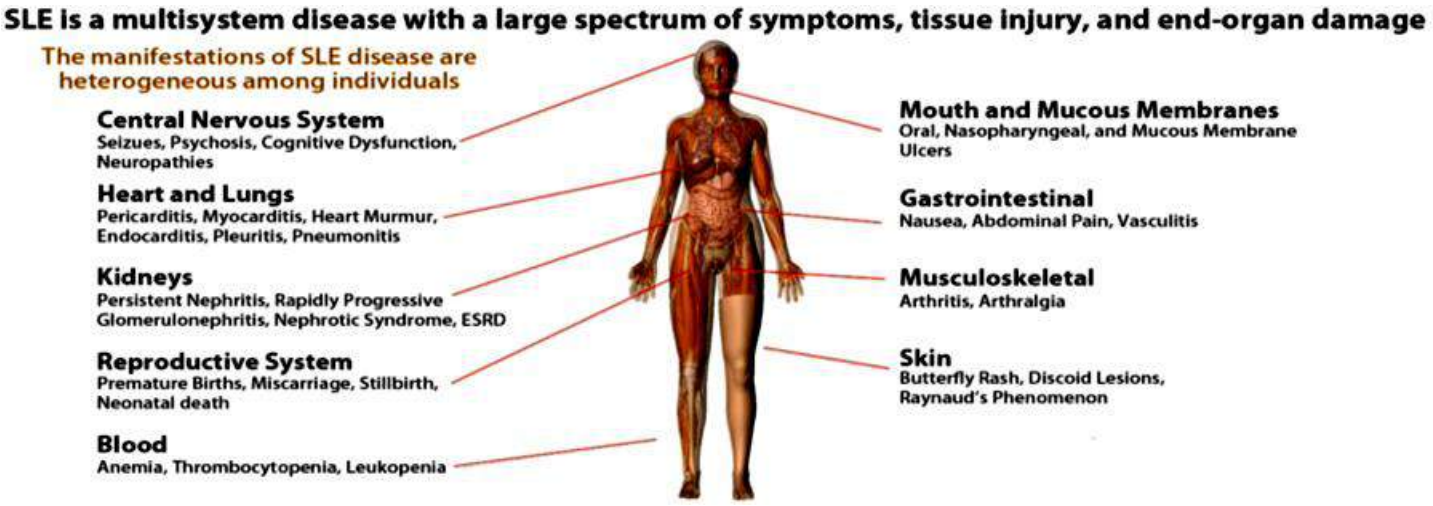
➢ Pathogenesis

- "classical" autoimmune disease: antibodies to any thinkable proteins of our body have been described in SLE-patients
- High amount of antibodies => immune complexes
- Complement consumption => susceptibility to infections
- Cause is unknown but thought to be related to environmental, genetic, and hormonal factors

➢ Pathology

- Immunoglobulin deposits are commonly seen
- Occasionally there is evidence of vasculitis both on pathology and clinically evident

➢ Clinical Features

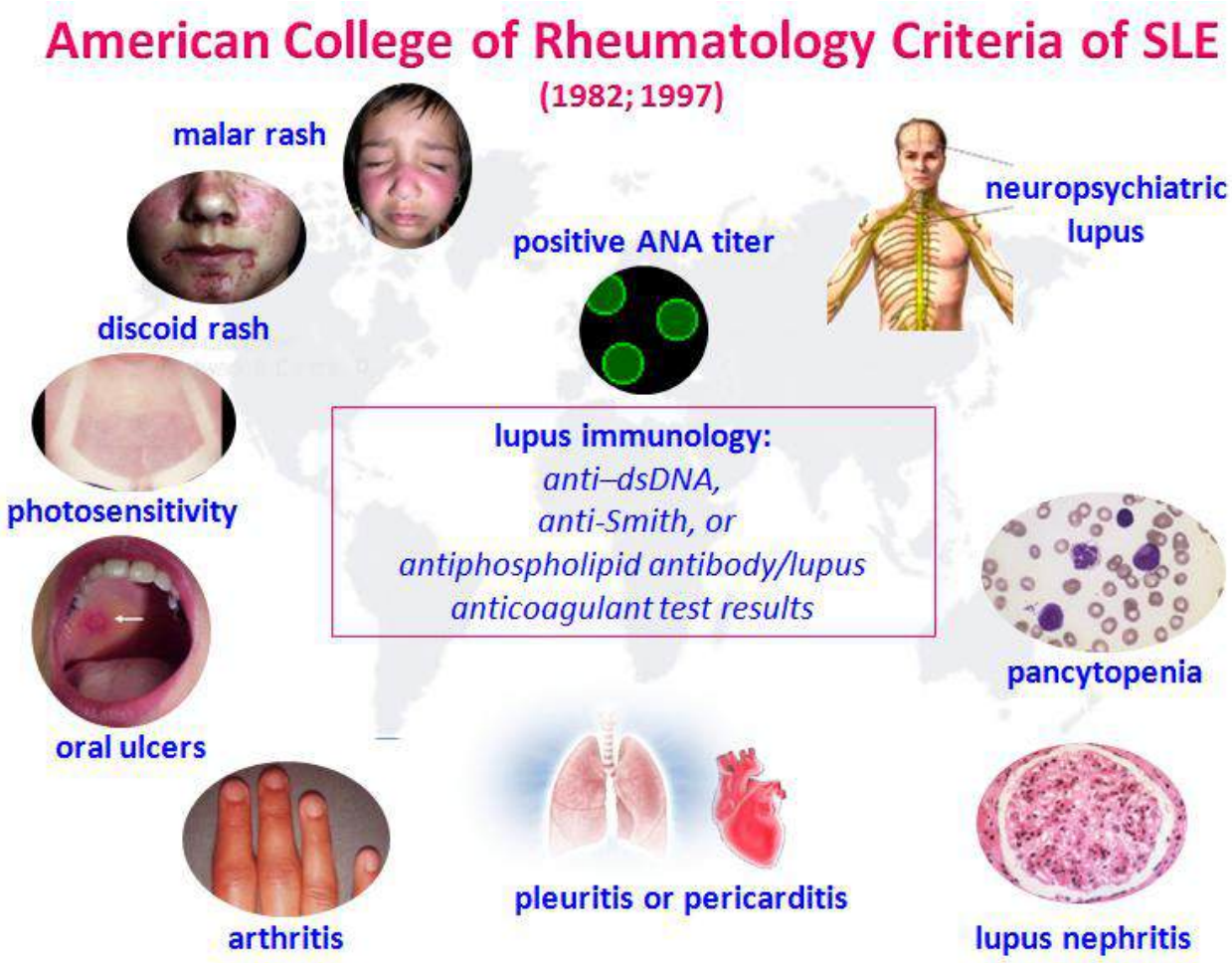


1. Constitutional symptoms: fatigue, fever, weight loss
2. Cutaneous
   - Malar rash: photosensitive "butterlly" rash on cheeks and nasal bridge but sparing nasolabial folds
   - Discoid rash: annular, scaly rash on scalp, face, and extremities that can lead to scarring
   - Photosensitivity, alopecia, painless oral and/or nasal ulcers
3. Cardiopulmonary: pericarditis, Libman-Sacks endocarditis, myocarditis, Raynaud phenomenon (vasospasm in hands triggered by cold exposure), pleuritis, pleural effusion, pulmonary hypertension, pulmonary hemorrhage
4. Renal: proteinuria, hematuria, pyuria, hypertension, renal insufficiency
5. GI: pancreatitis, hepatitis, intestinal vasculitis, protein-losing enteropathy
6. Musculoskeletal: arthritis, myositis, avascular necrosis
7. CNS: stroke, psychosis, seizures, chorea, transverse myelitis, cranial neuropathies, depression
8. Hematologic: leukopenia (particularly lymphopenia), anemia, thrombocytopenia, thrombosis

MANIFESTATION	ONSET (1st yr)	ANYTIME
Fever	55%	86%
Arthritis	78%	80%
Skin rash	79%	86%
Malar rash	36%	38%
Renal	55%	69%
CVS	14%	17%
Pulmonary	18%	18%
CNS	25%	34%
GI	19%	24%
Lymphadenopathy	34%	34%
Hepatosplenomegaly	30%	30%

➢ Diagnosis

The clinical diagnosis of SLE is based on the American College of Rheumatology criteria, which include the following: malar rash; discoid rash; pleuritis or pericarditis; oral ulcers; arthritis; a positive ANA titer; photosensitivity; proteinuria or evidence of nephritis; hemolytic anemia, thrombocytopenia, leukopenia; positive anti–double-stranded DNA, anti-Smith, or antiphospholipid antibody/lupus anticoagulant test results; and seizure or psychosis. *Of the 11 listed criteria, 4 are sufficient for classification.*



➢ Laboratory findings

- Leukopenia, anemia, and thrombocytopenia are common
- Electrolyte abnormalities, elevated kidney function tests, or hypoalbuminemia due to renal involvement
- ESR is usually elevated
- CRP is rarely elevated in SLE and warrants investigation for infection
- C3 and C4 are low with active disease due to complement consumption in process of clearing immune complexes
- ANA is positive in >95% of patients, usually with titers of 1:320 or higher
- Negative ANA virtually excludes SLE, but false positives are common
- Obtain testing for **antiphospholipid antibodies** because 50%-60% of pediatric SLE patients have these antibodies, which puts them at increased risk for arterial and venous thrombosis

➢ **Kidney biopsy** is performed to classify histologic subtype of lupus nephritis; different subtypes have different prognosis

➢ Treatment

1. Dependent on organ system involved

2. Mainstay is with oral prednisone (2 mg/kg/day) or intravenous (IV) methylprednisolone for significant organ involvement

3. Antimalarials such as hydroxychloroquine (5-7 mg/kg/day) can be used for skin manifestations, fatigue, arthritis, and antiphospholipid antibodies

4. NSAIDs help manage pleuritic chest pain, headaches, and arthritis

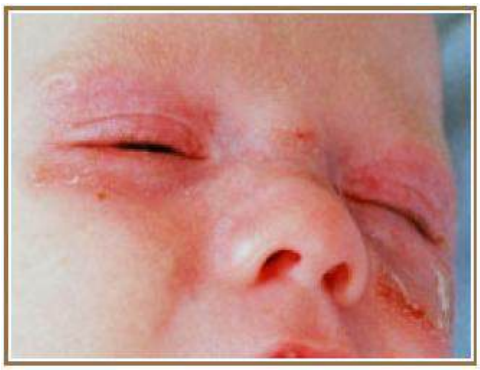
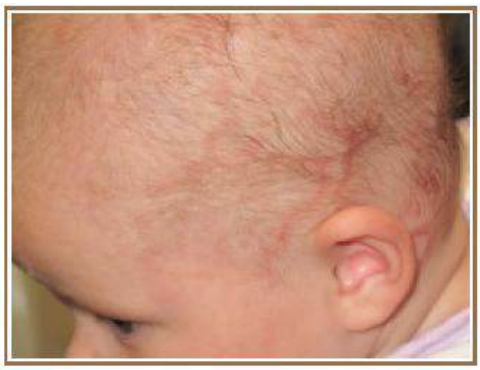
5. For persistent disease, mycophenolate mofetil, methotrexate, azathioprine, cyclophosphamide, or rituximab should be added

6. Presence of antiphospholipid antibodies should be treated with baby aspirin every day to prevent thrombosis

7. Sun precautions should be discussed because skin manifestations can be exacerbated by sun exposure

➢ Neonatal Lupus Syndrome

- Transplacental transfer of antibodies from mother to child
- Congenital heart block => hydrops fetalis, neonatal problems
- Postnatal rash (3-6 weeks after birth)
- Neonatal lupus is not a „disease“. Complete recovery except for the heart block. No increased risk for connective tissue disease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Abdominal Aspects of Familial Mediterranean Fever (FMF)

FMF is the most widespread and best-characterized monogenic auto-inflammatory disease (AID), affecting mainly ethnic groups originating in or around the Mediterranean basin: Sephardic Jews, Armenians, Turks, and Arabs. This disease is characterized by irregular, selflimited febrile episodes of inflammation of serous membranes and marked elevation of acute-phase proteins.

Although FMF is considered a periodic disease, some forms of FMF morbidity may be persistent rather than episodic. These include *protracted febrile myalgia, FMF-associated vasculitis, and persistently elevated inflammatory markers without apparent clinical signs*. Other long-term complications include peritoneal adhesions, which may lead to intestinal obstructions and female infertility; and amyloidosis involving the gastrointestinal tract, liver and spleen. These complications occur mainly in untreated or colchicine-non-adherent patients, and are associated with certain ethnicities and countries of residence. Amyloidosis of the kidney is the most serious long-term complication of FMF, potentially progressing to end-stage renal disease.

FMF is inherited with an autosomal recessive pattern and is caused by mutations in the **MEFV gene** located on chromosome 16p13.3. More than 310 MEFV sequence variants have been reported to Infevers (http://fmf.igh.cnrs.fr/ISSAID/infevers/), an online registry of AID mutations. Most are located in exon 10, including the most common M694V, V726A, M680I and M694I mutations. The wide clinical variability in FMF is partly explained by genetic heterogeneity. **More severe disease** is associated with the M694V as well as the M680I mutation and the complex allele V726A-E148Q.

FMF is generally considered to be an autosomal recessive disease. However, Stoeffels and colleagues described an autosomal dominant auto-inflammatory disease associated with MEFV mutations affecting amino acid 577 in three families, each of different ethnic background. Febrile attacks in these patients were prevented by colchicine, but differed from typical FMF in that attacks were prolonged, lasting up to weeks. The dominant inheritance pattern implies these patients had a gain-of-function mutation, suggesting that the mechanism of disease in these patients may also be different to that of classical FMF.

The diagnosis of FMF is based on clinical symptoms and supported by ethnic origin and family history. As discussed above, some patients may present with incomplete or atypical attacks, especially small children and patients with mild disease. In such cases, diagnosis can be difficult, resulting in delayed initiation of treatment. Since the discovery of the MEFV gene, molecular genetic testing is used as a diagnostic adjunct in these cases. In patients with possible clinical disease, a finding of two mutations in MEFV gene confirms the diagnosis of FMF. In patients with atypical attacks and one mutation (heterozygotes) or no mutation, the genetic test is considered non-diagnostic, and a therapeutic trial of colchicine is given for 3–6 months to ascertain whether there is a decrease in the severity and frequency of attacks.

Clinical rather than genetic criteria have remained the basis for diagnosis of FMF; the use of genetic testing for diagnosing asymptomatic patients or for screening of unaffected family members of patients with FMF is not currently recommended.

The minimal and most current criteria for diagnosis of FMF are the **Tel Hashomer clinical criteria**. Genetic testing only has a 70-80 % positive predictive value.

Major criteria

- Recurrent febrile episodes associated with peritonitis, pleuritis or synovitis
- Amyloidosis of AA-type without a predisposing disease
- Favorable response to daily colchicine

Minor criteria

- Recurrent febrile episodes
- Erysipelas-like erythema
- Positive history of familial Mediterranean fever in a first degree relative

Definite Diagnosis: 2 major or 1 major + 2 minor criteria.
Probable Diagnosis: 1 major + 1 minor criteria.

It is important to make the correct diagnosis in individuals with recurrent monoarthritis. The criteria that suggest a diagnosis of FMF in persons with monoarthritis include a high fever, favorable response to colchicine, history of FMF in sibs and other family members, and an appropriate genotype.

ABDOMINAL ATTACKS AND RELATED MANIFESTATIONS

Acute Peritonitis

The most frequent manifestation of FMF is episodic abdominal pain of sudden onset and short duration (days). Abdominal attacks are experienced by 95% of FMF patients during at least some of their attacks, with about 50% citing such episodes as the first symptom. The pain may be diffuse, spreading over the entire abdomen, or much less commonly, localized to a limited area. The intensity of abdominal pain is usually severe. Patients prefer to stay in bed, motionless and flexed, in an attempt to reduce the pain. Most patients experience either constipation or intact bowel habit, yet in 20% of the patients diarrhea may occur. After 12–24 h, the intensity of the signs and symptoms is reduced and usually within 72 h the attack recedes, leaving the patient in the same condition as before the attack. The time interval to the next attack ranges from days to months or even longe.

Pelvic Attacks in Female FMF Patients

An FMF attack, when restricted to the pelvic region, simulates acute pelvic inflammatory disease (PID). In theses cases, attacks are frequently precipitated by menstruation or pelvic instrumentation. Many of the attacks last between several hours and up to 24 h. The awareness of the possibility of pelvic attacks is important to avoid unnecessary surgery.

Mechanical Intestinal Obstruction

Peritonitis results in sterile exudate in the peritoneal cavity, containing fibrin and polymorphonuclear cells. The organization of this exudate may lead to adhesions, which may in turn cause adhesive small bowel obstruction.

Involvement of the Alimentary System with Amyloidosis

Amyloidosis in FMF develops independently of the frequency, duration, and intensity of flare-ups. Established data indicate that male sex, recurrent arthritis, and homozygosity to the M694V mutation of MEFV and to the α-allele of serum amyloid A1 increase the risk of developing amyloidosis.

FMF amyloidosis affects many organs, including the kidneys, adrenals, intestine, spleen, liver, stomach, thyroid gland, heart, and lungs. Of these, kidney involvement is by far the most clinically significant. The amyloid gradually fills the glomerular tufts, causing proteinuria and nephrotic syndrome at an early stage and ultimately leading to renal failure. Colchicine treatment has prevented the development of kidney amyloidosis. Because of the present widespread use of colchicine, only a minority of FMF patients now presents with end stage renal disease.

The GI tract is a site of amyloid deposition early in the course of FMF. However, amyloidosis of the GI tract becomes clinically overt only in some patients and only after many years of asymptomatic amyloid deposition. Hemodialysis, kidney transplantation, and colchicine treatment have prolonged lives of FMF patients with amyloidosis. Therefore, more patients with non-renal amyloidosis-related clinical manifestations are currently seen. In some of them, the digestive system becomes the center of the clinical picture. FMF-related amyloid deposition throughout the entire wall of the small intestine may cause *constipation, intractable diarrhea, and severe malabsorption*. Reduced motility permits bacterial overgrowth, bile acid deconjugation, and, consequently, worsening diarrhea and steatorrhea. The main practical issue is to differentiate amyloid-induced from colchicine-induced diarrhea. Parenteral alimentation is the only answer for patients in whom amyloidosis is the culprit.

FMF-Associated Diseases Affecting the Alimentary Tract

1. Inflammatory Bowel Disease (IBD)

IBD is a condition that has recently been shown to be more frequent and severe in non–Ashkenazi Jewish patients with FMF than in an ethnically matched general population. IBD was present in 0.5% of FMF patients, compared to < 0.1% in the general population.

FMF associated with IBD shows a higher attack rate and is more frequently complicated with amyloidosis.

2. Vasculitides Associated With FMF

Vasculitis	GI Features of the Vasculitis	General Features	Features That Mark the Combined Disease
Henoch Schonlein purpura	Bloody diarrhea, abdominal pain	Fever, purpura, arthralgia, glomerulonephritis	Prolonged and severe disease
Polyarteritis nodosa	Perforation, ischemia, abdominal pain, GI-bleeding, cholecystitis	Fever, nephropathy, arthritis, hypertension, neuropathy, rash, cardiomyopathy	Young age, severe course, perirenal hematoma
Protracted febrile myalgia	Abdominal pain	Fever, myalgia, rash, arthralgia	PFM is FMF specific
Behçet's disease	Diarrhea, abdominal pain	RAS, genital ulcer, eye lesions, arthritis, thrombophlebitis, erythema nodosum, epididymitis	Lessened response to colchicine, prominent GI manifestation

PFM = protracted febrile myalgia; RAS = recurrent apthous stomatitis.

3. Irritable bowel syndrome

It is a GI disorder that is characterized by altered bowel habits and abdominal pain without any detectable structural abnormalities.

IBS is commonly associated with, or may arise from fibromyalgia, which is another FMF-related disease. It is characterized by widespread musculoskeletal pain, stiffness, and fatigue, along with multiple tender points that are widely and symmetrically distributed. In addition to IBS, fibromyalgia is also associated with other diseases including irritable bladder, premenstrual syndrome, restless legs syndrome, sicca syndrome, rheumatoid arthritis, and other connective tissue diseases.

COLCHICINE AND THE GI TRACT

Therapeutic doses of colchicine for FMF patients, ranging from 1 to 2 mg p.o., may cause abdominal pain and cramping, hyperperistalsis, heartburn, vomiting, bulky stools, and frank diarrhea. The overall incidence of these GI complaints is around 20%. GI side effects are reversible, at least in part, upon dose adjustment or by administration of colchicine in specifically prepared capsules.

Pediatric Pancreatitis

Pancreatitis is an inflammatory condition of the pancreas. Two major forms of pancreatitis, acute and chronic, are recognized. Acute pancreatitis is a reversible process, whereas chronic pancreatitis (CP) is irreversible. Acute pancreatitis is more prevalent, and most patients have a single episode of pancreatitis. A small number of patients have recurrent episodes of acute pancreatitis and are at risk of developing CP.

Acute Pancreatitis (AP)

Definition of Acute Pancreatitis

Acute pancreatitis (AP), defined as the acute nonbacterial inflammatory condition of the pancreas, is derived from the early activation of digestive enzymes found inside the acinar cells, with variable compromise of the gland itself, nearby tissues and other organs.

AP is broadly classified as mild or severe. **Mild AP** is often referred to as **interstitial pancreatitis**, based on its radiographic appearance. **Severe AP** implies persistent failure of one or more end organs. Most children (≥90%) have mild disease.

Epidemiology of Acute Pancreatitis

Acute pancreatitis occurs in all age groups, even in infants. Currently, the best estimates suggest that there are 3.6 to 13.2 pediatric cases per 100,000 individuals per year, an incidence that approaches the incidence of disease in adults.

Causes of Acute Pancreatitis

Common	*Less common*	*Rare*
Biliary disorders Systemic conditions Medications Trauma Idiopathic	Infection Metabolic diseases Genetic/hereditary disorders	Autoimmune pancreatitis Anatomic pancreaticobiliary abnormalities

Pathophysiology of Acute Pancreatitis

Acute pancreatitis results from injury of the pancreas and a subsequent inflammatory response that may involve adjacent and distant tissues and organs. The prevailing theory of the pathophysiology of pancreatitis includes several distinct steps. First, an event initiates a process of acinar cell injury. The cell injury produces pancreatic edema and a local inflammatory response, with release of inflammatory mediators. The production of cytokines and chemokines provoke a systemic inflammatory response. The magnitude of this inflammatory response determines the clinical severity of acute pancreatitis and can lead to complications such as pancreatic necrosis, shock, and distant organ failure.

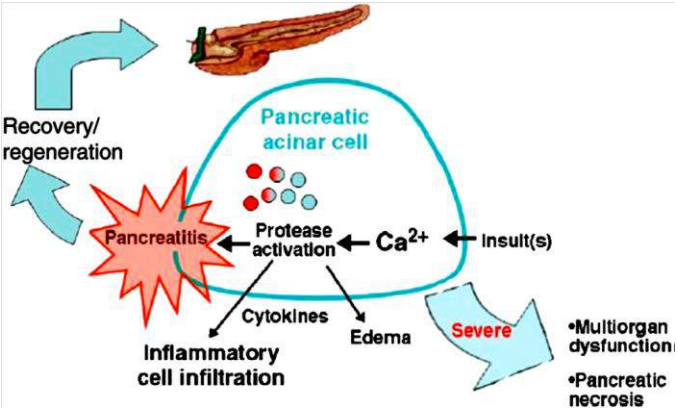


Figure 1. Pathophysiology of acute pancreatitis. Multiple causes of acute pancreatitis can lead to abnormal intra-acinar calcium signaling. This signaling leads to intra-acinar zymogen activation and resulting pancreatic injury and cytokine response, as well as potential systemic inflammatory response.

{from *Bai HX et al. What have we learned about acute pancreatitis in children? J Pediatr Gastroenterol Nutr. 2011;52(3):263*}

Diagnosis of Acute Pancreatitis

Acute pancreatitis in pediatric patients requires at least two of three criteria: (1) **abdominal pain** suggestive of or compatible with acute pancreatitis (ie, abdominal pain of acute onset, especially in the epigastric region); (2) **serum amylase or lipase*** activity at least three times greater than the upper limit of normal; and (3) **imaging findings**** compatible with acute pancreatitis.

** Other pancreatic products like phospholipase A2, trypsin, trypsinogen activation peptide and elastase are elevated in acute pancreatitis, but none have gained widespread use in the clinical laboratory. Although levels of lipase and amylase that are three times the upper reference limit suggest pancreatitis, the level of elevation is not diagnostic.* ***Both enzymes can be elevated in conditions unrelated to pancreatitis (table1) and both can be normal when there is radiographic evidence of acute pancreatitis.***

*** Computed tomography (CT) and ultrasound images of the pancreas serve to confirm the presence of pancreatitis, to identify complications and to investigate other causes for the symptoms.*

- Ultrasound findings included enlargement of the pancreas, altered echogenicity of the pancreas, a dilated main pancreatic duct, gallstones, biliary sludge, dilated common and intrahepatic ducts, pancreatic calcification, choledochal cysts, and fluid collections.

- A CT scan will show similar findings, except that abnormal attenuation is seen rather than altered echogenicity.

- Studies in animals indicate the CT contrast given early in the course of acute pancreatitis may further diminish blood flow to ischemic areas of the pancreas and increase the likelihood of necrosis. Although similar studies have not been done in humans, it is reasonable to avoid CT scans early in the course of pancreatitis and save this study for patients that do not show improvement. Endoscopic retrograde cholangiopancreatography (ERCP) is reserved for patients with unexplained recurrent episodes of pancreatitis, prolonged episodes of pancreatitis where a structural defect or duct disruption is suspected, and in some cases of gallstone pancreatitis. **Magnetic resonance cholangiopancreatography (MRCP)** can be helpful in defining abnormalities of the ductal system and with the development of improved software MRCP may supplant ERCP as the method of choice for evaluating the anatomy of the ductal system.

Table1 Conditions Associated With Elevation of Amylase or Lipase Levels

Condition	Amylase	Lipase
Abdominal	• Acute pancreatitis • Biliary tract disease • Intestinal obstruction/ischemia • Mesenteric infarction • Peptic ulcer • Appendicitis • Ruptured ectopic pregnancy • Ovarian neoplasm	• Nonpancreatic abdominal pain • Acute cholecystitis • Esophagitis • Intestinal obstruction/ischemia • Peptic ulcer
Salivary gland	• Trauma • Infection (ie, mumps) • Sialolithiasis • Irradiation	
Thoracic	• Pneumonia • Pulmonary embolism • Myocardial infarction • Cardiopulmonary bypass	
Infectious	• Viral gastroenteritis • Pelvic inflammatory disease	• Human immunodeficiency virus infection
Metabolic	• Diabetic ketoacidosis • Pheochromocytoma	• Diabetic ketoacidosis • Hypertriglyceridemia
Neoplastic	• Ovarian, lung, esophageal, or thymic tumors	
Drugs	• Opiates	
Trauma	• Cerebral trauma • Burns	
Renal	• Renal insufficiency • Renal transplantation	• Renal insufficiency
Inflammatory	• Macroamylasemia • Celiac disease	• Macrolipasemia • Celiac disease
Miscellaneous	• Cystic fibrosis • Acute liver failure • Viral gastroenteritis • Pregnancy • Eating disorders: anorexia, bulimia	

Management of Acute Pancreatitis

The management of acute pancreatitis traditionally has consisted of pancreatic rest (no enteral feeding), antiemetics, analgesia, fluid support, and monitoring for complications.

Complications of Acute Pancreatitis

Local		Systemic	
Inflammation • Localized to pancreas • Systemic extension Ileus Pancreatic edema Pancreatic necrosis Pancreatic abscess	Fat necrosis pancreatic hemorrhage Pancreatic pseudocyst Pancreatic duct rupture Pancreatic duct stricture Thrombosis of adjacent blood vessels	Shock Sepsis Hypermetabolic state Hypocalcemia Hyperglycemia Vascular leak syndrome	Multiorgan system failure Disseminated intravascular coagulation (DIC) Pleural effusions Acute renal failure Splenic artery pseudoaneurysm

Acute Recurrent Pancreatitis (ARP)

ARP is defined as at least two episodes of acute pancreatitis per year, or more than three episodes over a lifetime, in a patient without CP or a pancreatic pseudocyst.

The diagnostic criteria for each ARP episode and its treatment are the same as described earlier for acute pancreatitis. It is important to thoroughly explore all potential causes and triggers because many are preventable and knowledge of the cause can guide management and prognosis.

Causes of Acute Recurrent and Chronic Pancreatitis

Biliary calculi
- Macrolithiasis
- Microlithiasis (<2 mm)[a]
- Sludgea

Congenital pancreaticobiliary abnormalities
- Anomalous pancreaticobiliary junction
- Choledochal cyst
- Annular pancreas
- Pancreas divisum[b]

Genetic[c]
- Hereditary pancreatitis, PRSS-1 mutation
- SPINK-1 mutation
- CFTR mutation

Duodenal inflammation
- Crohn disease
- Celiac disease
- Infection

Medications

Sphincter of Oddi dysfunction

Metabolic
- Hypercalcemia
- Hypertriglyceridemia

Intestinal duplication cyst
- Gastric
- Duodenal

Autoimmune
- Localized to pancreas
- Systemic disorder

Idiopathic[c]

CFTR = cystic fibrosis transmembrane conductance regulator; **PRSS-1**= cationic trypsinogen; **SPINK-1**= serine protease inhibitor Kazal type 1.

a Controversial associations.

b Only causative if present with another predisposing factor (eg, CFTR heterozygote mutation).

c Most common causes of chronic pancreatitis in pediatric patients.

Normally, the pancreas synthesizes trypsinogen and SPINK1 at a molar ratio of 5 to 1. If trypsinogen activation is brisk, the capacity of SPINK1 to inhibit trypsin becomes overwhelmed and the next tiers of defense mechanisms come into play.

In cases of ARP, genetic screening for PRSS-1 and SPINK-1 mutations should be conducted.

Although complete gene sequencing of CFTR is available, this investigation is not necessary for all patients. A sweat test should be performed. Patients who have mild/variable CFTR mutations will have values in the indeterminate or low positive zones. The presence of a CFTR mutation can then be confirmed by using complete gene sequencing. Patients who have CFTR mutations should be referred to a CF center for additional evaluation.

Chronic Pancreatitis (CP)

CP is defined as a process leading to irreversible destruction of the pancreatic parenchyma and ducts and loss of exocrine function. Many of these patients have a history of ARP before the irreversible changes in pancreatic anatomy and function become apparent.

CP can present at all ages in children. Classic cystic fibrosis is the most common cause in children. The incidence and prevalence of CP in childhood are not known.

The causes of CP are the same as those of ARP. In children, CP is usually idiopathic or associated with mutations in PRSS-1, SPINK-1, CFTR, or CTRC genes, alone or in combination.

In pediatrics, cystic fibrosis is the most common cause of chronic pancreatitis!

CP results from the sequelae of long-standing destructive inflammation. Current theory suggests that CP begins with acute pancreatitis and progresses to fibrosis. Instead of resolution, as in acute pancreatitis, the destructive process continues in susceptible individuals. Susceptibility and rate of progression are likely influenced by genetic and environmental modifiers.

Diagnosis

The diagnosis of CP is clinical and based on a combination of symptoms, imaging studies, and functional insufficiency. It is important to consider all of these parameters when CP is suspected in a patient, because diagnosis often is delayed. With advanced disease, amylase and lipase levels will not be elevated, even in the presence of disabling pain.

CLINICAL FEATURES. For many patients, recurrent episodes of pancreatitis will raise concerns about CP. Patients present with mild to intense abdominal pain, usually epigastric. The pain can be constant or intermittent and often is described as deep and penetrating, with radiation to the back. Many times the pain is episodic, as in ARP. There are numerous causes of this pain. The pain can result from obstruction of pancreatic ducts by fibrosis or stones, inflammation of the parenchyma (acute-on-CP), perineural inflammation, or pain imprinting in the peripheral or central nervous system. Rarely, patients present with symptoms of malabsorption, such as weight loss, fatty stools, or diarrhea. Even rarer are patients who present with jaundice from extrahepatic biliary obstruction caused by pancreatic fibrosis or a pseudocyst. An occasional patient will have an upper gastrointestinal hemorrhage from venous thrombosis as the presenting sign. Diabetes develops late in the course of CP, and children seldom, if ever, present with symptoms of diabetes.

IMAGING. Imaging studies provide evidence of morphologic change in the gland or ducts. Currently, **MRCP is the imaging method of choice.** This modality has limitations in that the side branches of the main pancreatic duct are not well defined. ERCP is better at defining ductal anatomy but usually is not required. CT can reliably detect calcification, gland atrophy, fat replacement, and ductal dilation but is not as sensitive for duct changes as MRCP or ERCP. In adults, endoscopic ultrasonography (EUS) has gained acceptance for detecting changes in CP, although there is disagreement about the standards for diagnosing chronic changes by using this method.

PANCREATIC FUNCTION TESTING. Pancreatic function testing can identify pancreatic insufficiency and support the diagnosis of CP.

- In recent years, **fecal elastase** has been used to screen for pancreatic insufficiency. This test is widely available, easy to conduct, and can be performed even if patients are taking pancreatic enzyme supplements. Like all indirect tests, fecal elastase has poor sensitivity for detecting mild to moderate pancreatic insufficiency.
- **72-hour fecal fat collection** remains the best test for steatorrhea. As with other noninvasive tests, the 72-hour fecal fat collection result is abnormal only with advanced disease. Fat testing should not be used alone for diagnosis because disease of the intestinal mucosa can cause steatorrhea.

Management of CP

The stage and etiology of CP determine its management.

- When recurrent episodes of acute pancreatitis dominate the clinical course, the management is identical to that of acute pancreatitis.

- With disease progression, chronic pain management and therapy for pancreatic insufficiency are required. In a few pediatric patients, diabetes will require treatment. Because unrelenting pain affects many patients, most of the therapeutic effort centers on pain control.
  - At first, acetaminophen may be effective, but therapy generally advances to narcotics.
  - Pancreatic insufficiency is treated with pancreatic enzyme replacement therapy. The goal is to restore digestive function and maintain weight gain and growth. Because no studies of the effective dose range exist for patients who have pancreatitis, the recommendations for treating patients who have cystic fibrosis are used for enzyme dosing in patients who have CP.
  - Antioxidant therapy (selenium, ascorbic acid, b-carotene, a-tocopherol, and methionine) is prescribed frequently as a therapeutic trial.

- Endoscopic treatment for CP should be considered only when ductal strictures or pancreatic duct stones are present or for symptomatic pseudocysts. The role of endoscopic sphincterotomy and stent placement remains controversial.

- Surgical approaches are still used in select patients.
  - Localized disease can be treated with ***partial pancreatic resection***.
  - ***Total pancreatectomy with islet cell autotransplant*** is currently offered to patients who have genetic causes of pancreatitis and to those afflicted with unrelenting pain.

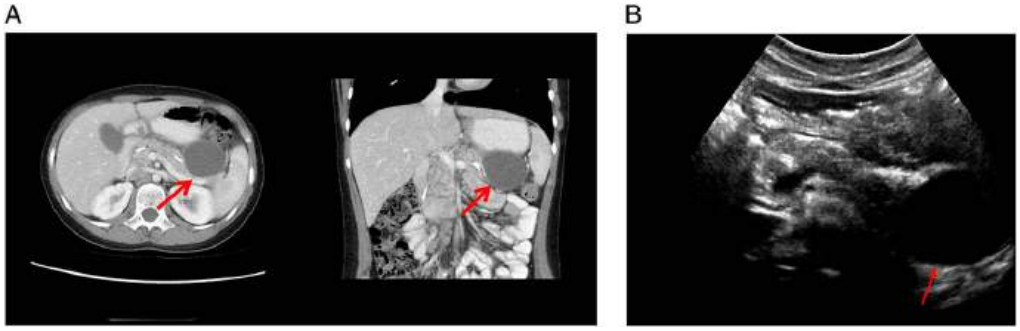
Complications of CP

Long-term natural history studies are beginning to delineate the prognosis of CP. Contrary to previous teaching, the pain of CP does not "burn out." The pain may vacillate in intensity and frequency, but it will not resolve with time.

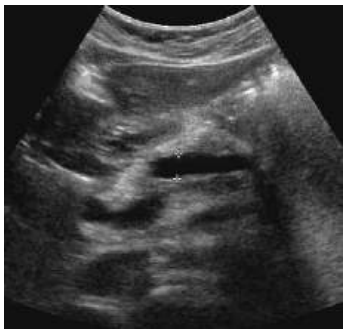
Both pancreatic insufficiency and diabetes appear later in the course. Diabetes may take 2 or 3 decades to become clinically significant. Even so, pediatric patients will likely develop diabetes in their lifetime.

Pancreatic cancer is a long-term risk for all pediatric patients who have CP. In hereditary pancreatitis, pancreatic cancer appears first in the fourth decade (incidence of 0.5%), and the incidence increases with age. The high probability of pancreatic cancer is a factor in deciding whether to proceed with total pancreatectomy and islet cell autotransplant.

IMAGING FINDINGS



Scans of pancreatic pseudocyst (arrow). A. Computed tomography. B. Ultrasonography.



Chronic pancreatitis. Ultrasound image with an enlarged pancreatic duct (+) with a paucity of surrounding pancreatic tissue.

FEATURES OF METABOLISM IN CHILDREN. FLUIDS AND ELECTROLYTES

Metabolism involves:

- all chemical reactions that provide energy and substances needed for growth
- **catabolic reactions** that break down large, complex molecules to provide energy and smaller molecules
- **anabolic reactions** that use ATP energy to build larger molecules

Pediatric peculiarities of metabolism:

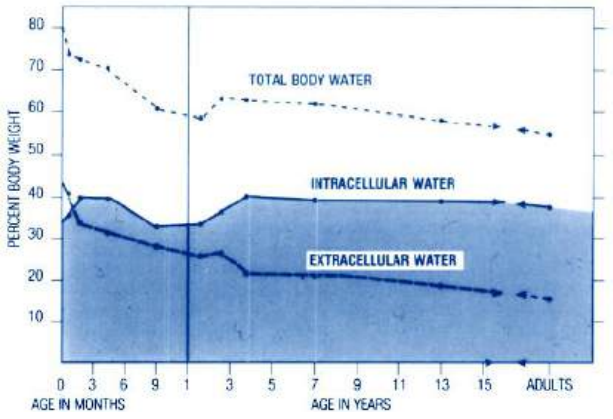
1. intense anabolic process and growth => higher needs for energy, nutrients, water and oxygen

2. higher metabolic rate

Fluid Physiology in Children

Water is the most abundant substance in the human body, constituting about 60% of body mass in a reference man, or 50% in a reference woman [Wilmore and Costill, 1994], although this percentage can change, depending on sex, age, and percentage of body fat. As a person grows older and develops a greater percentage of body fat, the percentage of total body water (TBW) gradually decreases.

Neonates contain more water than adults: 75-80% water with proportionately more extracellular fluid (ECF) than adults. By the age of 12 months, the percentage of total body water (TBW) has decreased to 60% which is the adult value.



The TBW is distributed among two major components:
1) intracellular fluid (ICF) - 2/3 (40 %),
2) extracellular fluid (ECF) - 1/3 (20 %), which includes:

- *blood volume (5%)*
- *interstitial volume (15%)*

Water turnover is considered in terms of external balance and internal fluxes.

External balance refers to the comparison between the water input from and the water output to the external environment. Over any period of time, input equals output and the organism is in water balance.

Internal balance or flux refers to the movement of water across the capillaries of the body (including the secretion and absorption of the various transcellular fluids) and movement of water between interstitial and intracellular fluids.

Why Infants are more vulnerable to water loss?

1. Larger water turnover (1/2 of ECF every day versus 1/7 of ECF in adults)

Table. Body Water Turnover per Body Weight *[J Physiol Anthropol 19(5):207-212, 2000]*

	Age group (months)				Age group (years)				
	1-3	4-6	7-9	10-12	1-3	4-6	7-9	10-12	13--15
Mean	160	119	114	97	64	63	54	46	40
SD	34	19	27	29	21	17	13	9	7

Water turnover is high in neonates and decreases with increasing age and the concomitant decreases of metabolic rate and growth velocity.

2. Larger body surface area

3. Poorly developed thirst mechanism

4. Reduced ability to concentrate urine

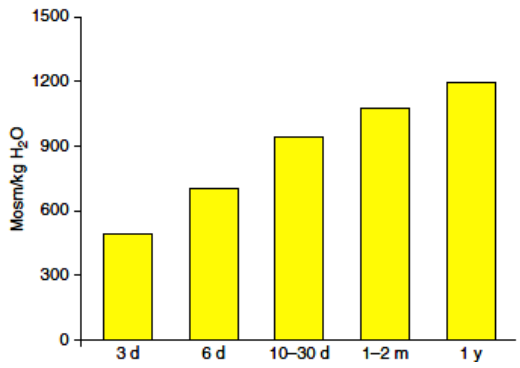


FIG. Maturation of the concentrating ability during the first year of life in term infants. *(Adapted from Polácek E, Vocel J, Neugebauerová L, et al: The osmotic concentrating ability in healthy infants and children,*Arch Dis Child *40:291-295, 1965.)*

Immaturity of the distal nephron with an anatomically shortened loop of Henle lead to reduced ability to concentrate urine. Maximum urinary concentrations are up to 550 mosm/l in preterm infants, and 700 mosm/l in term infants, compared to 1200 mosm/l in adults.

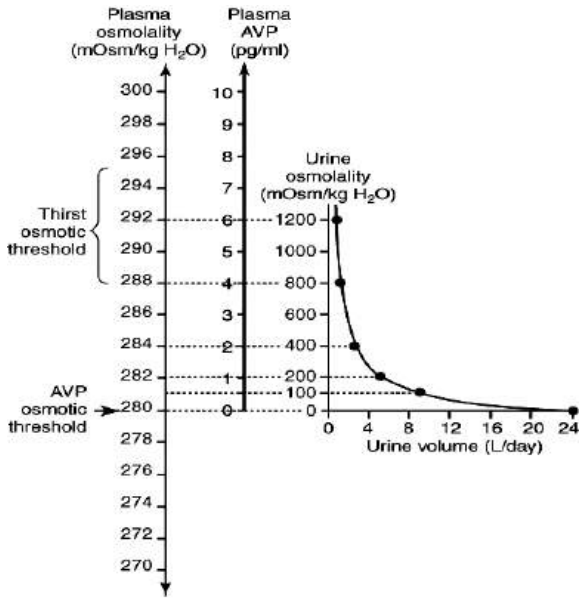
An infant's renal system can maintain a healthy fluid and electrolyte status. However, it doesn't function as efficiently as an adult's during periods of stress. For example, if a child doesn't receive enough fluid to meet his needs, his kidneys can't adequately concentrate urine to prevent dehydration. Conversely, if a child receives too much fluid, he may be unable to dilute urine appropriately to get rid of the increased volume.

Infants are also vulnerable to water gain due to reduced GFR and frequent development of syndrome of inappropriate antidiuretic hormone secretion (SIADH).

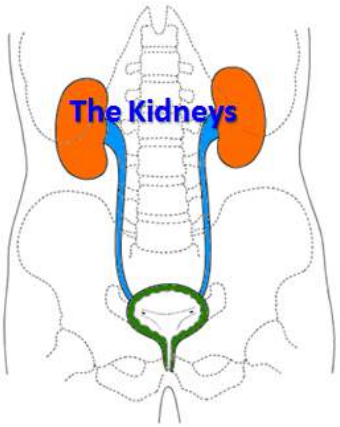
Changes in the osmolality of plasma lead to **antidiuretic hormone (ADH)** secretion at a much lower threshold than they lead to thirst.
The value of **280 mOsm/kg** is the threshold value (or set-point) of the osmoreceptor.
Very small increases in ADH lead to very large changes in urine volume.

In addition to changes in osmolality, there are several other non-osmotic factors which increase ADH secretion (SIADH). These include input from higher cerebral centres and various drugs.

SIADH is the most frequent cause of hyponatremia.



The Pediatric Urinary System



Upper Urinary Tract:

- renal calices and pelvis
- ureter

Lower Urinary Tract:

- urinary bladder
- urethra

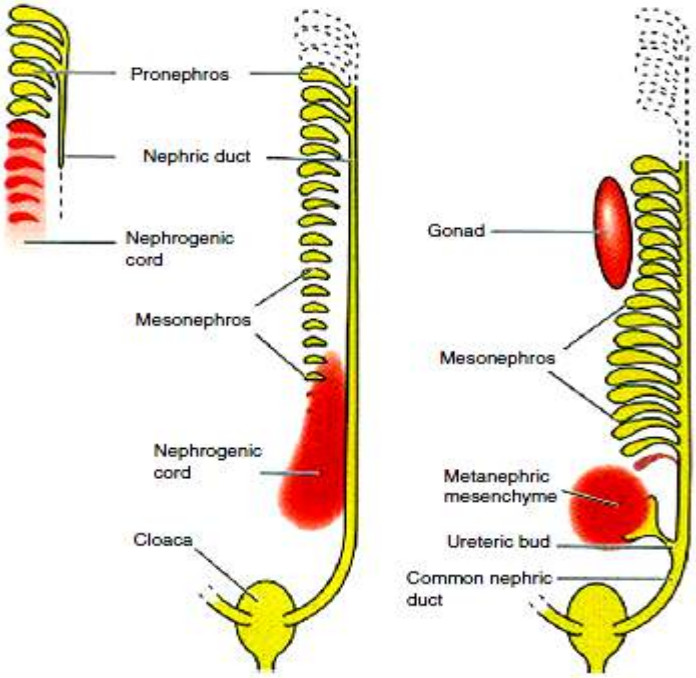
Development of the Renal Anlage

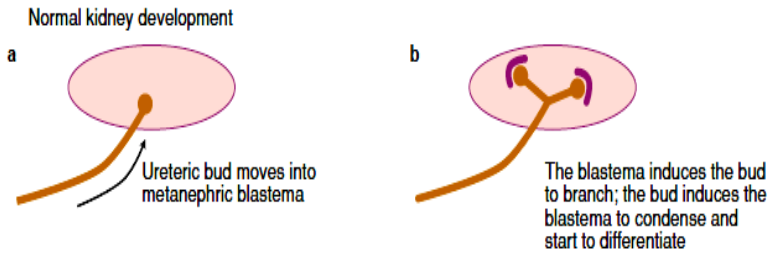
The embryonic development of the kidney commences during the third week of gestation from the intermediate mesoderm (Mac-Gregor, 2010). The developing baby's kidney will begin to produce urine between 9 and 12 weeks of gestation, and this is excreted into the amniotic fluid. Failure of any part of the renal system to develop correctly will have implications for the infant. As kidney development and genitourinary tract development are interdependent, if there is any abnormality of one system, then abnormalities in the other system should also be considered.

The kidneys develop along a cranio-caudal gradient. Typically, the development passes through three stages:

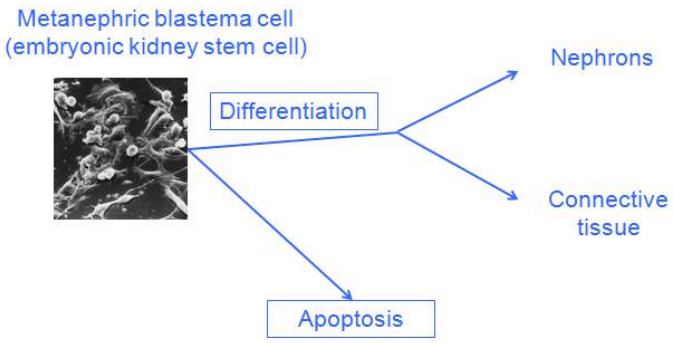
- *Pronephros*
- *Mesonephros*
- *Metanephros*

The first two developmental stages have a transitory character and the definitive kidneys actually develop from the metanephros stage.

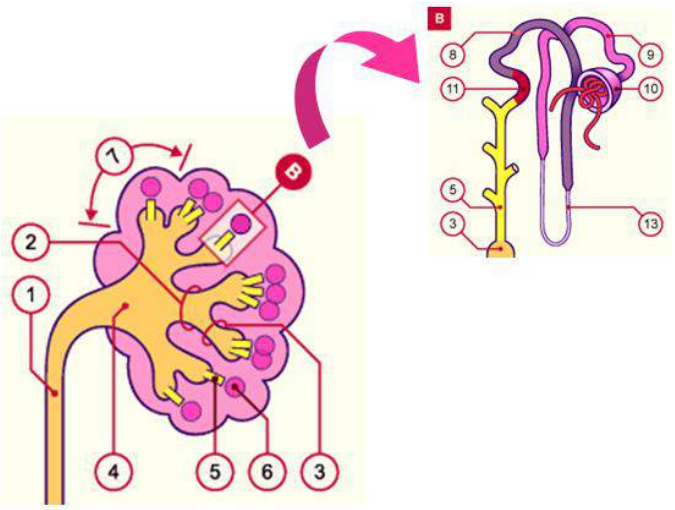




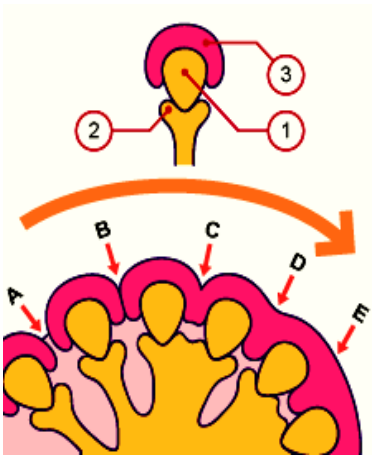
(a) Development of the definitive kidney begins with the ureteric bud (which develops into the ureter and collecting ducts) moving into the metanephric blastema. (b) In a two-way inductive interaction, the blastema induces the ureteric bud to branch, and the bud induces the blastema to condense around it and begin to differentiate.



The metanephric blastema cells are normally induced to differentiate into epithelial cells (which go on to form the mature nephrons) or stromal cells (which make up the connective tissue). Those cells that are not induced to differentiate undergo apoptosis (programmed cell death).



The cranial end of the ureter anlage subdivides dichotomically many times due to the inductive effect of the metanephric blastema. As a result **major and minor calices** are formed. Further dichotomic branching follow - up to the 15th generation (roughly 32 weeks). Thereby the caliber of the tubules is reduced more and more so that finally **1-3 millions collecting ducts** are formed in the periphery of the metanephric blastema.



At birth the kidneys have a multilobular appearance, due to the development of the ureter anlage in the metanephric blastema. Normally, towards the end of the fetal period, the lobes are considerably smoothed, but they still exist until after birth.
Completion of the smoothing follows during childhood by the increase in volume of the connective tissue and the increase in size of the nephrons without any change in their number. With only few exceptions, adult kidneys no longer exhibit any lobulation.

Location

The kidneys form in the pelvis, and by week 9 of gestation they have risen into the posterior abdominal wall to meet the suprarenal (adrenal) glands (England, 1996). As they ascend into the abdominal cavity they also rotate and locate themselves on either side of the vertebra between T12 and L3 when fully developed. During the migration into the abdominal cavity, changes to the blood supply to the kidneys occur. Initially blood is supplied from the common iliac artery, but as they migrate upwards the blood supply now comes from branches of the abdominal aorta, and this becomes the permanent renal artery eventually with all the accessory branches deleted (Moore and Persaud, 2003). When migration is complete the kidneys are retroperitoneal organs, as they are situated on the posterior aspect of the abdominal wall behind the peritoneum. The left kidney is located slightly more superior to the right kidney, with the right kidney slightly inferior due to the positioning of the right lobe of the liver. The adrenal glands are located on the superior aspects of each kidney.

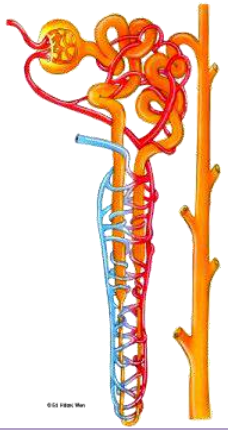
Clinical application
Failure of the kidney to migrate upwards into the abdominal cavity can lead to several conditions arising. These include:
- horseshoe kidneys (kidneys that fuse during ascent);
- pelvic kidney (kidney that fails to ascend);
- malrotation of the kidney;
- accessory branches of the renal artery.

The kidney is designed to perform a number of **essential functions**:

- Excretion of waste products
- Regulation of body fluid volume and composition (salt, water and pH balance)
- Endocrine and metabolic (renin, prostaglandins, erythropoietin, vitamin D metabolism)

All these functions of the kidney are due to its unique microanatomy. The main structural and functional unit of the kidney is the **nephron**. There are 200 000 to 2 million nephrons in each kidney.
No new nephrons are formed after 34-36 weeks of gestation and in extrauterine life.

Each nephron is composed of an **initial filtering component (the "renal corpuscle")** and a tubule specialized for reabsorption and secretion (**the "renal tubule"**).
The renal corpuscle consists of two structures: a glomerulus and a Bowman's capsule. It filters out solutes from the blood, delivering water and small solutes to the renal tubule for reabsorption and modification.



Urine output (diuresis) is a net result of glomerular filtration and tubular reabsorption.

Despite the reduced rate of glomerular filtration, the relative magnitude of diuresis per kg of body weight is higher in children than in adults. This is due to a high rate of water turnover and reduced tubular reabsorption of water in children.

The kidney and urine production at birth

Newborn infant	Renal function
Fetal kidneys have no function in homeostasis	Their function is to produce urine to add to the volume of amniotic fluid
Low glomerular filtration rate (GFR) in newborn	GFR in healthy newborn is 30 mL/min per 1.73 m^2 compared with an adult, whose GFR is 120 mL/min per 1.73 m^2
Newborn kidney main aim is to optimize dietary solutes for growth and not excretion	Newborns undergo rapid growth and have little excess dietary solute that requires excretion; therefore, the newborn kidney is optimized for retention of essential substances such as sodium and other minerals Also in the presence of periods where growth ceases due to ill health, the infant has insufficient renal reserve; thus, homeostasis can become unbalanced quickly
At term the infant's kidney conserves sodium, while the pre-term infant's kidney loses sodium	Term infant's urine is mostly salt free and can thrive on human milk that is low in sodium. Consequently, a pre-term infant will become sodium depleted and need added dietary sodium in order to prevent hyponatraemia
Low urine osmolarity	Inability to concentrate urine as a newborn

- The neonate has an immature kidney function at birth which makes it **vulnerable to water loss and fluid gain**, such as losing fluid through rapid breathing or failure to feed.
- The neonate's kidneys weigh about **23 g** but have their full complement of filtering units (nephrons); this weight will double in six months and treble by the end of the first year eventually growing to its adult size by puberty which shows a ten-fold increase from birth. The growth of the kidney depends on its work; if one kidney is removed the other will double in size and take on the function of both.
- When the infant is born the loss of placenta flow, followed by a rapid increase in the infant's own renal blood flow, causes **a high vascular resistance in the neonate kidney**. This results in a temporarily reduced renal blood flow and filtration through the filtering units to produce urine; however, as the infant starts to feed and the load presented to the kidney increases, 95% of infants will pass urine in the first 24 hours after birth.
- **The kidney capillary network resistance reduces over the first few weeks of life**, which allows increasing filtration ability by the glomeruli, however, the newborn kidney glomeruli capsules are formed of **cuboid epithelium** and are not fully replaced by **thin pavement epithelium** and fully functional until after the first year. These small, immature nephrons also have **short Loops of Henle** where water and sodium are normally adjusted; salt (sodium) should not be added to an infant's diet as it cannot excrete the excess to requirements easily and the excess sodium will retain water in the arteries and veins, raise blood pressure and dilate the developing heart. The infant's distal convoluted tubules in the nephron are relatively resistant to the hormone aldosterone, released from the adrenal cortex in response to high blood sodium, which results in limited excretion of sodium and thus concentrating ability of urine in the infant.
- **A reduced glomerulus filtration rate (GFR) 28–30 ml/min/m2 at birth** increases over time to approximately 100 ml/min/m2 at nine months; the GFR increases fourfold during the first 1–2 years of life, at which point the adult glomerular filtration rate is attained (Dean RFA and McCance RA1947; Rubin MI 1949). This developmental change in glomerular filtration rate is not due to an increase in

glomerular number as no new nephrons are formed after 34–36 weeks of gestation. However, there are changes in renal hemodynamics and the glomerular basement membrane that result in an increase in the glomerular filtration rate during postnatal development. The most important factor that leads to an increase in glomerular filtration rate is the **postnatal increase in glomerular surface area**. If there was no increase in solute and water reabsorption that parallels the increase in glomerular filtration, the neonate would become volume-depleted with a minor developmental increase in glomerular filtration rate. Thus, there is a balance between changes in glomerular filtration rate and transport designated **glomerulotubular balance**. Glomerulotubular balance persists in the adult nephron so that changes in glomerular filtration rate seen with changes in extracellular fluid volume are paralleled by appropriate changes in tubular transport. However, in very premature neonates, there is some glomerulotubular imbalance evidenced by glucosuria,with normal serum glucose levels.

- **Difficulty in excretion of acids** impairs the ability of the kidney to correct acidosis – for example, if the infant is underfed it will breakdown body fat for energy (ketones are released as a waste product in fat breakdown which reduces the blood pH acidity and may irritate the brain). The infant blood pH average is slightly lower (more acidic) than the older child at 7.3–7.35 (normal range 7.35–7.45) thus the blood acidity will fall more quickly the younger the child and body responses will occur more rapidly.

Fluid homeostasis in the neonate is compromised because

• The kidneys receive only 15–20 % of the cardiac output (25 % in adults).
• The GFR (ml/min/1.73m 2) in the premature infant is 10–15 and 15–20 in the term infant. These values double over the first 2 weeks after birth and reach adult values of 80–120 by 1–2 years of age.
• Maximum urine concentrating capacity is low at birth (up to 600mOsm/kg) and increases over the first 2 months of life and then progressively over the first year of life.

Neonatal hypernatraemic dehydration

• A complication of inadequate breast milk production that may go unrecognized, particularly in the first child who is exclusively breast fed.
• If severe, venous and/or arterial thrombosis, and AKI (acute kidney injury) may occur.

Developing continence

Bladder capacity and volume increase with age.

Urinary frequency is closely related to urine formation and bladder capacity. The neonate will pass 20–35 ml of urine four times a day while intake is low and milk production establishes in the mother, but this soon rises to 100–200 ml ten times a day by the tenth day of life. Then the newborn urinates almost every hour: 20-24 times per day. Later, when the baby is not fed at night, the total number of voids decreases. After toilet training normal urinary frequency ranges from 4 to 7 times per day. This is due to an increase in bladder capacity and the acquisition of bladder control. **Daily control** of bladder function appears at the age of 2-3 years, while the **night control** mechanism is generated at the age of 3–7 years.

Assessment of the Urinary Tract in Children

Urinary tract diseases occur with or without appearent clinical manifestations (eg., urine frequency; urgency; changes of urine output and urine color; edema; hypertension; tachypnea etc.). Asymptomatic renal diseases may be detected via urinary screening tests.

➢ Important factors in the antenatal and birth history

• 90-95 % of infants pass urine within 24h.
• Weight loss over 10 % of birth weight is significant.
• Transient proteinuria may occur in the first days of life.
• Plasma creatinine reflects maternal levels at birth.
• Plasma creatinine may rise in the first 3 weeks of life in premature infants due to tubular reabsorption.
• Plasma bicarbonate may be lower than expected as the renal threshold for bicarbonate is 18–20mmol/L, rising to 24–26mmol/L by 1 year of age.

Commonly used drugs administered during pregnancy that affect the fetal kidney
• Angiotensin converting enzyme inhibitors (ACEIs) affect placental perfusion and inhibit nephrogenesis.
• Non-steroidal anti-inflammatory drugs (NSAIDs) affect fetal renal perfusion. May cause renal cysts and chronic kidney disease (CKD).

Polyhydramnios
Polyhydramnios occurs in approximately 1 % of pregnancies. In the majority of cases there is no underlying fetal abnormality, but maternal problems such as diabetes may be present. If a fetal abnormality is present, the majority are in the gastrointestinal (GI) tract (decreased swallowing of liquor). Only a small proportion of polyhydramnios is caused by fetal renal disease, typically Bartter syndrome.

Oligohydramnios
• Bilateral urinary tract obstruction.
• Renal agenesis.

Raised alfa-fetoprotein
Present in all conditions with leakage of fetal protein, such as:
• Neural tube defects.
• Congenital nephrotic syndrome (CNS).
• Epidermolysis bullosa.

➢ Assessment of renal function in children

Plasma creatinine concentration (PCr)	Main test of renal function. Rises progressively throughout childhood according to height and muscle bulk. May not be outside laboratory 'normal range' until renal function has fallen to less than half normal
Estimated glomerular filtration rate (eGFR)	The formula eGFR = k × height (cm) ÷ creatinine (μmol/L) provides estimate of GFR. Better measure of renal function than creatinine and useful to monitor renal function serially in children with renal impairment (k is 40 if creatinine measured using Jaffe method or 30 if measured enzymatically)
Inulin or EDTA glomerular filtration rate	More accurate as clearance from the plasma of substances freely filtered at the glomerulus, and is not secreted or reabsorbed by the tubules. Need for repeated blood tests limits use in children
Creatinine clearance	Requires timed urine collection and blood tests. Rarely done in children as inconvenient and inaccurate
Plasma urea concentration	Increased in renal failure, often before creatinine starts rising, and raised levels may be symptomatic. Urea levels also increased by high protein diet and if in a catabolic state.

➢ Radiological investigation of the kidneys and urinary tract

Ultrasound (US)	Standard imaging procedure of the kidneys and urinary tract, provides anatomical assessment but not function. Excellent at visualising urinary tract dilatation, stones and nephrocalcinosis (small, multiple calcium deposits in renal parenchyma) Advantages: non-invasive, mobile Disadvantages: operator-dependent, will not detect all renal scars
DMSA scan (^{99m}Tc dimercaptosuccinic acid)	*Static* scan of the renal cortex Detects functional defects, such as scars, but very sensitive, so need to wait at least 2 months after a urinary tract infection to avoid diagnosing false 'scars'
Micturating cystourethrogram (MCUG)	Contrast introduced into bladder through urethral catheter. Can visualise bladder and urethral anatomy. Detects vesicoureteric reflux (VUR) and urethral obstruction Disadvantages: invasive and unpleasant investigation especially beyond infancy, high radiation dose
MAG3 renogram (mercapto-acetyl-triglycine, labelled with ^{99m}Tc)	*Dynamic* scan, isotope-labelled substance MAG3 excreted from the blood into the urine. Measures drainage, best performed with a high urine flow. In children old enough to cooperate (usually >4 years), scan during micturition is used to identify VUR
Plain abdominal X-ray	Identifies unsuspected spinal abnormalities May identify renal stones, but poor at showing nephrocalcinosis.

➢ **Renal biopsy with histology and immunohistochemistry** helps in confirmation of the diagnosis and are indicated:

- in case of the renal failure of unknown etiology
- to determine the case of the renal hematuria and proteinuria

etc.

➢ Collecting urine

Urine samples are often required of small children, and there are many ways to catch them! A **'mid-stream' sample** is the best, but difficult to obtain if the child is uncooperative. Older children can be washed with water round the perineal area and then instructed to allow some urine to pass into the toilet before they sample the urine into a sterile pot before completing their voiding. Another way is to **attach a collecting plastic bag** over the urethral opening, easier in boys than girls, or **place a collection pad/cotton ball** in the nappy/pants/knickers. The parent/carer can also be requested **to catch a clean sample** from a toddler who is left without a nappy until they void. This method is time-consuming but less traumatic for some children who are sore.

Methods to collect urine from children

Specimen	Indication	Potential problems
Clean catch	Infants	Difficult to time Three samples ideally needed prior to treatment
Suprapubic aspirate	May use in infants < 1 year Standard in sick infants	*'Gold standard'* sample Invasive technique
Catheter sample	If catheter *in situ* In sick older child	Contamination possible
Mid-stream urine (MSU)	Children > 3 years old (or younger with patience)	Contamination possible

➢ Observing urine

Routine observation of the child's urine is helpful in detecting change in general health as well as for the laboratory test.

• **Smell** that is strongly ammoniacal may be the sign of infection; or if the child is taking medication it may reflect that of the oral preparation, for example antibiotics. Some foods also produce a characteristic smell in the urine, for example asparagus.

• Appearance should be **straw coloured**; if concentrated it will be a dark orange, and if diluted a pale lemon colour. Red urine may reflect the diet of the previous day, for example beetroot. Jaundiced babies will have dark orange/brown urine due to the excretion of bile salts which should be excreted through the gut. Pink deposits from small babies are urates, not blood.

• Children normally void urine five or six times per day depending on their drinking volumes and environment conditions (on hot days they may pee less frequently). Those who are dehydrated may not void for eighteen to twenty-four hours and still not have a distended bladder. However, some children are embarrassed to void in the presence of strangers or in strange environments; standing them or sitting them in an appropriate position will often get results.

URINE TESTS

Urinalysis (dipstick)	Sticks can be used to test for: glucose, protein, ketones, pH, urobilinogen, nitrates and nitrites, leukocyte esterase
Microscopy	White cells, red cells and bacteria (Gram stain) – seen in infection Casts and red cells – seen in glomerular inflammation/nephritis
Culture	Bacteria, white cells – seen in infection

• **Protein in the urine** is normal in small amounts (normally 100 mg/m2/day). In children, two-thirds of the physiologic urine protein consists of albumin and one-third represents a mixture of Tamm-Horsfall protein and globulin. This ratio is reversed in adults.

Normal protein excretion must be differentiated from that which is caused by disease states. Persons who do not have renal disease may have proteinuria after strenuous exercise or during dehydration. Functional (nonrenal) proteinuria may also be seen in congestive heart failure (CHF), cold exposure, and fever. Postural (orthostatic) proteinuria may also occur in a small percentage of normal individuals. In this situation, the client spills protein while in an upright posture but not when recumbent. Postural proteinuria is evaluated by having the client collect a urine sample on first arising and then approximately 2 hours later after having been up and about. The second sample should be positive for protein; the first should be negative. Orthostatic proteinuria is generally a benign condition, although the client should be reevaluated periodically for persistent, nonpostural proteinuria.

Renal disease resulting in proteinuria may be a result of damage to the glomerulus or to the renal tubules. When the glomerular membrane is damaged, greater amounts of albumin pass into the glomerular filtrate. If damage is more extensive, large globulin molecules are also excreted. Nephrotic syndrome is an example of renal disease primarily associated with glomerular damage. In this disorder there is heavy proteinuria accompanied by decreased serum albumin. In contrast, renal disease resulting from tubular damage is characterized by loss of proteins that are normally reabsorbed by the tubules (i.e., low-molecular-weight proteins). An example of renal disease primarily associated with tubular damage is pyelonephritis. The proteinuria that occurs in disorders involving the renal tubules is generally not as profound as that associated with glomerular damage.

• **Glucose** is not usually present unless the child is anxious, for example from injury or chronic stress, or has eaten a large amount of sugary foods and the blood sugar levels are higher than the usual limits.

• **Ketones** are commonly found in children's urine where they have not eaten recently, for example in the morning if they have not had breakfast or in the evening after a long day at school. Children who are feverish have a raised metabolic demand (their bodies are working faster), as do children who are very active. Their bodies are breaking down their fat reserves to release energy; their glycogen (carbohydrate energy reserves in the muscles and liver) stores are quickly used up if they do not eat. Release of ketones is the by-product of this fat metabolism.

• **The acidity of normal urine** is 5.5 – acidic. Small children often have a higher score; their urine is more alkaline due to their diet of milk and milk products. Children who have a high vegetable diet may also have an alkaline result. Urine is acid because the kidney is filtering hydrogen ions out to maintain a blood pH of approximately 7.3.

• **The specific gravity (SG) of urine** is useful to detect dehydration, together with other observable signs such as small and infrequent volume passed. The specific gravity of water is 1,000, so the more solutes in the urine the higher the number will be.

Poststreptococcal Glomerulonephritis (PSGN)

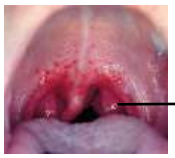
PSGN is an immune-mediated inflammatory disease of the kidneys that develops 1-3 weeks after acute infection with specific nephritogenic strains of group A beta–hemolytic streptococci (pharyngotonsillitis, scarlet fever, skin infections). The disease damages the glomeruli, letting protein and red blood cells leak into the urine.

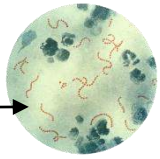
Clinical manifestations may range from asymptomatic microscopic hematuria to severe nephritic syndrome with

- gross hematuria (red to dark brown urine),
- proteinuria (may reach to nephrotic values),
- edema,
- hypertension,
- impaired renal function, up to the development of acute renal failure (ARF).

The overwhelming majority of patients develop a full recovery. Very rarely, the disease progresses to end-stage renal failure, and mortality is seen in less than 1% of patients at the onset of the disease as a result of pulmonary or brain edema.

Clinical Course of PSGN





Nephritogenic strains of group A beta–hemolytic streptococci

latent phase 1-3 wk

PSGN

Microscopic hematuria

Gross hematuria

Proteinuria

Edema

Hypertension

Reduced glomerular filtration rate

Full recovery

Progression to end-stage renal failure:
- in children - 2% of cases
- in adults - 30% of cases

Mortality at the onset of the disease: <1% of cases

General investigations in acute nephritic syndrome

Urine	Urinalysis (protein, blood, casts)
	M, C & S (haematuria, proteinuria, casts, features of infection)
Blood	FBC, ESR
	U&E, creatinine, LFTs
	Complement levels (C3 and C4)
	Viral titres, ASOT
	HBsAg, ANA
Throat swab	M, C & S (features of infection)

Specific investigations to look for previous streptococcal infection:
– Antistreptolysin O titre (ASOT)
– Anti-DNAse B antibodies
– Strep test

* M, C & S microscopy, culture and sensitivities
U&E urea and electrolytes

Management

The management is *supportive*:

- Fluid restriction – give **insensible loss** (300–400 mL/m^2/day) + **urine output**
- Sodium restriction – difficult in children, hence often use 'no added' salt diet
- Management of hypertension, e.g. diuretics
- Penicillin if positive throat swab or nephrotic range proteinuria
- Renal dialysis if necessary, e.g. if marked hyperkalaemia

NEPHROTIC SYNDROME

Nephrotic syndrome is characterized by *heavy proteinuria* and the consequences of hypoalbuminaemia. It occurs in 1 in 50 000 children, is twice as common in boys, and the typical age of presentation is 1–6 years.

Diagnostic tetrad

- **Proteinuria >40 mg/m2/h, or >1000 mg/m2/day, or >50 mg/kg/day, or >3.5 g/1.73m2/day**
- **Hypoalbuminaemia <25 g/L**
- **Generalized edema**
- **Hyperlipidaemia (raised LDL and triglycerides)**

Nephrotic syndrome as a glomerular disorder can be clasified according to etiology:
1. primary or idiopathic
2. secondary (in systemic diseases, eg. SLE)
3. congenital

Major types of idiopathic nephrotic syndrome in childhood:

Minimal change disease (85–90%)	No changes seen under normal microscope but podocyte foot process fusion on electron microscopy
Focal segmental glomerular sclerosis (10–15%)	Focal because not all glomeruli affected (usually deeper ones) and segmental because only segments of each glomeruli are affected
Membranous nephropathy (1–5%)	Associated with hepatitis B and malignancy such as lymphomas (more often seen in adults)

Congenital nephrotic syndrome presenting *in utero* or within the first month of life is rare. Several mutations have been found, most notably in the nephrin gene (Finnish congenital nephrotic syndrome).

Other types of nephrotic syndrome fall into an overlap pattern with nephritis, where there is marked inflammation in the glomerulus – hence there will be additional features secondary to the inflammation, such as red and white cells ± casts in the urine. Unlike uncomplicated nephrotic syndrome, it is rare for the plasma albumin to fall below 20 g/dL in these conditions. Causes include:

- Poststreptococcal glomerulonephritis (GN)
- Henoch–Schönlein purpura (HSP), anaphylactoid, drugs
- Heavy metals, malaria, systemic lupus erythematosus (SLE)

Clinical features

- **Classical presentation** is with **dependent oedema**, i.e. oedema collects at the lowest part, particularly of the face and eyes in the morning, since children often sleep face down; frequently misdiagnosed as allergies in the early stages
- As hypoproteinaemia worsens, the **oedema** becomes widespread and does not improve during the day; sites include the ankles and lower legs, scrotum and **sacrum**. Ascites can develop and shortness of breath with pleural effusions
- **Non-specific symptoms** – progressive lethargy and anorexia, occasionally diarrhoea
- **Infections**, particularly encapsulated organisms such as pneumococcus more likely. Peritonitis also possible (primary or pneumococcal)
- **Frothy urine** (rare)
- **Intravascular hypovolaemia** (secondary to hypoalbuminaemia) may present with abdominal pain, circulatory collapse/shock or venous thrombosis

NB: These children do not appear dehydrated because they are so oedematous, but they can have profound intravascular hypovolaemia because their fluid is in the wrong compartments.

Features of intravascular hypovolaemia

Orthostatic hypotension	Tachycardia
Oliguria	Abdominal pain
Cool peripheries	Rising haematocrit
Prolonged capillary refill time	Urine sodium < 20 mmol/L (severe if < 5)
Significant core–periphery temperature gap	

NB: The blood pressure will *not* fall in children until there is *severe* hypovolaemia due to their compensatory mechanisms, therefore these features must be checked regularly

Initial investigations

Urine	Dipstick for proteinuria – will have +3 or +4 proteinuria Albumin:creatinine ratio – > 200 mg/mmol Sodium concentration – < 20 mmol/L is an indication of hypovolaemia Microscopy – no or minimal cells in uncomplicated nephrotic syndrome (cf red and white cell casts in glomerulonephritis)
Blood	FBC, ESR – ↑ haematocrit or haemoglobin (signs of hypovolaemia), ?signs of infection U&E, creatinine – raised urea may indicate hypovolaemia Albumin – <25 g/L (by definition) Cholesterol, triglyceride – ↑; whether treatment is required in acute stages is controversial (Hep B S Ag – if membranous GN and from Middle/Far East or at-risk group)

Other investigations if there is a suggestion of overlap with glomerulonephritis:

Blood	Complement factors – C3 and C4 ↓ (except in minimal change) ASOT, anti-DNAse B – positive if streptococcal infection
Throat swab	M, C & S – ? streptococcal sore throat
Renal biopsy	Done if: – No response to steroids after 4–6 weeks – Atypical features at presentation, e.g. hypertension, high creatinine, infant < 1 year

Management

- Oral corticosteroids – 60 mg/m^2/day (2 mg/kg/day) for 4 weeks (NB: this is longer than older regimens, which reduced when clear of proteinuria for 3–4 days, because there is increasing evidence that a longer initial course reduces chance of relapse and hence overall steroid dosage), then 40 mg/m^2/day alternate days for 4 weeks. If no response to steroids consider renal biopsy
- Oral penicillin prophylaxis
- Monitor intravascular volume (see below)
- Daily weight, electrolytes and albumin and fluid input–output chart
- Diuretics as needed (in hospital only)
- Monitor proteinuria (by urine dipstick at home when recovered to assess for a relapse)

Complications

- Hypovolaemia – see above
- Infection – high risk of infection, classically pneumococcal peritonitis, although Gram-negative sepsis now becoming commoner as the penicillin reduces Gram-positive cases (due to low immunoglobulins)
- Intravascular thrombosis – DVT and renal vein thrombosis (due to hypovolaemia and hypercoagulable state)
- Hypercholesterolaemia
- Acute tubular necrosis (if severe hypovolaemia)

Prognosis

Steroid sensitive disease	One-third no relapses One-third occasional relapses One-third regular relapses
Steroid resistant disease	Alternative immunosuppressive therapy needed High proportion (up to 50%) will progress to chronic renal failure

If the child is well, then yearly follow-up is required, checking particularly for BP and growth.

Urinary Tract Infection (UTI) in Children

Definition

Urinary tract infection (UTI) – bacterial growth in different parts of urinary system with a potential inflammation producing clinical symptoms corresponding to bacterial inflammation locus (pyelonephritis, cystitis, urethritis etc.).

Epidemiology of UTI

- Urinary tract infection will occur in up to 2% of boys and 8% of girls prior to sexual activity, and 20% to 50% of these will have VUR if examined. Seven percent of febrile infants will have UTI, making the urinary tract second only to the respiratory tract in areas affected by bacterial infection at this age. During the first 3 months of life, uncircumcised boys have the highest incidence of UTI at any age, which has been estimated as 20 to 30 times higher than in circumcised boys and higher than in female infants. The female/male ratio of UTI in children of all ages is 5:1 in populations in which most boys are circumcised at birth but only 3:1 in populations in which boys are usually not circumcised.
- There is no plausible explanation for why UTI is observed less commonly in black children (both boys and girls) in Africa or North America, but all other races are affected similarly.

Most UTIs are caused by **Gram-negative bacteria** representing the usual colorectal flora: Escherichia coli predominates, followed by Klebsiella, Enterobacter, Pseudomonas, and Proteus; Enterococcus is the only Gram-positive organism considered a urinary pathogen in a normal urinary tract. Bacteria gain access to the urinary tract either by blood (rarely) or the bladder (usually). Bacteria gain entry into the bladder through the urethral meatus, which accounts for the higher rate of UTI in the girl whose bladder is relatively less well protected due to a short urethra. Fortunately, most girls do not develop UTI unless they empty their bladders infrequently or incompletely. Obstruction to urine flow anywhere in the urinary tract, but especially in the bladder outflow tract, results in residual urine, which provides a medium conducive to bacterial growth. Relative obstruction occurs with VUR when the bladder urine refluxes into the ureter during micturition and subsequently returns to the empty bladder. When the infected urine reaches the papilla, pyelitis, and the papillary collecting duct, pyelonephritis may develop. P-fimbriated E coli attach to uroepithelial cells in the urethra and bladder and have been reported to cross the UVJ, even in the absence of VUR, to cause pyelonephritis. In the urinary tract, bacteria double in number every 20 minutes but must reach about 100,000 organisms/mL of urine before the inflammatory response produces symptoms. A single organism remaining undisturbed in bladder urine would exceed 100,000 organisms in less than 6 hours or even more overnight in a person who fails to empty the bladder completely before going to sleep. This is primarily the case in girls. Although much has been made over the causality of cystitis due to bubble bath, there is no direct evidence for this. There are 2 more likely explanations. First, the chemical in bubble bath remains on the vaginal or urethral mucosa when a girl gets out of a bath and dries off without rinsing her skin and genitalia with clean water. Later, dysuria is experienced as urine flows over the irritated mucosa, but in this case, the urine remains sterile. Unless dysuria leads to micturition avoidance or partial urinary retention, UTI more likely results from the prolonged time that girls spend in dirty bath water enjoying the bubbles and allowing dirty bath water to enter the urethra and bladder. If a girl does not empty her bladder soon after a bubble bath, bacterial growth may occur.

Risk factors of UTI

- Urodynamic disturbancies (VUR, bladder dysfunction, obstruction, stones)
- Constipation
- Iatrogenic (bladder catheters and procedures)
- Immune deficiency (?)
- Bacterial virulence (adhesion, a\b resistance etc.)

Descriptions and Criteria for Urinary Tract Colonization/Infection

[Feld, 1989; Leonard and Mattoo, 2010; Tsigin, 2015]

Symptomatic bacteriuria	Upper or lower urinary tract symptoms and urine culture with significant bacterial colony counts
Significant bacteriuria	Presence of 50 000 microbial cells in 1 ml of urine
Urethritis	Inflammation of the urethral mucosa, with symptoms of dysuria, frequency, secondary enuresis, pyuria, and low urine colony counts ($<10^3$) (rule out vaginitis in sexually active patients)
Acute cystitis	Inflammation of bladder mucosa and symptoms of lower tract infections: urgency, dysuria, frequency, and hematuria
Parenchyma infection/acute pyelonephritis	Inflammation of renal parenchyma and symptoms of upper tract infection: high fever (temperature >39°C), abdominal or flank pain, and other systemic symptoms (eg, vomiting)
Chronic pyelonephritis	Long lasting or recurrent inflammation, usually with anatomic abnormalities, reflux or obstruction leading to scarring and pelvic and calyceal deformation (The term no more used by most)
Reflux nephropathy	Renal scarring associated with vesico-uretheral reflux (VUR)
Urosepsis	Bacteremia with acute systemic inflammation and predominant renal involvement
Asymptomatic bacteriuria	Urine culture with significant bacterial colony count in an asymptomatic patient
Complicated bacteriuria	Urine culture with significant bacterial colony count and associated urologic abnormalities (hydroureter, hydronephrosis, and vesicoureteral reflux)

Diagnosis of UTI

- **Presenting symptoms and signs in infants and children with UTI**

Age group		Symptoms and signs Most common ⟷ Least common		
Infants younger than 3 months		Fever Vomiting Lethargy Irritability	Poor feeding Failure to thrive	Abdominal pain Jaundice Haematuria Offensive urine
Infants and children, 3 months or older	Preverbal	Fever	Abdominal pain Loin tenderness Vomiting Poor feeding	Lethargy Irritability Haematuria Offensive urine Failure to thrive
	Verbal	Frequency Dysuria	Dysfunctional voiding Changes to continence Abdominal pain Loin tenderness	Fever Malaise Vomiting Haematuria Offensive urine Cloudy urine

The symptoms of a febrile UTI are very non-specific, particularly in small children. The clinician assessing a febrile infant with no apparent source for the fever should always consider the possibility of a UTI, and in all these children a urine sample should be obtained.

- **Urine tests**

- Leukocyturia/pyuria
  - boys > 10 WBCs/μl
  - girls > 50 WBCs/μl
  - may be nonspecific due to fever of any origin, nephrocalcinosis, urolithiasis
- Leukocyte esterase (LE) test (for pyuria)
- Nitrite test (for bacteriuria)
- Hematuria and proteinuria per se are not a signs of UTI but does not exclude it
- Urine culture

  For several decades, the accepted cut-off limit for a true UTI has been a bacterial count of more than 10^5 bacteria per millilitre. AAP acknowledges that this definition is operational and not absolute and recommends that a lower threshold of 5×10^4 bacteria per millilitre should be used as this will increase the sensitivity of the culture but at the expense of decreased specificity.

Urine collection for culture

[Hellerstein S. 1982; Johnson CE et al. 2003, AAP 2011]

Bag	non reliable due to high contamination risk
Suprapubic Aspiration	Any growth of gram-negative bacilli or $>10^3$ colony forming units/mL of gram-positive cocci
Urethral Catheterization	Greater than 10^3 colony forming units/mL for circumcised males and all females, $>10^5$ colony forming units/mL for uncircumcised males (if 10^4 to 10^5 colony forming units/mL, consider repeat sample)
Midstream Clean Catch	> 50000 (5×10^4) colony forming units/mL.

These values pertain to pure, one-pathogen colony growth and should be interpreted based on the child's symptom complex.

Sensitivity and Specificity of Components of the Urinalysis

	Test Sensitivity %(Range)	Specificity %(Range)
Leukocyte esterase	83 (67–94)	78 (64–92)
Nitrite	53 (15–82)	98 (90–100)
Leukocyte esterase *or nitrite* positive	93 (90–100)	72 (58–91)
Microscopy: WBCs	73 (32–100)	81 (45–98)
Microscopy: bacteria	81 (16–99)	83 (11–100)
Leukocyte esterase *or nitrite or* microscopy positive	99.8 (99–100)	70 (60–92)

Ultrasound

The AAP recommends that all small children who have had a febrile UTI should undergo a renal and bladder ultrasound (RBUS).

Other imaging

New guidelines (AAP, NICE) recommend radically reducing the number of further investigations. AAP recommends no more MCUG in children with a first time acute febrile UTI if there are no additional features indicated by the RBUS, i.e. hydronephrosis, scarring or other signs of high grade VUR or urinary tract obstruction. NICE agrees and recommends a MCUG only in the youngest infants below the age of 6 month if they have had an atypical UTI (NICE provides a list of situations when a UTI should be regarded as atypical, including a seriously ill child, poor urine flow, abdominal or bladder mass, raised serum creatinine, septicaemia, failure to respond to treatment with antibiotics within 48 h and an infection with a non-Escherichia coli organism). An MCUG is not recommended in slightly older infants, aged more than 6 months, even in the presence of an atypical infection. Further evaluation should, according to AAP, be performed after a recurrent infection, and NICE agrees on the need for a MCUG but only in those with recurrences below the age of 6 months. Regarding nuclear imaging, typically DMSA, NICE recommends this be done 4–6 months after the acute infection in children younger than 3 years who have had a recurrent or atypical infection. AAP is much less impressed by the need to do a DMSA and states that this is not recommended as part of the routine evaluation of infants after their first febrile UTI.

Differential Findings in Urinary Tract Infection

Arguments in favor of pyelonephritis

- High fever
- General illness
- Age
- Blood test (neutrophilic leukocytosis, ↑ ESR)
- Ultrasound
- Elevated C reactive protein
- Procalcitonin test

Treatment

Oral antibiotic treatment works equally well as IV in infants and children that are not septic and who reliably can take the drug by mouth. Children who need IV treatment should be switched to oral medication as soon as feasible. The choice should take into account local bacterial susceptibility patterns in collaboration with the local bacteriological laboratory. There is no scientific evidence for whether 7, 10 or 14 days are better.

Some Empiric Antimicrobial Agents for Parenteral Treatment of UTI

Antimicrobial Agent	Dosage
Ceftriaxone	75 mg/kg, every 24 h
Cefotaxime	150 mg/kg per d, divided every 6–8 h
Ceftazidime	100–150 mg/kg per d, divided every 8 h
Gentamicin	7.5 mg/kg per d, divided every 8 h
Tobramycin	5 mg/kg per d, divided every 8 h
Piperacillin	300 mg/kg per d, divided every 6–8 h

Some Empiric Antimicrobial Agents for Oral Treatment of UTI

Antimicrobial Agent	Dosage
Amoxicillin-clavulanate	20–40 mg/kg per d in 3 doses
Sulfonamide	
Trimethoprim-sulfamethoxazole	6–12 mg/kg trimethoprim and 30-60 mg/kg sulfamethoxazole per d in 2 doses
Sulfisoxazole	120–150 mg/kg per d in 4 doses
Cephalosporin	
Cefixime	8 mg/kg per d in 1 dose
Cefpodoxime	10 mg/kg per d in 2 doses
Cefprozil	30 mg/kg per d in 2 doses
Cefuroxime axetil	20–30 mg/kg per d in 2 doses
Cephalexin	50–100 mg/kg per d in 4 doses

Prophylactic antibiotics

Prophylactic antibiotics should not be routinely used even in children with VUR.

Who may benefit from prophylaxis?

- Not recommended routinely but may be efficient in several groups (girls under 2 years without toilet training)
- Unlikely may help in boys after 2 years and in VUR I-II
- Consider individual indication
- More extended studies are required

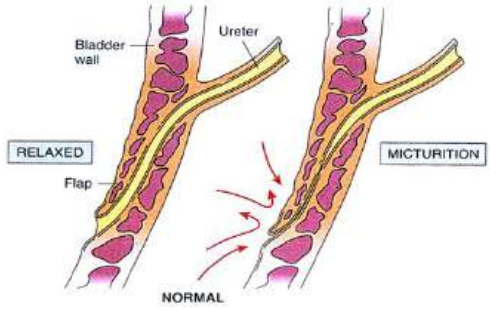
Antimicrobial drugs for long term low-dose prophylaxis in VUR

- Nitrofurantoin 1 mg/kg once a day
- Trimethoprim/co-trimoxazol 2 mg/kg once a day

Vesicoureteric Reflux (VUR) in Children

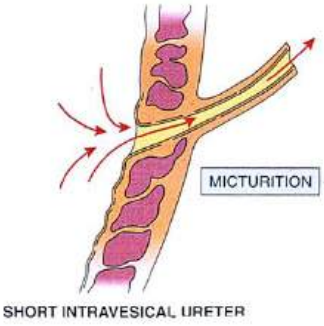
Vesicoureteric reflux (VUR) is retrograde flow of urine from the bladder into the ureters ± renal pelvis, due to incompetence at the vesicoureteric junction or abnormality of the whole ureter.

Normal Ureterovesical Junction (UVJ)



In the normal ureterovesical junction, the ureter tunnels through the detrusor muscle of the bladder before terminating at the ureteral hiatus; this is the 'intramural' ureter. The intramural ureter is compressed passively as the bladder fills, preventing retrograde flow of urine.

Refluxing Ureterovesical Junction (UVJ)

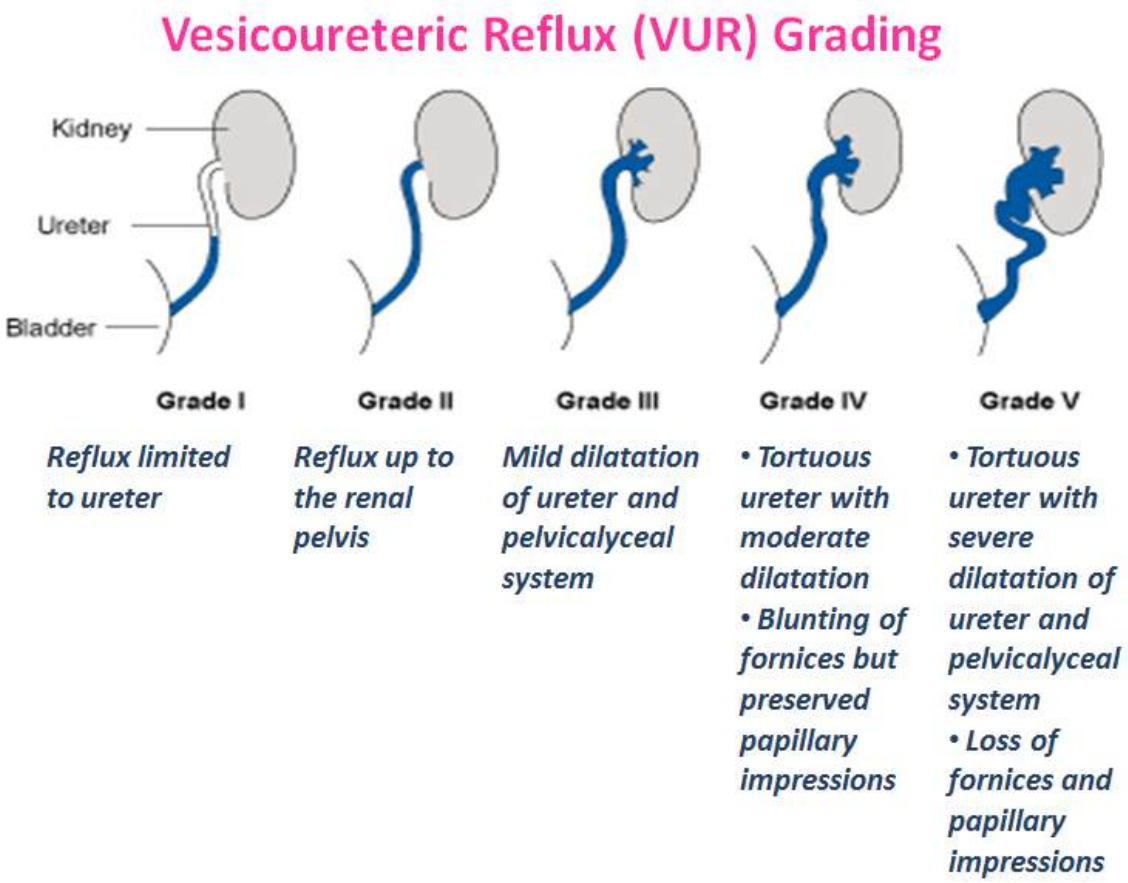


If the intramural tunnel is too short, this flapvalve mechanism fails and VUR ensues. ***Primary VUR*** *is, therefore, caused by an anatomic abnormality.* ***Secondary VUR*** *results from any situation that creates an abnormally high pressure within the bladder (neurogenic bladder, posterior urethral valves). This pressure is transmitted to the ureter and causes a failure of the flap-valve mechanism.*

Traditional teaching is that reflux can result in renal scarring (**reflux nephropathy**) because:

- Renal pelvis is exposed to high pressures (during urination)
- Reflux facilitates the passage of bacteria into the renal pelvis

But many of the kidneys are already abnormal at birth because of combined maldevelopment of the lower urinary tract (ureters and bladder) and kidneys, i.e. urinary tract 'field defect'.



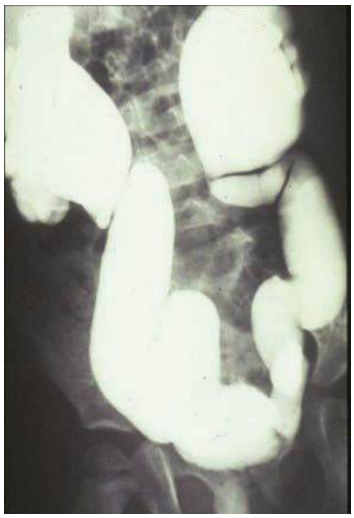


Figure Severe bilateral vesicoureteric reflux with gross ureteric dilatation seen on MCUG

Management of reflux and renal scarring

NB: Most centres have specific local protocols, hence this is only a guide.

- Cystoscopic injection of reinforcing material around ureteric orifices in the bladder or surgical reimplantation of ureters (old fashioned) if medical management fails (rarely necessary)
- If there is bilateral scarring, perform regular renal growth and function tests

BLADDER DYSFUNCTION (VOIDING DYSFUNCTION). URINARY INCONTINENCE

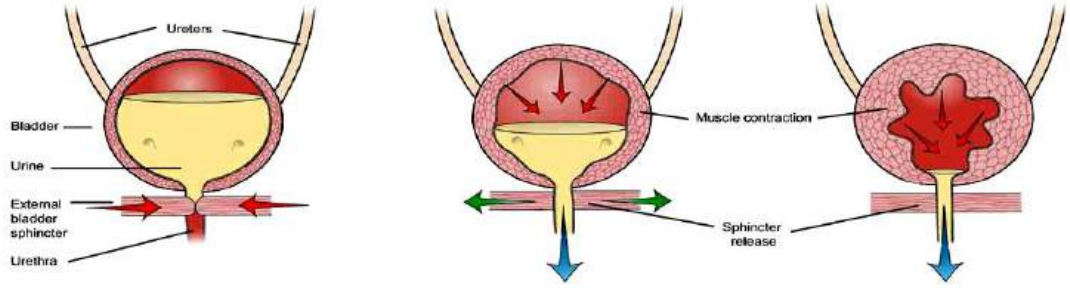
Normal voiding is a complex, tightly orchestrated neuromuscular cascade of events coordinating low-pressure storage of urine in the bladder and efficient emptying of stored urine.

Bladder filling and urine storage require the following:

1. Accommodation of increasing volumes of urine at a low intravesical pressure and with appropriate sensation
2. A bladder outlet that is closed at rest and remains so during increases in intra-abdominal pressure
3. Absence of involuntary bladder contractions

Bladder emptying requires the following:

1. Coordinated contraction of the bladder smooth musculature of adequate magnitude and duration
2. Concomitant lowering of resistance at the level of the smooth and striated sphincter
3. Absence of anatomic (as opposed to functional) obstruction

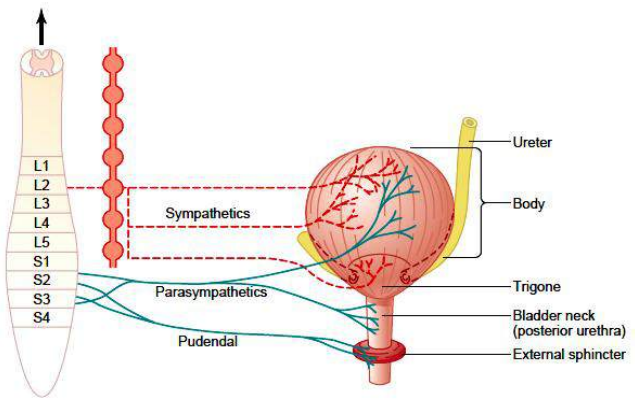


The **smooth sphincter** refers to the smooth musculature of the bladder neck and proximal urethra. This is a physiologic but not an anatomic sphincter and one that is not under voluntary control. The **striated sphincter** refers to the striated musculature, which is a part of the outer wall of the proximal urethra in males and females (this portion is often referred to as the *intrinsic* or *intramural striated sphincter*), and the bulky skeletal muscle group that surrounds the urethra at the level of the membranous portion in the male and the middle segment in the female (often referred to as the *extrinsic* or *extramural striated sphincter*). The extramural portion is the classically described *external urethral sphincter* and is under voluntary control.

Coordination of micturition involves control by two main centres in the CNS:

(1) the **Pontine Centre** in the brainstem, which is responsible for co-ordinated activity between the detrusor and the bladder outlet, and

(2) the **Sacral Centre** which controls local reflexes and initiates detrusor contraction.



A problem in bladder filling or emptying is called a **voiding dysfunction**. It is a common problem in children and constitutes up to 40% of pediatric urology clinic visits.

ETIOLOGY — There are neurogenic, anatomic, or functional causes.

- **Neurogenic causes** — Neurogenic causes of voiding dysfunction disrupt the innervation of the bladder or external sphincter. Neurogenic causes are due to either congenital anomalies, such as myelomeningocele, or trauma to the central nervous system (eg, spinal cord injury). Any child with a suspected neurologic abnormality should be evaluated for occult neurologic lesion.

NEUROGENIC BLADDER = **VOIDING DYSFUNCTION** + **NEUROLOGIC DIAGNOSIS** ↓

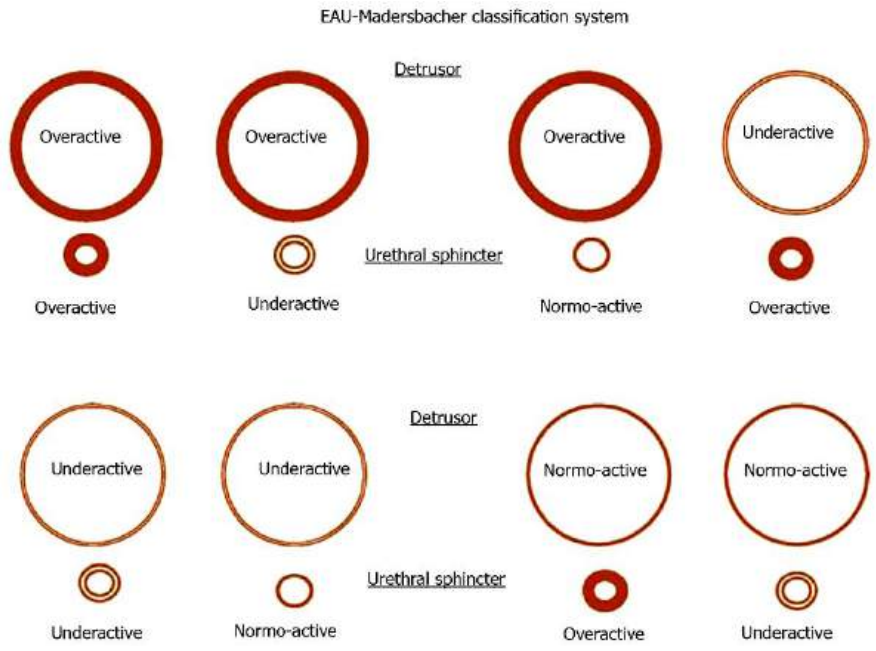
- *spinal dysraphism*
- *sacral agenesis*
- *cerebral palsy*
- *spinal cord lesions*
- …

- **Anatomic causes** — Children with an anatomic abnormality generally have a history of never gaining urinary control because the anatomic defect either bypasses the bladder outlet, such as ectopic ureter with insertion distal to the bladder neck, or there is obstruction of the bladder outlet (eg, posterior urethral valves).

- **Functional causes** — Functional refers to idiopathic bladder dysfunction with no known anatomic or neurologic cause. Proposed theories regarding the pathogenesis of functional voiding dysfunction include maturation delay, prolongation of infantile bladder behavior, or abnormal acquired toilet training habits.

In voiding dysfunction there may be different combinations of activity/contractility of bladder muscle (detrusor) and urethral sphinter, *for example:*

- overactive detrusor and normo-active sphincter
- underactive (atonic) detrusor and overactive sphincter
- overactive detrusor and overactive sphincter **(detrusor-sphincter dyssynergia)**:



DEFINITIONS OF SYMPTOMS OF VOIDING DYSFUNCTION

[The International Children's Continence Society (ICCS), 2006]

<table>
<tr><th colspan="3">SYMPTOM</th><th>AGE</th></tr>
<tr><td colspan="3">Increased daytime frequency - voiding eight or more times during waking hours after</td><td rowspan="2">relevant from age 5 onwards or from the attainment of bladder control</td></tr>
<tr><td colspan="3">Decreased daytime frequency - three or fewer voids</td></tr>
<tr><td rowspan="3">Incontinence - uncontrolled leakage of urine</td><td colspan="2">continuous</td><td>applicable to children of all ages</td></tr>
<tr><td rowspan="2">intermittent</td><td>daytime</td><td rowspan="2">applicable to children who are at least 5 years old</td></tr>
<tr><td>nocturnal (enuresis)</td></tr>
<tr><td colspan="3">Nocturia – awakening to void at night</td><td>relevant from the age of 5 years</td></tr>
<tr><td colspan="3">Urgency - the sudden and unexpected experience of an immediate need to void</td><td>relevant from age 5 onwards or from the attainment of bladder control</td></tr>
<tr><td colspan="3">Hesitancy - difficulty in the initiation of voiding or if a child must wait a considerable amount of time before voiding starts</td><td>relevant from age 5 onwards or from the attainment of bladder control</td></tr>
<tr><td colspan="3">Weak stream - the observed ejection of urine with a weak force</td><td>applicable to children of all ages</td></tr>
<tr><td colspan="3">Straining - the application of abdominal pressure (Valsalva maneuver) by the child to initiate and maintain voiding</td><td>applicable to children of all ages</td></tr>
<tr><td colspan="3">Intermittency - a voiding stream of urine that occurs in several discrete bursts rather than the normal continuous stream</td><td>This may be described in all age groups but is regarded as physiological up to 3 years of age if not accompanied by straining</td></tr>
<tr><td colspan="3">Holding maneuvers - observed behavior used to either postpone voiding or suppress urgency. Common maneuvers include standing on tiptoe, forcefully crossing the legs, or squatting with a hand or heel pressed into the perineum</td><td>These may be observed in children who have achieved bladder control regardless of age</td></tr>
</table>

Different types of voiding dysfunction

- **Daytime wetting:** Daytime wetting can consist of either small urine leaks that spot or dampen underwear to the complete soaking of undergarments. Wetting occurs more commonly in the afternoon, as most children are anxious about wetting in school and work hard to stay dry.
- **Giggle/stress incontinence:** This is the complete emptying of the bladder that occurs with vigorous laughter or giggling.
- **Urge syndrome:** frequent attacks of the need to void (at least seven times a day) countered by hold maneuvers, such as squatting. Urine loss is mild, represented by a dampening of undergarments.
- **Bedwetting (enuresis):** a sleeping child cannot control his/her urination at night. This problem begins to be considered abnormal after the age of five.

URODYNAMIC TESTS

Bladder function is estimated by urodynamic tests.

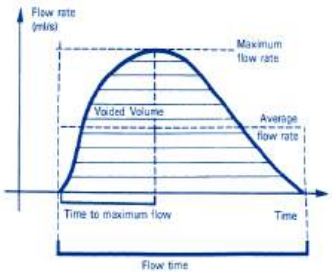
Instrument	Age	Data
Bladder diary	From 5 years	Voided volumes Voiding frequency Urine output Symptom (leakage, etc.) frequency other data (see table 2)
Uroflow + residual	From 5 years	Voided volume Curve shape Urine flow rate Residual urine
Cystometry	All ages	Detrusor pressure and activity Cystometric bladder capacity compliance Sphincter competence and activity other data (see specific section)
4 hr voiding observation	Infancy	Voided volumes Voiding frequency Residual urine Observation of symptoms

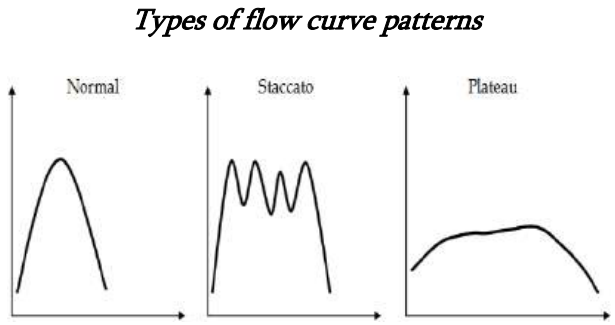
- **THE BLADDER DIARY FORM**

1. Time	2. Intake Type	3. Intake Amount	Urge (X)	4. Voided (X)	5. Leak (X)	6. Activity

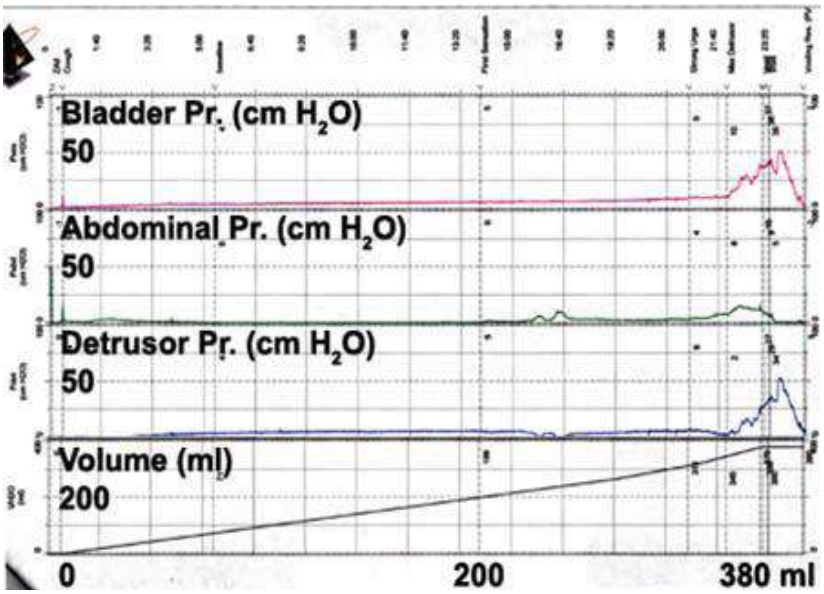
7. Measured Urine: Time:_____ Amount:_____

➢ UROFLOWMETRY



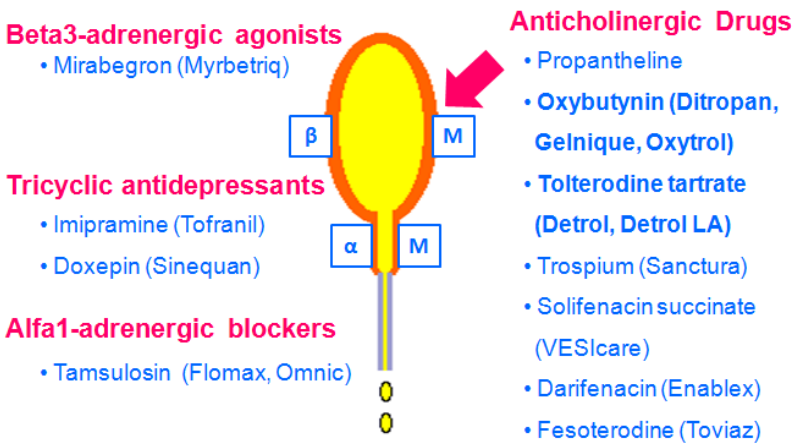


➢ CYSTOMETRY



* bladder filling at low pressures = normal bladder compliance
* normal bladder contraction with voiding

DRUGS AFFECTING BLADDER FUNCTION



GLOMERULAR DISEASES

Synonims

- Glomerulonephritis (GN)
- Glomerulopathy

Definition

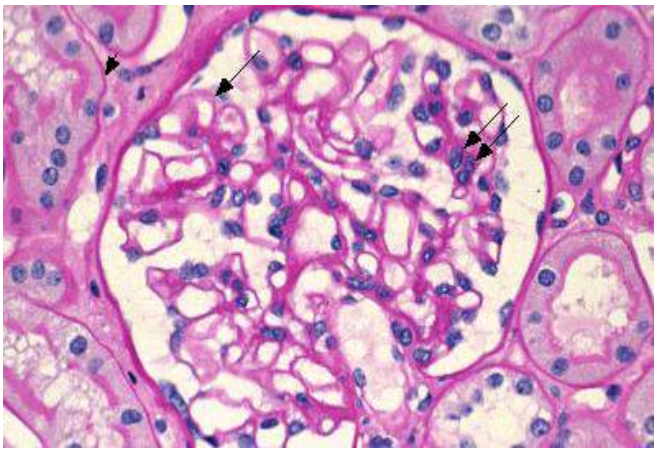
- A group of conditions in which glomerular injury occurs

Pathogenesis

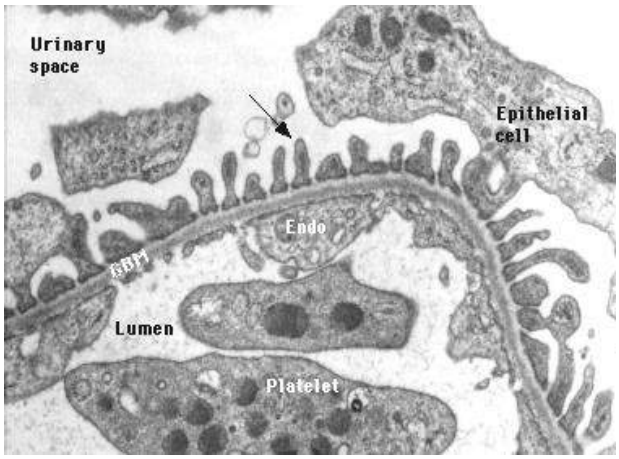
Glomerular injury includes several mechanisms:

- Damage by immune complexes
- Damage by autoantibodies
- Cell-mediated immune injury
- Damage by complement and proinflammatory mediators

Normal Glomerulus



Light micrograph of a normal glomerulus. There are only 1 or 2 cells per capillary tuft, the capillary lumens are open, the thickness of the glomerular capillary wall (long arrow) is similar to that of the tubular basement membranes (short arrow), and the mesangial cells and mesangial matrix are located in the central or stalk regions of the tuft (arrows).



Electron micrograph of a normal glomerular capillary loop showing the fenestrated endothelial cell (Endo), the glomerular basement membrane (GBM), and the epithelial cells with its interdigitating foot processes (arrow). The GBM is thin and no electron dense deposits are present. Two normal platelets are seen in the capillary lumen.

➢ Classification of glomerular diseases

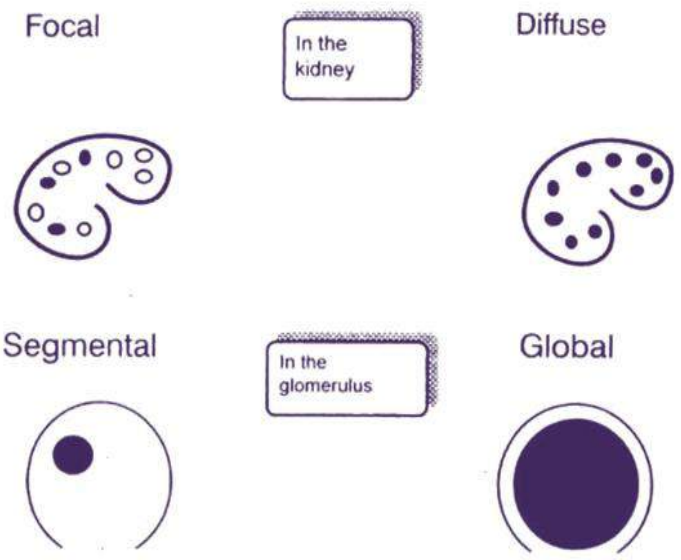
I. Classification according to etiology

Primary (idiopathic)	Hereditary	Secondary
Idiopathic forms of • *Crescentic (rapidly progressive) GN* • *Membranous GN* • *Minimal change disease (MCD)* • *Focal segmental glomerulosclerosis (FSGS)* • *Membranoproliferative GN* • *IgA nephropathy*	Alport's syndrome	**Infections** ● Hepatitis B, C ● Human immunodeficiency virus ● Malaria ● Toxoplasmosis ● Syphilis **Drugs** ● Gold ● Non-steroidal anti-inflammatory drugs ● Pamidronate ● Interferon ● Heroin ● Lithium **Malignancies** ● Lymphoma ● Leukemia **Associated with Systemic Diseases:** ● SLE ● Diabetes Mellitus ● Goodpasture's syndrome ● Amyloidosis ● Polyarteritis nodosa ● Wegener's granulomatosis ● Henoch-Schonlein purpura ● Post-Infectious Glomeruloneph

II. Classification according to light (LM) and electron microscopy (EM)

Distribution of glomerular lesions (LM)

"focal": <50% of all glomeruli
"diffuse": ≥50% of all glomeurli
"segmental": part of individual glomerulus
"global": entire glomerulus



"proliferative" GN: increased glomerular cells (hypercellularity):

a) "intracapillary/endocapillary" (proliferation of endothelial or mesangial cells)

b) "extracapillary" cells in Bowman's space -> "crescent" formation: half-moon-shaped collection of cells in Bowman's space (often associated with rapidly progressive GN)

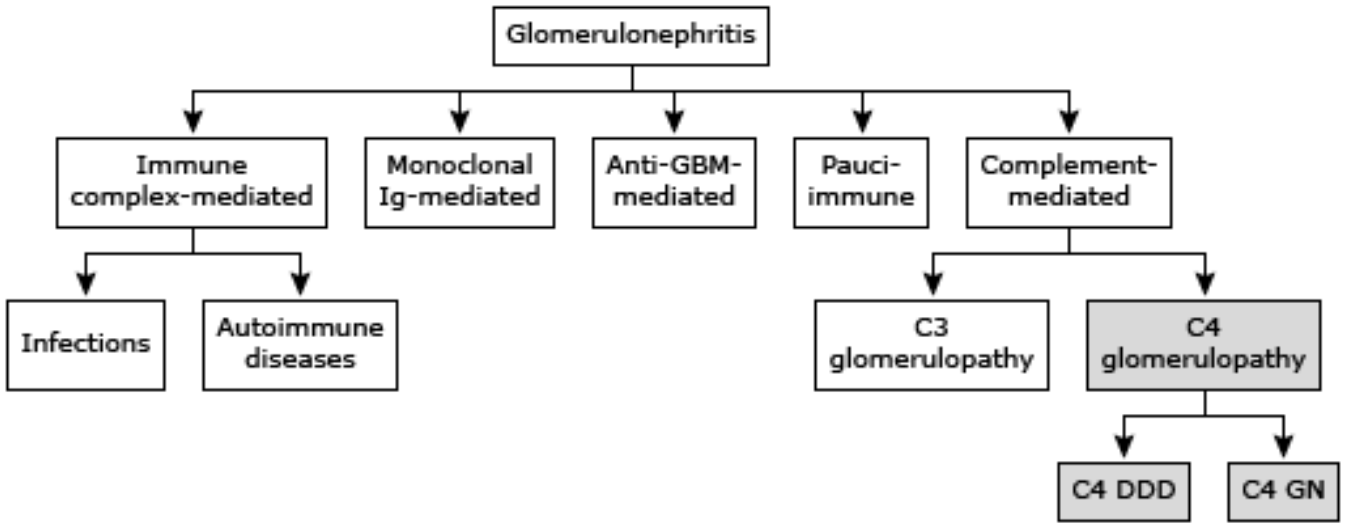
"membranous" GN: - expansion of glomerular basement membrane as a dominant feature

"sclerosis": - increased amount of homogenous non-fibrillar extracellular material (similar to GBM and mesangeal matrix)

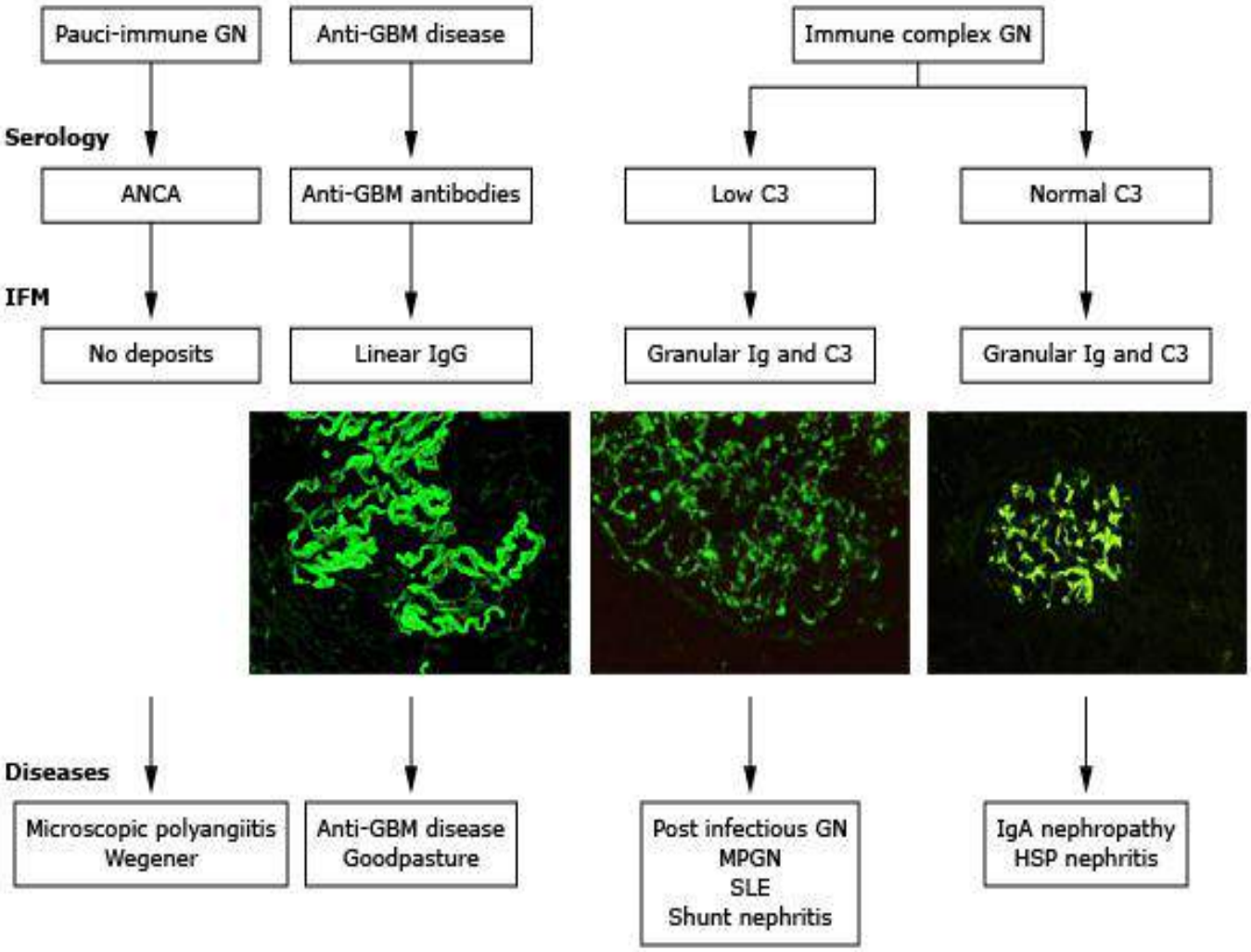
"fibrosis" - deposition of type I and III collagen - commonly as a consequence of healing of crescents or tubulointerstitial inflammation

EM delineates:
- specific basement membrane abnormalities (thinning, thickening)
- immune complex deposits (subepithelial, subendothelial)
- changes of endothelium and podocytes (foot process effacement)

III. Classification according to serology testing and immunofluoresence microscopy (immunologic classification)



Complement-mediated glomerulonephritis, that is, glomerulonephritis characterized by predominant deposition of complement factors with little or no immunoglobulin (Ig) can therefore be further subdivided into C3 glomerulopathy and C4 glomerulopathy. C3 glomerulopathy is characterized by bright staining for C3 with minimal or no immunoglobulin. However, C4 glomerulopathy is characterized by bright staining for C4d with minimal or no immunoglobulin. The difference in C4 glomerulopathy and C3 glomerulopathy lies in the essentially absent or minimal staining for C3 in C4 glomerulopathy. Why there is no staining for C3, because activation of C4 should presumably lead to the formation of C4 convertase and activation of C3, is not known at this time.
GBM: glomerular basement membrane; DDD: dense deposit disease; GN: glomerulonephritis.
Reproduced from: Sethi S, Quint PS, O'Seaghdha CM, et al. C4 glomerulopathy: A disease entity associated With C4d deposition. Am J Kidney Dis 2016. Illustration used with the permission of Elsevier Inc. All rights reserved.


Pauci-immune GN
Anti-GBM disease
Immune complex GN
Serology
ANCA
Anti-GBM antibodies
Low C3
Normal C3
IFM
No deposits
Linear IgG
Granular Ig and C3
Granular Ig and C3
Diseases
Microscopic polyangiitis
Wegener
Anti-GBM disease
Goodpasture
Post infectious GN
MPGN
SLE
Shunt nephritis
IgA nephropathy
HSP nephritis

III. Classification according to clinical features (glomerular syndromes)

1. Asymptomatic urinary abnormalities	Isolated glomerular hematuria or/and proteinuria
2. Nephritic syndrome	- Nephritic pattern has variable proteinuria, and an "active" urine sediment. An "active sediment" is urine that contains proteinuria; red cells > I0/hpf; white cells; and often red cell, white cell, or granular casts. *Casts always originate in the tubules. Know the following:* *• Red cell casts are a very specific finding. They are seen only in glomerulonephritis.* *• White cell casts are typically seen in pyelonephritis or AIN.* *• Granular casts can be nonspecific; in the setting of acute kidney injury with an appropriate clinical picture, they are characteristic of acute tubular necrosis.* *• Waxy casts typically indicate advanced renal disease.* *• In patients with a lot of proteinuria, free fat can assemble into a cast (called a fatty cast) or oval fat bodies, characterized by "Maltese crosses" under polarized light; or fat can suspend in the urine as droplets.* *• Hyaline casts do not indicate disease and are seen with concentrated urine.*
3. Nephrotic syndrome	- is characterized by **heavy proteinuria**, edema, hypoalbuminemia, hyperlipidemia
4. Combined Nephrotic-nephritic syndrome	Features of both nephrotic and nephritic syndromes
5. Rapidly progressive GN (RPGN)	- is characterized clinically by a rapid decrease in the glomerular filtration rate (GFR) of at least 50% over a short period, from a few days to 3 months. The main pathologic finding is extensive glomerular crescent formation.

RPGN is classified pathologically into three categories:

(1) **Anti-GBM antibody disease** (approximately 3% of cases)	• Goodpasture syndrome (lung and kidney involvement) • Anti-GBM disease (only kidney involvement) • Note: 10-40% of patients may be ANCA positive
(2) **Immune complex disease** (45% of cases)	• Postinfectious (staphylococci/streptococci) • Collagen-vascular disease • Lupus nephritis • Henoch-Schönlein purpura (immunoglobulin A and systemic vasculitis) • Immunoglobulin A nephropathy (no vasculitis) • Mixed cryoglobulinemia • Membranoproliferative glomerulonephritis • Fibrillary glomerulonephritis • Idiopathic • Note: Of all patients with crescentic immune complex GN, 25% are ANCA positive; however, less than 5% of patients with noncrescentic immune complex glomerulonephritis are ANCA positive
(3) **Pauci-immune disease** (50% of cases)	• Granulomatosis with polyangiitis (Wegener granulomatosis) • Microscopic polyangiitis (MPA) • Renal-limited necrotizing crescentic glomerulonephritis (NCGN) • Churg-Strauss syndrome • Note: 80-90% of patients are ANCA positive

* ANCA - *antineutrophil cytoplasmic antibodies*

QUESTIONS

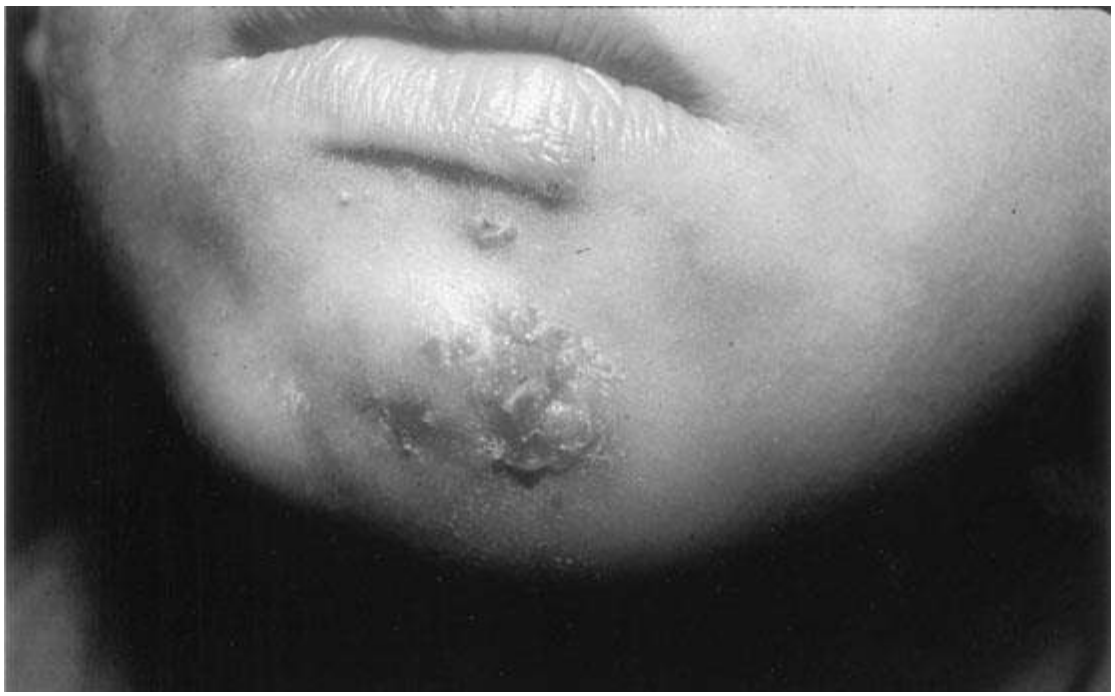
1. Which of the following are complications of nephrotic syndrome?

1. Peritonitis
2. Pleural Effusions
3. Pulmonary Edema
4. Thromboembolism

A. 2 and 3
B. 1, 2, and 3
C. 2, 3, and 4
D. 1, 2, and 4

---

2. A boy has returned home from visiting his grandmother in a rural area. He spent most of his time swimming, playing in the yard, helping in the gardens, and chasing his Chihuahua; his grandma says “he was generally dirty!” He was noted 2 weeks ago to have “infected mosquito bites” on his neck and chin for which the local doctor had him just scrub with soap; a few remain and are shown in the photograph below. His mother brings him into the office with the complaint of dark urine, swelling around his eyes, and shortness of breath. You also find him to have hypertension and hepatomegaly. Which of the following is the most likely cause of his problem?



a. IgA nephropathy
b. Poststreptococcal glomerulonephritis
c. Idiopathic hypercalciuria
d. Pyelonephritis
e. Sexually transmitted disease

Renal Amyloidosis

In pediatrics, the most common form of amyloidosis is **reactive AA amyloidosis** due to

- *chronic infections (e.g. tuberculosis, bronchiectasis),*
- *chronic inflammatory diseases, (e.g. JIA),*
- *autoinflammatory diseases (e.g. FMF)*
- *neoplasias*

Amyloid fibrils are most commonly deposited in the **kidneys**, but may also attack the heart, peripheral nerves, thyroid, gastrointestinal system, and bone marrow.

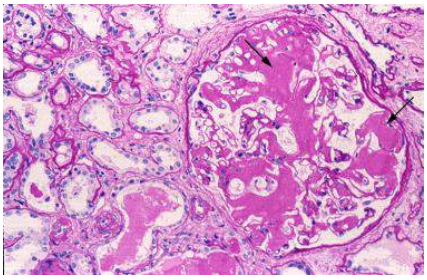
Major manifestations of renal amyloidosis:

- asymptomatic proteinuria (initial presentation)
- nephrotic syndrome
- chronic renal failure

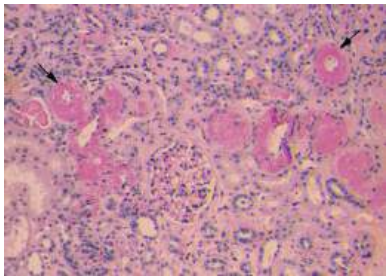
The most common and earliest sign of amyloidosis in FMF is proteinuria, gradually progressing to nephrotic syndrome and/or renal dysfunction.

Signs of tubular dysfunction such as type 1 (distal) renal tubular acidosis, nephrogenic diabetes insipidus related polyuria, and acquired Fanconi syndrome have been rarely reported as well.

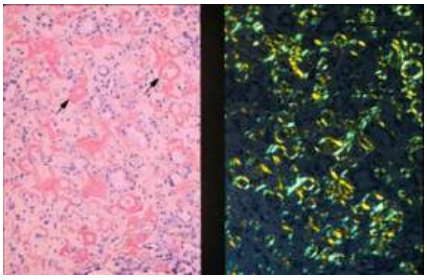
Glomerular amyloidosis



Vascular renal amyloidosis



Tubular amyloidosis



The amount of proteinuria and renal function vary in each case, which is related to the amount and/or site of amyloid deposition. Patients having glomerular amyloid deposition are more common and have a poorer prognosis than patients having vascular and tubular amyloid deposition in AA amyloidosis.

Risk factors for amyloidosis in familial Mediterranean fever (FMF):
- early onset of the disease,
- frequent attacks,
- protracted articular syndrome,
- homozygous genotype of MEFV mutant alleles (M694V/M694V) and SAA1 (α/α):

Colchicine is the mainstay treatment for the prevention of amyloidosis in FMF.

INTRODUCTION TO PREVENTIVE PEDIATRICS. CHILDHOOD IMMUNIZATION

Keeping our children healthy and safe is the responsibility of all of us - parents, doctors, nurses, teachers. Each of these five components of preventive pediatrics will help us accomplish this task.

- Nutrition promotes good health
  - *Good nutrition is every child's birthright*
  - *Every child will instinctively choose the right food in the right amount at the right time if it is available to him*

- Health care and health maintenance
  - Benefits of well child checks-ups
  - Schedule for check-ups
  - Each assessment will include:
    - *growth/development*
    - *head-to-toe physical assessment*
    - *health teaching*
    - *immunizations*
    - *screening for problems*

- Safety and accident prevention

- Emotional climate in the home

- Immunizations prevents childhood diseases

CHILDHOOD IMMUNIZATION

Immunisation is one of the most important weapons for protecting individuals and the community from serious diseases. Immunity to an infectious disease can be acquired through a natural process, e.g. active clinical infection by a microorganism or a subclinical inapparent infection.
Immunisation is a process of inducing immunity against an infectious agent, and is generally used in reference to the artificial means of inducing immunity by giving vaccines, i.e. vaccination. Immunisation can also be achieved by a passive process wherein antibodies to the infectious agent produced by another individual or animal who has been exposed to it, are extracted, and are used to provide protection. These antibodies provide protection for a short duration as their level decreases over a period of time leading to waning of immunity. Also, the level of protection provided by such methods is not as good as by the individual's own response.

The examples of passive immunisation are:

1. Immunoglobulin from human source

• General non-specific pooled immunoglobulin, e.g. intravenous immunoglobulin.
• Specific antibodies against an infectious agent, e.g. antirabies or antitetanus globulins.
• Transplacental transfer from mother to foetus of various immune globulins.

2. From animal sources
• Pooled sera, e.g. anti-diphtheritic serum (ADS—diphtheria antitoxin).

Various Types of Vaccines Used for Active Immunisation

Killed Vaccines
The whole infectious agent is killed artificially, and made into a suitable vaccine, e.g. whole cell pertussis vaccine, cholera vaccine.

Live Attenuated Vaccines
In this type of vaccine, the microorganisms are subjected to processes which attenuate their disease causing capabilities while retaining the immunity generating components. After administration, the microorganisms multiply in the recipient, and thus generate an immune response similar to a natural infection, e.g. BCG, measles vaccine.
Toxoids
Toxoids are detoxified toxins with the capacity to stimulate formation of antitoxin in the recipient, e.g. tetanus toxoid, diphtheria toxoid.

Sub-unit Vaccines
A part of the microorganism, which has the capability to generate the immune response, is utilised for making the vaccine, e.g. acellular pertussis, vi antigen typhoid vaccine.

Recombinant Vaccines
The recombinant vaccines are synthesised using a nonpathogenic organism carrying immunogenic components of the pathogenic organism, e.g. Hepatitis B vaccine. These can be *Live Attenuated Vector Vaccines* which involve incorporation of a pathogen's antigenic peptides into a harmless carrier virus or bacteria, or *Chimeric Vaccines* where genes from the target pathogen are substituted for similar genes in a safe but closely related organism. In DNA vaccines, a DNA plasmid encodes a viral gene that can be expressed inside cells of the animal to be immunised.

Vaccination schedule

There are ten routine childhood vaccines that protect children from the 14 diseases described in this booklet:
DTP: Protects against Diphtheria, Tetanus & Pertussis
MMR: Protects against Measles, Mumps & Rubella
HepA: Protects against Hepatitis A
HepB: Protects against Hepatitis B
Hib: Protects against Haemophilus influenzae type b
Flu: Protects against Influenza
PCV13: Protects against Pneumococcal disease
Polio: Protects against Polio
RV: Protects against Rotavirus
Varicella: Protects against Chickenpox
(also **BCG** in many countries: protects against tuberculosis)

Some bacteria or viruses – for example, pneumococcal, rotavirus, and influenza – have many strains, and existing vaccines protect only against selected strains . . . generally the most common or those most likely to cause illness in children.
All childhood vaccines are given as a series of 2 or more doses. For some of these vaccines, a booster dose at 4-6 years is also recommended.
- Influenza (flu) vaccine is recommended every winter for children 6 months of age and older.

Here is the routine childhood schedule. *(For a more detailed and comprehensive version of this schedule, you can visit the CDC website at: http://www.cdc.gov/vaccines/recs/schedules/default. htm#child)*

at birth	HepB (and BCG in many countries)
2 months	HepB (1-2 mos) + DTP + PCV13 + Hib + Polio + RV
4 months	DTP + PCV13 + Hib + Polio + RV
6 months	HepB (6-18 mos) + DTP + PCV13 + Hib + Polio (6-18 mos) + RV
12 Months	MMR (12-15 mos) + PCV13 (12-15 mos) + Hib (12-15 mos) + Varicella (12-15 mos) + HepA (12-23 mos)
15 months	DTP (15-18 mos)

Route of Administration

Intramuscular (IM)	Subcutaneous (SC)	Oral	Intradermal
■ DTP ■ Hep A & B ■ HiB ■ Influenza ■ Pneumococcal ■ Meningococcal ■ Typhoid	■ Measles ■ Mumps ■ Rubella ■ MMR ■ Varicella ■ Pneumococcal ■ Meningococcal	■ OPV ■ Typhoid ■ Rotavirus	■ BCG

Where to inject?

General rules:

- For children < 1 year old – lateral thigh
- For children > 1 year old - deltoid
- Buttocks should not be used for active vaccinations because of the potential risk of injury to the sciatic nerve
- If the buttocks are to used – use only the upper outer quadrant

Contraindications

Every child has a right for immunisation, and withholding it for some common minor illness or for any other reason is not justifiable. There are few contraindications to vaccination, and one must apply them judiciously so as not to have a missed opportunity for immunisation in a child.

- Severe acute illness—infectious or noninfectious
- Immunocompromised states, especially for live vaccines
- History of allergic reaction to vaccine
- Egg allergy in case of egg/chicken protein containing vaccines
- History of previous severe reaction to DPT

Live attenuated vaccines is contraindicated in:

- Pregnant woman
- Immunocompromised person – leukemia, lymphoma, malignancy, therapy with steroids, alkylating agents, antimetabolites
- Radiotherapy

Adverse events

The present day vaccines, which have been approved for use in children, are expected to be safe. Sometimes, they can cause certain mild adverse reactions and rarely serious events. Various components of the vaccine can lead to an allergic reaction, e.g. the microorganism, antibiotics or other stabilising agents used in the vaccine. The usual adverse events and the causative vaccines are shown here:

Fever of short duration	*Local reaction*	*Transient rash*	*Shock like state*	*Rare events*
• DTP • Measles • Typhoid • T. toxoid	• DTP • Typhoid • T. toxoid	• Measles • Varicella	• DTP • Measles (contaminated)	• *Seizure* DTP • *Paralysis* OPV • *Anaphylaxis* measles • *Guillian Barre* T. toxoid • *Inconsolable crying* DTP

Post-immunisation pyrexia in infants

The parent(s) should be advised that if pyrexia develops after childhood immunisation, the infant can be given a dose of paracetamol and if necessary, a second dose given 6 hours later; ibuprofen may be used if paracetamol is unsuitable. For post-immunisation pyrexia in an infant aged 2–3 months, the dose of paracetamol is 60 mg; the dose of ibuprofen is 50 mg.