I. A. KAZYRA

PEDIATRIC DISEASES

Minsk BSMU 2024

МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ РЕСПУБЛИКИ БЕЛАРУСЬ
БЕЛОРУССКИЙ ГОСУДАРСТВЕННЫЙ МЕДИЦИНСКИЙ УНИВЕРСИТЕТ
1-я КАФЕДРА ДЕТСКИХ БОЛЕЗНЕЙ

И. А. Козыро

ДЕТСКИЕ БОЛЕЗНИ

PEDIATRIC DISEASES

Допущено Министерством образования Республики Беларусь
в качестве учебного пособия для иностранных студентов
учреждений высшего образования по специальности «Лечебное дело»,
по профилю субординатуры «Общая врачебная практика»

Минск БГМУ 2024

УДК 616-053.2(075.8)
ББК 57.33я73
К59

Р е ц е н з е н т ы: д-р мед. наук, проф., зав. 2-й каф. детских болезней Гродненского государственного медицинского университета; каф. педиатрии № 2 Витебского государственного ордена Дружбы народов медицинского университета

Учебное пособие издано при поддержке Гранта
Президента Республики Беларусь в образовании

Козыро, И. А.

К59 Детские болезни = Pediatric diseases : учебное пособие / И. А. Козыро. – Минск : БГМУ, 2024. – 347 с.

ISBN 978-985-21-1697-8.

Включает следующие разделы педиатрии: история развития и болезни ребенка, методы обследования ребенка, оценка физического развития ребенка, новорожденный ребенок и основные проблемы периода новорожденности, питание ребенка и его нарушения, рахит, аллергические заболевания (пищевая аллергия, атопический дерматит, бронхиальная астма), болезни дыхательной системы, болезни сердечно-сосудистой системы, болезни желудочно-кишечного тракта, болезни органов мочевой системы, болезни соединительной ткани, болезни крови, неотложные состояния у детей, а также схема написания учебной истории болезни ребенка. Отражены современные представления об этиологии, патогенезе, клинических проявлениях, классификационных критериях, принципах лабораторной, инструментальной и других видах диагностики, а также подходах к дифференциальной диагностике, лечению и профилактике заболеваний детского возраста.

Предназначено для использования при реализации программ в системе первой ступени высшего образования и ориентировано на студентов 4–6-го курсов медицинского факультета иностранных учащихся, обучающихся по специальности «Лечебное дело» 1-79 01 01 на английском языке, по учебной дисциплине «Педиатрия».

УДК 616-053.2(075.8)
ББК 57.33я73

ISBN 978-985-21-1697-8

ABBREVIATIONS

AB — antibodies
ACE — angiotensin-converting enzyme
ACEIs — angiotensin converting enzyme inhibitors
AG — antigens
AHD — Acquired heart disease
AKI — acute kidney injury
ALL — acute lymphoblastic leukemia
AML — acute myeloblastic leukemia
ANA — anti-nuclear antibodies
ANCA — antineutrofilic cytoplasmic antibodies
APGN — acute post-streptococcal or post-infectious glomerulonephritis
ARBs — angiotensin receptor blockers
ARNI — angiotensin receptor and neprilysin inhibitor
ARF — acute renal failure
ASD — atrial septal defect
ASLO — antistreptolysin O
BMI — body mass index
BP — blood pressure
BR — breath rate
BUN — blood urea nitrogen
BW — body weight
CAP — community-aquiered pneumonia
CBC — complete blood count
CHD — congenital heart disease
CKD — chronic kidney disease
CML — chronic myeloid leukemia
CMV — cytomegalovirus
CNS — central nervous system
CoA — coarctation of the aorta
CO — cardiac output
CRP — C-reactive protein
CSF — cerebral spinal fluid
CT — computed tomography
DCMP — dilated cardiomyopathy
DNA — deoxyribonucleic acid
EBV — Epstein-Barr virus
ECG — electrocardiogram
EDP — end-diastolic pressure
EDV — end-diastolic volume
EEG — electroencephalogram
EF — ejection fraction
EPO — erythropoietin

ESR — erythrocyte sedimentation rate
EGDS — esophagogastroduodenoscopy
FC — functional classes
GA — gestation age
GBM — glomerular basement membrane
GBS — Group B Streptococcus infection
GER — gastroesophageal reflux
GERD — gastroesophageal reflus disease
CSF — cerebrospinal fluid
G-6-PD — glucose-6-phosphate dehydrogenase
GI — gastrointestinal
eGFR — estimated glomerular filtration rate
GFR — glomerular filtration rate
GN — glomerulonephritis
HAP — hospital-aquired pneumonia
Hb — hemoglobin
HBV — hepatitis B
HC — head circumference
HCV — hepatitis C
HDN — hemolytic disease of the newborn
HSV — herpes simplex virus
HFA — height for age
HF — heart failure
HFmrEF — heart failure with mildly reduced ejection fraction
HFpEF — preserved ejection fraction heart failure
HFrEF — heart failure with reduced ejection fraction
HIV — human immunodeficiency virus
HR — heart rate
HUS — hemolytic uremic syndrome
IBD — inflammatory bowel diseases
IC — immune complex
ICU — intensive care unit
Ig — immunoglobulins
IDA — iron deficiency anemia
IL — interleukin
IM — intramuscular
US — ultrasound
IVIG — intravenous immunoglobulin
IV — intravenous
LA — left atrium
LABA — long-acting β2-agonists
LBW — low birth weight
LDH — lactate dehydrogenase
LV — left ventricle

LVHF — left ventricular heart failure
LP — lumbar puncture
MCH — mean corpuscular hemoglobin
MCHC — mean corpuscular hemoglobin concentration
MCV — mean corpuscular volume
Mo — month
MUAC — mid-upper arm circumference
NSAIDS — non-steroidal antiinflamatory drugs
PCR — polymerase chain reaction
PDA — patent ductus arteriosus
PH — pulmonary hypertension
PMNs — polymorphonuclear neutrophils
PPIs — proton pomps inhibitors
PTH — parathyroid gormon
PUD — peptic ulcer disease
RA — right atrium
RAAS — renin-angiotensin-aldosterone system
RBC — red blood cell
RDA — recommended daily allowance
RDW — red cell distribution width
RES — reticuloendothelial system
RI — reticulocyte index
RPGN — rapidly progressive glomerulonephritis
RRT — renal replacement therapy
RV — right ventricle
RVHF — right ventricular heart failure
SABA — short-acting β2-agonists
SCD — sudden cardiac death
SD — standard deviation
SV — stroke volume
SF — serum ferritin
SI — serum iron
Tf — transferring
TfR — transferrin receptor
TMA — thrombotic microangiopathy
TORCH — toxoplasma, others, rubella, cytomegalovirus, herpes simplex virus
TTP — thrombotic thrombocytopenic purpura
UTI — urinary tract infection
VSD — ventricular septal defect
WFA — weight for age
WFH — weight for height
WHO — World Health Organization
Wk — week
Yr — year

CHAPTER 1
HISTORY-TAKING AND EXAMINATION

The cornerstone of clinical practice continues to be history-taking and clinical examination. Good doctors will continue to be admired for their ability to distil the important information from the history, for their clinical skills, for their attitude towards patients and for their knowledge of diseases, disorders and behavior problems. Parents are acutely interested in and anxious about their children. They will quickly recognize doctors who demonstrate interest, empathy and concern. They will seek out doctors who possess the appropriate skills and attitudes towards their children.

In approaching clinical history and examination of children, it is helpful to visualize some common clinical scenarios in which children are seen by doctors:

– an acute illness, e.g. respiratory tract infection, meningitis, appendicitis;

– a chronic problem, e.g. failure to thrive, chronic cough;

– a newborn or infant with a congenital malformation (abnormality), e.g. developmental dysplasia of the hip, Down syndrome;

– suspected delay in development, e.g. slow to walk, talk or acquire skills;

– behavior problems, e.g. temper tantrums, hyperactivity, eating disorders.

The aims and objectives in clinical history and examination are to:

– establish the relevant facts of the history; this is always the most fruitful source of diagnostic information;

– elicit all relevant clinical findings;

– collate the findings from the history and examination;

– formulate a working diagnosis or differential diagnosis on the basis of logical deduction;

– assemble a problem list and management plan.

The above can be summarized by the acronym HELP: H — history, E — examination, L — logical deduction, P — plan of management.

Key points in pediatric history and examination are:

– the child's age — a key feature in the history and examination as it determines;

– the nature and presentation of illnesses, developmental or behavior problems;

– the way in which the history-taking and examination are conducted;

– the way in which any subsequent management is organized;

– the parents, who are astute observers of their children. Never ignore or dismiss what they say.

Introduction:

• Make sure you have read any referral letter and scanned the notes before the start of the interview.

• Observe the child at play in the waiting area and observe their appearance, behavior and gait as they come into the clinic room. The continued observation of the child during the whole interview may provide important clues to the diagnosis and management.

• When you welcome the child, parents and siblings, check that you know the child's first name and gender. Ask how the child prefers to be addressed.

• Introduce yourself.

• Determine the relationship of the adults to the child.

• Establish eye contact and rapport with the family. Infants and some toddlers are most secure in parents' arms or laps. Young children may need some time to get to know you.

• Ensure that the interview environment is as welcoming and unthreatening as possible. Avoid having desks or beds between you and the family, but keep a comfortable distance.

• Have toys available. Observe how the child separates, plays and interacts with any siblings present.

• Do not forget to address questions to the child, when appropriate.

• There will be occasions when the parents will not want the child present or when the child should be seen alone. This is usually to avoid embarrassing older children or teenagers or to impart sensitive information. This must be handled tactfully, often by negotiating to talk separately to each in turn.

Presenting symptoms (complaints). Full details are required of the presenting symptoms. Let the parents and child recount the presenting complaints in their own words and at their own pace. Note the parent's words about the presenting complaint: onset, duration, previous episodes, what relieves/aggravates them, time course of the problem, if getting worse and any associated symptoms. Has the child's or the family's lifestyle been affected? What has the family done about it?

Pain — if pain is a symptom, clarify the details of the pain using SOCRATES:

– Site — where exactly is the pain / where is the pain worst?

– Onset — when did it start? / did it come on suddenly or gradually?

– Character — what does it feel like? (sharp stabbing / dull ache / burning?)

– Radiation — does the pain move anywhere else? (e.g. chest pain with left arm radiation).

– Associations — any other symptoms associated with the pain (e.g. chest pain with shortness of breath).

– Time course — does the pain have a pattern (e.g. worse in the mornings)?

– Exacerbating / Relieving factors — anything make it particularly worse or better?

– Severity — on a scale of 0–10, with 0 being no pain & 10 being the worst pain you've ever felt.

Make sure you know: what prompted referral to a doctor; what the parents think or fear is the matter.

The history and examination should be goal-oriented, based on the presenting complaint. The scope and detail of further history-taking are determined by the nature and severity of the presenting complaint and the child's age. While the comprehensive assessment listed here is sometimes required, usually a selective approach is more appropriate. This is not an excuse for a short,

slipshod history, but instead allows one to focus on the areas where a thorough, detailed history is required.

General enquiry. Check:

– General health — how active and lively?

– Normal growth.

– Pubertal development (if appropriate).

– Feeding/drinking/appetite.

– Any recent change in behavior or personality.

Systems review. Selected, as appropriate:

General rashes, fever (if measured);

– Respiratory — cough, wheeze, breathing problems.

– ENT (ear, nose and throat) — throat infections, snoring, noisy breathing (stridor).

– Cardiovascular — heart murmur, cyanosis, exercise tolerance.

– Gastrointestinal — vomiting, diarrhea/constipation, abdominal pain.

– Genitourinary — dysuria, frequency, wetting, toilet-trained.

– Neurological — seizures, headaches, abnormal movements.

– Musculoskeletal — disturbance of gait, limb pain or swelling, other functional abnormalities.

Make sure that you and the parent or child means the same thing when describing a problem.

An approach to examining children. Obtaining the child's cooperation:

– Make friends with the child.

– Be confident but gentle.

– Avoid dominating the child.

– Short mock examinations, e.g. auscultating a teddy or the mother's hand, may allay a young child's fears.

– When first examining a young child, start at a non-threatening area, such as a hand or knee.

– Explain what you are about to do and what you want the child to do, in language he/she can understand. As the examination is essential, not optional, it is best not to ask his permission, as it may well be refused!

– A smiling, talking doctor appears less threatening, but this should not be overdone as it can interfere with one's relationship with the parents.

– Leave unpleasant procedures until last.

Adapting to the child's age. Adapt the examination to suit the child's age. While it may be difficult to examine some toddlers and young children fully, it is usually possible with resourcefulness and imagination on the doctor's part.

• Babies in the first few months are best examined on an examination couch with a parent next to them.

• A toddler is best initially examined on his/her mother's lap or occasionally over a parent's shoulder.

• Distracting a toddler with a toy allows auscultation of the heart. Parents are reassuring for the child and helpful in facilitating the examination if guided as to what to do.

• Preschool children may initially be examined while they are playing.

• Older children and teenagers are often concerned about privacy. Teenage girls should normally be examined in the presence of their mother, or a nurse or suitable chaperone. Be aware of cultural sensitivities in different ethnic groups.

• A quiet condition of the child is preferred. It is not necessary to awake the sleeping child suddenly. Please keep in mind: while sleeping, the parameters of some systems are optimal.

Undressing children. Be sensitive to children's modesty. The area to be examined must be inspected fully but this is best done in stages, re-dressing the child when each stage has been completed. It is easiest and kindest to ask the child or parent to do the undressing.

Warm, clean hands. Hands must be washed before (and after) examining a child. Warm smile, warm hands and a warm stethoscope all help.

Developmental skills. A good overview of developmental skills can be obtained by watching the child play. A few simple toys, such as some bricks, a car, doll, ball, pencil and paper, pegboard, miniature toys and a picture book, are all that is required, as they can be adapted for any age. If developmental assessment is the focus of the examination, it is advisable to assess this before the physical examination, as cooperation may then be lost.

Examination. Initial observations. Careful observation is usually the key to success in examining children. Look before touching the child. Inspection will provide information on:

– severity of illness;

– growth and nutrition;

– behavior and social responsiveness;

– level of hygiene and care.

Severity of illness. Is the child sick or well? If sick, how sick? For the acutely ill infant or child, perform the "60-second rapid assessment":

– airway and breathing — respiration rate and effort, presence of stridor or wheeze, cyanosis;

– circulation — heart rate, pulse volume, peripheral temperature, capillary refill time;

– disability — level of consciousness.

Measurements. As abnormal growth may be the first manifestation of illness in children, always measure and plot growth on centile charts for:

– weight, noting previous measurements from personal child health record;

– length (in infants, if indicated) or height in older children;

– head circumference (HC) in infants.

Measurements of length, weight and HC between the 25th and 75th percentiles are likely to represent normal growth. Measurements between

the 10th and 25th percentiles represent less than average data and between the 75th and 90th — bigger than average data. These measurements may or may not be normal, depending on previous and subsequent measurements and on genetic and environmental factors. Measurements between the 10th and 3rd, and the 90th and 97th percentiles belong to low and high data, which require further examination. Measurements below the 3rd and above the 97th percentiles are extremely low and extremely high and reflect pathological deviations of physical development (Appendix 2).

Also, as appropriate: temperature; blood pressure (BP); peak expiratory flow rate.

General appearance. The face, head, neck and hands are examined. The general morphological appearance may suggest a chromosomal or dysmorphic syndrome. In infants, palpate the fontanelle and sutures.

Respiratory system. Cyanosis. Central cyanosis is best observed on the tongue. Clubbing of the fingers and/or toes. Clubbing is usually associated with chronic suppurative lung disease, e.g. cystic fibrosis, or cyanotic congenital heart disease. It is occasionally seen in inflammatory bowel disease or cirrhosis. Rate of respiration is age-dependent (Table 1.1).

Table 1.1

Normal respiratory rate in children

Age	Respiratory rate, breaths/minute
Under 3 months.	40–45
4–6 months	35–40
7–12 months	30–35
2–3 years	25–30
5–6 years	Approx. 25
10–12 years	20–22
14–15 years	18–20

Tachypnea (age — breaths/minute): < 2 months — > 60; from 2 to 12 months — > 50; from 12 months to 5 years — > 40; greater than 5 years — > 30.

Dyspnea. Labored breathing. Increased respiratory rate (may be the only sign of increased work of breathing). Increased work of breathing is judged by: nasal flaring; expiratory grunting — to increase positive end-expiratory pressure; use of accessory muscles, especially sternomastoids; retraction (recession) of the chest wall, from use of suprasternal, intercostal and subcostal muscles; difficulty speaking (or feeding).

Chest shape:

– Hyperexpansion or barrel shape, e.g. asthma.

– Pectus excavatum (hollow chest) or pectus carinatum (pigeon chest).

– Harrison’s sulcus (indrawing of the chest wall from diaphragmatic tug), e.g. from poorly controlled asthma or rickets.

– Asymmetry of chest movements.

Palpation:

– Chest expansion: this is 3–5 cm in school-aged children. Measure maximal chest expansion with a tape measure. Check for symmetry.

– Trachea: checking that it is central is seldom helpful and is disliked by children. To be done selectively.

– Location of apex beat to detect mediastinal shift.

Percussion:

– Needs to be done gently, comparing like with like, using middle fingers.

– Seldom informative in infants.

– Localized dullness: collapse, consolidation, fluid.

Auscultation (ears and stethoscope):

– Note quality and symmetry of breath sounds and any added sounds.

– Harsh breath sounds from the upper airways are readily transmitted to the upper chest in infants.

– Hoarse voice — abnormality of the vocal cords.

– Stridor — harsh, low-pitched, mainly inspiratory sound from upper airways obstruction.

– Breath sounds — normal are vesicular; bronchial breathing is higher-pitched and the length of inspiration and expiration is equal.

– Wheeze — high-pitched, expiratory sound from distal airway obstruction.

– Crackles — discontinuous "moist" sounds from the opening of bronchioles.

Cardiovascular system. Cyanosis. Observe the tongue for central cyanosis, clubbing of fingers or toes (check if present).

Pulse: Check Rate (Tables 1.2, 1.3).

Check *Rhythm* — sinus arrhythmia (variation of pulse rate with respiration) is normal. Check *Volume* — small in circulatory insufficiency or aortic stenosis; increased in high-output states (stress, anemia); collapsing in patent ductus arteriosus, aortic regurgitation.

Inspection. Look for:

– respiratory distress;

– precordial bulge — caused by cardiac enlargement;

– ventricular impulse — visible if the patient is thin, hyperdynamic circulation or left ventricular (LV) hypertrophy is present;

– operative scars — mostly sternotomy or left lateral thoracotomy.

Table 1.2

Normal resting pulse rate in children (beats/minute)

Age	Heart rate, beats/minute
< 3 months	120–170
4–6 months	100–150
7–12 months	80–120
1–3 years	70–110
3–6 years	65–110
6–12 years	60–95
12 years and older	60–85

Table 1.3

Heart rate (centiles)

Age	Centiles			
	10	**25**	**75**	**90**
Newborn	110	120	130	140
1	100	110	120	130
2	80	95	110	120
3–4	80	90	105	120
5–7	75	82	100	110
8–10	72	80	95	108
11–13	70	80	95	108
14–15	70	80	95	108
16–17	65	80	95	110

Palpation. Thrill = palpable murmur.

Apex (4–5th intercostal space, mid-clavicular line):

– not palpable in some normal infants, plump children or dextrocardia;

– heave from LV hypertrophy.

Right ventricular heave at lower left sternal edge — right ventricular (RV) hypertrophy.

Percussion. Cardiac border percussion in children is Table 1.4.

Table 1.4

Borders of relative heart dullness and transversal heart distance

Border	Age of child			
	Under 2 years	**2–7 years**	**7–12 years**	**Over 12 years**
Right	The right parasternal line	Inwards from the right parasternal line	In the middle between the right parasternal line and the right sternal line	
Upper	the 3rd rib	the 2nd intercostal space	the 3rd rib	the 3rd rib or 3rd intercostal space
Left	2 cm outwards from the left mid-clavicular line	1 cm outwards from the left mid-clavicular line	0.5 cm outwards from the left mid-clavicular line	On the left mid-clavicular line or 0.5 cm inwards
Transversal heart distance	6–9 cm	8–12 cm	9–14 cm	9–14 cm

Auscultation. Listen for heart sounds and murmurs. Heart sounds: splitting of second sound is usually easily heard and is normal; fixed splitting of second heart sound in atrial septal defects; third heart sound in mitral area is normal in young children.

Murmurs:

– Timing — systolic/diastolic/continuous.

– Duration — mid-systolic (ejection)/pansystolic.

– Loudness — systolic murmurs graded: 1–2 — soft, difficult to hear; 3 — easily audible, no thrill; 4–6 — loud with thrill.

– Site of maximal intensity — mitral/pulmonary/aortic/tricuspid areas.

– Radiation: to the neck in aortic stenosis, to the back in coarctation of the aorta or pulmonary stenosis.

Femoral pulses. In coarctation of the aorta:

– decreased volume or may be impalpable in infants;

– Brachiofemoral delay in older children.

Heart disease is more common in children with other congenital abnormalities or syndromes, e.g. Down and Turner syndromes.

Features of heart failure in infants:

– poor feeding/failure to thrive;

– sweating;

– tachypnea;

– tachycardia;

– gallop rhythm;

– cardiomegaly;

– Hepatomegaly. Important sign of heart failure in infants (an infant's liver is normally palpable 1–2 cm below the costal margin).

Features suggesting that a murmur is significant: conducted all over the precordium; loud; thrill (equals grade 4–6 murmur); any diastolic murmur; accompanied by other abnormal cardiac signs.

Blood pressure. *Abdominal palpation*. Abdominal examination is performed in three major clinical settings:

– the routine part of the examination;

– an "acute abdomen" — cause;

– recurrent abdominal pain/distension/constipation mass.

Associated signs — examine:

– the eyes for signs of jaundice and anemia;

– the tongue for coating and central cyanosis;

– the fingers for clubbing.

Inspection. The abdomen is protuberant in normal toddlers and young children. The abdominal wall muscles must be relaxed for palpation. Generalized abdominal distension is most often explained by the five "F"s:

– Fat;

– Fluid (ascites — uncommon in children, most often from nephrotic syndrome);

– Faeces (constipation);

– Flatus (malabsorption, intestinal obstruction);

– Fetus (not to be forgotten after puberty).

Occasionally, it is caused by a grossly enlarged liver and/or spleen or muscle hypotonia.

Causes of localized abdominal distension are:

– upper abdomen — gastric dilatation from pyloric stenosis, hepato/splenomegaly;

– lower abdomen — distended bladder, masses.

Other signs: dilated veins in liver disease, abdominal striae; operative scars (draw a diagram); peristalsis — from pyloric stenosis, intestinal obstruction.

Are the buttocks normally rounded, or wasted as in malabsorption, e.g. celiac disease or malnutrition?

Palpation:

• Use warm hands, explain, relax the child and keep the parent close at hand. First ask if it hurts.

• Palpate in a systematic fashion — liver, spleen, kidneys, bladder, through four abdominal quadrants.

• Ask about tenderness. Watch the child's face for grimacing as you palpate. A young child may become more cooperative if you palpate first with their hand or by putting your hand on top of theirs.

Tenderness. Location — localized in appendicitis, hepatitis, pyelonephritis; generalized in mesenteric adenitis, peritonitis. Guarding — often unimpressive on direct palpation in children. Pain on coughing, on moving about / walking / bumps during car journey suggests peritoneal irritation. Back bent on walking may be from psoas inflammation in appendicitis. By incorporating play into examination, more subtle guarding can be elicited. For example, a child will not be able to jump on the spot if they have localized guarding.

Liver: palpate from right iliac fossa; locate edge with tips or side of finger; edge may be soft or firm; unable to get above it; moves with respiration; measure (in cm) extension below costal margin in mid-clavicular line.

Liver boarders (Table 1.5).

Table 1.5

Liver boarders

Lines	1–3 years	4–7 years	8–12 years	Over 12 years
The right mid-clavicular line	5 cm	6 cm	8 cm	10 cm
The medium line	4 cm	5 cm	7 cm	9 cm
The left oblique line	3 cm	4 cm	6 cm	8 cm

Percuss downwards from the right lung to exclude pseudohepatomegaly due to lung hyperinflation. Liver tenderness is likely to be due to inflammation from hepatitis. Cause of hepatomegaly (Table 1.6).

Table 1.6

Cause of hepatomegaly

Infection	Congenital infection, mononucleosis, hepatitis, malaria, parasitic infection
Hematological	Sickle cell anemia, thalassemia
Liver disease	Chronic active hepatitis, portal hypertension, polycystic disease
Malignancy	Leukemia, lymphoma, neuroblastoma, Wilms' tumor, hepatoblastoma
Metabolic	Glycogen and lipid storage disorders, mucopolysaccharidoses
Cardiovascular	Heart failure
Apparent	Chest hyperexpansion from bronchiolitis or asthma

Spleen. Palpate from left iliac fossa. Edge is usually soft. Unable to get above it; Notch occasionally palpable if markedly enlarged. Moves on respiration (ask the child to take a deep breath). Measure size below costal margin (in cm) in mid-clavicular line. If uncertain whether it is palpable: use bimanual approach to spleen; turn child onto right side. A palpable spleen is at least twice its normal size! Lung hyperexpansion in bronchiolitis or asthma may displace the liver and spleen downwards, mimicking hepato/splenomegaly. Cause of splenomegaly (Table 1.7).

Table 1.7

Cause of splenomegaly

Infection	Viral, bacterial, protozoal (malaria, leishmaniasis), parasites, infective endocarditis
Hematological	Haemolytic anemia
Malignancy	Leukaemia, lymphoma
Other	Portal hypertension, systemic juvenile idiopathic arthritis (Still's disease)

On examining the abdomen:

– inspect first, palpate later;

– superficial palpation first, deep palpation later;

– guarding is unimpressive in children;

– silent abdomen — serious!

– immobile abdomen — serious!

Kidneys. These are not usually palpable beyond the neonatal period unless enlarged or the abdominal muscles are hypotonic. On examination palpate by balloting bimanually, they move on respiration, one can get above them. Tenderness implies inflammation.

Abnormal masses:

– *Wilms' tumour* — renal mass, sometimes visible, does not cross midline.

– *Neuroblastoma* — irregular firm mass, may cross midline; the child is usually very unwell.

– *Faecal masses* — mobile, non-tender, indentable.

– *Intussusception* — acutely unwell, mass may be palpable, most often in right upper quadrant.

Percussion. Liver — dullness delineates upper and lower border. *Spleen* — dullness delineates lower border. *Ascites* — shifting dullness. Percuss from most resonant spot to most dull spot.

Auscultation. Not very useful in "routine" examination, but important in "acute abdomen":

– increased bowel sounds — intestinal obstruction, acute diarrhea;

– reduced or absent bowel sounds — paralytic ileus, peritonitis.

Genital area. The genital area is examined routinely in young children, but in older children and teenagers this is done only if relevant, e.g. vaginal discharge. Is there an inguinal hernia or a perineal rash?

In *males*:

– Is the penis of normal size?

– Is the scrotum well developed?

– Are the testes palpable? With one hand over the inguinal region, palpate with the other hand. Record if the testis is descended, retractile or impalpable.

– Is there any scrotal swelling (hydrocele or hernia)?

In *females*: Do the external genitalia look normal?

Does the anus look normal? Any evidence of a fissure?

Rectal examination. This should not be performed routinely, and only for specific reasons. Unpleasant and disliked by children. Its usefulness in the "acute abdomen" (e.g. appendicitis) is debatable in children, as they have a thin abdominal wall and so tenderness and masses can be identified on palpation of the abdomen. Some surgeons advocate it to identify a retrocaecal appendix, but interpretation is problematic as most children will complain of pain from the procedure. If intussusception is suspected, the mass may be palpable and stools looking like redcurrant jelly may be revealed on rectal examination.

Urinalysis. Normal daily diuresis in children: newborns — 300 ml; 2 years — 700 ml; 5–6 years — 1000 ml; 10 years — 1500 ml. Diuresis (ml/kg/hour) is shown in Table 1.8.

Table 1.8

Age	Diuresis, ml/kg/hour	Density
10 day	2.5	1.002–1.004
2 month	3.5	1.002–1.006
1 year	2	1.006–1.010
2–7 years	1.7	1.010–1.020
11–14 years	1.4	1.008–1.022
Adults	0.8	1.011–1.025

Clean catch urine specimen preferred and the use of urine bags in the diagnosis of urine tract infection is not advisable. Dipstick testing for proteinuria, hematuria, glycosuria, leukocyturia. Examination of the microscopic appearance of urine is helpful for determining the origin of hematuria (crenated red cells, red cell casts).

Brief neurological screen. A quick neurological and developmental overview should be performed in all children. Use common sense to avoid unnecessary examination, adapt it to the child's age, and take into consideration the parent's account of developmental milestones. Watch the child play, draw or write. Are the manipulative skills normal? Can he walk, run, climb, hop, skip, and dance? Are the child's language skills and speech satisfactory? Are the social interactions appropriate? Does vision and hearing appear to be normal?

In infants, assess primarily by observation:

– Observe posture and movements of the limbs.

– When picking the infant up, note their tone. The limbs and body may feel normal, floppy or stiff. Head control may be poor, with abnormal head lag on pulling to sitting.

Most children are neurologically intact and do not require formal neurological examination of reflexes, tone, etc. More detailed neurological assessment is performed only if indicated. Specific neurological concerns or problems in development or behavior require detailed assessment.

Neck. ***Thyroid.*** Inspect — swelling uncommon in childhood; occasionally at puberty. Palpate from behind and front for swelling, nodule, thrill. Auscultate if enlarged. Look for signs of hypo / hyperthyroidism.

Lymph nodes. Examine systematically — occipital, cervical, axillary, inguinal. Note size, number, consistency of any glands felt:

– small, discrete, pea-sized, mobile nodes in the neck, groin and axilla — common in normal children, especially if thin;

– small, multiple nodes in the neck — common after upper respiratory tract infections (viral/bacterial);

– multiple lymph nodes of variable size in children with extensive atopic eczema — frequent finding, no action required;

– large, hot, tender, sometimes fluctuant node, usually in neck — infected/abscess;

– variable size and shape: infections: viral, e.g. infectious mononucleosis, or TB;

– rare causes: malignant disease (usually non-tender), Kawasaki disease, cat-scratch.

Blood pressure. *Indications:* must be closely monitored if critically ill, if there is renal or cardiac disease or diabetes mellitus, or if receiving drug therapy which may cause hypertension, e.g. corticosteroids. Not measured often enough in children.

Technique: when measured with a sphygmomanometer:

– Show the child that there is a balloon in the cuff and demonstrate how it is blown up.

– Use largest cuff which fits comfortably, covering at least two-thirds of the upper arm.

– The child must be relaxed and not crying.

– Systolic pressure is the easiest to determine in young children and clinically the most useful.

– Diastolic pressure is when the sounds disappear. May not be possible to discern in young children. Systolic pressure used in clinical practice.

Measurement. Must be interpreted according to a centile chart. BP is increased by tall stature and obesity. Charts relating BP to height are available and preferable; however, for convenience, charts relating BP to age are often used. An abnormally high reading must be repeated, with the child relaxed, on at least three separate occasions.

Cuff should be $^{2}/_{3}$ upper arm (smaller cuffs give artificially high reading). Upper limit of normal systolic BP for children 1–5 years — 110 mmHg, 6–10 years — 120 mmHg.

Eyes. *Examination.* Inspect eyes, pupils, iris and sclerae. Are eye movements full and symmetrical? Is nystagmus detectable? If so, may have ocular or cerebellar cause, or testing may be too lateral to the child. Are the pupils round (absence of posterior synechiae), equal, central and reactive to light? Is there a squint? Epicanthic folds are common in Asian ethnic groups.

Ophthalmoscopy:

- In infants, the red reflex is seen from a distance of 20–30 cm. Absence of red reflex occurs in corneal clouding, cataract, retinoblastoma.
- Fundoscopy — difficult. Requires experience and cooperation. In infants, mydriatics are needed and an ophthalmological opinion may be required. Retinopathy of prematurity and retinopathy of congenital infections and choroido-retinal degeneration show characteristic findings. Retinal hemorrhages may be seen in head trauma or in 'shaken baby syndrome' (non-accidental injury).
- In older children with headaches, diabetes mellitus or hypertension, optic fundi should be examined. Mydriatics are not usually needed.

Ears and throat. Examination is usually left until last, as it can be unpleasant. Explain what you are going to do. Show the parent how to hold and gently restrain a younger child to ensure success and avoid possible injury.

Throat. Try quickly to get a look at the tonsils, uvula, pharynx and posterior palate. Older children (5 years +) will open their mouths as wide as possible without a spatula. A spatula is required for young children. Look for redness, swelling, pus or palatal petechiae. Also check the teeth for dental caries and other gross abnormalities.

Ears. Examine ear canals and drums gently, trying not to hurt the child. Look for anatomical landmarks on the ear drum and for swelling, redness, perforation, dullness, fluid.

CHAPTER 2
GROWTH, DEVELOPMENT AND NUTRITION

Health is defined as a total physical, mental and social well-being according to the World Health Organization (WHO).

Criteria that determine a child's health:

1. Presence or absence of chronic (including congenital) disease.
2. The functional state of organs and systems.
3. Body resistance and reactivity.
4. Normal physical and pshycho-neurological development.

Pediatricians need to understand growth and development in order to monitor children's progress, to identify delays or abnormalities in development, and to counsel parents and prescribe treatment. In addition to clinical experience and personal knowledge, effective practice requires familiarity with major theoretical perspectives and evidence-based strategies for optimizing growth and development. In order to target factors that increase or decrease risk, pediatricians need to understand how biologic and social forces interact within the parent-child relationship, within the family, and between the family and the larger society. By monitoring children and families, pediatricians can observe the interrelationships between physical growth and cognitive, motor, and emotional development.

All periods of child's life are divided into two stages: intrauterine (gestational, antenatal) and extra uterine (postnatal).

Fetal growth and development. The most dramatic events in growth and development occur before birth. Intrauterine period continues for 280 days (40 weeks).

Embryonic period. By 6 days postconceptual age, as implantation begins, the embryo consists of a spherical mass of cells with a central cavity (the blastocyst). By 2 wk, implantation is complete and the uteroplacental circulation has begun; the embryo has two distinct layers, endoderm and ectoderm, and the amnion has begun to form. By 3 wk, the third primary germ layer (mesoderm) has appeared, along with primitive neural tube and blood vessels. Paired heart tubes have begun to pump. During wk 4–8, lateral folding of the embryologic plate, followed by growth at the cranial and caudal ends and the budding of arms and legs, produces a human-like shape. Precursors of skeletal muscle and vertebrae (somites) appear, along with the branchial arches that will form the mandible, maxilla, palate, external ear, and other head and neck structures. Lens placodes appear, marking the site of future eyes; the brain grows rapidly. By the end of wk 8, as the embryonic period closes, the rudiments of all major organ systems have developed; the average embryo weighs 9 g and has a crown-rump length of 5 cm.

Fetal period. From the 9th wk on, somatic changes consist of increases in cell number and size and structural remodeling of several organ systems. By 10 wk, the face is recognizably human. The midgut returns from the umbilical cord into the abdomen, rotating counterclockwise to bring the stomach, small intestine, and

large intestine into their normal positions. By 12 wk, the gender of the external genitals becomes clearly distinguishable. Lung development proceeds with the budding of bronchi, bronchioles, and successively smaller divisions. By 20–24 wk, primitive alveoli have formed and surfactant production has begun; before that time, the absence of alveoli renders the lungs useless as organs of gas exchange. During the 3rd trimester, weight triples and length doubles as body stores of protein, fat, iron, and calcium increase. Low birthweight may be due to prematurity, intrauterine growth retardation (small for dates), or both.

Neurologic development. During the 3rd wk, a neural plate appears on the ectodermal surface of the trilaminar embryo. Infolding produces a neural tube that will become the central nervous system (CNS) and a neural crest that will become the peripheral nervous system. Neuroectodermal cells differentiate into neurons, astrocytes, oligodendrocytes, and ependymal cells, whereas microglial cells are derived from mesoderm. By the 5th wk, the three main subdivisions of forebrain, midbrain, and hindbrain are evident. The dorsal and ventral horns of the spinal cord have begun to form, along with the peripheral motor and sensory nerves. Myelinization begins at midgestation and continues throughout the 1st 2 yr of life. By the end of the embryonic period, the gross structure of the nervous system has been established. On a cellular level, the growth of axons and dendrites and the elaboration of synaptic connections continue at a rapid pace, making the CNS vulnerable to teratogenic or hypoxic influences throughout gestation.

Behavioral development. Muscle contractions first appear around 8 wk, soon followed by lateral flexion movements. By 13–14 wk, breathing and swallowing motions appear and tactile stimulation elicits graceful movements. The grasp reflex appears at 17 wk and is well developed by 27 wk. Eye opening occurs around 26 wk. By midgestation, the full range of neonatal movements can be observed. During the 3rd trimester, fetuses respond to external stimuli with heart rate elevation and body movements. As with infants in the postnatal period, reactivity to auditory (vibroacoustic) and visual (bright light) stimuli vary depending on their behavioral state, which can be characterized as quiet sleep, active sleep, and awake.

Threats to fetal development. Mortality and morbidity are highest during the prenatal period. Some 30 % of pregnancies end in spontaneous abortion, most often during the 1st trimester as a result of chromosomal or other abnormalities. Major congenital malformations requiring neonatal surgical intervention occur in approximately 2 % of live births. Teratogens associated with gross physical and mental abnormalities include various infectious (toxoplasmosis, rubella, syphilis), chemical agents (mercury, thalidomide, antiepileptic medications, ethanol), high temperature, and radiation. For any potential teratogen, the extent and nature of its effects are determined by characteristics of the host as well as the dose and timing of the exposure. Inherited differences in the metabolism of ethanol may predispose certain individuals to fetal alcohol syndrome, eg.

Organ systems are most vulnerable during periods of maximum growth and differentiation, generally during the 1st trimester (organogenesis). Teratogenic effects may include not only gross physical malformation but also decreased growth and cognitive or behavioral deficits that only become apparent later in life. Prenatal exposure to cigarette smoke is associated with lower birthweight, shorter length, and smaller head circumference, as well as decreased IQ and increased rates of learning disabilities. The effects of prenatal exposure to cocaine remain controversial, and may be less dramatic than popularly believed. In addition to direct neurotoxic effects and effects mediated by reduced placental blood flow, associated risk factors include other prenatal exposures (e.g., alcohol and cigarettes used in large amounts by many cocaine-addicted women) as well as "toxic" postnatal environments frequently characterized by instability, multiple caregivers, and abuse and neglect. The wide range of outcomes observed reflects the complex interactions among biologic and social risk and protective factors. High levels of psychologic stress during pregnancy may also adversely affect fetal development.

Postnatal period *(from birth till 18 years of age)* is divided into the following periods:

– neonatal — the first 28 days of life: early (the first 7 days of life) and late (from 8th to the 28th days of life);

– infancy — from 29 days to 1 year of life;

– toddler — from the 1st to the 3rd yrs of life;

– preschool — 4–6 yrs of life;

– junior school — 7–11 yrs of life;

– senior school — 12–18 yrs of life.

In children *growth is one of the best indicators of health*. It's reflected in increases in the body weight and length, head circumference and other indexes along expected pathways and within certain limits. Disorders of growth and development are often associated with chronic or severe illness or may be the only symptom of parental neglect or abuse. Although normal growth and development does not eliminate a serious or chronic illness, in general, it supports a judgment that a child is healthy except for acute, often benign, illnesses that do not affect growth and development.

The processes of growth and development are intertwined. However, it is convenient *to refer to growth as* the increase in size and *development* as an increase in function of processes related to body and mind. Being familiar with normal patterns of growth and development allows those practitioners who care for children to recognize and manage abnormal variations.

The genetic makeup and the physical, emotional, and social environment of the individual determine how a child grows and develops throughout childhood. One goal of pediatrics is to help each child achieve his or her individual potential through periodically monitoring and screening for the normal progression or abnormalities of growth and development. The American Academy of Pediatrics recommends routine office visits in the 1st week of life (depending on timing of

nursery discharge); at 2 weeks; at 1, 2, 4, 6, 9, 12, 15 and 18 months; at 2, 2.6 and 3 years; and then annually through adolescence/young adulthood (the Bright Futures' "Recommendations for Preventive Pediatric Health Care", https://www.aap.org/en-us/documents/periodicity_schedule.pdf).

Deviations in growth patterns may be nonspecific or may be important indicators of serious and chronic medical disorders. An accurate measurement of length/height, weight, and head circumference should be obtained at every health supervision visit and compared with statistical norms on growth charts. Serial measurements are much more useful than single measurements to detect deviations from a particular growth pattern even if the value remains within statistically defined normal limits (percentiles).

Rules of Thumb for Growth.

Weight:

– weight loss in first few days: 5–10 % of birthweight;

– return to birthweight: 7–10 days of age;

– double birthweight: 4–5 months;

– triple birthweight: 1 year;

– daily weight gain: 20–30 g for first 3–4 months, 15–20 g for rest of the first year.

Height:

– average length: 20 in. at birth, 30 in. at 1 year, 50–55 cm and 75 cm respectively;

– at age 4 years, the average child is double birth length or 40 in. (1 m respectively).

Head circumference (HC):

– average HC: 35 cm at birth (13.5 in.);

– HC increases: 1 cm per month for first year (2 cm per month for first 3 months, then slower).

Growth is assessed by plotting accurate measurements on growth charts and comparing each set of measurements with previous measurements obtained at health visits (Fig. 2.1, 2.2). Complete charts can be found at www.cdc.gov/growthcharts.

The body mass index is defined as body weight in kilograms divided by height in meters squared; it is used to classify adiposity and is recommended as a screening tool for children and adolescents to identify those overweight or at risk for being overweight.

Normal growth patterns have spurts and plateaus, so some shifting on percentile graphs can be expected. Large shifts in percentiles warrant attention, as do large discrepancies in height, weight, and head circumference percentiles.

When caloric intake is inadequate, the weight percentile falls first, then the height, and the head circumference is last. Caloric intake may be poor as a result of inadequate feeding or because the child is not receiving adequate attention and stimulation (nonorganic failure to thrive). Caloric intake also may be inadequate because of increased caloric needs. Children with chronic illnesses,

such as heart failure or cystic fibrosis, may require a significantly higher caloric intake to sustain growth. An increasing weight percentile in the face of a falling height percentile suggests hypothyroidism.

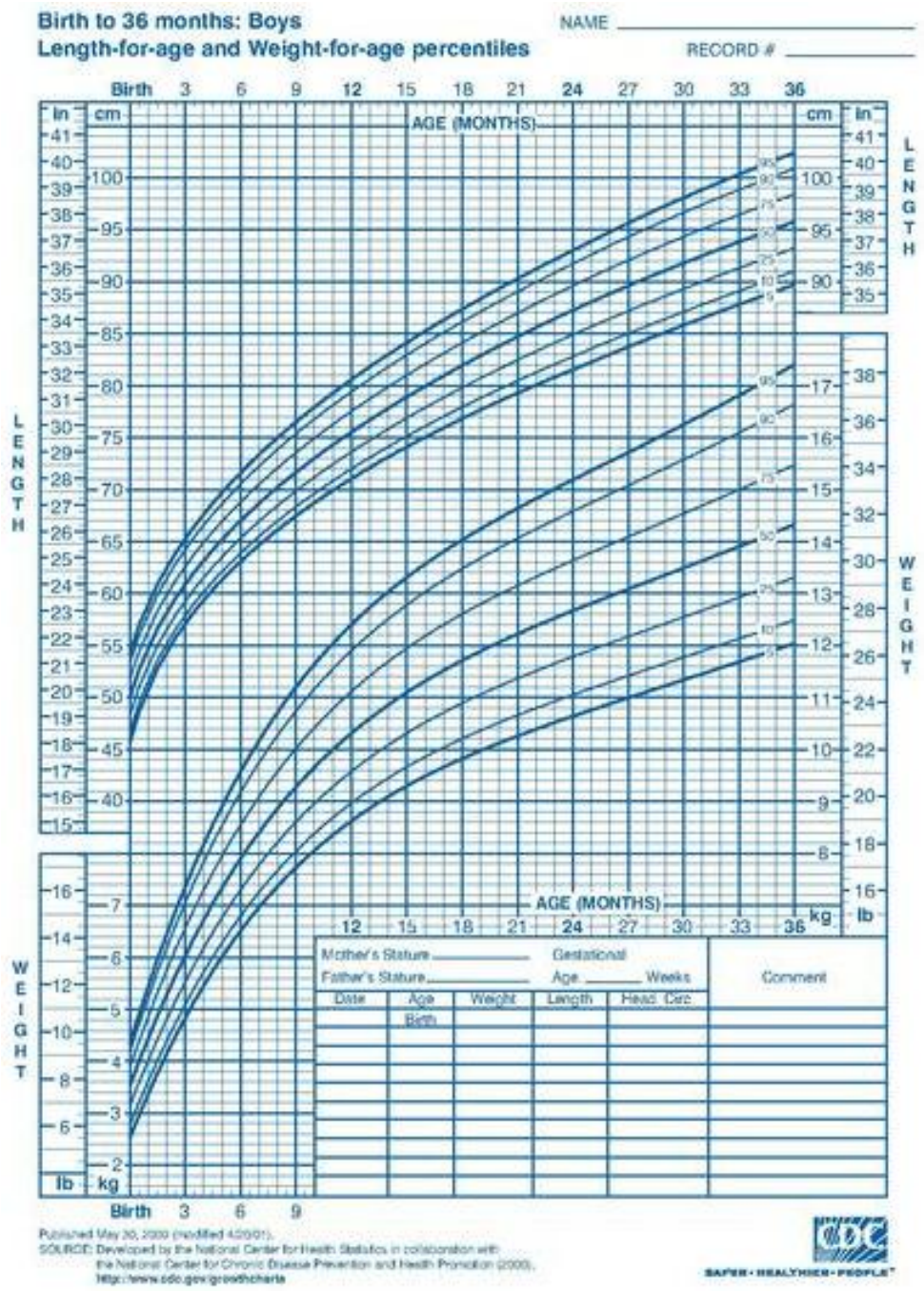


Fig. 2.1. Length-by-age and weight-by-age percentiles for boys, birth to 2 years of age. Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (From Centers for Disease Control and Prevention. WHO Child Growth Standards. Atlanta, GA; 2009. Available at http://www.cdc.gov/growthcharts/who_charts.htm)

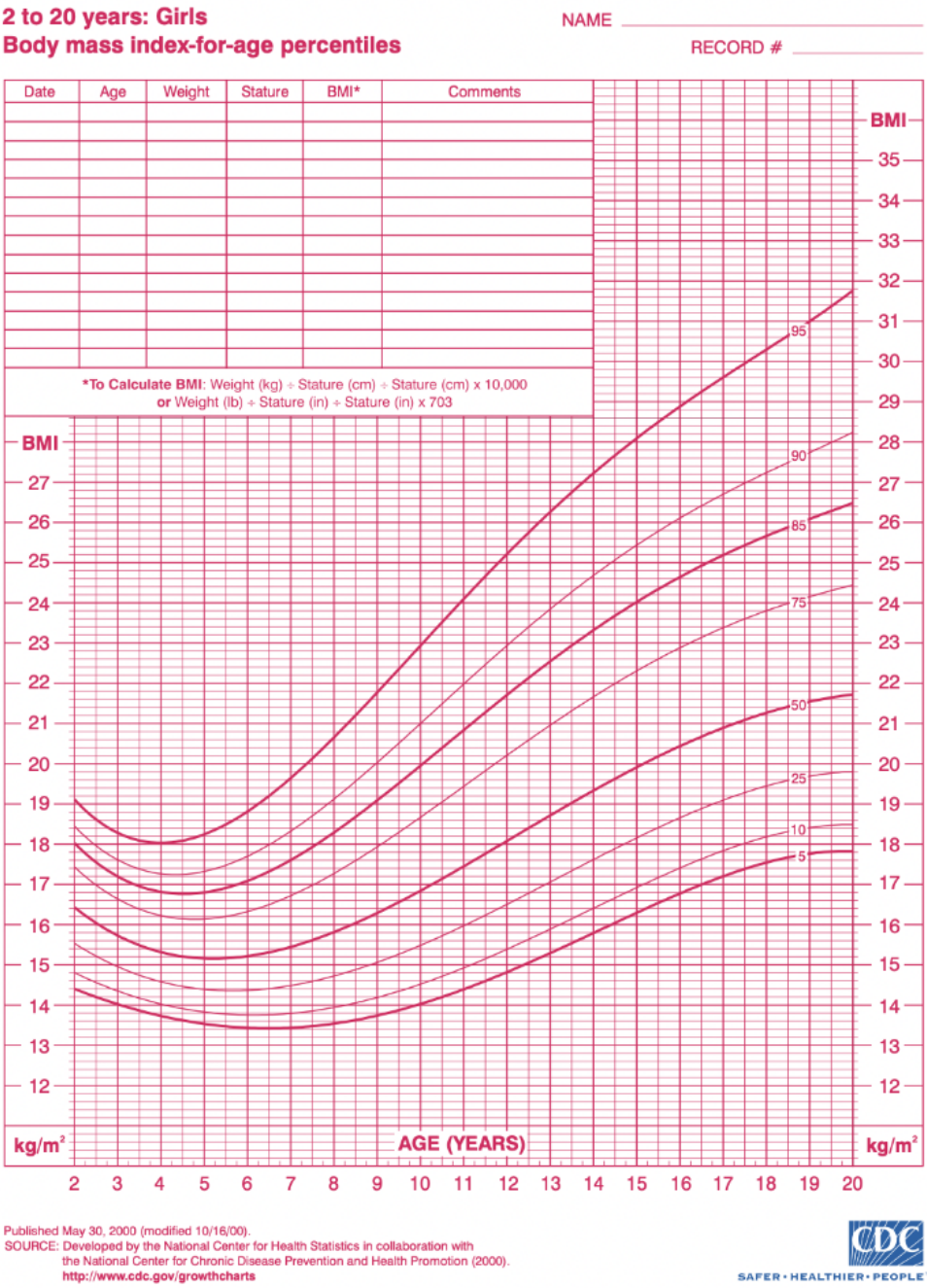


Fig. 2.2. Body mass index-for-age percentiles for girls, 2–20 years of age. Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (From Centers for Disease Control and Prevention. Atlanta, GA; 2001. Available at http://www.cdc.gov/growthcharts)

Head circumference may be disproportionately large when there is familial megalocephaly, hydrocephalus, or merely catch-up growth in a neurologically normal premature infant. A child is considered microcephalic if the HC is less than the 3rd percentile, even if length and weight measurements also are proportionately low. Serial measurements of HC are crucial during infancy, a period of rapid brain development, and should be plotted regularly until the child is 2 years of age. Any suspicion of abnormal growth warrants at least a close follow-up, further evaluation, or both.

Separate growth charts are available and should be used for very low birthweight infants (weight < 1,500 g) and for those with Turner syndrome, Down syndrome, achondroplasia, and various other dysmorphology syndromes.

Evaluating a child over time, coupled with a careful history and physical examination, helps determine whether the growth pattern is normal or abnormal. Parental heights may be useful when deciding whether to proceed with a further evaluation. Children, in general, follow their parents' growth pattern, although there are many exceptions.

For a girl, midparental height is calculated as follows:

$$\frac{\text{Paternal height (inches)} + \text{Maternal height (inches)}}{2} - 2.5$$

For a boy, midparental height is calculated as follows:

$$\frac{\text{Paternal height (inches)} + \text{Maternal height (inches)}}{2} + 2.5$$

Normal growth:

• Standard growth charts are used; they are available free from the CDC.

• For 0–2 years, use the WHO growth charts and measure weight, recumbent length, and head circumference and plot these as well as the weight for length.

• For > 2 years, use the CDC growth charts and measure weight, standing height, and calculate BMI. All should be plotted.

• Rules of thumb: double birthweight in 4–5 months; double birth length by age 4 years.

Disorders of growth:

• The pattern of decreased growth may assist in the evaluation.

• Weight decreases first, then length, then head circumference: caloric inadequacy.

• May be organic (increased work of breathing with congestive heart failure).

• Often is nonorganic (neglected child, material depression).

• All growth parameters less than the fifth percentile.

• Normal variants: familial short stature, constitutional delay.

• Endocrine disorders (especially with pituitary dysfunction).

• Declining percentiles but otherwise normal 6–18 months: “catch-down growth”.

Disorders of development:

• Developmental surveillance at every office visit; more careful attention at health maintenance visits.

• Developmental screening using validated tool.

• Done at 9, 18, and 30 months at a minimum.

• Most common tools are Ages and Stages and Parents’.

Evaluation of developmental status:

• Abnormalities require definitive testing.

• Autism screening using validated tool is done at 18 and 24 months.

• Most common is the M-CHAT-R.
• Abnormalities require definitive testing.
• Language development is critical in early childhood.
• Highly correlates with cognitive development.
• Even with newborn hearing test, may need to re-test hearing at any age.
• Speech therapy is more effective the younger it is started.
• After age 6, school performance is assessed; if there are performance issues (academic or behavioral), there should be elaborated testing; testing should be done by psychologists, psychiatrists, developmental pediatricians, or educational experts.
• Context of Behavioral problems.
• Parental factors: mismatch in temperament of expectations between parent and child, depression, other health issues.
• Social determinants of health.
• Stress, lack of parental support, perceived prejudice, and racism.
• Poverty: housing with environmental exposures, poor access to quality education, poor access to healthy nutrition (food deserts), toxic stress.
• Adolescents are a special challenge; developing rapport and open communication is critical.
• Adolescents may usually consent for sexual health, mental health, and substance abuse services.
• As long as they are not homicidal, suicidal, or unable to give informed consent, adolescents should consent for above issues.
• Confidentiality is critical unless there is information that would seem to allow harm to come to the individual or others.

Growth of the nervous system is most rapid in the first 2 years, correlating with increasing physical, emotional, behavioral, and cognitive development. There is again rapid change during adolescence. Osseous maturation (bone age) is determined from radiographs on the basis of the number and size of calcified epiphyseal centers; the size, shape, density, and sharpness of outline of the ends of bones; and the distance separating the epiphyseal center from the zone of provisional calcification. Developmental Milestones are shown in the Table 2.1.

Table 2.1

Developmental Milestones

Age	Gross motor	Fine motor-adaptive	Personal-social	Languige	Other cognitive
2 wk	Moves head side to side	–	Regards face	Alerts to bell	–
2 mo	Lifts shoulder while prone	Tracks past midline	Smiles responsively	Cooing Searches for sound with eyes	–
4 mo	Lifts up on hands Rolls front to back If pulled to sit from supine, no head lag	Reaches for object Raking grasp	Looks at hand Begins to work toward toy	Laughs and squeals	–

End of Table 2.1

Age	Gross motor	Fine motor-adaptive	Personal-social	Languige	Other cognitive
6 mo	Sits alone	Transfers object hand to hand	Feeds self Holds bottle	Babbles	–
9 mo	Pulls to stand Gets into sitting position	Starting to pincer grasp Bangs two blocks together	Waves bye-bye Plays pat-a-cake	Says Dada and Mama, but nonspecific Two-syllable sounds	–
12 mo	Walks Stoops and stands	Puts block in cup	Drinks from a cup	Imitates others Says Mama and Dada, specific Says one to two other words	–
15 mo	Walks backward	Scribbles Stacks two blocks	Uses spoon and fork Helps in housework	Says three to six words Follows commands	–
18 mo	Runs	Stacks four blocks Kicks a ball	Removes garment “Feeds” doll	Says at least six words	–
2 yr	Walks up and down stairs Throws overhand	Stacks six blocks Copies line	Washes and dries hands Brushes teeth Puts on clothes	Puts two words together Points to pictures Knows body parts	Understands concept of today
3 yr	Walks steps alternating feet Broad jump	Stacks eight blocks Wiggles thumb	Uses spoon well, spilling little Puts on T-shirt	Names pictures Speech understandable to stranger 75 % Says three-word sentences	Understands concepts of tomorrow and yesterday
4 yr	Balances well on each foot Hops on one foot	Copies O, maybe + Draws person with three parts	Brushes teeth Without help Dresses without help	Names colors Understands adjectives	–
5 yr	Skips Heel-to-toe walks	Copies □	–	Counts Understands opposites	–
6 yr	Balances on each foot 6 sec	Copies Δ Draws person with six parts	–	Defines words	Begins to understand right and left

Developmental screening involves the use of standardized screening tests to identify children who require further diagnostic assessment.

Nutrition. Proper nutrition in infancy is essential for normal growth, resistance to infections, long-term adult health, and optimal neurologic and cognitive development. Healthy nutrition is especially important during the first

6 months, a period of exceptionally accelerated growth and high nutrient requirements relative to body weight. Breast feeding is associated with a reduced risk of many diseases in infants, children, and mothers.

Breast feeding. Human milk and breast feeding are the ideal and normative standards for infant feeding and nutrition. The American Academy of Pediatrics (AAP) recommends human milk as the sole source of nutrition for the first 6 months of life, with continued intake for the first year, and as long as desired thereafter. Breast feeding has short- and long-term advantages for infant neurodevelopment. Pediatric health care providers should approach breast feeding at multiple levels (individual, community, social, and political).

The goals of the U.S. Department of Health and Human Services "Healthy People 2020" include 82 % of infants with any breast feeding, 25.5 % of infants with exclusive breast feeding for the first 6 months of life, and lactation support at work of 38 %. In collaboration with national and global organizations, including the AAP, WHO, United Nations Children's Fund (UNICEF), the Centers for Disease Control and Prevention (CDC), and the Joint Commission, hospitals are asked to promote and facilitate breast feeding. The first 2 days of breast feeding, and perhaps the first hour of life, may determine the success of breast feeding. There is greater emphasis to improve and standardize hospital practices with "Baby-Friendly" programs for breast feeding support, utilizing the "Ten Steps to Successful Breastfeeding" recommendations by the UNICEF/WHO.

Human-milk feeding decreases the incidence and severity of diarrhea, respiratory illness, otitis media, bacteremia, bacterial meningitis, and necrotizing enterocolitis, as documented by the Agency for Healthcare Research and Quality (AHRQ). Mothers who breast feed experience both short- and long-term health benefits. Decreased risk of postpartum hemorrhages, more rapid uterine involution, longer period of amenorrhea, and decreased postpartum depression have been observed. There is an association between a long lactation of 12–23 months (cumulative lactation of all pregnancies) and a significant reduction of hypertension, hyperlipidemia, cardiovascular disease, and diabetes in the mother. Cumulative lactation of more than 12 months also correlates with reduced risk of ovarian and breast cancer. Feeding preterm infants human milk has beneficial effects on their long-term neurodevelopment (IQ). Preterm breast fed infants also have a lower readmission rate in the first year of life.

Adequacy of milk intake can be assessed by voiding and stooling patterns of the infant. A well-hydrated infant voids 6–8 times a day. Each voiding should soak, not merely moisten, a diaper, and urine should be colorless. By 5–7 days, loose yellow stools should be passed approximately 4 times a day. Rate of weight gain provides the most objective indicator of adequate milk intake. Total weight loss after birth should not exceed 7 %, and birth weight should be regained by 10 days. The mean feeding frequency during the early weeks postpartum is 8–12 times per day. An infant may be adequately hydrated while not receiving enough milk to achieve adequate energy and nutrient intake.

In the newborn period, elevated concentrations of serum bilirubin are present more often in breast fed infants than in formula-fed infants. Feeding frequency during the first 3 days of life of breast fed infants is inversely related to the level of bilirubin; frequent feedings stimulate meconium passage and excretion of bilirubin in the stool. Infants who have insufficient milk intake and poor weight gain in the first week of life may have an increase in unconjugated bilirubin secondary to an exaggerated enterohepatic circulation of bilirubin (known as breast feeding jaundice). Attention should be directed toward improved milk production and intake. The use of water supplements in breast fed infants has no effect on bilirubin levels and is not recommended. After the 1st week of life in a breast fed infant, prolonged elevated serum bilirubin may be due to the presence of an unknown factor in milk that enhances intestinal absorption of bilirubin. This is termed breast milk jaundice, which is a diagnosis of exclusion and should be made only if an infant is otherwise thriving, with normal growth and no evidence of hemolysis, infection, biliary atresia, or metabolic disease. Breast milk jaundice usually lasts no more than 1–2 weeks. The AAP recommends vitamin D supplementation (400 IU/day starting soon after birth) for breast fed infants.

Maternal contraindications and recommendations for breast feeding:

• Tuberculosis (active): Should not breast feed; expressed milk may be provided to child.

• Varicella: Should not breast feed; expressed milk may be provided to child.

• H1N1 influenza: Should not breast feed; expressed milk may be provided to child. Alternately provide prophylaxis to infant and continue nursing.

• Herpes simplex infection of the breast: Should not breast feed; expressed milk may be provided to child.

• Human immunodeficiency virus: In industrialized countries, mothers are not recommended to breast feed. In developing countries, women are recommended to combine breast feeding with antiretroviral therapy for 6 months.

• Use of phencyclidine (PCP), cocaine, or amphetamines: Recommended to stop use of drugs because they can affect infant neurobehavioral development. Mothers enrolled in supervised methadone programs are encouraged to breast feed.

• Alcohol: Limit ingestion to < 0.5 mg of alcohol per kg of body weight due to association with motor development.

• Radiopharmaceutical agents: Express milk before exposure to feed infant. Express milk and discard during therapies. Radioactivity may be present in milk from 2–14 days, depending on agent. Consult with nuclear medicine expert.

• Antineoplastic and immunosuppressive agents: Substitute formula.

Formula feeding. Cow's milk-based formulas are the vast majority of commercial formulas. Most milk-based formulas have added iron, which the AAP recommends, and parents should use only iron-fortified formula unless advised otherwise by the primary health care provider. Infant formula manufacturers have begun to examine the benefits of adding a variety of nutrients and biologic factors to infant formula to mimic the composition and quality of breast milk. These include long-chain polyunsaturated fatty acids, nucleotides, prebiotics, and probiotics.

Soy-based formulas, which sometimes have added iron, may be used for newborns who may be allergic to cow's milk. However, some newborns allergic to cow's milk are also allergic to the protein in soy formulas.

There are hypoallergenic formulas for infants who cannot tolerate the basic formulas, such as those with allergies to milk or soy proteins. The proteins in these hypoallergenic formulas are broken down to their basic components and are therefore easier to digest. Specialized formulas are designed for premature, low birth weight babies.

The carbohydrate in standard formulas is generally lactose, although lactose-free cow's milk–based formulas are available. The caloric density of formulas is 20 kcal/oz (0.67 kcal/mL), similar to that of human milk. A relatively high-fat and calorically dense diet (human milk or formula) is needed to deliver adequate calories. Formula-fed infants are at higher risk for obesity later in childhood; this may be related to self-regulation of volumes ingested by the newborns and infants.

Complementary foods. By approximately 6 months, complementary feeding of semisolid foods is suggested. By this age, an exclusively breast fed infant requires additional sources of several nutrients, including protein, iron, and zinc. Cereals are commonly introduced around 6 months of age, and initially they are mixed with breast milk, formula, or water and later with fruits. By tradition solid cereals are usually introduced first; however, there is no medical evidence that a particular order is better than others for the infants. Baby-cereals are available premixed or dry, to which parents add breast milk, formula, or water. Single-grain iron-fortified cereals (rice, oatmeal, barley) are recommended as starting cereals to help identify possible allergies or food intolerances that may arise, especially when new foods and solids are added to the diet.

Infants do not need juices, but if juice is given, it should be started only after 12 months of age, given in a cup (as opposed to a bottle), and limited to 4 oz (for toddlers age 1–3 yr) daily of 100 % natural juice, and it should be unsweetened; juices should also be offered only with meals or snacks. If these recommendations are not followed, the infant may have reduced appetite for other more nutritious foods, including breast milk and/or formula. Too much juice may cause diaper rash, diarrhea, and weight gain. An infant should never be put to sleep with a bottle or sippy cup filled with milk, formula, or juice because this can result in early childhood caries.

For the first 2 months it is important to set the stage for making a distinction between sleeping and feeding time. Healthy infants do not need extra water; breast milk and formula provide all the fluids needed. However, with the introduction of solid foods, water can be added to the infant's diet. During the 4–6 months of age, starting actively to separate mealtime from bedtime is recommended. After 6 months of age other foods may be introduced as the infant shows signs of readiness to solid feedings. Once the infant learns to eat solid cereals, parents gradually introduce one food at a time, and they should wait 3–5 days before introducing a new one and watch for signs of an allergic reaction such as diarrhea, rash, or vomiting.

In general meats and vegetables have more nutrients per serving than fruits and cereals. Green vegetables bring nutrients, vitamins, minerals, and micronutrients. The avoidance of foods with high allergic potential in infancy (e.g., fish, tree nuts, peanuts, dairy products, and eggs) is no longer supported, and early introduction may actually help to prevent food allergies. Once the child can sit and bring her hands or other objects to the mouth, parents may provide finger food to help the infant learn to feed themselves. To avoid choking, make sure that anything given to the infant is easy to swallow, soft, and cut in very small pieces. Initially the infant should be eating approximately 4 ounces of solids at each daily meal. If the food fed to the infant is prepared by the adult, it should be prepared without preservatives or high salt.

All foods with the potential to obstruct the young infant's main airway should be avoided in general until 4 years of age or older. Honey (risk of infant botulism) should not be given before 1 year of age. Commercially prepared or homemade foods help meet the nutritional needs of the infant. If the introduction of solid foods is delayed, nutritional deficiencies can develop, and oral sensory issues (texture and oral aversion) may occur. General signs of readiness include the ability to hold the head up, big enough (around double the birth weight), opening their mouths wide showing eager anticipation of eating food and interest in foods, sitting unassisted, bringing objects to the mouth, the ability to track a spoon and take food from the spoon, and stopping when they are full. The choice of foods to meet micronutrient needs may be less critical for formula-fed infants because formulas are fortified with those nutrients. With the introduction of solid foods, the infants' stools may have appropriate changes; they become more solid and/or have a stronger odor as new and more sugars may be added. Exposure to different textures and the process of self-feeding are important neurodevelopmental experiences for infants.

Since children will stick anything into their mouths during the “oral stage,” take advantage of this and introduce the tooth brush. There are ergonomically designed toothbrushes that are comfortable and safe for infants and used to rub their gums and create the habit of oral hygiene. Children will become accustomed to having a toothbrush in their mouth. Cavities are tooth infections in baby teeth that can lead to problems with adult teeth and health issues. Early caries of childhood are caused by a misbalance of increased sugars and bacteria in the mouth and decreased saliva flow at as early as 6 months of age. Eating a healthy diet and brushing regularly will control the sugar factor and bacteria. Transmission of bacteria from the caretakers can also be prevented by avoiding sharing food or utensils with the infant.

General recommendations. “ChooseMyPlate” by the U.S. Department of Agriculture can provide parents with a general guideline for the types of foods to be offered on a regular basis. A child should eat three meals a day and two healthy snacks. A general rule for the quantity of food to offer to a child is one tablespoon per age of each food provided per meal, with more given if the child

requests. As a rule of thumb, children should not be eating more than an adult palm per serving. By 1 year of age, infants should be eating meals with the family, have a regular schedule of meals and snacks, and be encouraged to self-feed with appropriate finger foods. The "plate" image is divided into five sections: fruits, grains, vegetables, protein, and dairy (Fig. 2.3).

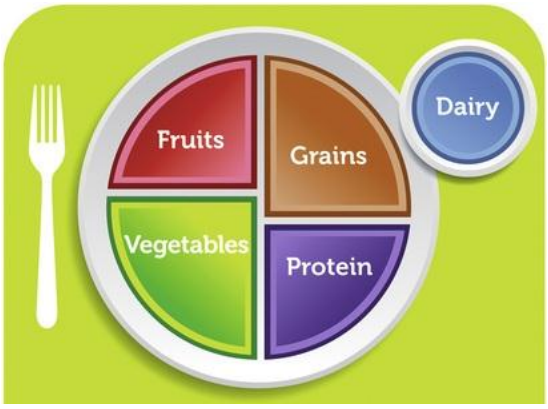


Fig. 2.3. "ChooseMyPlate" guidelines developed by the U.S. Department of Agriculture. (www.ChooseMyPlate.gov)

Half of the "plate" should be vegetables and fruits and the other half grains and proteins, with dairy on the side. The "plate" is simple, organized, and serves as a guide for healthy eating. Other suggestions include the following: switch to fat-free or low-fat (1 %) milk after age 2 years; make at least half of the grains whole instead of refined grains; avoid oversize proportions; compare sodium (salt) in foods such as soup, bread, and frozen meals; choose foods with lower sodium content; and drink water instead of sugary drinks. After 2 years, it is recommended that the fat intake gradually be reduced to approximately 30 % and not less than 20 % of calories. Replace proteins from red meat with a mix of fish, chicken, nuts, and legumes. Power struggles over eating are common between parents and toddlers. The parent's role is to decide the what, when, and where of the meals. The child's role is to decide if, what, and how much to eat.

Recommendations of a nutritious diet for a child are based on the following nutrient-dense foods:

• *Protein.* Provide seafood, lean meat and poultry, eggs, beans, peas, soy products, and unsalted nuts and seeds.

• *Fruits*. Encourage the child to eat a variety of fresh, canned, frozen, or dried fruits rather than fruit juice. If the child drinks juice, make sure it is 100 % juice without added sugars and limit his or her servings. Look for canned fruit that says it is light or packed in its own juice, meaning it is low in added sugar. Keep in mind that one-half cup of dried fruit counts as one cup-equivalent of fruit. When consumed in excess, dried fruits can contribute to extra calories.

• *Vegetables.* Serve a variety of fresh, canned, frozen, or dried vegetables. Aim to provide a variety of vegetables, including dark green, red, and orange, beans and peas, starchy and others, each week. When selecting canned or frozen vegetables, look for options lower in sodium.

• *Grains.* Choose whole grains, such as whole-wheat bread, oatmeal, popcorn, quinoa, or brown or wild rice. Limit refined grains.

• *Dairy.* Encourage the child to eat and drink fat-free or low-fat dairy products, such as milk, yogurt, cheese, or fortified soy beverages. Aim to limit the child's calories from added sugar (limit added sugars); saturated and trans-fats; salt intake; iron Intake.

Puberty. Puberty is a time of rapid and complex changes involving overlapping components: hormonal, physical, and cognitive. Tanner Staging, also known as Sexual Maturity Rating (SMR), is an objective classification system that providers use to document and track the development and sequence of secondary sex characteristics of children during puberty. It was developed by Marshall and Tanner while conducting a longitudinal study during the 1940s to the 1960s in England. Based on observational data, they developed separate scales for the development of external genitalia: phallus, scrotum, and testes volume in males; breasts in females; and pubic hair in both males and females.

Tanner Stage 1 corresponds to the pre-pubertal form for all three sites of development with progression to Tanner Stage 5, the final adult form. Breast and genital staging, as well as other physical markers of puberty such as height velocity, should be relied on more than pubic hair staging to assess pubertal development because of the independent maturation of the adrenal axis.

Pubic Hair Scale (both males and females):

Stage 1: No hair

Stage 2: Downy hair

Stage 3: Scant terminal hair

Stage 4: Terminal hair that fills the entire triangle overlying the pubic region

Stage 5: Terminal hair that extends beyond the inguinal crease onto the thigh

Female Breast Development Scale:

Stage 1: No glandular breast tissue palpable

Stage 2: Breast bud palpable under the areola (1st pubertal sign in females)

Stage 3: Breast tissue palpable outside areola; no areolar development

Stage 4: Areola elevated above the contour of the breast, forming a “double scoop” appearance

Stage 5: Areolar mound recedes into single breast contour with areolar hyperpigmentation, papillae development, and nipple protrusion.

Male External Genitalia Scale:

Stage 1: Testicular volume < 4 ml or long axis < 2.5 cm

Stage 2: 4–8 ml (or 2.5 to 3.3 cm long), 1st pubertal sign in males

Stage 3: 9–12 ml (or 3.4 to 4.0 cm long)

Stage 4: 15–20 ml (or 4.1 to 4.5 cm long)

Stage 5: > 20 ml (or > 4.5 cm long)

CHAPTER 3
NEWBORN PERIOD: PHYSIOLOGY

The following definitions have been adopted by the World Health Assembly in relation both to statistics amenable to international comparison and to reporting requirements for the data from which they are derived.

The third week after conception marks the beginning of the **embryonic period**. It ends at the end of the tenth week, when the embryo comprises three layers from which all organs will develop.

Perinatal period — period commences at 22 completed weeks (154 days) of gestation (the time when birth weight is normally 500 g), and ends seven completed days after birth.

Neonatal period — period commences at birth and ends 28 completed days after birth.

Early neonatal period — first 7 days. *Late neonatal period* — after the seventh day till 28 days.

Epidemiologic approaches to the perinatal period must therefore be bidirectional — looking backward to examine the causes of adverse health conditions that arise during the perinatal period and looking forward to seeing how these conditions shape disorders of health found later in life.

Perinatal mortality rate (PMR) refers to the number of stillbirths and neonatal deaths in the first week of life per 1000 live births and stillbirths. ***The WHO recommends this rate as an index of quality of perinatal health services.***

Neonatal mortality rate (NMR) refers to the number of deaths of live-born infants in the first 28 days of life per 1000 live births. Neonatal deaths may be subdivided into early neonatal deaths, occurring during the first seven days of life, and late neonatal deaths, occurring after the 7th day but before 28 completed days of life.

Postneonatal (infant) mortality rate refers to the number of death of live-born infants dying after 28 days but before 1 year of age per 1000 live births. Infant mortality rate refers to the number of deaths of all live-born infants in the firstyear of life per 1000 live birth.

The causes of neonatal deaths vary between countries. In developed countries four main causes account for more than 75 % of all neonatal deaths: disorders related to prematurity or low birth weight (LBW), congenital anomalies, neonatal infections, birth asphyxia and birth trauma. Neonatal mortality increases progressively with a lowering of gestational age (GA) and birth weight (BW). Many other factors affect the survival of preterm and low birth weight infants (gender, ethnicity, multiple pregnancy, maternal health and complications of pregnancy, mode and place of delivery, prenatal administration of corticosteroids, and condition at birth and clinical problems after birth). Perinatal, neonatal and infant mortality rates have decreased in the past decade in many parts of the world but remain high in most developing countries.

Gestational age. The duration of gestation is calculated from the 1st day of the last normal menstrual period. This assumes a regular 28-day cycle and that ovulation occurred 14 days after bleeding commenced. By this reckoning the duration of pregnancy (really the period of amenorrhea) is between 37 and 42 weeks (259–294 days).

Full-term delivery occurs between 37 and 42 gestational weeks (259–294 days) from the date of last normal menstrual period.

Pre-term delivery — if the infant is born between 22 and 37 weeks (154–258 days) from the first day of the last normal menstrual period.

Post-term delivery occurs if the infant is born after 42 completed weeks (294 days) from the first day of the last normal menstrual period.

Live birth. Is one in which there are signs of life (breathing, heart beat or spontaneous movement of voluntary muscles, pulsation of the umbilical cord, whether or not the umbilical cord has been cut or the placenta is attached) after complete expulsion from the mother, irrespective of the gestational age.

Stillbirth or fetal death (dead born fetus). Fetal death is death prior to the complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of pregnancy; the death is indicated by the fact that after such separation 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.

Birth weight. The first weight of the fetus or newborn obtained after birth. For live births, birth weight should preferably be measured within the first hour of life before significant postnatal weight loss has occurred.

Normal birth-weight (NBW) refers to any infant who weighs 2500–4000 g at birth.

Low birth weight (LBW): 1500–2500 g at birth.

Very low birth weight: 1000–1500 g at birth.

Extremely low birth weight: 499–1000 g at birth.

High birth-weight (HBW) refers to any infant who weighs 4000–4500 g at birth.

Very high birth-weight refers to any infant who weighs > 4500 g at birth.

Appropriate size for gestational age (AGA): birth weight between 10th and 90th percentile for gestational age.

Small for gestational age (SGA) is defined as 2 SD below the mean weight for gestational age or below the 10th percentile. SGA is commonly seen in infants of mothers who have hypertension or preeclampsia or who smoke, or associated with TORCH (toxoplasmosis, other, rubella, CMV, and herpes simplex virus) infections, chromosomal abnormalities, and other congenital malformations.

Large for gestational age (LGA) is defined as 2SD above the mean weight for GA or above the 90th percentile. LGA can be seen in infants of diabetic mothers, infants with Beckwith's syndrome, constitutionally large infants with large parents, or infants with hydrops fetalis (Fig. 3.1).

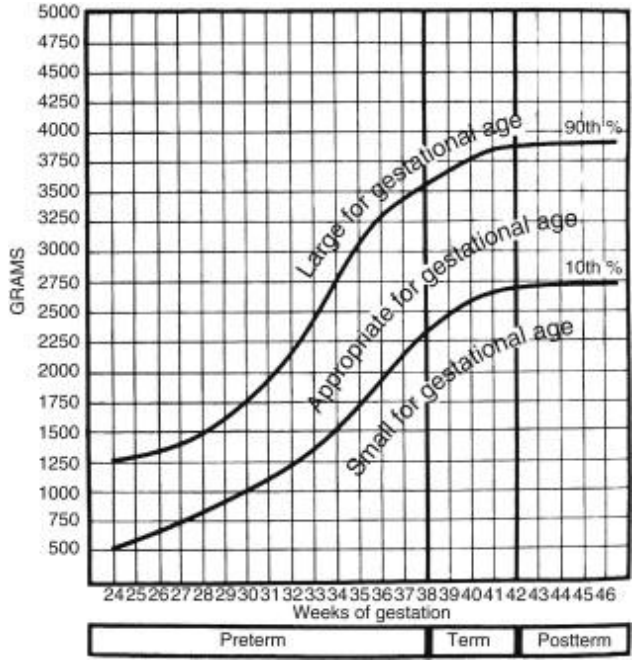


Fig. 3.1. Birth weight for gestational age chart

Gestational age assessment. Rapid delivery room assessment. The most useful clinical signs in differentiating among premature, borderline mature, and full-term infants are (in order of usefulness): creases in the sole of the foot, size of the breast nodule, nature of the scalp hair, cartilaginous development of the ear lobe, and scrotal rugae and testicular descent in males.

New Ballard Score. The Ballard maturational score has been expanded and updated to include extremely premature infants. It has been renamed the New Ballard Score (NBS) (Fig. 3.2). The score now spans from 10 (correlating with 20 weeks' gestation) to 50 (correlating with 44 weeks' gestation). It is best performed at < 12 h of age if the infant is < 26 weeks' gestation. If the infant is > 26 weeks' gestation, there is no optimal age of examination up to 96 h.

The examination consists of two parts: neuromuscular maturity and physical maturity. The 12 scores are totaled, and maturity rating is expressed in weeks of gestation, estimated by using the chart provided on the form.

a. Neuromuscular maturity:

– *Posture.* Score 0 if the arms and legs are extended, and score 1 if the infant has beginning flexion of the knees and hips, with arms extended; determine other scores based on the diagram.

– *Square window.* Flex the hand on the forearm between the thumb and index finger of the examiner. Apply sufficient pressure to achieve as much flexion as possible. Visually measure the angle between the hypothenar eminence and the ventral aspect of the forearm. Determine the score based on the diagram.

– *Arm recoil.* Flex the forearms for 5 s; then grasp the hand and fully extend the arm and release. If the arm returns to full flexion, give a score of 4. For lesser degrees of flexion, score as noted on the diagram.

– *Popliteal angle.* Hold the thigh in the knee-chest position with the left index finger and the thumb supporting the knee. Then extend the leg by gentle pressure from the right index finger behind the ankle. Measure the angle at the popliteal space and score accordingly.

– *Scarf sign.* Take the infant's hand and try to put it around the neck posteriorly as far as possible over the opposite shoulder and score according to the diagram.

– *Heel to ear.* Keeping the pelvis flat on the table, take the infant's foot and try to put it as close to the head as possible without forcing it. Grade according to the diagram.

Neuromuscular Maturity

Score	–1	0	1	2	3	4	5
Posture							
Square window (wrist)	>90°	90°	60°	45°	30°	0°	
Arm recoil		180°	140–180°	110–140°	90–110°	<90°	
Popliteal angle	180°	160°	140°	120°	100°	90°	<90°
Scarf sign							
Heel to ear							

Physical Maturity

Skin	Sticky, friable, transparent	Gelatinous, red, translucent	Smooth, pink; visible veins	Superficial peeling and/or rash; few veins	Cracking, pale areas; rare veins	Parchment, deep cracking; no vessels	Leathery, cracked, wrinkled
Lanugo	None	Sparse	Abundant	Thinning	Bald areas	Mostly bald	
Plantar surface	Heel-toe 40–50 mm: –1 <40 mm: –2	>50 mm, no crease	Faint red marks	Anterior transverse crease only	Creases anterior 2/3	Creases over entire sole	
Breast	Imperceptible	Barely perceptible	Flat areola, no bud	Stippled areola, 1–2 mm bud	Raised areola, 3–4 mm bud	Full areola, 5–10 mm bud	
Eye/Ear	Lids fused loosely: –1 tightly: –2	Lids open; pinna flat; stays folded	Slightly curved pinna; soft; slow recoil	Well curved pinna; soft but ready recoil	Formed and firm, instant recoil	Thick cartilage, ear stiff	
Genitals (male)	Scrotum flat, smooth	Scrotum empty, faint rugae	Testes in upper canal, rare rugae	Testes descending, few rugae	Testes down, good rugae	Testes pendulous, deep rugae	
Genitals (female)	Clitoris prominent, labia flat	Clitoris prominent, small labia minora	Clitoris prominent, enlarging minora	Majora and minora equally prominent	Majora large, minora small	Majora cover clitoris and minora	

Maturity Rating

Score	Weeks
–10	20
–5	22
0	24
5	26
10	28
15	30
20	32
25	34
30	36
35	38
40	40
45	42
50	44

Fig. 3.2. New Ballard score

b. Physical maturity:

– *Skin.* Carefully look at the skin and grade according to the diagram. Extremely premature infants have sticky, transparent skin and receive a score of –1.

– *Lanugo hair* is examined on the infant's back and between and over the scapulae.

– *Plantar surface.* Measure foot length from the tip of the great toe to the back of the heel. If the results are < 40 mm, then give a score of –2. If it is between 40 and 50 mm, assign a score of –1. If the measurement is > 50 mm and no creases are seen on the plantar surface, give a score of 0. If there are creases, score accordingly.

– *Breast.* Palpate any breast tissue and score.

– *Eye and ear.* This section has been expanded to include criteria that apply to the extremely premature infant. Loosely fused eyelids are defined as closed,

but gentle traction opens them. Score this as –1. Tightly fused eyelids are defined as inseparable by gentle traction. Base the rest of the score on open lids and the examination of the ear.

– *Genitalia.* Score according to the diagram.

Scores from neuromuscular and physical domains are added to obtain total score. Adapted from Ballard J. L., Khoury J. C., Wedig K. et al. New Ballard score, expanded to include extremely premature infants (Pediatrics 119 (3): 417–423, 1991. doi: 10.1016/s0022-3476(05)82056-6; used with permission of the CV Mosby Company) is shown on Fig. 3.2.

History of the pregnancy and delivery:

1. The mother's medical history is important, including the possibility of maternal diabetes mellitus, other illnesses and immune status (HBV, HCV, HIV, TORCH, and syphilis).

2. The results of antenatal checks should be noted: fetal growth and ultrasound results, amniotic fluid volume, maternal anemia, urine results and maternal diabetes mellitus, pregnancy- induced hypertension or pre-eclampsia.

3. The results of vaginal or anal bacterial swabs within the month before delivery should be noted (group B streptococci or Listeria monocytogenes) and whether the mother was given appropriate intrapartum antibiotic prophylaxis.

A history of the pregnancy should include:

– note of drugs (taken during the pregnancy and their indications.);

– consider evidence of infectious illnesses or fever close to the time of delivery;

– the timing of membrane rupturing and the quantity and color (blood ormeconium staining) of the amniotic fluid.

Details of the delivery should be noted, i.e., whether:

– vaginal, operative (forceps of vacuum extraction);

– cesarean section (planned or emergency, before or during the labor);

– evidence of fetal distress.

The baby's presentation should be noted because abnormal limb position may be due to a breech presentation. The possibility of birth trauma (e.g., cephalhematoma, fracture of the clavicle) should be considered.

Physical examination of the newborn. At birth, a healthy newborn should be immediately put skin-to-skin on his/her mother, dried and covered by dry warm blankets. The newborn infant should undergo a complete physical examination within 24 h of birth. Newborn assessment includes observation, auscultation, and palpation, proceeding in a systematic head-to-toe fashion, although it can be adapted to the particular infant and situation. In order to obtain quality data, the assessment is organized to minimize stress for the infant. It is best to begin by observing the symmetry, respirations, movement, and behavior of the baby.

Before undertaking clinical examination, familiarize yourself with maternal history and pregnancy, family health, history of congenital diseases. Identify drugs mother may have taken during pregnancy and in labor. Identify pregnancy complications, blood tests, ultrasound scans, admissions to hospital, maternal

blood group, presence of antibodies, serology results for sexually transmitted diseases, duration of labor, type of delivery, duration of rupture of membranes, condition of liquor.

Procedure includes:

• Assessment of gestational age, birth weight, length, head circumference (see Fig. 3.1).

The 10th to 90th percentile for weight at 40 weeks' gestation for a male infant is 2.9 to 4.2 kg (mean 3.6 kg), and for a female infant it is 2.8 to 4 kg (mean 3.5 kg). The birthweight percentile can be ascertained from the growth chart. If the infant's gestational age is uncertain, it can be determined (±2 weeks' gestational age) using a standardized scoring scheme. The HC should be measured at its maximum and plotted on a growth chart to identify microcephaly or macrocephaly and to serve as a reference for future measurements. However, the measurement can change markedly in the first few days because of molding of the head during delivery.

The 10th to 90th percentile is 33 to 37 cm at 40 weeks. The infant's length (48 to 53 cm at 40 weeks) is measured routinely. Because the hips and lower legs need to be held extended by an assistant, the length is rarely measured accurately enough to identify short stature or serve as a reliable reference value when measured routinely. The length of the arms and legs relative to that of the trunk is observed, although short limbs from skeletal dysplasias can be difficult to appreciate in the immediate newborn period.

• Apgar scores and whether resuscitation required.

• Temperature: rectal, oral, axillary. The normal axilla temperature ranges from 36.3–37.2 °C.

• *Skin examination.* Much valuable information can be gleaned by simply observing the newborn. The skin of a newborn looks reddish pink. He or she may appear plethoric from polycythemia or unduly pale from anemia or shock. If polycythemia or anemia is suggested, the Hb concentration or hematocrit should be checked. Jaundice within the first 24 hours of birth, unless mild, is most likely to be hemolytic and requires investigation and treatment.

Central cyanosis is best observed on the tongue. If present, it requires urgent investigation. If there is any doubt, the newborn's oxygen saturation should be checked with a pulse oximeter. Polycythemic infants sometimes appear cyanotic because they have more than 5 g of reduced Hb per 100 mL of blood, even though they are adequately oxygenated.

Rashes: including erythema toxicum, milia, miliaria, staphylococcal skin infection, and candida. Bruises: traumatic lesions, petechiae. Cutis aplasia. Tufts of hair other than on head. Vascular lesions: haemangioma, port wine stain, simple nevus. Color: pink / cyanosis / jaundice / pallor / plethora / acrocyanosis.

• *Facial examination.* General facial appearance to identify common syndromes. Assessment of eyes (shape, size, position, strabismus, nystagmus), of nose, ears (shape, position). Lips, gums and palate must be examined to exclude the presence of a cleftor other malformation. If the face is abnormal, does

the newborn have a syndrome? Observe the newborn's posture and tone. Is he or she moving all four limbs fully and are they held in a normal, flexed position?

• *Head*. Palpate skull for sutures and shape / cranio-synostosis, swellings on scalp, especially crossing suture lines, cephalhaematoma, signs of trauma associated with birth (e.g. chignon from vacuum extraction), subgaleal haemorrhage. The fontanelle and sutures are palpated. The size of the anterior fontanelle is very variable. After delivery, the sagittal sutures are often separated and the coronal sutures are overriding. The posterior fontanelle is often open, but small. If the fontanelle is tense when the newborn is not crying, this may be from elevated intracranial pressure, and cranial ultrasonography should be performed. A tense fontanelle is also a late sign of meningitis.

The *eyes* should be checked both by inspection and with an ophthalmoscope. The red reflex should be elicited using an ophthalmoscope. The red retinal reflex can be seen if the lens is clear but not if it is opaque from a congenital cataract or glaucoma. If the red reflex is abnormal, an ophthalmologist should be consulted urgently. Congenital cataract is the most common form of preventable childhood blindness.

Ears. The shape, size, and position of the ears are checked. Low-set ears are positioned so that the top of the pinna falls below a line drawn from the outer canthus of the eye at right angles to the face. Low-set or abnormal ears are a characteristic of a number of syndromes.

Palate. The palate must be inspected, including posteriorly, excluding a posterior cleft palate. It should also be palpated to detect an indentation of the posterior palate from a submucous cleft or a posterior cleft palate.

• Examine (inspection, palpation, auscultation) each system.

• Respiratory system. The normal respiratory rate in a newborn is 40–60 breaths/min. Examination of the chest should note any asymmetry during respiration, subcostal or intercostal retraction, ancillary nipples, grunting, and nasal flaring. Auscultate for breath sounds. If the breathing is normal, it is very rare for any significant abnormalities to be detected on auscultation. If the infant has respiratory distress, further evaluation is required immediately.

• *Cardiovascular system*. Examination should include skin colour /cyanosis, palpate: precordium for thrills, peripheral and femoral pulses for rate and volume, central perfusion, auscultate for heart sounds, murmur(s), rate, rhythm. Pulse rate — usually 140–160 beats/min when awake but can drop to 85 beats per minute during sleep. Blood pressure (BP) — correlates directly with gestational age, postnatal age of the infant and birth weight. The heart sounds should be loudest on the left side of the chest, and no murmurs should be present. Femoral pulses are palpated when the infant is quiet. Their pulse pressure is reduced if there is coarctation of the aorta. If coarctation is suggested clinically, it can be confirmed by comparing the BP in the arms and legs. The pulse pressure is increased with a patent ductus arteriosus.

• *Abdomen.* Observation readily reveals abdominal distention. For palpation, the infant must be relaxed. The abdomen is palpated to identify any masses.

The liver is normally palpable 1 to 2 cm below the costal margin. The spleen tip and left kidney are often palpable.

• *The hips* should be examined to exclude congenital dislocation. Clavicles, arms, legs, fingers, and toes should be examined to identify any abnormality (e.g., webbing, number, length, symmetry of movement).

• *Neurological system.* Before beginning examination, observe baby's posture. Assess: muscle tone, grasp, responses to stimulation, behavior, ability to suck, limb movements, cry, head size in relation to body weight, spine, presence of sacral pits, midline spinal skin lesions/tufts of hair. If neurological concerns, initiate Moro and stepping reflexes. Responses to passive movements: pull-to-sit, ventral suspension. Palpate anterior fontanels size.

• *Gastrointestinal tract*. Ask mother how well baby is feeding, whether baby has vomited, color of vomit. Bilious vomiting may have a surgical cause and needs prompt stabilization and referral. Chek abdominal shape, presence of distension. Cord stump for discharge or inflammation/umbilical hernia. Presence and position of anus and patency. Stools passed. Palpate abdomen for tenderness, masses and palpable liver. Auscultation is not routinely undertaken unless there are abdominal concerns.

• *Genito-urinary system*. Ask mother if baby has passed urine, and how frequently. The diaper area should be examined to look for anomalies of the external genitalia, an imperforate or anterior anus, and hairy tufts or dimples over the sacrum. Male genito-urinary: look for hypospadias, position of urethral meatus, inguinal hernia, and urinary stream. Palpate scrotum for presence of 2 testes and absence of hydrocele. Female genito-urinary system: presence of vaginal discharge, inguinal hernia, proximity of genitalia to anal sphincter. Routine palpation of kidneys is not always necessary as antenatal scans will have assessed presence.

Neurological chek-up. First, observe the infant for any abnormal movement (e.g., seizure activity) or excessive irritability. Then evaluate the following parameters.

A. Muscle tone.

1. Hypotonia. Floppiness and head lag are seen.

2. Hypertonia. Increased resistance is apparent when the arms and legs are extended.

Hyperextension of the back and tightly clenched fists are often seen.

B. Reflexes. The following reflexes are normal for a newborn infant.

1. Rooting reflex. Stroke the lip and the corner of the cheek with a finger and the infant will turn in that direction and open the mouth.

2. Glabellar reflex (blink reflex). Tap gently over the forehead and the eyes will blink.

3. Grasp reflex. Place a finger in the palm of the infant's hand and the infant will grasp the finger

4. Neck-righting reflex. Turn the infant's head to the right or left and movement of the contralateral shoulder should be obtained in the same direction.

5. Moro reflex. Support the infant behind the upper back with one hand, and then drop the infant back 1 cm or more to but not on the mattress. This should cause abduction of both arms and extension of the fingers. Asymmetry may signify a fractured clavicle, hemiparesis, or brachial plexus injury.

C. Cranial nerves. Note the presence of gross nystagmus, the reaction of the pupils, and the ability of the infant to follow moving objects with his or her eyes.

D. Movement. Check for spontaneous movement of the limbs, trunk, face, and neck. A fine tremor is usually normal. Clonic movements are not normal and may be seen with seizures.

E. Peripheral nerves.

1. Erb-Duchenne paralysis involves injury to the fifth and sixth cervical nerves. There is adduction and internal rotation of the arm. The forearm is in pronation; the power of extension is retained. The wrist is flexed. This condition can be associated with diaphragm paralysis.

2. Klumpke's paralysis involves the seventh and eighth cervical nerves and the first thoracic nerve. The hand is flaccid with little or no control. If the sympathetic fibers of the first thoracic root are injured, ipsilateral ptosis and miosis can occur.

F. General signs of neurologic disorders.

1. Symptoms of increased intracranial pressure (bulging anterior fontanelle, dilated scalp veins, separated sutures, and setting-sun sign).

2. Hypotonia or hypertonia.

3. Irritability or hyperexcitability.

4. Poor sucking and swallowing reflexes.

5. Shallow, irregular respirations.

6. Apnea.

7. Apathy.

8. Staring.

9. Seizure activity (sucking or chewing of the tongue, blinking of the eyelids, eye rolling, and hiccups).

10. Absent, depressed, or exaggerated reflexes.

11. Asymmetric reflexes.

Apgar score. A quick initial physical examination of all newborns should be performed in the delivery room to check that there are no major anomalies or birth injuries, that the newborn’s tongue and body appear pink, and that breathing is normal. A baby’s condition during the minutes just after birth is described by the Apgar score (originally described by Virginia Apgar, an anesthesiologist, in 1953). **Apgar score** is a numerical expression of a newborn infant on a scale of 0–10. The score is usually recorded at 1 and 5 min after delivery and become a permanent part of the health record (Table 3.1). They have clinical usefulness not only during the nursery stay but at later child health visits also, when clinical status at delivery may have a bearing on current diagnostic assessments.

Table 3.1

Apgar score

Sign	Score		
	0	**1**	**2**
Appearance (color)	Blue or pale	Pink body with blue extremities	Completely pink
Pulse (heartrate)	Absent	Slow (< 100 beats/min)	> 100 beats/min
Grimace (reflexirritability)	Noresponse	Grimace	Cough or sneeze
Activity (muscletone)	Limb	Some flexion	Active movement
Respirations	Absent	Slow, irregular	Good, crying

Newborn adaptation to extrauterine life. The immediate postpartum period is a time of significant physiological adaptation for both the mother and baby. The newborn must adapt from being completely dependent on another for life sustaining oxygen and nutrients to an independent being, a task accomplished over a period of hours to days. Successful transition from fetal to neonatal life requires a complex interaction between the following systems:

– respiratory;
– cardiovascular;
– thermoregulatory;
– immunologic.

Establishing respirations is critical to the newborn's transition, as lungs become the organ of gas exchange after separation from maternal uteroplacental circulation. Over 90 % of newborns make the transition from intrauterine life to extrauterine life without difficulty, requiring little to no assistance. However, for the 10 % of newborns who do require assistance, about 1 % requires extensive resuscitative measures to survive.

Fetal circulation. In utero, oxygenated blood flows to the fetus from the placenta through the umbilical vein. Although a small amount of oxygenated blood is delivered to the liver, most blood diverts the hepatic system through the ductus venosus, which forms a connection between the umbilical vein and the inferior vena cava. Oxygenated blood from the inferior vena cava enters the right atrium (RA) and most of it is directed through the foramen ovale to the left atrium (LA), then to the left ventricle (LV), and onto the ascending aorta, where it is primarily directed to the fetal heart and brain. Deoxygenated blood from the head and upper extremities comes back to the RA by the superior vena cava, where it blends with oxygenated blood from the placenta. This blood enters the RV and pulmonary artery, where 90 % of it is shunted across the ductus arteriosus and into the descending aorta, providing oxygen to the lower half of the fetal body and eventually draining back to the placenta through the two umbilical arteries. The remaining 10 % of the blood coming from the RV perfuses lung tissue to meet metabolic needs.

Neonatal circulation. With the infant's first breath and exposure to increased oxygen levels, there is an increased blood flow to the lungs causing the closure of

the foramen ovale. Constriction of the ductus arteriosus is a gradual process that results from a reduction of pulmonary vascular resistance, increasing systemic vascular resistance and sensitivity to a rise in arterial PaO_2 levels. The removal of the placenta decreases prostaglandin levels (which helped to maintain ductal patency) further influencing closure. At birth, the clamping of the umbilical cord eliminates the placenta as a reservoir for blood, triggering an increase in systemic vascular resistance, an increase in blood pressure, and increased pressures in the left side of the heart. The removal of the placenta also eliminates the need for blood flow through the ductus venosus, causing functional elimination of this fetal shunt. Systemic venous blood flow is then directed through the portal system for hepatic circulation. Umbilical vessels constrict, with functional closure occurring immediately. Fibrous infiltration leads to anatomic closure in the first week of life. Successful transition and closure of fetal shunts creates a neonatal circulation where deoxygenated blood returns to the heart through the inferior and superior vena cava. Blood then enters the RA to the RV and travels through the pulmonary artery to the pulmonary vascular bed. Oxygenated blood returns through pulmonary veins to the LA, the LV, and through the aorta to systemic circulation. Hypoxia, acidosis and congenital heart defects are conditions that lead to a sustained high pulmonary vascular resistance and may interfere with the normal sequence of events.

Respiratory adaptation. The initiation of breathing is a complex process that involves the interaction of biochemical, neural and mechanical factors. Pulmonary blood flow, surfactant production, and respiratory musculature also influence respiratory adaptation to extrauterine life. Umbilical cord clamping decreases oxygen concentration, increases carbon dioxide concentration, and decreases the blood pH. This stimulates the fetal aortic and carotid chemoreceptors, activating the respiratory centre in the medulla to initiate respiration. Mechanical compression of the chest during the vaginal birth forces approximately $^1/_3$ of the fluid out of the fetal lungs. As the chest is delivered, it re-expands, generating a negative pressure and drawing air into the lungs. Passive inspiration of air replaces fluid. As the infant cries, a positive intrathoracic pressure is established which keeps the alveoli open, forcing the remaining fetal lung fluid into the lymphatic circulation. In order for the respiratory system to function effectively, the infant must have: adequate pulmonary blood flow; adequate amount of surfactant; respiratory musculature strong enough to support respiration.

Adaptation to postnatal life should be considered, bearing in mind that during the first hours after birth the baby is in a transitional period, passing from intra- to extrauterine life. With the first breath after birth, changes in the cardiopulmonary system occur.

The first challenge for a newborn is the provision of oxygen by independent breathing instead of utilizing placental oxygen. With the first breaths, there is a fall in pulmonary vascular resistance and an increase in the surface area available for gas exchange. As the pulmonary vascular resistance falls, there is a corresponding increase in systemic vascular resistance due to loss of the low-resistance placental

circulation. These two changes result in a rapid redistribution of blood flow to the pulmonary vascular bed from approximately 4 % to 100 % of the cardiac output, with an increase in blood oxygen delivery. The consequent increase in pulmonary venous return results in the left atrial pressure being slightly higher than the right atrial pressure, which closes the foramen ovale. This changed flow pattern results in decreased blood flow across the ductus arteriosus and the higher blood oxygen content stimulates the constriction and ultimately the closure of this fetal circulatory shunt. The umbilical vein and the ductus venosus close off within two to five days after birth, leaving behind the ligamentum teres and the ligamentum venosus of the liver, respectively. These cardiovascular system changes result in a transition from fetal to adult circulation pattern. During this transition, some types of congenital heart disease that were not symptomatic in utero when there was a fetal circulation will present with cyanosis or respiratory signs.

Conditions that resolve spontaneously. A number of conditions that could be observed during the routine examination might alarm parents but resolve spontaneously.

Peripheral and traumatic cyanosis. Peripheral cyanosis confined to the hands and feet is common during the first day of life and is of no clinical significance. Traumatic cyanosis is blue discoloration of the skin, often with petechiae. It can affect the presenting part in a face or breech presentation or of the head and neck if the umbilical cord was wrapped around the infant's neck. However, the tongue remains pink.

Bruising of the head. The head can be markedly molded from having to squeeze through the birth canal. Newborns that have been in the breech position in utero often have a prominent occipital shelf. A caput succedaneum is bruising and edema of the presenting part of the head. It extends beyond the margins or of the skull bones. A cephalhematoma is caused by bleeding between the periosteum and the skull bone. It is confined within the margins of the skull sutures and usually affects the parietal bone. Bruising and abrasions after forceps deliveries, from scalp electrodes, or from fetal blood sampling are relatively common.

Swollen eyelids. Swelling of the eyelids is common in newborns and resolves over the first few days of life. There may also be a mucoid discharge, often called a "sticky eye". When present on the first day of life, it usually resolves spontaneously. The eyelids can be cleansed with sterile water. This must be contrasted with the erythematous, swollen eyelids with purulent eye discharge seen in conjunctivitis in the first day of life from gonococcal infection.

Subconjunctival hemorrhages. Subconjunctival hemorrhages are common. They occur during delivery and resolve in 1 to 2 weeks.

Dry, peeling skin. Dry skin is common, especially in post-term infants.

Capillary hemangioma (stork bites). Capillary hemangiomas are pink macules appearing on the upper eyelids, the mid forehead, and the nape of the neck from distention of dermal capillaries. Those on the eyelids and forehead fade over the first year, whereas those on the neck become covered with hair.

Neonatal urticaria (erythema toxicum). It's a common rash that usually starts on the second or third day of life. There are white pinpoint papules at the center of an erythematous base. Eosinophils are present on microscopy. The lesions migrate to different sites.

Milia. Benign white cysts may be present on the nose and cheeks from retention of keratin and sebaceous material in the pilaceous follicles.

Epstein pearls and cysts of the gums. Small white pearls may be visible along the midline of the palate (Epstein pearls). Cysts of the gums (epulis) and on the floor of the mouth (ranula) are mucus-retention cysts and do not need any treatment.

Harlequin color change. There is longitudinal reddening down one half of the body and a sharply demarcated blanching down the other side. This lasts for a few minutes. It is thought to be due to vasomotor instability.

Breast enlargement. This can occur in newborns of either sex. A small amount of milk ("witch's milk") may be discharged.

Hydroceles. Hydroceles are relatively common in boys and usually resolve spontaneously.

Vaginal discharge. There may be a white vaginal discharge or small amount of bleeding from maternal hormone withdrawal. There may also be prolapse of a ring of vaginal mucosa.

Mongolian blue spots. Mongolian blue spots are blue-black macular discolorations at the base of the spine or on the buttocks. They occasionally also occur on the legs and other parts of the body. They occur most often in African-American or Asian infants and fade slowly over the first few years of life. They are of no clinical significance but are occasionally misdiagnosed as bruises.

Umbilical hernia. Umbilical hernias are common, especially in African-American infants. No treatment is indicated because they usually resolve within the first few years of life.

The risk groups of newborns.

1. *Risk of infection.*

Newborns may acquire early-onset neonatal infection "vertically" (mother-to-newborn during birth) from endogenous bacteria in the mother's reproductive tract, which may or may not cause disease in the mother but can cause disease in the newborn. These bacteria may be transmitted to newborns during the delivery process, when newborns come into direct contact with bacterial flora. Ascending infections from the mother to the fetus may occur before orduring labor when colonized bacteria from the maternal perineum spread through the vaginal canal, amniotic sac, and into the once-sterile amniotic fluid. Amniotic fluid infection, orchorioamnionitis, and bacteremia are additional sources of bacterial transmission from the mother to fetus in utero. Antibiotic prophylaxis during labor, early diagnosis of sepsis, and neonatal antibiotic treatment has been highly effective in reducing mortality from early-onset neonatal bacterial sepsis.

2. *Risk of CNS damage.*

3. *Risk of developing jaundice.*

4. *Risk of respiratory disorders.*

5. *Risk of hemorrhagic disorders.*

6. *Risk of anemia.*

7. *Risk of HDN.*

8. *Risk of hypoglycemia.*

Feeding. There are different types of feeding:

1. Breast feeding — is a feeding of a newborn / infant child with breast milk of his biological mother. Separate could be defined: feeding of breast milk from another woman (nurse), expressed milk feeding and donor's milk feeding (human milk bank).

2. Artificial feeding — feeding with special babies'milk formulas.

3. Mixed (compound) feeding — combined breastfeeding (not less than 150–200 ml) and artificial milk formulas.

Breast milk is the best food for infants as it has all necessary substances for the right postnatal intellectual and physical growth and development. After birth the child's intestine is abacterial and microorganisms settle it in few hours. In cases when breast milk takes place there is a Bifidobacterium flora in the bowel, when mixed or artificial feeding takes place Colibacillus, Lactobacillus acidophilus, Bifidobacterium flora and Enterococcus are present.

Mother's contraindications to breast feeding directly after birth:

– Severe forms of gestosis;

– Massive bleeding in the intra- and postnatalperiods;

– Open tuberculosis;

– Decompensating stage of cardiac, kidney and liver diseases;

– Relative contraindication — Cesarean section (breast feeding can be started after the recovery from anesthesia).

Child's contraindications to breast feeding directly after birth:

– Apgar score is less than 7 points;

– Severe disorders (2nd–3rd degree) of cerebral circulation;

– Severe prematurity with sucking reflex absence;

– Severe congenital malformations of the heart, gastro-intestinal tract, maxillofacial region.

Methods for determining the quantity of milk necessary for feeding infants.

During the first 10 days:

• Finkilshtein's formula in A. F. Tur's modification: milk ml amount for 24 hours (ml) n × 70 or 80: where n — day of life; coefficient 70 — at birth weight less than 3200 g, and 80 — at birth weight higher than 3200 g;

• Shabalov's formula: Amount of milk for 1 feeding (ml) = 3 ml × day of life × body mass (kg);

• Filatov's in Zaitseva's modificaition formula: 24 hours' amount of milk (ml) = 2 % from body weight x day of life.

From 10 days of life: 24 hours' milk amount:

• Gejbner–Cherni's formula: from 10 days till 2 months — $^1/_5$ part from real body mass; 2–4 months — $^1/_6$; 4–6 months — $^1/_7$;

Older than 6 months — $^1/_8$ (no more than 1 liter).

• Maslov's method: 120–115 Cal/kg — 1–6 months; 110 Cal/kg — 6–12 months; 1 liter of breast milk — 700 Calories.

The preterm infant. Maturity is determined by the length of gestation, and the severity of problems related to pre-maturity are directly related to gestation. Weeks of gestation are generally considered as completed weeks.

The WHO has defined preterm infants as those with gestational age less than 37 weeks.

Classification by birth weight is as follows:

– low birth weight (LBW): less than 2500 g (up to and including 2499 g);

– very low birth weight: less than 1500 g (up to and including 1499 g);

– extremely low birth weight: less than 1000 g (up to and including 999 g).

Because of the survival of very light and premature babies, the term "incredibly low birth weight" has been used to refer to babies weighing less than 750 g.

A fundamental problem for all preterm infants is their poor ability to maintain body temperature, because of reduced glycogen stores (depending on gestational age) and thinner skin, with the most immature lacking the ability to shiver. Thus a primary aim is to avoid heat loss (and insensible water losses) by drying, heating, and covering the baby. This also decreases glucose consumption, reducing the risk of hypoglycemia.

The preterm baby often experiences delayed respiratory adaptation. Depending on the degree of immaturity, the lungs are morphologically immature and lack surfactant. Such babies may require the endotracheal administration of exogenous surfactant and mechanical ventilation. Bronchopulmonary dysplasia (chronic lung disease with oxygen dependency) is a complication of severe prematurity, which may continue to cause problems during subsequent years.

Premature infants have reduced immune defenses. Furthermore, infection may be the primary cause of preterm delivery, sometimes affecting the baby before birth. Such infections, in combination with lung and brain immaturity, increase the risk of later disability.

The gastrointestinal (GI) tract is not yet adapted to enteral feeds, posing considerable challenges to those responsible for their care. Early non-nutritive feeding should be considered. Milk, preferably from the mother or a human milk bank may be started early but cautiously, particularly for the most immature infant. Careful note should be taken of early signs of GI intolerance, e.g., increased volume or bile-staining of gastric aspirates or abdominal swelling. The most immature infants require parenteral nutrition (partial or total) to provide adequate nutrients and calories for growth, and this may need to be continued for several weeks. This practice requires a central, indwelling catheter, increasing the risk of infection.

Survival at early gestation and the associated risks of neurodevelopmental impairment are considered elsewhere. Not only babies at extremely low gestation,

but also those born late preterm are at risk. Light, painful interventions, development in air instead of surrounded by amniotic fluid, noise, stress, sleep-wake cycles interrupted by nursing procedures, continuous intravenous nutrition (without the intermittent glycemic peaks of normal feeding and maternal ingestion), fluctuations in oxygen delivery, carbon dioxide and pH levels and blood pressure may all interfere with normal brain development. A high tech/soft touch approach may be beneficial and a mother's touch and breastfeeding should be encouraged even for very tiny babies.

Risk factors associated with preterm delivery.

• Maternal medical conditions:

– poor obstetric history;

– uterine or cervical malformations;

– myomas;

– exposure to diethylstilbestrol;

– hypertension;

– diabetes;

– other medical conditions.

• Current pregnancy complications:

– multiple gestations;

– excess or decreased amniotic fluid;

– vaginal bleeding;

– low body mass index;

– fetal anomalies;

– infection (systemic or local);

• demographic factors: age, race, socio-economic status;

• behavioral factors: smoking, substance abuse, poor nutrition, absent or inadequate prenatal care.

The main problems of preterm infants:

– birth asphyxia;

– thermal instability;

– lack of primitive survival reflexes, suck, swallow and gag, which may predispose the infant to milk aspiration;

– jaundice;

– pulmonary disease;

– metabolic disturbances — hypoglycemia, hypocalcaemia, hypomagnesaemia, hyponatraemia, hypernatraemia, hyperkalaemia;

– intracranial haemorrhage, especially intravenrticular haemorrhage and subarachnoid harmmorrhage;

– suspectibility to infection;

– gastrointestinal intolerance and necrotizing enterocolitis;

– ophthalmic problems;

– haematological problems;

– renal immaturity.

CHAPTER 4
NEWBORN PERIOD: PATHOLOGY

4.1. NEONATAL JAUNDICE

Jaundice is seen in approximately half of all newborns. Although neonatal hyperbilirubinemia is usually a benign and physiologic condition, very high bilirubin levels occur in certain pathologic conditions and are potentially injurious to the central nervous system.

Bilirubin metabolism. Bilirubin is a product of heme catabolism. Red cell Hb accounts for approximately 85 % of all bilirubin. In newborns, the normal Hb level is 15–18 mg/dl. The rate of neonatal RBC destruction is higher than in adults resulting in greater quantity of Hb release. Excessive bruising from birth trauma or abnormal blood collections such as in a cephalohematoma may further add to the rate of RBC destruction and bilirubin formation.

Heme is catabolized to unconjugated bilirubin in the reticuloendothelial system (RES). Unconjugated bilirubin is bound to albumin in the plasma and transported bound to albumin to the liver and is conjugated with glucuronic acid in the hepatocytes; the conjugation is catalyzed by glucuronyl transferase. Conjugated bilirubin is secreted into the bile and enters the duodenum. In the small bowel, some of the bilirubin is hydrolyzed to yield unconjugated bilirubin and glucuronic acid. Most unconjugated bilirubin is excreted in the stool, but some is reabsorbed and returned to the liver for re-conjugation (enterohepatic circulation).

The level of glucuronyl transferase is initially low in the newborn and any increase in the rate of bilirubin formation can overwhelm the capacity to conjugate, thus resulting in elevated bilirubin levels.

Bilirubin toxicity. When the serum level of unconjugated bilirubin exceeds the albumin binding capacity, bilirubin diffuses into the central nervous system and may result in permanent neurological damage or death (bilirubin encephalopathy with kernicterus). Conjugated bilirubin is water soluble and does not diffuse into the CNS so it is not capable of causing kernicterus.

Factors such as acidosis and hypoalbuminemia may reduce the ability of albumin to bind to conjugated bilirubin. The specific serum level of unconjugated bilirubin that results in kernicterus is unknown, but for the term infant it has traditionally been defined as a concentration of 20 mg/dl. In the low birthweight infant, the level is proportionately lower.

During the first week of life all newborns have increased bilirubin levels by adult standards, with approximately 60 % of term babies and 85 % of preterm babies having visible jaundice. Most of these cases are benign but it is important to identify those babies at risk (although rare) of acute bilirubin encephalopathy and kernicterus/chronic encephalopathy. Jaundice may also be a sign of a serious underlying illness.

Jaundice (Hyperbilirubinemia) — the yellow coloration of the skin and sclera as a result of accumulation of bilirubin. Visible bilirubin level (bilirubin

higher than normal blood) in adults: > 34 μmol/l (1.99 mg/dl), in term infants: > 85 μmol/l (5 mg/dl), in preterm infants: > 120 μmol/l (7 mg/dl).

Visual assessment of jaundice does not permit a reliable conclusion about the level of bilirubin. Sources of bilirubin:

– RBC Hb (major source 1 g Hg = 34 mg bilirubin);

– haem from ineffective erythropoiesis in bone marrow;

– other haem containing proteins — myoglobin, cytochromes, catalase, peroxidase);

– free haem.

1 g albumin binds 14.4 mcmol bilirubin. Unconjugated bilirubin = Indirect bilirubin (fat soluble). Unconjugated bilirubin + albumin = protein-bound unconjugated bilirubin (Indirect bilirubin). Conjugated bilirubin = Direct bilirubin (water soluble).

Special characteristic of bilirubin metabolism in neonates.

1. *Increased production of bilirubin:*

– physiological polycythemia (180–220 g/l 1–3 days after birth);

– shorter life span of HbF (70–90 days).

2. *The low capability of albumin on unconjugated bilirubin transportation:*

– less albumin in neonates (28–44 g/l interm neonates, 18–30 g/l in preterm neonates first few days).

3. *Defective conjugation:*

– transient deficiency of Y & Z acceptor proteins.

4. *Reduced hepatic clearance:*

– reduced UDPG enzymes (UDP-glucuronosyltransferase).

5. *High workload of the hepato-enteric circulation:*

– increased activity of β-glucuronidase;

– less bacterial;

– low enzymatic activity in intestine;

– low intestinal motility.

Jaundice of newborns could be of the following types — Physiological and Pathological.

Characteristics of physiological jaundice:

• Appears after 24 hours.

• Maximum intensity by 4–5th day in term, 7th day in preterm.

• Maximum serum bilirubin level less than 256 μmol/l (15 mg/dl).

• Umbilical cord bilirubin levels less than 35 μmol/l (2 mg/dl).

• Direct bilirubin 10–15 % of total bilirubin.

• Clinically not detectable after 14 days.

• Disappears without any treatment.

Note. Treatment usually is not required. Baby should, however, be watched for worsening jaundice.

Characteristics of pathological jaundice:

• Clinical jaundice detected before 24 hours of age (after 72 hours of age).

• Umbilical cord bilirubin levels more than 42 μmol/l (2.5 mg/dl).

• Serum bilirubin more than 256 μmol/l (15 mg/dl) in term and 150 μmol/l (8.8 mg/dl) in preterm at any time.

• Clinical jaundice persisting beyond 14 days of life.

• Clay/white colored stool and/or dark urine.

• Direct bilirubin more then 10–15 % of total bilirubin at any time.

Note: Treatment must be initiated as soon as possible.

Indirect hyperbilirubinemia. More common causes:

• Disorders of Production (HDN, drug hemolysis: menadione, oxytocin, penicillin, RBC structural abnormalities, RBC enzyme defects (glucose-6-phosphate dehydrogenase), sequestration, infection, polycythemia, hemoglobinopathy).

• Disorders of Hepatic Uptake (Gilbert Syndrome).

• Disorders of Conjugation (Crigler Najjar Syndrome Type I&II, Lucey Driscoll Syndrome, hypothyroidism).

• Other Causes (Breastfeeding jaundice — lack of volume, Breast milkjaundice, Infant of diabetic mother).

Direct hyperbilirubinemia. More common causes:

• Hepatitis: idiopathic, infectious, toxic.

• Infection: sepsis, TORCH.

• Biliary atresia.

• Inspissated bile plug.

• Choledochal cyst.

• Alpha-1-antitrypsin deficiency, galactosemia.

Less common causes: cholelithiasis, rotor's syndrome, Dubin–Johnson syndrome (due to decreased excretion of bilirubin), storage diseases (Niemann–Pick, Guacher's), metabolic disorders (tyrosinemia, fructosemia), Alagille syndrome, Zellweger syndrome.

Day 1: always pathological.

• Usually due to hemolysis: hemolytic disease of newborn: Rh, ABO incompatibility.

• Exclude sepsis.

• Rarer causes may include:

– other blood group incompatibilities (Kell, Duffy, anti-E);

– red cell enzyme defects (glucose-6-phosphate dehydrogenase deficiency — G6PD);

– red cell membrane defects (hereditary spherocytosis).

• Obstructive jaundice in neonatal hepatitis due to rubella, CMV and syphilis is occasionally present (conjugated).

Investigations: mother and baby's blood group; direct Coomb's test; reticulocyte count, Hct, Hb and blood film. Repeat serum bilirubin.

Serological tests for TORCH infections if indicated.

Day 2–9.

• Sepsis.

• Polycythemia.

• Breakdown of extravasated blood due to: cephalhaematoma; CNS haemorrhage.

• Increased enterohepatic circulation which may be due to gut obstruction.

• Physiological jaundice (mostly).

Investigations: CBC; urine for microscopy and culture; investigations for bacterial infections; glucose-6-phosphate dehydrogenase screen; blood groups; direct Coomb's test.

Day 10 – 4 weeks.

• Sepsis.

• Pyloric stenosis (especially greater than 2 weeks).

• Conjugated hyperbilirubinaemia due to:

– idiopathic neonatal hepatitis;

– infections (hepatitis B, TORCH, sepsis);

– congenital malformations (biliary atresia, choledochal cyst, bileduct stenosis);

– metabolic disorders (galactosaemia, hereditary fructose intolerance, alpha-1 antitrypsin deficiency, tyrosinaemia, hypothyroidism).

• Breast milk jaundice.

Investigations: CBC; investigations for bacterial infections; thyroid function tests; urine for reducing substances to exclude galactosaemia.

Workup for pathological jaundice:

1. Review maternal and perinatal history: family history of jaundice, liver disease, previous sibling with jaundice forblood group incompatibility, maternal illness during pregnancy, traumatic delivery, delayed cord clamping, oxytocin use, birth asphyxia, delayed feeding, delay in meconium passage, breast feeding.

2. Physical examination: extent of jaundice, prematurity, small for gestation (polycythemia, hepatosplenomegaly, cataract, rash), extravascular bleed (cephalhematoma); pallor (hemolysis, blood loss); petechiae (sepsis, TORCH infections); hepatosplenomegaly (Rh-isoimmunization, sepsis, TORCH infections).

3. Laboratory tests: serum bilirubin total and direct, blood group and Rh for mother and baby, direct, indirect Coomb's test on infant, hematocrit, RBC morphology, evidence of hemolysis, reticulocyte count, sepsis screen, liver and thyroid function tests in cases with prolonged jaundice, TORCH titres.

Physical examination. Extent of jaundice. Kramer's index describes the relationship between serum bilirubin level and progression of skin discoloration (Fig. 4.1).

Transcutaneous bilirubinometry. Since 2006 transcutaneous bilirubinometry has been adopted as the first-line screening tool for jaundice in well, full-term babies. This leads to about 50 % of blood test previously required being avoided. To take a measurement, the device is calibrated prior to each measurement; the disposable probe is applied on the forehead level below the hairline or on the chest and five readings are used to generate one measurement. The correlation between bilirubin concentration in derma and bilirubin concentration in blood is caused by existing

dynamical balance between bilirubin concentration in blood and subcutaneous tissues due to reversible diffusion of a bilirubin between blood and tissues.

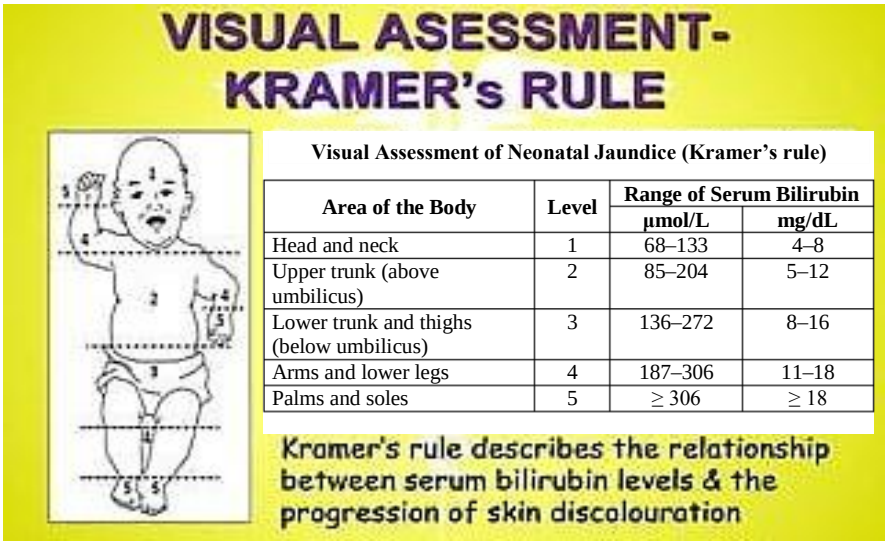


Fig. 4.1. Kramer's index

Assess each jaundiced baby to see whether the following danger signs are present:

– family history of significant haemolytic disease;
– pallor, bruising, petechiae;
– lethargy;
– poor feeding;
– fever;
– vomiting;
– dark urine and light stools;
– hepatosplenomegaly;
– high pitched cry.

Laboratory tests. The total serum bilirubin continues to be the "gold standard" for deciding if a baby's jaundice requires intervention. In the case of preterm infants, greater caution should be exercised. These babies are at risk of kernicterus at lower serum bilirubin levels.

Other labs: hematocrit; examination of a blood sample under a microscope to look for signs of RBC breakdown; reticulocyte count; albumin; coombs test (which checks for certain antibodies attached tored blood cells); measurement of different types of bilirubin; blood type and Rh status (positive or negative) of the newborn and mother; congenital infection screen; liver function tests (ALT, AST, albumin, GGT); coagulation profile; thyroid function tests, metabolic investigations, G6PD screen.

Common drugs that displace bilirubin from the albumin-binding sites: Ceftriaxone; Sulfisoxazole; Cefmetazole; Sulfamethoxazole; Cefonicid; Cefotetan; Moxalactam; Salicylates; Carbenicillin; Ethacrynic acid; Aminophylline; Ibuprofen.

Ampicillin, cefotaxime, and vancomycin can be safely given to an infant with jaundice.

Breast milk jaundice (BMJ). *Causes:*

– not completely understood;

– associated with nonesterified long-chain fatty acids, metabolite of progesterone in breast milk that competitively inhibit glucuronyltransferase, also glucoronidase which will increase deconjugation and enterohepatic recirculation of bilirubin;

– in 2–4 % EBF (exclusivley breastfeeding) babies;

– appears after the fourth day of life;

– SBr > 170 μmol/l beyond 3rd – 4th week.

Management:

• Some babies may require therapy.

• Should be differentiated from hemolyticjaundice, hypothyroidism, G6PD deficiency, breastfeeding jaundice.

• Interrupt breastfeeding for 24–48 hours to reduce bilirubin level.

• Continue breastfeeding if bilirubin levels are not critical.

• Usually declines over a period of time.

Disorders of hepatic uptake.

Gilbert syndrome is due to a mutation in the UGT1A1 gene which results in decreased activity of the glucuronosyltransferase enzyme, the capture of bilirubin by hepatocytes is disturbed. Affects ~ 9 % of the population. Usually not diagnosed in the neonatal period and occurs asphysiological jaundice. Conjugated bilirubin is usually within the normal range and is less than 20 % of the total. Newborns with Gilbert syndrome may have severe hyperbilirubinemia and even kernicterus, if they have a concurrent hemolytic disorder such as ABO incompatibility or glucose-6-phosphate dehydrogenasedeficiency.

Disorders of conjugation. *Crigler–Najjar Syndrome Type I&II.* Crigler–Najjar syndrome type I is characterized by a nearly complete lack of glucuronosyltransferase enzyme activity and severe symptoms. Type II (Arias syndrome) is characterized by partial enzyme activity and milder symptoms. Both forms are inherited as autosomal recessive traits and are caused by errors or disruptions (mutations) of the UGT1A1 gene. Type 1 is characterized by a serum bilirubin usually above 345 μmol/L (20 mg/dl). Therapy includes: exchange transfusions in the immediate neonatal period; 12 hours/day phototherapy; hemeoxygenase inhibitors, oral calcium phosphate and carbonate; liver transplantation.

Disorders due to decreased excretion of bilirubin. ***Rotor syndrome***. Autosomal recessive disease and a rare cause of mixed conjugated (mostly) and unconjugated hyperbilirubinemia. The mutations of SLCO1B1 and SLCO1B3 genes are involved and lead to abnormally short, nonfunctional OATP1B1 and OATP1B3 proteins or an absence of these proteins. Without the function of either transport protein, bilirubin is less efficiently taken up by the liver and removed from the body. Jaundice is usually evident shortly after birth or in childhood and may come and go. Conjunctival icterus is often the only symptom. Total serum

bilirubin typically elevated between 2 to 5 mg/dL but may be as high as 20 mg/dL. It's a benign disease requiring no treatment. Should be differentiated from Dubin–Johnson syndrome, Gilbert syndrome, extra-hepatic biliary obstruction, drug-induced hepatotoxicity.

Dubin–Johnson syndrome. Dubin–Johnson syndrome is a rare, autosomal recessive, benign disorder that causes an increase of conjugated bilirubin in the serum. Caused by mutations in the ABCC2 gene and associated with a defect in the ability of hepatocytes to secrete conjugated bilirubin into the bile, and is similar to Rotor syndrome. It is usually asymptomatic, but may be diagnosed in early infancy based on laboratory tests, the bilirubin elevation is usually mild, 2–3 mg/dl. It's causes a black liver due to the deposition of a pigment similar to melanin. Onset usually occurs during puberty or adulthood, but it has rarely been described in the newborn period. No treatment is usually needed.

Prevention of hyperbilirubinemia:

– early and frequent feeding;

– promote and support successful breastfeeding;

– measure the total serum bilirubin or conjugated bilirubin to a baby with jaundice in the first 24 hours;

– evaluate systemic all infants with severe risk of hyperbilirubinemia;

– adequate hydration. This may require IV administration of fluid.

Treatment of unconjugated hyperbilirubinemia: phototherapy or/and administration of Immunoglobulin; exchange transfusion.

1. *Feeding*. Increase feeding frequency to 8–12 feeds in 24 hours to meet the increased fluid needs due to insensible water. Check the baby's weight to gauge his/her hydration. Supplementation with expressed breast milk and/or formula is appropriate if weight loss is excessive despite frequent feeds. Intravenous therapy may be indicated in severe cases;

2. *Phototherapy* involves exposure of the naked baby to blue, cool white or green light of wave length 450–460 nm. The light waves convert the bilirubin to water soluble nontoxic forms which are then easily excreted. Positon phototherapy units no more than 30.5 cm from the patient. Expose as much of the skin surface as possible to the phototherapy light. Eye shades should be fixed; external genitalia may be covered. Recent studies show that phototherapy converts bilirubin to more polar photoisomers. Recent studies show that phototherapy converts bilirubin to more polar photoisomers quite rapidly, and it accounts for about 10 % of TSB by 15 minutes of treatment, increasing to 20 % to 25 % of TSB by 2 hours of exposure.

Indications for phototherapy:

• If in the first 48 hours of life bilirubin level reaches 260 μmol/l (15 mg/dl), it is necessary to think about the presence of a child of any disease and to examine him.

• On the 3 day of life FT carried out at the level of bilirubin 310 μmol/l (18 mg/dl) or higher, from the 4th day of life — more than 340 μmol/l.

• If, in spite of the ongoing FT for 4–6 hours, total bilirubinmore than 430 μmol/l (25 mg/dl), it is replacing bloodtransfusions.

• If total bilirubin level above 510 μmol/l (30 mg/dl), exchangetransfusion is carried out in any case.

• During phototherapy increase the volume of fluid injected is 1 mL/kg/h.

Complications:

• Babies with congenital erythropoietic porphyria can develop severe blistering and photosensitivity during phototherapy.

• Intestinal hypermotility, diarrhea.

• Separation of mother and baby causing interference of mother baby interaction.

• Changes in the baby's thermal environment lead to increased peripheral blood flow and water loss.

• Babies with cholestatic jaundice may development "bronze baby syndrome" and rarely purpura and bullous eruptions.

• Concomitant use of certain drugs or agents may cause Photosensitivity.

3. *Exchange Transfusions* is the removal of an infant's blood with high bilirubin levels and/or antibody-coated red blood cells (RBCs) and replacement with fresh donor blood.

Indications:

1. Alloimmune haemolytic disease of the newborn.

2. Significant unconjugated hyperbilirubinaemia with risk of kernicterus due to any cause when intensive. Phototherapy is unsuccessful.

3. Severe anaemia (where there is normal or increased circulating blood volume).

4. Antibodies in maternal autoimmune disease.

5. Polycythemia;

4. *Ursodeoxycholic acid* — may improve bile flow and lower bilirubin concentrations.

5. *Phenobarbitone (Phenobarbital)* — may improve bile flow but is not recommended for treatment of hyperbilirubinaemia.

Treatment of conjugated hyperbilirubinemia. Treat underlying cause:

• TPN-associated cholestasis: Stop TPN or at least reduce (especially lipid) and advancefeeds, "TPN-Cholestasis protocol" (remove trace elementscertain days).

• Biliary atresia with Kasai procedure +/– liver transplant.

• Alpha-1-antitrypsin with liver transplant.

• Choledochal cyst with surgical removal.

• Galactosemia with dietary elimination.

• Supportive care if no treatment possible.

Note!

• Infection must be ruled out in jaundice appearing any time.

• Even after extensive investigations, cause remains uncertain in over one third of cases.

• Neonatal jaundice may be multifactorial in origin.

• Never discharge a baby with conjugated hyperbilirubinaemia without attempting to find the cause.

• Assess all babies for risk of developing severe hyperbilirubinaemia at hospital discharge.

• Visual estimation of bilirubin levels can lead to errors, especially in darkly pigmented babies and in infants who have received phototherapy.

• Parents should be advised to contact a healthcare professional if: their baby becomes jaundiced, baby's jaundice is worsening, jaundice is persisting beyond 14 days, or their baby is passing pale stools.

• Identify ways to reduce maternal stress and anxiety to promote lactation.

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.

4.2. HEMOLYTIC DISEASE OF THE NEWBORN

Hemolytic disease of the fetus and newborn (HDN, erythroblastosis fetalis, isoimmunization). HDN is a blood disorder that occurs when the blood types of a mother and baby are incompatible. The first description of HDN is thought to be in 1609, the underlying cause of HDN was clarified in 1950.

The frequency of HDN is 3–6 %, mortality — 0.01–0.02 ‰.

Causes of hemolytic disease of the newborn:

– Rh (D) incompatibility;

– ABO incompatibility;

– minor blood group incompatibility.

50 known membrane proteins 25 proteins carry the various antigens.

Rh-Incompatibility. Rh positive (+) denotes presence of D antigen. The number of antigenic sites on RBCs varies with genotype. D/D — Rh positive (+). D/d — Rh positive (+). d/d — Rh negative (–). Pathophysiology: the process of antibody formation is called maternal sensitization.

ABO incompatibility. ABO disease can occur in first pregnancies without any transfusion. The mechanism of ABO HDN is similar to the RH HDN. In contrast to the Rh antigens, the ABO blood group antigens are expressed by a variety of fetal tissues, reducing the chances of anti-A and anti-B binding their target antigens on the fetal RBCs. Generally, it's less severe than Rh disease. The risk of sensitization to the Rh D antigen is decreased if the fetus is ABO incompatible.

Minor blood group incompatibility. Uncommon, responsible for 3–5 % of hemolytic disease of the newborn. Others Rh antigens: C, c, E, e, combination (c and E occurring together, can be severe). Other antigens: Kell, Duffy, Diego, Kidd, and MNSs antigen systems. Clinical presentation is similar to Rh (D) disease.

Hemolytic disease of the fetus and newborn. Clinical symptoms: varies from mild jaundice and anemia to hydrops fetalis (with ascites, pleural and pericardial effusions);

– chief risk to the fetus is anemia;

– extramedullary hematopoiesis due to anemia results in hepatosplenomegaly;

– risks during labor and delivery include: asphyxia and splenic rupture.

Postnatal problems include:

– asphyxia;

– pulmonary hypertension;

– pallor (due to anemia);

– edema (hydrops, due to low serum albumin);

– respiratory distress;

– coagulopathies (↓ platelets & clotting factors);

– jaundice;

– kernicterus (from hyperbilirubinemia);

– hypoglycemia (due to hyperinsulinemnia from islet cell hyperplasia).

Acute bilirubin encephalopathy. Unconjugated bilirubin is lipid soluble and toxic, it can cross the blood-brain barrier and it will penetrate neuronal and glial membrane thus causes neurotoxicity. The following areas in the brain are most commonly affected: Basal nuclei, Hippocampus, Substantia nigra, Cranial nerve nuclei, Inferior olivary nuclei, Reticular formation of the pons. Acute bilirubin encephalopathy results from high levels of unconjugated bilirubin in the blood which is more than 342 μmol/l (20 mg/dl) (in term newborns).

Early phase. In the first 3–5 days of the disease, the nonspecific symptoms of slight lethargy, poor feeding, poor sucking, slight hypotonia and hyperreflexia, slightly high pitch cry are seen.

Intermediate phase. At the end of 1st week of life acute bilirubin encephalopathy presented with moderate stupor, irritability, fever, hypo and hypertonia as an alternative symptom, back arching and hyperextension of extensor muscles (opisthotonos, retrocollis) and high-pitched cry.

Late (advanced) phase. Deep stupor or coma, high pitch crying, pronounced retrocollis-opisthotonos, and no feeding is observed.

Kernicterus. *Clinical signs:* abnormal motor functions (choreoathetosis, delayed motor skill, spasticity, muscular rigidity); disturbance in hearing, oculomotor impairment; mental retardation; dental enamel hypoplasia; digestive dysfunction.

Prevention. It is important to monitor the serum bilirubin levels of a newborn baby, especially in the first 24 hours. Premature babies need to be monitored even more closely because they have a higher risk. If symptoms of jaundice appear, it is treated early by light therapy or exchange transfusion therapy in severe cases.

Managing the levels of bilirubin in the early stages can prevent the development of kernicterus. The prognosis of kernicterus depends on the severity of the condition and the time of intervention.

Hydrops fetalis. If Rh isoimmunization occurs early greater rapid and prolonged destruction of RBCs leads to severe anemia in the fetus. The liver, spleen, and other organs increase their production of RBCs to compensate for their loss. The drive to produce RBCs causes the liver and spleen to increase in size (hepatosplenomegaly) and liver dysfunction can occur. A complication of severe HDN is hydropsfetalis, in which the fetal tissues become swollen (edematous). This condition is usually fatal. Characterized by an abnormal collection of fluid with at least two of the following:

1. Edema (fluid beneath the skin, more than 5 mm).
2. Ascites (fluid in abdomen).
3. Pleural effusion (fluid in the pleural cavity, the fluid-filled space that surrounds the lungs).
4. Pericardial effusion (fluid in the pericardial sac, covering that surrounds the heart).

In addition, hydrops fetalis is frequently associated with polyhydramnios and a thickened placenta (> 6 cm).

Management of HDN:

1. Determine Rh, ABO status of the mother. All D-negative pregnant women should undergo an antibody screen (an increase of antibodies represents sensitize) at the first prenatal visit then routine repeat screen at 28 weeks.

2. If the mother is not sensitized, reduce the risk of future sensitization. Rh D-negative mothers receive on injection of anti-D immunoglobulin at 28 weeks' gestation, another dose at about 34 weeks, a few weeks before labor begins. A final dose of anti-D Ig is given after the baby (D-positive) has been delivered (300 micrograms within 72 hours of delivery).

3. If the mother is sensitized, determine whether the fetus is at risk and monitor accordingly. Monitoring includes regular ultrasound scans of the fetus and monitoring of the amount of anti-D in the mother's serum, fetal blood test.

Diagnostics. Laboratory Findings vary with severity of HDN and include:

– anemia;
– hyperbilirubinemia;
– reticulocytosis (6 to 40 %);
– ↑ nucleated RBC count;
– thrombocytopenia;
– leucopenia;
– positive Antiglobulin Test (Coombs test);
– hypoalbuminemia;
– Rh negative blood type;
– smear: polychromasia, anisocytosis, no Spherocytes;
– cord blood bilirubin > 68 μmol/l indicates severe isoimmunization.

Treatment:

1. Intrauterine therapy. This procedure is done when a baby that is still in the womb suffers from severe anemia caused by Rh incompatibility. Usually, between 30–200 ml RBC is transfused during a single procedure (transfusion volume is calculated by the fetal medicine specialist using a formula based on the haematocrits of the donor blood and fetus, the estimated feto-placental blood volume and the target haematocrit). High-risk pregnancies are monitored by: weekly fetal Doppler ultrasound scans to measure middle cerebral artery peak systolic velocity an indication of the severity of fetal anemia, and regular ultrasound monitoring of fetal growth. Monitoring is indicated if severe anemia before 24 weeks' gestation is suspected, if there has been a previous intrauterine death.

2. If the infant is hydropic, intubate immediately and begin assisted ventilation with oxygen. If ventilation is difficult, drain pleural and ascitic fluid.

3. Insert umbilical arterial and venous catheters immediately measure BP, arterial pH and blood gas tensions, hematocrit and blood sugar.

4. *Exchange transfusions:*

– exchange transfusions are performed using either one catheter or two catheter push-pull method;

– simultaneous exchange;

– two catheter push-pull technique: blood is removed from the artery while infusing fresh blood through a vein at the same rate. The goals:

1) to decrease the level of bilirubin and prevent kernicterus.;

2) to remove baby's sensitized red blood cells;

3) to provide compatible red blood cells adequate oxygen carrying capacity;

4) to decrease the level of incompatible antibody in the baby;

5) the exchange transfusion is done if the total bilirubin level is approaching 342 μmol/l (20 mg/dl) and continues to rise despite the baby undergo the phototherapy;

6) the blood should be reconstituted from fresh, O_2 negative packed RBCs cross-matched against the mother and typespecific fresh frozen plasma;

7) 30 min before the exchange transfusion, give albumin 1 g/kg to increase the bilirubin bound to albumin in the circulation and make the exchange transfusion more effective;

8) exchange 2–3 times the blood volume (85 mL/kg).

Post exchange care:

• Remove the exchange circuit and prime new intravenous infusion set.

• Commence intravenous / arterial fluids as ordered on the Intravenous Infusion Order.

• Check all infusions, volumes and rates and document on the Intensive Care Chart.

• Ensure infant is clean and dry and repeat all observations.

• Notify parents that the procedure has been completed and their infant is comfortable.

• Perform blood glucose levels 30 minutes after exchange and as appropriate to keep bg > 2.5 mmol/l and to stabilise respiratory / metabolic condition.

• Repeat RBC, creatinine, sodium, potassium, magnesium, calcium, glucose and SBR as indicated Post Exchange.

• Monitor infant for abnormal signs and possible complications including thrombocytopenia, bleeding, and signs of infection, feed intolerance or abdominal distension.

• High intensity phototherapy needs to be continued and reviewed in relation to SBR results.

• Follow up should be arranged with attending staff specialist as requested.

5. Correct metabolic acidosis.

6. Correct anemia.

7. Use Intravenous Immunoglobulin (IVIG) — is made up from plasma isolated (dose 1 g/kg/day, 1–5 days). IVIG decrease hemolysis leading to reduction in serum bilirubin level, could act by occupying the FC receptors of RES cells preventing them from taking up and lysing antibody coated RBCs. This subsequently leads to decrease in the need for exchange transfusion.

8. Follow platelet counts; consider platelet transfusion for counts < 50,000.

9. Phototherapy.

Pearl: Approach to a jaundiced baby: ask 4 questions.

1. What is the birth weight?

2. What is the gestation?

3. What is the postnatal age in hours?

4. Is the jaundice physiological or pathological?

4.3. SEPSIS

The Sepsis-3 consensus defined adult sepsis as a “life-threatening organ dysfunction caused by a dysregulated host response to infection”. The Pediatric sepsis definition is under development by the International Pediatric Sepsis Definition Taskforce and has found strong associations of organ dysfunction markers linked with clinical outcomes suitable for inclusion in the validation phase of the definition. However, neonatal sepsis definitions are not aligned with those in adults and children as many clinicians still rely on microbiological results rather than organ dysfunction. In addition to the lack of an internationally accepted consensus definition of neonatal sepsis, there are no long-term outcomes or core outcome datasets to standardize clinical trials of sepsis and allow comparison between trials.

The most common classification of neonatal sepsis is by age at onset. While most EOS is classified as sepsis in the first 72 hours after birth, for GBS infection, early-onset disease (EOD) is classified in the first 7 days after birth. Subsequently, late-onset disease occurs from 1 week to 3 months of age, and very-late-onset disease occurs more than 3 months after birth.

Early-onset infection. Clinical manifestations of early-onset infection occur within the first 7 days of life (95 % present within the first 72 hours). Frequently, maternal complications of labor or delivery lead to this infection. Organisms from the maternal genital tract during the intrapartum period colonize the infant's skin and gastrointestinal and respiratory tracts. The reasons for progression from colonization to infection are not well understood. The most common organisms causing early-onset infection are group B streptococci (GBS), E. coli, and, occasionally, Listeria monocytogenes.

Late-onset infection. Clinical manifestations of late-onset infection occur between 7 and 30 days of life. Infection may be the result of colonization during birth or during hospitalization in the intensive care unit. Although most infants do not become ill as a result of this colonization, necessary invasive procedures put them at increased risk for infection. The most common organisms causing late-onset infection are coagulase-negative staphylococci, Staphylococcus aureus, Enterococcus spp., GBS, E. coli, Klebsiella pneumoniae, and Candida spp.

Late, late-onset infection. The improved survival rate of very low-birth-weight infants (< 1.500 g) has prompted the addition of this third category: late, late-onset infection (generally between 31 and 90 days of life). Although these infants are no longer neonates, their "corrected" gestational age (usually 28 to 34 weeks) and continued need for hospitalization because of complications of prematurity accord them "newborn" status. A quarter of all very low birthweight infants who survive beyond 3 days of life have at least one episode of late-onset or late, late-onset sepsis. These infants usually have central venous catheters or endotracheal tubes in place. Infection in this group is nosocomially acquired and often caused by coagulase-negative staphylococci, Pseudomonas aeruginosa, Enterobacter spp., Klebsiella spp., Serratia marcescens, and Candida spp.

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. **Sepsis involves organ dysfunction**, indicating a pathobiology more complex than infection plus an accompanying inflammatory response alone. Under this terminology, "severe sepsis" becomes superfluous.

Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to increase mortality. Patients with septic shock can be identified with a clinical construct of sepsis with persisting hypo tension requiring vasopressors to maintain MAP 65 mm Hg and having a serum lactate level > 2 mmol/L (18 mg/dL) despite adequate volume resuscitation. With these criteria, hospital mortality is in excess of 40 %. *(Singer M et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) JAMA 2016; 315(8): 801-810).*

Common pathogens. ***Group B Streptococcus infection (GBS).*** The maternal colonization rate for GBS is 15 % to 30 %, and 50 % of these women deliver infants who are colonized at birth; 1 % of colonized infants develop invasive GBS infection. Women with prenatal colonization are 25 times more likely to deliver an infant with early-onset GBS disease.

Maternal Risk Factors for GBS: prior infant with GBS sepsis, GBS bacteriuria, Prolonged rupture of membranes (≥ 18 hr), Premature rupture of membranes (< 37 wk of gestation), Preterm labor (< 37 wk of gestation), Intrapartum fever > 37.9 °C.

The most common clinical manifestations for early-onset infection are sepsis, pneumonia, and, less often, meningitis (5 % to 10 % of early-onset GBS cases). Early-onset GBS infection has a fulminant presentation; 50 % of infected infants are symptomatic at birth. Initial manifestations include respiratory distress, hypoxia, and shock. The mortality rate is 5 % to 10 %.

Late-onset infections typically occur within the first month of life, but a small subset of infants develops GBS infection 3 to 6 months after birth. Late-onset infections include sepsis, meningitis (30 % to 40 % of late-onset GBS cases), and, occasionally, skin or soft tissue infections, osteomyelitis, or septic arthritis. The mortality rate is 2 % to 6 %. Permanent neurologic sequelae occur in ~ 50 % of patients with meningitis caused by GBS infection.

The use of intrapartum antibiotics to treat GBS colonized women has decreased the incidence of early-onset GBS infection in neonates by about 30 %; the incidence of late-onset disease remains unchanged because intrapartum antibiotic administration does not effectively eradicate neonatal colonization. Currently, half of all cases of invasive GBS disease are late onset.

American Academy of Pediatrics and American College of Obstetrics and Gynecology recommendations include vaginal and rectal GBS screening of all pregnant women at 35 to 37 weeks of gestation. Intrapartum penicillin is administered in the following situations: previous infant with GBS; GBS bacteriuria; positive GBS screening culture; and unknown GBS status if there is preterm labor, membrane rupture > 18 hours, or intrapartum temperature > 38 °C. Cefazolin, clindamycin, erythromycin, or vancomycin may be given to penicillin-allergic women based on results of GBS isolate susceptibility testing. Other factors that increase the risk of neonatal sepsis include a multiple gestation pregnancy and maternal chorioamnionitis.

E. coli infection: E. coli, like GBS, is passed from mother to infant and the ratio of infected to colonized babies is similar. Early-onset and late-onset infections occur. Organisms that have the K1 surface antigen are more apt to cause infection, especially meningitis.

Escherichia coli infections. Historically, E. coli is the 2nd most common pathogen causing sepsis and meningitis in newborns, up to 80 % of the strains causing meningitis and 40 % bacteremia or sepsis express the K1 antigen. The capsular K1 polysaccharide Ag is highly homologous to the capsular Ag of group B Neisseria meningitis. Because a high percentage of women have bacteriuria with strains of E. coli that express the K1 antigen or are colonized with it at the time of delivery, it is surprising that E. coli sepsis or meningitis is not more common. Surveillance data from the National Institute of Child Health and Human Development Neonatal Research Network, a consortium of 16 US

academic neonatal centers, revealed that in the era of widespread implementation of antibiotic prophylaxis, the rate of E. coli sepsis increased from 3.2 to 6.8 cases per 1000 live births. This increase was observed in the 1998–2000 era and persisted from 2002 to 2003. Up to 85 % of E. coli infections in VLBW infants were ampicillin-resistant. Yet, while most evidence suggests that IAP has not been associated with a concomitant increase in the incidence of E. coli or other non-GBS bacterial causes, other evidence demonstrates that the incidence of E. coli and ampicillin-resistant E. coli infections increased significantly among preterm infants. Furthermore, neonates who developed E. coli infections with ampicillin-resistant strains are more likely to be born from mothers with IAP with ampicillin. In VLBW neonates, the incidence of EOS with E. coli has increased, with nearly 85 % of cases having resistance to ampicillin. Thus, while the benefits of IAP on reducing EOS attributable to GBS are well-documented, the balance of preventing resistance by other bacterial pathogens is still under investigation.

Coagulase-negative staphylococcal infection. Coagulase-negative staphylococci (primarily S. epidermidis) are most commonly associated with nosocomial infection. Risk factors include prematurity and the use of indwelling catheters. The organism produces a slime coating that allows it to adhere to the surfaces of synthetic polymers used to make central venous catheters and also enables it to evade the immune system. Clinical manifestations of staphylococcal sepsis are often subtle, and a high index of suspicion is needed to diagnose the infection early.

Fungal infection. Candida albicans has been the most common cause of neonatal fungal infection; however, C. parapsilosis and other non-albicans Candida species (C. tropicalis, C. glabrata) are becoming more prevalent. Risk factors for fungal infection include gestational age < 32 weeks, indwelling intravascular catheter, endotracheal intubation > 7 days, receipt of intra lipids or parenteral nutrition, and broad-spectrum antibiotic use, especially 3rd-generation cephalosporins. Systemic infection occurs after hematogenous dissemination. Infants with persistently positive blood cultures for Candida spp. (> 3 days) with a central venous catheter in place are three times more likely to have disseminated disease. The most commonly involved sites are the heart (15 %), retina (6 %), kidneys (5 %), and liver (3 %).

Differential diagnosis. Neonatal sepsis may present with a variety of clinical presentations. These same presentations can have a variety of other causes simulating or accompanying sepsis.

Differential diagnosis for sepsis: metabolic (hypoglycemia, hypocalcemia, inborn errors of metabolism), pulmonary (RDS, meconium aspiration, transient tachypnea of the newborn), cardiac (congenital heart diseases, heart failure), neurologic (hemorrhage, cerebral infarct), GI (necrotizing enterocolitis, malrotation), hematologic (profound anemia).

Evaluation of sepsis. All infants with suspected sepsis should receive antibiotics while awaiting blood culture results. The remainder of the evaluation, including lumbar puncture (LP), can be completed once the infant is stabilized.

Patient history:

• Are there maternal factors that place the infant at risk for sepsis?

• Is there a family history of infection or other diseases (e.g., galactosemia) in newborns?

• Does the infant have poor feeding, feeding intolerance (e.g., vomiting, abdominal distention), decreased activity, lethargy, or irritability?

Physical examination. Signs of infection in the newborn infant are nonspecific and include the following disturbances:

– temperature — fever (> 37.9 °C) or hypothermia (< 36.0 °C);

– neurologic — bulging fontanel, lethargy, irritability, weak suck or cry, hypotonia, hypertonia;

– respiratory — tachypnea (respiratory rate > 60/min), grunting, nasal flaring, retractions, hypoxemia, apnea;

– cardiovascular — tachycardia, bradycardia, hypo tension (systolic blood pressure < 60 mm Hg in term infants), delayed capillary refill (< 2 seconds);

– cutaneous — jaundice, mottled skin, cyanosis, or petechiae;

– skeletal — focal bone tenderness.

Standard sepsis workup:

1. CBC.
2. Blood culture.
3. Lumbar puncture (LP) and cerebrospinal fluid (CSF) analysis.
4. Urinalysis and urine culture.
5. Chest X-ray.

Laboratory studies. ***Complete blood count (CBC).*** The ranges of normal values for the WBC count and differential changes correlate with the gestational and chronological age of the baby. The normal WBC count is 10,000 to 30,000/mm^3 at birth and decreases to 5,000 to 15,000/mm^3 by the second week of life. Although elevated total WBC and absolute neutrophil counts (ANCs) are not helpful as single indicators of sepsis, neutropenia (ANC < 1,500/mm^3) and an elevated immature-to-total WBC ratio > 0.2 are more often associated with infection. Positive and negative predictive values in large enough studies have not been established to use these values for treatment decisions. The initial WBC count may be normal in an infected newborn, with abnormalities developing 24 to 48 hours later. Several non-infectious conditions can cause neutropenia in newborns, including pregnancy-induced hypertension, asphyxia, intraventricular hemorrhage, hemolytic disease, and alloimmune neutropenia.

Cerebrospinal fluid (CSF) analysis. The CSF sample should be evaluated for the cell count and differential and protein and glucose levels. Newborns have higher CSF cell counts and protein levels than older children and adults. The average CSF WBC count in an uninfected newborn is 6 WBCs/mm^3, and several studies have determined the normal range to be up to 20 WBCs/mm^3. The average value for protein in the CSF is 90 mg/dL in full-term infants and 120 mg/dL in preterm infants. Normal babies may have CSF protein of 150 mg/dL. Traumatic

("bloody") LPs can give results that are difficult to interpret. The correction factor applied to a traumatic LP is based on the WBC-to-RBC ratio in the CSF and in the peripheral blood. Unfortunately, it is often inaccurate in determining the true WBC and protein counts of the CSF.

Other studies. Additional tests to consider include C-reactive protein (CRP, normal value 0–10 mg/l for 1st day neonates, for older children 0–6 mg/l), procalcitonin (normal level less than 0.05 ng/ml; 0.05–0.49 ng/ml — local infection possible; 0.5–1.99 ng/ml — systemic infection possible; 2.0–9.99 ng/ml — sepsis possible; 10 ng/ml — severe sepsis), D-dimers, hepatic function panel, serum electrolytes, glucose, CSF viral testing (e.g., enterovirus, parechovirus, herpes simplex virus (HSV) by polymerase chain reaction (PCR), and viral cultures of nasopharyngeal secretions, rectal swabs, or CSF.

CRP and procalcitonin. The level of CRP, an acute phase reactant, is often increased in response to infection. The negative predictive value of two CRP measurements < 1 mg/dL measured 24 hours apart and within 48 hours of birth was > 97 % in one study. Serum procalcitonin measurements are also elevated in neonatal sepsis; values > 40 ng/mL are reported in infected infants compared with values < 5 ng/mL in uninfected infants. However, routine use of CRP and procalcitonin to guide initiation of antibiotic therapy in the asymptomatic newborn infant is not advocated because of insufficient data.

Treatment of sepsis. *Stabilization and monitoring.* ABCs: airway, breathing, and circulation. Close monitoring of the respiratory status, perfusion, and urine output is necessary in all newborns with sepsis.

Initial empirical antibiotic therapy. Empirical antimicrobial therapy for suspected bacterial infections is guided by knowledge of pathogens suspected, associated focus of infection, and the antimicrobial susceptibility patterns in a particular intensive care unit. The standard therapy for suspected early-onset sepsis is *ampicillin* (which is effective against GBS, L. monocytogenes, most enterococci, and 50 % of E. coli strains) *plus gentamicin* (provides good gram-negative coverage and is synergistic with ampicillin against many organisms). For hospital-acquired infections, Vancomycin plus an aminoglycoside (e.g., gentamicin, amikacin, tobramycin) is appropriate. Imipenem should be added for empiric treatment of gram-negative meningitis or when resistance to aminoglycosides is suspected. Obviously, the therapy should be altered appropriately when an organism is isolated and susceptibilities are available.

Specific antibiotic therapy:

• *Group B Streptococcus.* Bacteremia or pneumonia can be treated with administration of ampicillin alone. If meningitis is present, aminoglycoside administration should be continued.

• *L. monocytogenes.* Ampicillin plus an aminoglycoside is recommended.

• *E. coli and K. pneumonia.* Cefepime is preferred as empiric therapy. Alternate agents include Imipenem. For susceptible organisms, cefazolin or cefotaxime are appropriate. Meningitis requires combination therapy with an aminoglycoside.

Other gram-negative organisms. Therapy is more complicated because of development of strains resistant to gentamicin and cephalosporins. Administration of a carbapenem and amikacin (or tobramycin) should be considered. This decisionshould be made in conjunction with a specialist in pediatric infectious diseases. Cephalosporins should not be used as monotherapy to treat certain gram-negative rod bloodstream infections (e.g., Serratia spp., P. aeruginosa, Citrobacter spp., Enterobacter spp.) because of the risk of inducing resistant strains.

• *Coagulase-negative staphylococci.* Vancomycin is generally used; however, oxacillin can be used if sensitivity to this agent is demonstrated in vitro.

• *C. albicans.* Treat with amphotericin B. For meningitis, add oral flucytosine. For severe amphotericin B-associated toxicity (e.g., renal insufficiency), consider lipid amphotericin B, fluconazole, or caspofungin. Removal of the infected catheter is an important part of treatment of candidemia. Failure to remove the catheter as soon as candidemia is detected results in prolonged duration of candidemia and increased mortality rates.

Duration of antibiotic therapy. Expected duration of therapy depends on many variables, including virulence of pathogen, rapidity of clinical response, removal of infected catheter, and adequacy of drainage of purulent foci, if present. In cases of bacterial meningitis, a LP should be repeated several days into therapy to document sterilization of the CSF for gram-negative meningitis and meningitis caused by highly resistant bacteria. Therapy should continue 2 weeks after obtaining a negative culture result for gram-positive meningitis and 3 weeks after obtaining a negative culture result for gram-negative meningitis.

Other Treatment Modalities:

• Blood products. Some centers treat coagulation disorders with administration of fresh-frozen plasma (15 mL/kg) to replenish clotting factors. Platelets should be given to maintain a count of > 20,000/mm^3 (or > 50,000/mm^3 if there is evidence of bleeding).

• Alternative therapies. Various strategies for prophylaxis or treatment of sepsis in the newborn have been studied, including exchange transfusion, neutrophil transfusion, administration of IV Ig, and cytokine therapy. Unfortunately, none has consistently proven effective for routine use. Hemopoietic colony-stimulating factors in recent trials increased ANC and decreased mortality rates in critically ill neutropenic neonates.

Approach to the asymptomatic patient with risk factors for sepsis. The decision on whether to evaluate an asymptomatic newborn for infection should be based on maternal and fetal risk factors. In asymptomatic infants with gestational age > 35 weeks, the duration of intrapartum prophylaxis before delivery determines subsequent management. If two or more doses of maternal prophylaxis were given before delivery, no laboratory evaluation or antimicrobial treatment is required. These infants should be observed in the hospital for at least 48 hours. If fewer than two doses were given, the AAP and American College of Obstetrics and Gynecology recommend a limited evaluation (CBC and blood

culture) and at least 48 hours of observation before discharge from the hospital. Premature neonates have at least a 10-fold higher risk for early-onset GBS sepsis compared with term neonates. Furthermore, as the degree of prematurity increases, clinical evaluation for signs and symptoms of sepsis are less reliable. Therefore, asymptomatic infants < 35 weeks of gestation should receive limited evaluation (CBC and blood culture) and at least 48 hours of observation prior to hospital discharge. Empirical antibiotic therapy is not required. If, during the period of observation, the clinical course suggests systemic infection, complete diagnostic evaluation and administration of empiric antibiotic therapy are indicated. This degree of surveillance and treatment is justified by the high morbidity and mortality rates associated with neonatal infection.

Congenital (TORCH) and perinatal infections:

– toxoplasmosis;

– other (includes HIV, syphilis, enterovirus, parvovirus, hepatitis B virus, varicella-zoster virus);

– Rubella;

– Cytomegalovirus (CMV);

– Herpes simplex virus (HSV).

A congenital infection is acquired by the infant transplacentally during the first, second, or early third trimester. The classic acronym for the agents that cause these congenital infections is TORCH. Infections that are acquired in the perinatal period are frequently included in this group.

Clinical features suggesting infection with TORCH agents:

– intrauterine growth retardation;

– hydrops;

– microcephaly, hydrocephalus, intracranial calcifications;

– eye abnormalities (chorioretinitis, cataracts, glaucoma);

– cardiac malformations, myocarditis;

– pneumonitis;

– hepatosplenomegaly;

– anemia;

– thrombocytopenia, petechiae;

– jaundice (especially conjugated hyperbilirubinemia);

– bone abnormalities (osteochondritis, periostitis).

Evaluation of the infant with a suspected TORCH infection.

Cerebrospinal fluid: CSF cell count, protein, glucose (enterovirus, rubella, syphilis), CSF PCR (enterovirus, HSV), CSF VDRL (syphilis).

Blood: IgG (specify Toxoplasma or rubella — if positive, send IgM), RPR (syphilis), Hepatitis B surface antigen, PCR (enteroviruses, HIV).

Skin lesions: darkfield examination (syphilis), direct fluorescent antibody (HSV, varicella), PCR (HSV, varicella), tzanck smear (HSV), culture (HSV).

Urine: PCR (CMV, enteroviruses), culture (CMV).

Mucosa: conjunctiva culture (HSV), mouth or nasopharynx culture (HSV, enterovirus), rectum culture (enterovirus, HSV).

Other studies: audiologic evaluation (CMV, rubella, toxoplasmosis), head CT (CMV, toxoplasmosis), ophthalmologic examination (toxoplasmosis, rubella, CMV, HSV, varicella, syphilis), radiograph of long bones (rubella, syphilis).

Laboratory studies. It is not necessary to perform a complete TORCH evaluation for every baby with suspected congenital infection. A thorough history and physical examination of the baby and knowledge of maternal prenatal laboratory studies (rubella, syphilis, hepatitis, and HIV serologies) can narrow the differential diagnosis.

• *Serology.* Maternal IgG antibody crosses the placenta; therefore, the absence of rubella- or Toxoplasma-specific IgG in the infant excludes congenital infection. However, positive IgG titers in the infant for rubella or Toxoplasma are not diagnostic of congenital infection. If the serology is positive, check specific IgM titers. In suspected congenital syphilis, serum RPR and CSF VDRL should be tested.

• *Viral culture.* All infants with suspected HSV should have surface viral cultures performed. Urine CMV PCR testing should be performed to assess for congenital CMV infection; shell-vial culture is occasionally used in lieu of PCR. Testing for CMV must be sent within 2 weeks of birth, otherwise postnatal acquisition cannot be excluded. Enteroviral culture of nasopharyngeal and rectal swabs and CSF may be indicated for a baby with myocarditis, hepatitis, or aseptic meningitis.

• *Other laboratory studies* include a CBC, bilirubin (conjugated and unconjugated), and transaminases. Darkfield examination of nasal discharge in patients with "snuffles" may reveal syphilis.

Systemic inflammatory response syndrome (SIRS) is an exaggerated defense response of the body to a noxious stressor (infection, trauma, surgery, acute inflammation, ischemia or reperfusion, or malignancy, to name a few) to localize and then eliminate the endogenous or exogenous source of the insult. *Clinically, the SIRS is identified by two or more symptoms including fever or hypothermia, tachycardia, tachypnea and change in blood leucocyte count.*

Multisystem inflammatory syndrome in neonates (MIS-N) related to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has increasingly been reported worldwide amid the spread of the SARS-CoV-2 pandemic. There is a clear definition of MIS-C in children as described by the WHO and Centers for Disease Control. In general, the MIS-C definition includes fever with multi-organ involvement (2 or more organs) and evidence of SARS-CoV-2 infection. Currently, there is no agreed definition of MIS-N. Newborns are proposed to be classified as neonates as having confirmed MIS-N when they fulfilled either the CDC or WHO criteria for MIS-C and had a confirmed infection or exposure to SARS-CoV-2 infection before 28 days of age after excluding other causes.

The fulfilment of one of the criteria was sufficient to confirm the diagnosis of MIS-N. Neonates with confirmed infection or exposure to SARS-CoV-2

infection before 28 days of age and who presented without fever and had three-organ involvement were categorized as suspected MIS-N after excluding other possible causes, such as sepsis, birth asphyxia, and others.

Early MIS-N hypothesized as presenting due to the transplacental transfer of maternal SARS-CoV-2 antibodies (AB) when a neonate is born to a mother who is SARS-CoV-2 positive, and the neonate is demonstrating clinical/laboratory features within 72 h after birth. *Late MIS-N* hypothesized as occurring due to AB produced secondarily to SARS-CoV-2 infection in the newborn when the neonate presents with clinical and laboratory features beyond the first 72 h of age.

Common focal infections. Inflammation is a stereotypic, mostly local response of the organism followed by systemic signs of different intensity, induced by tissue damage or destruction.

Focal infections of bones, skin and soft tissues:

– focal skin infections: bullous impetigo, Staphylococcal scalded skin syndrome, cellulitis;

– omphalitis;

– neonatal mastitis;

– lymph node disorders: lymphadenitis;

– necrotizing soft tissue infections;

– osteomyelitis: acute hematogenous osteomyelitis, subacute hematogenous osteomyelitis, chronic osteomyelitis, exogenousosteomyelitis, neonatal osteomyelitis.

Impetigo. Impetigo is a group of superficial skin infections caused by S. aureus, group A streptococcus (GAS), or both.

Clinical findings:

• Manifests as flaccid vesicles/bullae or pustules on an erythematous base.

• Ruptured lesions leave behind a moist red base with a characteristic collarette of scale.

• Aggressive cases of S. aureus bullous impetigo may also present as widespread desquamation in a de gloving pattern.

Treatment:

• Extremely limited infections may be treated with topical mupirocin, butthis form of therapy should be used with caution in neonates.

• More extensive lesions require a systemically administered penicillinase-resistant antibiotic for 7–10 days.

• Outbreaks of S. aureus may present as multiple cases of staphylococcal scalded skin syndrome (SSSS), pustulosis, bullous impetigo, abscesses, or other varied presentations of staphylococcal infection.

• Aggressive monitoring of patients via active surveillance cultures and subsequent treatment of S. aureus-colonized neonates with topical mupirocin therapy and chlorhexidine baths have also been successful in limiting staphylococcal infections.

Staphylococcal scalded skin syndrome (SSSS) is a generalized manifestation of-circulating toxin produced by S. aureus.

Clinical findings:

• Abrupt onset of temperature instability, lethargy, and irritability.

• Subsequent generalized skin tenderness and erythema.

• Facial swelling, conjunctivitis, and significant periorificial crusting.

• Focal or widespread flaccid bullae may develop within hours to days with subsequent desquamation. This is easily elicited by light stroking of intact skin (Nikolsky sign).

• Thermoregulation disorder, fluid and electrolyte balance, and superinfection.

Streptococcus species infections. Common manifestation and treatment:

– omphalitis;

– cellulitis;

– pustular eruptions, paronychia;

– dissemination may occur and often presents as respiratory distress, a toxic shock-like syndrome, lethargy, abdominal distension, and poor oral intake;

– meningitis is more commonly seen in affected individuals 5 days of age or older;

– infants should be identified and treated promptly with strict isolation;

– disinfection of the umbilical stump reservoir and antibiotic prophylaxis for carriers and exposed infants;

– penicillin or ampicillin is effective as first-line therapy.

Omphalitis is an infection of the umbilical stump.

• Omphalitis typically presents as a superficial cellulitis that may spread to involve the entire abdominal wall and may progress to necrotizing fasciitis, myonecrosis, or systemic disease.

• Omphalitis is most commonly caused by bacteria. The most common are Staphylococcus aureus, group A Streptococcus, E. coli, Klebsiella pneumoniae, and Proteus mirabilis. Normally, the cord area is colonized with potential bacterial pathogens during or soon after birth.

• Omphalitis is more common in those patients who have a deficient immune system or who are hospitalized and subject to invasive procedures.

• Omphalitis can quickly progress to sepsis and presents a potentially life-threatening infection.

• Clinically, neonates with omphalitis present within the first two weeks of life with signs and symptoms of infection (cellulitis) around the umbilical stump (redness, warmth, swelling, pain), pus from the umbilical stump, may be accompanied by signs of a systemic infection if infection progresses, fever, tachycardia, arterial hypotension, poor feeding, jaundice.

• Treatment includes topical therapy (Cleaning 1–3 times a day with some antiseptics); a short antibiotic therapy of 7 days is adequate for simple uncomplicated omphalitis. Complications such as respiratory failure, hypotension, and disseminated intravascular coagulation arising from infection may require

supportive care in the form of intravenous fluids, fresh whole blood, fresh frozen plasma, platelets, or cryoprecipitate. The surgical treatment is handled according to the surgical complication.

• Complications of omphalitis: septic umbilical arteritis; suppurative thrombophlebitis of the umbilical or portal veins (resulting in portal vein thrombosis and portal hypertension); liver abscess; endocarditis; abdominal wall necrotizing fasciitis; peritonitis; intestinal gangrene; infection of the urachal remnant.

Osteomyelitis. Osteomyelitis and septic arthritis result either from hematogenous seeding in babies antibacterial, or direct extension from a skin infection. Signs include localized erythema, swelling, pain on movement, or lack of spontaneous movement of the involved joint or extremity. The hip, knee and wrist are the usual joints involved. The femur, humerus, tibia, radius and maxilla are the bones most commonly affected.

• S. aureus, GBS and gram-negative organisms are the typical causative organisms.

• Surgical drainage is often essential for infected joints, and orthopedic surgery should be consulted.

• In the preterm baby, orthopedics should be consulted emergently because of the potential of irreversible damage to a septic joint. Duration of therapy is 3–4 weeks, ideally with an antibiotic known to be effective for the specific infecting organism.

• Disability following osteomyelitis or septic arthritis can be significant due to the vulnerability of the growth plate at this age.

• Osteomyelitis usually occurs in the long bones, but in the neonate frequently occurs in other bones such as the clavicle and ribs. This infant demonstrates inflammation and swelling over the right clavicle due to a staphylococcal osteomyelitis.

Neonatal mastitis:

• Usually caused by Staphylococcus aureus, coliform bacteria, or group B streptococcus.

• Predisposing factors: maternal skin or soft-tissue infection in the postpartum period, manipulation of the neonatal breast.

• Clinical presentation: edema, induration, and tenderness of the breast tissue, fever and other systemic symptoms. Erythema and fluctuation to palpation ensue if treatment is delayed.

Differential diagnosis: it is important to differentiate mastitis from **physiologic breast hypertrophy** (sexual crisis in newborns), which resolves spontaneously. In contrast to mastitis, the breast bud is neither red nor tender. The nipple discharge (if present) is milky rather than purulent and does not contain white blood cells or bacteria.

CHAPTER 5
MALNUTRITION. OVERWEIGHT

Pediatric undernutrition is usually the result of:
– inadequate food supply, access, or utilization;
– poor access to health and sanitation;
– chronic health conditions;
– and/or inappropriate feeding or child-care practices.

WHO defines malnutrition as the cellular imbalance between supply of nutrients and energy and the body's demand for them to ensure growth, maintenance and specific functions. Malnutrition refers to deficiencies or excesses in nutrient intake, imbalance of essential nutrients or impaired nutrient utilization. The double burden of malnutrition consists of undernutrition and overweight (obesity), as well as diet-related non communicable diseases.

Undernutrition manifests in four broad forms: wasting, stunting, underweight, and micronutrient deficiencies.

Wasting is defined as low weight-for-height. It often indicates recent and severe weight loss, although it can also persist for a long time. It usually occurs when a person has not had food of adequate quality and quantity and/or they have had frequent or prolonged illnesses. Wasting in children is associated with a higher risk of death if not treated properly.

Stunting is defined as low height-for-age. It is the result of chronic or recurrent undernutrition, usually associated with poverty, poor maternal health and nutrition, frequent illness and/or inappropriate feeding and care in early life. Stunting prevents children from reaching their physical and cognitive potential.

Underweight is defined as low weight-for-age. A child who is underweight may be stunted, wasted or both.

Micronutrient deficiencies are a lack of vitamins and minerals that are essential for body functions such as producing enzymes, hormones and other substances needed for growth and development.

Globally in 2020, 149 million children under the 5 years of age were estimated to be stunted (too short for age), 45 million were estimated to be wasted (too thin for height), and 38.9 million were overweight or obese. Around 45 % of deaths among children under the 5 years of age are linked to undernutrition. These mostly occur in low- and middle-income countries. Moderately malnourished children face health risks four times greater than their well-nourished peers. The greatest risk of undernutrition is in utero through age 2 years.

Various guidelines can be used to classify pediatric malnutrition. International references are established that allow normalization of anthropometric measures in terms of z scores. Other measurements include height and weight for age, weight for height, BMI, and mid-upper arm circumference. The greatest consequence of undernutrition is death, but significant intellectual and physical disability exists in many who survive.

Definitions of malnutrition:

• Gomez (Weight below % median WFA): mild (grade 1) — 75–90 % WFA; moderate (grade 2) — 60–74 % WFA; severe (grade 3) < 60 % WFA;

• Waterlow (z scores (SD) (below median WFH)): mild — 80–90 % WFH; moderate — 70–80 % WFH; severe < 70 % WFH;

• WHO (wasting) z scores (SD) below median WFH: moderate — –3 ≤ z score < –2; severe — z score < –3;

• WHO (stunting) z scores (SD) below median HFA: moderate — –3 ≤ z score < –2; severe — z score < –3;

• Kanawati (MUAC divided by occipitofrontal head circumference): mild < 0.31; moderate < 0.28; severe < 0.25;

• Cole (z scores of BMI for age): grade 1 — z score < –1; grade 2 — z score < –2; grade 3 — z score < –3.

Protein-energy malnutrition (PEM) is a spectrum of conditions caused by varying levels of protein and calorie deficiencies.

• Primary PEM is caused by social or economic factors that result in a lack of food.

• Secondary PEM occurs in children with various conditions associated with increased caloric requirements (infection, trauma, cancer etc.), increased caloric loss (malabsorption), reduced caloric intake (anorexia, cancer, oral intake restriction, social factors), or a combination of these three variables.

Protein and calorie malnutrition may be associated with other nutrient deficiencies, which may be evident on physical examination (Table 5.1).

Table 5.1

Physical signs of nutritional deficiency disorders

System	Sign	Deficiency
General appearance	Reduced weight for height	Calories
Skin and hair	Pallor	Anemias (iron, vitamin B12, vitamin E, folate, and copper)
	Edema	Protein, thiamine
	Nasolabial seborrhea	Calories, protein, vitamin B6, niacin, riboflavin
	Dermatitis	Riboflavin, essential fatty acids, biotin
	Photosensitivity dermatitis	Niacin
	Acrodermatitis	Zinc
	Follicular hyperkeratosis (sandpaper-like)	Vitamin A
	Depigmented skin	Calories, protein
	Purpura	Vitamins C, K
	Scrotal, vulval dermatitis	Riboflavin
	Alopecia	Zinc, biotin, protein
	Depigmented, dull hair, easily pluckable	Protein, calories, copper
Subcutaneous tissue	Decreased	Calories

End of Table 5.1

System	Sign	Deficiency
Eye (vision)	Adaptation to dark	Vitamins A, E, zinc
	Color discrimination	Vitamin A
	Bitot spots, xerophthalmia, keratomalacia	Vitamin A
	Conjunctival pallor	Nutritional anemias
	Fundal capillary microaneurysms	Vitamin C
Face, mouth, and neck	Moon facies	Kwashiorkor
	Simian facies	Marasmus
	Angular stomatitis	Riboflavin, iron
	Cheilosis	Vitamins B6, niacin, riboflavin
	Bleeding gums	Vitamins C, K
	Atrophic papillae	Riboflavin, iron, niacin, folate, vitamin B12
	Smooth tongue	Iron
	Red tongue (glossitis)	Vitamins B6, B12, niacin, riboflavin, folate
	Parotid swelling	Protein
	Caries	Fluoride
	Anosmia	Vitamins A, B12, zinc
	Hypogeusia	Vitamin A, zinc
	Goiter	Iodine
Cardiovascular	Heart failure	Thiamine, selenium, nutritional anemias
Genital	Hypogonadism	Zinc
Skeletal	Costochondral beading	Vitamins D, C
	Subperiosteal hemorrhage	Vitamin C, copper
	Cranial bossing	Vitamin D
	Wide fontanel	Vitamin D
	Epiphyseal enlargement	Vitamin D
	Craniotabes	Vitamin D, calcium
	Tender bones	Vitamin C
	Tender calves	Thiamine, selenium, vitamin C
	Spoon-shaped nails (koilonychias)	Iron
	Transverse nail line	Protein
Neurologic	Sensory, motor neuropathy	Thiamine, vitamins E, B6, B12
	Ataxia, areflexia	Vitamin E
	Ophthalmoplegia	Vitamin E, thiamine
	Tetany	Vitamin D, calcium, Magnesium
	Retardation	Iodine, niacin
	Dementia, delirium	Vitamin E, niacin, thiamine
	Poor position sense, ataxia	Thiamine, vitamin B12

Pediatric undernutrition in the United States is often termed *failure to thrive* and describes circumstances in which a child fails to gain weight appropriately or, in more severe cases, experiences failure in linear growth or head circumference. The terms organic and nonorganic failure to thrive have lost favor in recognition of the frequent interplay between underlying medical conditions that may cause

maladaptive behaviors. Similarly, social and behavioral factors that initially may have been associated with feeding problems and poor growth may also be associated with medical problems, including frequent minor acute illnesses.

There are Child growth standards and computer programs:

– ***WHO Anthro for children from birth to five years old;***

– ***WHO Anthro Plus for children older than five years old;***

– ***AnthroCalc Provide both Percentile score and Z-score for length / height for age, weight for age, MUAC and BMI for age.***

Etiology of undernutrition. ***Prenatal:*** malnutrition in pregnant women; severe acute or chronic illnesses of women; intrauterine toxins exposure; infections (TORCH); genetic disease in fetus; feto-fetal transfisuon; premature birth.

Postnatal. *Primary* (non-organic, alimentary): inadequate food intake (parents cannot afford to buy the food (lack of money)), or Don't know which food is appropriate for their child (lack of education), or Don't want to care of their child (maltreatment or abuse).

Secindary (organic):

– malabsorption or maldigestion (infections of GI tract, celiac disease, chronic diarrhea) — inability to tolerate or proceed natural foods, significant losses of nutrients;

– chronic illnesses (discrepancy btw higher or specific demands and nutrients intake): congenital malformations (heart, lungs, kidneys, etc), cystic fibrosis, inborn errors of metabolism; malignancies; primary immune deficiencies; endocrine disorders; genetic syndromes.

Pathophysiology of undernutrition. Deficiency in nutrients' intake:

– slowing down of anabolic processes, then shift towards catabolic processes predominance;

– lack of substrate for production of body structural and effector molecules: low immunity, weak muscles, anemia;

– low levels of protein, lipids, glucose in serum, low glycogen storages;

– slowing of cognitive development;

– slowing down of metabolism — in severe cases bradycardia, apathy, lethargy, hypothermia.

Classification of undernutrition according to the severity:

– mild (Z-score btw –1 to –2 SD);

– moderate (Z-score btw –2 to –3 SD);

– severe (Z-score less than –3 SD);

– kwashiorkor (protein deficiency);

– marasmus (protein-energy deficiency).

According to the duration:

– acute (< 3 months) — height generally not affected;

– chronic (> 3 months) — stunting, wasting or both, when linear growth is slowed down and weight is not corresponding to age and height.

Mild undernutrition (or at risk patients, BMI z-score –1 to –2):

– mostly acute (infections);

– height is not affected;

– decreased subcutaneous fat predominantly on abdominal wall;

– cognitive development is normal;

– activity normal or slightly decreased;

– appetite normal or even increased.

Moderate undernutrition (BMI z-score –2 to –3):

– acute or chronic;

– weight is low for height (wasting);

– height is often affected (stunting);

– decreased subcutaneous fat predominantly on abdominal wall and extremities, low turgor;

– cognitive development delay — hardly or don't gain new skills;

– activity decreased, hypotony, decreased muscle mass;

– appetite might be decreased, food intolerance (secondary malabsorption);

– anemia (iron and protein deficiency).

*Severe undernutrition (*BMI z-score less than –3):

– acute (SAM) or chronic (severe chronic illnesses);

– height is affected (stunting), especially in chronic (z-score less than –3 for age);

– old person trapped in a young body appearance.

Marasmus (BMI z-score less than –3). Marasmus results from the body's physiologic response to inadequate calories and nutrients. Loss of muscle mass, hypotony and subcutaneous fat stores can be confirmed by inspection or palpation and quantified by anthropometric measurements. The head may appear large but generally is proportional to the body length. Edema usually is absent. The skin is dry and thin, and the hair thin, sparse, and easily pulled out. Children may be apathetic and weak and may be irritable when touched. Bradycardia and hypothermia signify severe and life-threatening malnutrition. Inappropriate or inadequate weaning practices and chronic diarrhea are common findings. Stunting results from a combination of malnutrition, especially micronutrients, and recurrent infections. Diffusely decreased subcutaneous fat including face (monkey face), low turgor — longitudinal skinfolds, flabby dry pale skin, sparse thin dry hair, alopecia. Cognitive development is significantly delayed — affected children hardly or do not gain new skills, loose developed ones. Appetite is decreased or absent: anorexia, food intolerance (secondary malabsorption) — vomits, diarrhea. Immune deficiency often complicated with severe infections (pneumonia, sepsis) or lack of symptoms. Anemia (iron deficiency), multiple vitamin deficiencies.

Kwashiorkor. Kwashiorkor results from inadequate protein intake in the presence of fair to good caloric intake. The hypoalbuminemic state leads in pitting edema that starts in the lower extremities and ascends with increasing severity. Acute infection, toxins, and possibly specific micronutrient or amino

acid imbalances, to contribute to the etiology. The major clinical manifestation is that the body weight is near normal for age; weight alone does not accurately reflect the nutritional status because of edema. A relative maintenance of subcutaneous adipose tissue and a marked atrophy of muscle mass are seen. Edema varies from a minor pitting of the dorsum of the foot to generalized edema with involvement of the eyelids and scrotum. The hair is sparse, easily plucked, and appears dull brown, red, or yellow-white. Nutritional repletion restores hair color, leaving a band of hair with altered pigmentation followed by a band with normal pigmentation (flag sign). Skin changes are common and range from hyperpigmented hyperkeratosis to an erythematous macular rash (pellagroid) on the trunk and extremities. In the most severe form of kwashiorkor, a superficial desquamation occurs over pressure surfaces ("flaky paint" rash). Angular cheilosis, atrophy of the filiform papillae of the tongue, and monilial stomatitis are common. Enlarged parotid glands and facial edema result in moon facies; apathy and disinterest in eating are typical of kwashiorkor. The abdomen is distended, and bowel sounds tend to be hypoactive, enlarged soft liver with an indefinite edge. Lymph node and tonsils are commonly atrophic. Chest examination may reveal basilar rales. Hypoproteinemia leads to low oncotic pressure and edema. Hypotony, lack of muscles. Appetite is decreased or absent — anorexia, food intolerance (vomiting, diarrhea). Immune deficiency (Igs are proteins) often complicated with severe infections (pneumonia, sepsis). Anemia (iron and protein deficiency). Multiple vitamin deficiencies.

Mixed marasmus-kwashiorkor. These children often have concurrent wasting and edema in addition to stunting, exhibit features of dermatitis, neurologic abnormalities, and fatty liver.

Management of malnutrition.

1. Anthropometric measurements:

– length or height;

– weight;

– MUAC (Mid-upper-arm circumference);

– head circumference: skinfold over triceps; length/height and weight velocity.

2. Assessment of:

– cognitive development (developmental milestones);

– overall health (immunity status, teething, symptoms of certain vitamin-deficiencies);

– risk factors (poor social-economic state, frequent or chronic illnesses, parenting problems).

3. Assessment of growth anthropometry:

– *Percentile growth charts*: height (two years and older) / length (birth to 2 years)-for-age, weight-for-age curves/tables; BMI-for-age curves (Fig. 5.1);

– *Z-score*: height (two years and older) / length (birth to 2 years)-for-age, weight-for-age, BMI-for-age (Fig. 5.2).

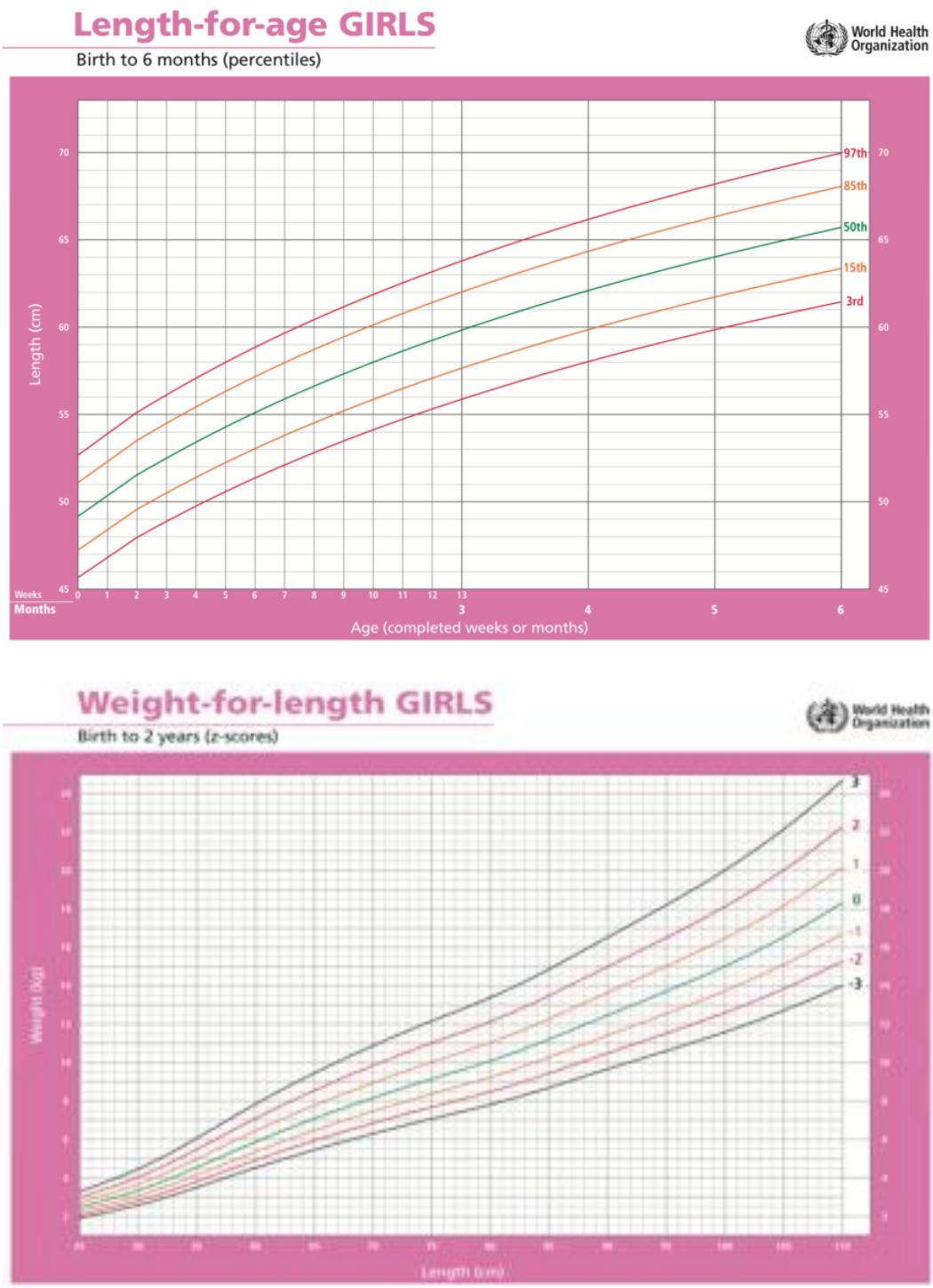


Fig. 5.1. Percentile growth charts

Fig. 5.2. Z-score growth charts

Mid-upper-arm circumference (MUAC) — less than 125 mm indicates malnutrition — good screening parameter in acute settings.

Growth assessment software applications. Desktop version: WHO Anthro Children birth to five years old; WHO Anthro Plus Children older than five years old.

Mobile App: AnthroCalc. Provide both Percentile score and Z-score for length/height for age, weight for age, MUAC and BMI for age.

To identify the underlying problem and complications: history, food diary, physical examination, labs, and investigations.

Major goal: to identify emergency conditions. Labs: CBC, Hb (infections, anemia); urine test and culture; blood biochemistry (protein, albumin, glucose, electrolytes); HIV; stool microscopy and culture; sweat test; thyroid hormones.

Investigations: chest X-ray; EchoCG; abdominal, kidney ultrasound.

Treatment of malnutrition. *Major steps:*

1. Treat the cause if possible.

2. Identify life-threatening conditions and treat them (infections, dehydration, electrolyte imbalance, severe anemia) — stabilization phase.

3. Supportive care — rehabilitation phase.

Initial stabilizations:

1. Mild (at risk) patients — not needed.

2. Moderate acute malnutrition (MAM): admit to ward

– ready to use supplementation food (RUSF) or energy dense milk formulas (F75) — 75 ccal/ml after successful passing Food tolerance test;

– oral rehydration solutions (ReSoMal);

– treatment of acute medical conditions.

Severe acute malnutrition (SAM): admit to intensive care

– ready to use therapeutic food (RUTF) or special milk formulas (F75, than F100) — 75 ccal/ml and later 100 ccal/ml after passing Food tolerance test. If fail to pass — consider tube feeding or parenteral feeding;

– parenteral rehydration solutions (IV normal saline and 5 % glucose with dotation of Potassium, Calcium as needed);

– treatment of acute medical conditions (antibiotics for infections, albumine transfusion, respiratory support).

Monitoring:

1. Body temperature.

2. Weight velocity (weight gain), adjust feeding as weight changes.

3. Blood glucose.

4. Pulse rate, breath rate.

5. Urine output, stool frequency, vomiting and adjust rehydration therapy as needed.

Further steps (rehabilitation) Diet therapy key points:

– initially decrease amount of food per single feeding and increase number of feedings than gradually decrease number and increase volume;

– always consider enteral feeding first with natural foods. Best for infants — breast milk or easily digestible energy-reach formulas (based on hydrolyzed protein);

– if fail to gain weight — enteral feeding (breast milk or milk formulas (with fortificator) or commercially available balanced formulas which can substitute single feeding) supplementation or complete enteral feeding;

– NGT feeding if fails to receive necessary amount (intermittent or continuous).

Rehabilitation. Supplementation: vitamin D, vitamin A; iron 2–3 mg/kg/day; zinc 2 mg/kg/day; folic acid 1 mg/day; normalization of GI tract microflora (probiotics); digestive enzymes (pancreatic lipase, lactase). Parenteral feeding on indications.

Always keep malnourished child: warm (ideal temperature regimen 24–26 °C); dry (change nappies as needed); happy (minimize unpleasant procedures, avoid unnecessary visits and crowdedness, noises), kangaroo posing.

The initial approach involves correction of dehydration and antiinfective (bacteria, parasites) therapy if indicated. Oral rehydration is recommended over intravenous fluid to avoid excessive fluid and solute load and resultant heart or renal failure.

When nutritional rehabilitation is initiated, calories can be safely started at 20 % above the child's recent intake. If no estimate of the caloric intake is available, 50–75 % of the normal energy requirement is safe. High-calorie oral solutions or ready-to-use therapeutic foods (a mixture of powdered milk, peanuts, sugar, vitamins, and minerals) are frequently used in developing countries. Nutritional rehabilitation can be complicated by refeeding syndrome, which is characterized by fluid retention, hypophosphatemia, hypomagnesemia, and hypokalemia. Careful monitoring of laboratory values and clinical status with severe malnutrition is essential.

When nutritional rehabilitation has begun, caloric intake can be increased 10–20 % per day, monitoring for electrolyte imbalances, poor cardiac function, edema, or feeding intolerance. If any of these occurs, further caloric increases are not made until the child's status stabilizes. Caloric intake is increased until appropriate regrowth or catch-up growth is initiated. Catch-up growth refers to gaining weight at greater than 50th percentile for age and may require 150 % or more of the recommended calories for an age-matched, well-nourished child. A general rule of thumb for infants and children up to 3 years of age is to provide 100–120 kcal/kg based on ideal weight for height. Protein needs also are increased as anabolism begins and are provided in proportion to the caloric intake. Vitamin and mineral intake in excess of the daily recommended intake is provided to account for the increased requirements; this is frequently accomplished by giving some age-appropriate daily multiple vitamins with other individual micronutrient supplements as warranted by history, physical examination, or laboratory studies. Iron supplements are not recommended during the acute rehabilitation phase, especially for children with kwashiorkor, for whom ferritin levels are often high. Additional iron may pose an oxidative stress; iron supplementation at this time is associated with higher morbidity and mortality.

In most cases, cow's milk-based formulas are tolerated and provide an appropriate mix of nutrients. Other easily digested foods, appropriate for the age, also may be introduced slowly. If feeding intolerance occurs, lactose-free or semi-elemental formulas should be considered.

Complications of Malnutrition. Malnourished children are more susceptible to infection, especially sepsis, pneumonia, and gastroenteritis. Hypoglycemia is common after periods of severe fasting but may also be a sign of sepsis. Hypothermia may signify infection or, with bradycardia, may signify a decreased metabolic rate to conserve energy. Bradycardia and poor cardiac output predispose to heart failure, which is exacerbated by acute fluid or solute loads. Micronutrient deficiencies also can complicate malnutrition. Vitamin A and zinc deficiencies are common and are an important cause of altered immune response and increased morbidity and mortality. Depending on the age at onset and the duration of the malnutrition, malnourished children may have permanent growth stunting (from malnutrition in utero, infancy, or adolescence) and delayed development (from malnutrition in infancy or adolescence). Environmental (social) deprivation may interact with the effects of the malnutrition to impair further development and cognitive function.

Overweight and obesity. The best and reliable parameter is body mass index (BMI). In younger children obesity is defined by weight-for-length — 97.7 percentile or +2 SD and more**.**

Overweight = BMI btw +1.0 +2.0 SD for age.

Obesity = BMI is more than +2.0 SD for age.

Classification. *On etiology:*

1. Exogenous: Alimentary (overconsumption + hypodynamy + predisposition).

2. Secondary (endogenous): hypotalamic; neuroendocrine disorders; medicamental (corticosteroids, antidepressants); monogenous (leptin gene mutations, etc.); syndromic (Down, Prader–Willy etc.).

Classification. *On severity:*

– overweight (BMI +1 to +2 SD);

– obesity:

- mild (BMI +2 to +2.5 SD);
- moderate (BMI +2.6 to +3 SD);
- severe (BMI +3 to +3.9 SD);

– morbid (BMI +4 SD and more).

Risk factors: family habits, large portions; addiction to junk food; “fast” carbohydrates: sweets, carbonated drinks, etc.; watching TV while taking meals; skipping breakfasts; insufficient night sleep.

Excess of nutrients intake:

– accumulation of body fat;

– low physical activity — low muscle strength, changes in body composition;

– high level of “unhealthy” lipids (low and very low density — predisposition to early atherosclerosis);

– high level of glucose in blood stimulates insulin resistance, high levels of insulin increase appetite and overconsumption;

– high blood pressure;

– fat accumulation in liver.

Note! Overconsumption doesn't exclude deficiency of certain nutrients (imbalanced, junk food). There can at the same time be protein or vitamin deficiency, mineral balance problems.

Complications:

– diabetes mellitus type 2;
– arterial hypertension;
– dyslipidemias;
– precocious puberty;
– joints problems (osteoarthrosis);
– fatty liver.

Diagnosis:

– all children with BMI greater +1 SD — check for comorbid conditions (DM type 2, dyslipidimia, AH, liver enzymes);
– children under two yo with weight for length at 97.7 percentile and higher OR early rebound of BMI should be referred to endocrinologist for assessment;
– history (birth weight and height, weight and height velocity, family history);
– physical activity;
– food diary;
– BMI, waist circumference; skin changes (striae);
– BP.

Additional methods: ECG; 24 hr BP monitoring; abdominal US; hand X-ray (bone age); hormonal studies; brain CT/MRI; molecular genetics if genetic cause is highly likely (specific phenotype), Genetic counseling; endocrinology counseling; neurological assessment; cardiologist counseling; parental height and weight.

Treatment. If overweight or mild obesity w/o complications:

– encourage healthy diet and appropriate physical activity;
– do not aim to achieve ideal body weight;
– gradually change diet to work out healthy food habits (Fig. 5.5);
– discuss which foods can be substituted by less "unhealthy";
– may propose to dilute juice with half-water;
– change salad dressings to less fatty.

Treatment: moderate to severe obesity. Aim: loose weight.

Therapeutic diets should be introduced stagely:

1st stage — initial. Transitional period for better adaptation 8 to 10 days of physiological balanced diet with Proten : Fat : Carb ratio 1 : 1 : 4.

2nd stage — therapeutic diet.

Decreased caloric intake by 20–30 % from normal for age:

– limited fat (25–30 % of daily caloric intake, saturated) and "fast" carbohydrates;
– protein normal per age (adolescents — exceeds by 10 % recommended for age);
– increase number of meals (3 main and 2 additional with snakes);
– majority of calories consumed in the first half of a day;

– decrease periods of non-activity (TV, gadgets, computer games);
– walk instead of drive, step rather than using elevator.
Physical activity. Sports: swimming, bicycle, dancing, yoga.

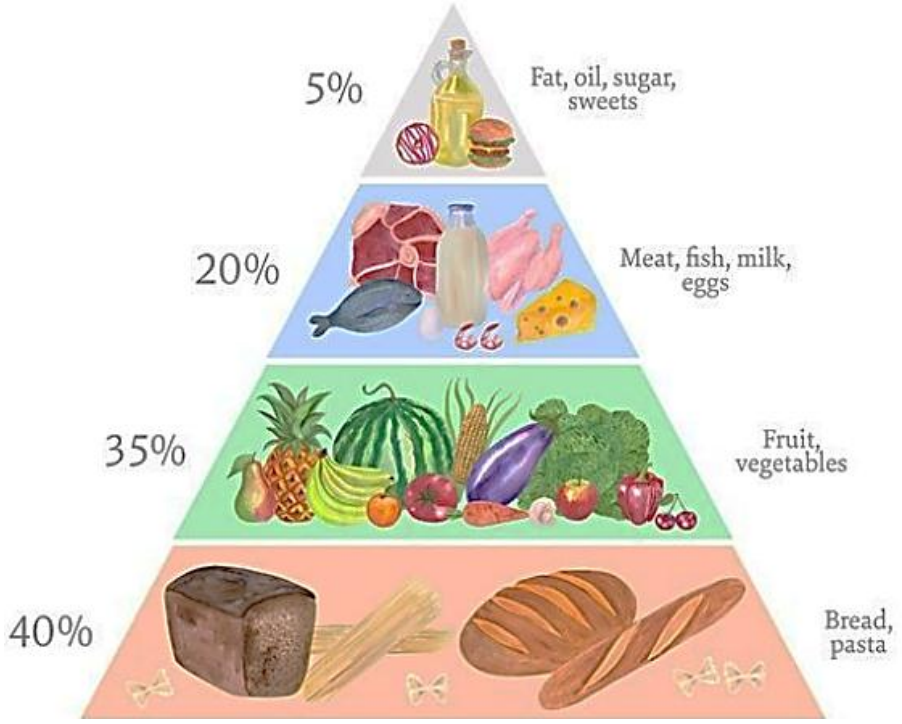


Fig. 5.3. Healthy food pyramid

In severe complicated obesity if diet is not effective:
– central acting agents (decrease appetite);
– peripheral acting (metformin, orlistat) — decrease insulin production or absorption of lipids.
– prevention:
– parents and children education;
– careful assessment and monitoring of all families to identify those at risk;
– growth assessment and follow up;
– community measures — decrease availability of junk foods and sweet drinks;
– promotion of healthy life-style and diet.

CHAPTER 6
RICKETS

Definition and history. Rickets is a disease of early-aged children, caused by a temporary mismatch between the needs of the growing body of the child in phosphorus and calcium deficiency and systems which ensure their delivery. Rickets is characterized by impaired mineralization of the rapidly growing bones and functions of the leading organs and body systems.

Rickets was known in antiquity. The first mention of rickets was found in the writings of Soranus of Ephesus (98–138 yrs.) and Galen (131–211 yrs.). The first medical description of rickets belongs to the British anatomist and orthopedic F. Glisson (1650). Due to the high prevalence of rickets in England this disease was called "the English disease", "rickets" (from old English "wrickken" — bend) or Glisson's disease. Later F. Glisson changed name to the Greek "rhachitis" (spine), based on the presence almost in all patients' significant spinal deformation.

Frequency:

1. Rickets is "a disease of the growing organism" as it affects children during one of the "fastest growing" age periods — from 2 months to 3 years old.

2. During the 1st year of life child increase body weight from birth weight 3–3.5 kg till 10–12 kg (triple) and body length from birth length 50–54 sm till 75–78 sm (50 %).

3. During the 1st year of life from 56 % to 80 % of children suffer from rickets.

Etiology. Rickets is understood as a polyethological metabolic disease, caused by the combined influence of many endogenous and exogenous causes as well as predisposing factors, acting both prenatally and postnatally, on mother's and child's side.

Influencing factors:

– deficiency of vitamin D or insufficient intake of vitamin D with food (leads to the lack of formation of cholecalciferol (vitamin D3) in the skin);

– insufficient intake of calcium and phosphorus;

– increasing function of the parathyroid glands;

– impairment of renal function;

– disturbances in the endocrine system which regulates Ca^{2+} and P^{3+} metabolism;

– variations in micro elemental status.

Predisposing factors. From mother's side:

– maternal age less than 17 and more than 35 years;

– gestosis of pregnancy;

– extra genital pathology (metabolic diseases, GI tract pathology, kidneys diseases);

– defects nutrition during pregnancy and lactation (protein deficiency, Ca, P, vit D, B1, B2, B6);

– day regimen (lack of insolation and physical activity);

– complications during delivery;
– poor socio-economic conditions.

From child's side:

– time of birth — autumn, winter (lack of sunlight);
– prematurity, morpho-functional immaturity;
– large birth weight (more than 4 kg);
– large weight gains during the first 3 months of life;
– breast-feeding, but the human-and long standing milk of nurse;
– early artificial and mixed feeding with non-adapted milk formulas;
– lack of exposure to fresh air;
– lack of physical activity (tight swaddling, lack of exercise therapy and massage);
– perinatal encephalopathy with lesions of the III ventricle;
– skin, liver, kidney diseases, malabsorption syndrome;
– frequent respiratory tract and intestinal infections;
– anticonvulsant medications;
– large quantities of cereals and vegetables consuming.

Endogen synthesis and transformation of vitamin D. Vitamin D was discovered in 1922 by Mc. Collum, later the opportunity to study its specific action on bone, muscle, intestine and renal tubules was found. Adequate Vit D intake, positive calcium balance and outdoor physical activity are essential for appropriate skeletal growth and bone mineralization. These environmental factors also show a liability to reduce risk of several diseases. A diverse diet rich in food containing large amounts of Vit D, including oily fish, is important. Main sources of Vit D: fish oil (150 IU/ml), egg yolk (20–50 IU/ yolk), caviar (3.2 IU/g), cow's milk (0.4–1.2 IU/100 ml), Infant formula (beginning formula 40–50 IU/100 ml; follow-up formula 40–80 IU/100 ml).

If the additive effect of dietary Vit D consumption and sunlight-induced Vit D synthesis in the skin is insufficient, taking supplements becomes essential to achieve optimal Vit D status. Most Vit D in the human body is produced in the skin after exposure to sunlight, specifically solar Ultraviolet-B irradiance. In Central Europe, solar angle and weather conditions suitable for Vit D synthesis occur between late April and early September; whereas skin synthesis does not occur from October to March. The efficacy of skin synthesis basically depends on two factors: the degree of skin pigmentation and age. For optimal effect, Central Europeans should expose, without sunscreen, 18 % of the body surface (i.e. uncovered forearms and partially exposed legs) to a half of one minimal erythemal dose two or three times per week. In practical terms, exposing 18 % of the body to the sun without sunscreen for approximately 15 minutes a day between 10 a.m. and 3 p.m. is likely to be adequate for fair-skinned Central Europeans.

Metabolism of vitamin D. Our body produces several metabolites of vitamin D but only 2 of them actively influence the metabolism of Ca^{2+} and P^{3+}: 1.25 dihydroxycholecalciferols and $24.25(OH)_2D_3$. In terms of normocalcemia

and hypercalcemia 24.25$(OH)_2D_3$ (mainly synthesized in kidneys) is formed. The formation of 1.25$(OH)_2D_3$ or calcitriol occurs under conditions of hypocalcemia. The process of vitamin D synthesis has some stages (Fig. 6.1).

1. Vitamin D is absorbed in the proximal part of the small intestine, necessarily in the presence of bile.

2. In the liver under the influence of 25-hydroxylase 25-hydroxyvitamin D or calcidiol is formed. The stock accumulates in muscle tissue and fat layer, the excretion of 25$(OH)D_3$ through the bile initially low, which leads to the accumulation of 25$(OH)D_3$ in the liver.

3. At the kidney level the formation of 1.25$(OH)_2D_3$ occurs under the influence of 1-hydroxylase enzyme (in the kidneys proximal tubular cells).

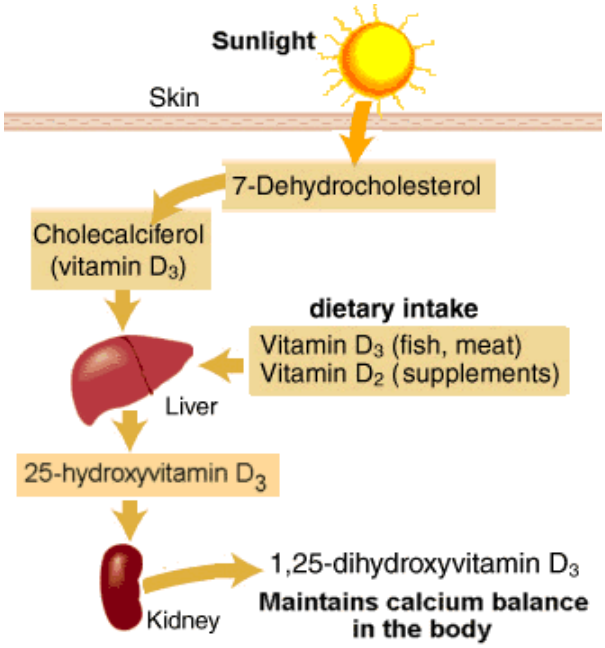


Fig. 6.1. Metabolism of vitamin D. Adopted

Role of metabolites of vitamin D:

– increases permeability of enterocytes cell membranes for Ca^{2+};

– stimulates the synthesis of Ca^{2+}-binding protein which provides transport of Ca^{2+} ions from enterocytes into the blood;

– stimulates the absorption of P^{3+} in the intestine;

– enhances the reabsorption of Ca^{2+} and P^{3+};

– stimulates the differentiation and proliferation of osteoblasts and chondrocytes which leads to protein synthesis increasing by the cells of the connective tissue — collagen;

– stimulates osteocalcin synthesis — the basic non-collagenous protein of bone tissue.

Role of Ca^{2+} in the body:

– is the basis of the skeleton;

– involved in processes of blood clotting; protein synthesis, cell division and differentiation; immunogenesis;

– involved in myocardial contraction, automatism of the heart;
– transmission of nerve impulses;
– regulation of membrane permeability;
– stimulation of the activity of certain enzymes;
– secretion of hormones.

Ca^{2+} concentration in blood is *from 2.1 to 2.8 mmol/l* and don't vary by more than 3 % due to hormonal control. The main mass of Ca^{2+} is concentrated in the bone skeleton where the Ca phosphate (85 %), carbonates (10 %), salts of organic acids (citric and lactic (about 5 %)) are represented. 50 % of the Ca^{2+} in the blood bound to plasma proteins, mainly to albumin. Ionized Ca^{2+} concentration in serum is *1.1–1.4 mmol/l*. Free Ca^{2+} is a regulator of a variety of intracellular processes and it ensures the implementation of a specific transmembrane signal into the cell. Elevated levels of ionized Ca^{2+} is lead to the increase synthesis of calcitonin (thyroid hormone) which reduces the number and activity of osteoclasts, enhances deposition of Ca^{2+} into the bone, increases Ca^{2+} excretion by the kidneys and works as the antagonist of parathyroid hormone (PTH).

Currently vitamin D is considered as steroid pregormon. Its activity is provided by specific receptors (VDR) in many organs and tissues, suggesting about integrated D-endocrine system in the body. Recently synthesis of the active form $1.25(OH)_2D_3$ is discovered. It directly exposed to ultraviolet irradiation in the skin. It promotes the synthesis of the antimicrobial protein cathelicidin with eliminating effect on Gr– microflora which is the important component of the anti-infectious immunity of the skin.

Main functions of vitamin D:
– maintaining mineral homeostasis;
– involved in the metabolism of lipids;
– maintaining the concentration of electrolytes and energy metabolism;
– participation in the maintenance of adequate bone mineral density;
– regulation of hair growth;
– stimulation of cell differentiation;
– inhibition of cell proliferation;
– implementation of immunological reactions;
– regulation of blood pressure.

A whole cascade of metabolic disorders develops with insufficient intake of vitamin D from food or its low synthesis. Scheme of pathogenesis of rickets is in the Fig. 6.2.

An important role in the pathogenesis is assigned to PTH which is activated in rickets. Its effect on kidneys and bones is as follows:
– increasing the tubular reabsorption of Ca^{2+} and Mg^{2+};
– decreasing reabsorption of potassium, non-organic P^{3+} and HCO_3^-;
– decreasing excretion of protons and ammonium ions;
– increasing the ability to form the active form of vitamin D — $1.25(OH)_2$;
– inhibition of collagen synthesis in active osteoblasts;

– activation of osteoclasts osteolysis;
– acceleration of maturation of osteoblasts and osteoclasts progenitor cells;
– the consequence of these effects is the mobilization of Ca^{2+} from the bone (release in the blood) and the depletion of matrix with collagen and proteoglicans.

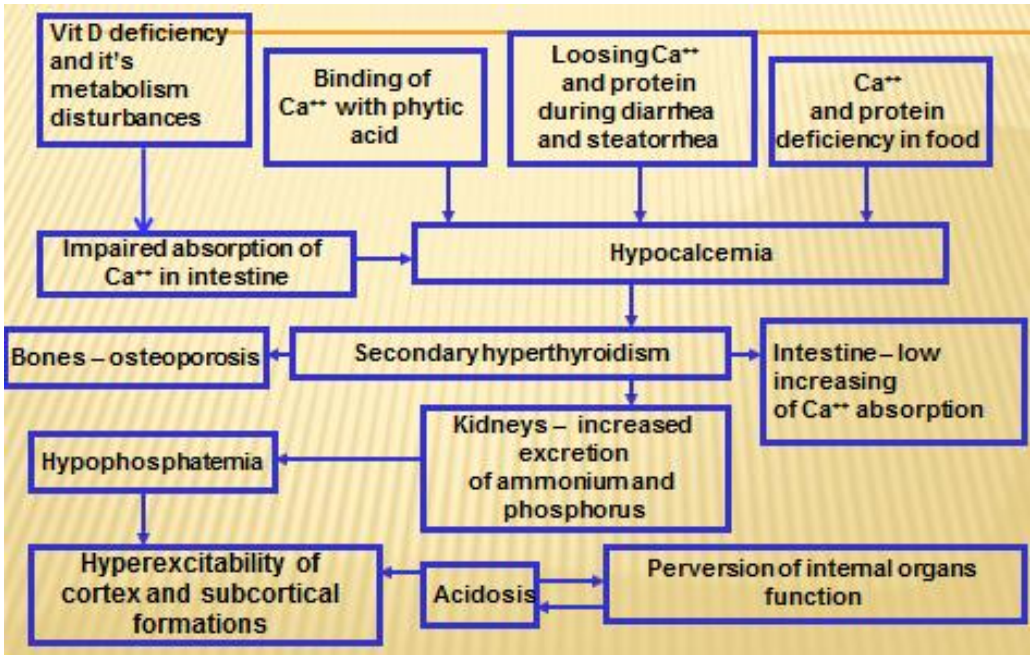


Fig. 6.2. Pathogenesis of rickets

It should be noted acidosis retains P^{3+}-Ca^{2+} salts in the dissolved state, and then prevents impregnation of cartilage and osteoid tissue. Accumulation in the blood serum of acidic products of metabolism at the same time with decreasing the level of Ca^{2+} impairs the function of the CNS and autonomic nervous system and increases their excitability. Upon cleavage of the pyruvic acid, the series of intermediate oxidized products are formed, one of which is the citric acid. Citrates form soluble compounds with Ca^{2+} and transport it from the bone into the blood and back again. Citric acid is also enhancing the reabsorption of P^{3+} in the kidneys.

Classification of rickets:

Stages of the disease:
– initial;
– clinical sings;
– recovery;
– residual sings.

Grade of severity:
– I grade — mild;
– II grade — moderate;
– III grade — severe.

Course:
– acute;
– sub-acute;
– relapsing.

Biochemical option:

– low Ca^{2+} level (Ca-penic);

– low P^{3+} level (P-penic);

– without Ca and P abnormalities.

Some diseases and conditions can lead to secondary rickets, e.g. malabsorption syndromes, chronic kidney disease, biliary tract pathology, metabolic diseases (tyrosinemia, cystinuria), hereditary diseases (vitamin D-resistant rickets), prolonged use of anticonvulsants (phenobarbital), diuretics, corticosteroids, parenteral nutrition.

Clinical signs of rickets depend on grades, course and biochemical changes but there are basic signs (Fig. 6.3).

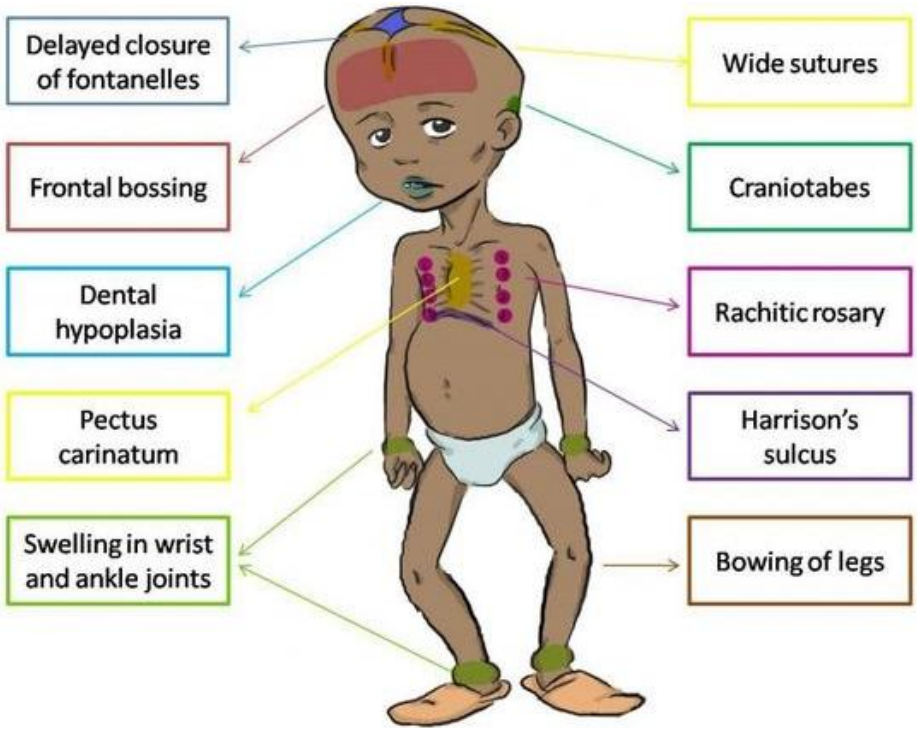


Fig. 6.3. Ten important clinical features of rickets. Adopted

Rickets I grade (mild) is characterized by a minor disturbance of the general state:

– restlessness; sweating; red dermographism;

– moderate hypotonia (constipation);

– initial bone changes — craniotabes (Fig. 6.4), flattening the occipital part of the head (Fig. 6.5) and a slight expansion in the areas of osteoid tissue growth (rosary).

Rickets II degree (moderate) is characterized by:

– impaired general condition and moderate changes in the nervous, muscular systems: hypotension, enlarged "frog belly" (Fig. 6.6), high standing of a diaphragm, slight enlargement of the liver and spleen, mild anemia;

but more pronounced changes in the bones: parietal bumps, rachitic "beads"; "bracelets", "string of pearls", spreads the lower thoracic inlet in the form of "hat brim", "Harrison's sulcus".

Fig. 6.4. Craniotabes in child with rickets

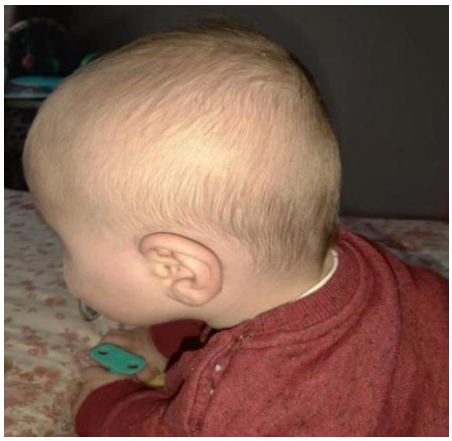


Fig. 6.5. Flattening the occipital part of the head

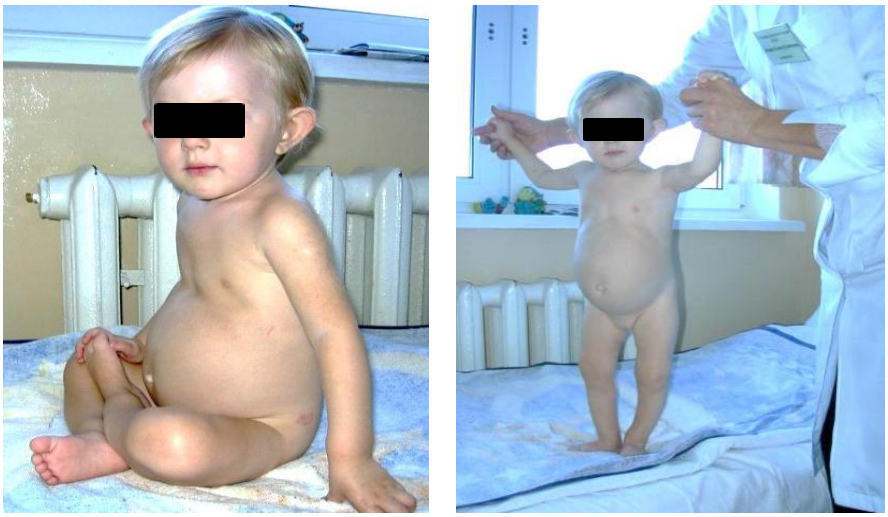


Fig. 6.6. Musular hypotonia and “frog belly”

Rickets III degree (severe) is characterized by severe skeletal deformities: “square” shape of the skull, increasing the frontal, occipital tubercules, “olympic” forehead, “saddle” nose, breaking the terms of teething, bite, chest deformity (“chest cobbler” and “chicken” chest (Fig. 6.7), kyphosis, lordosis, scoliosis), thecurvature of the long bones (Fig. 6.8), “flat” pelvis, atony of muscles, joint laxity and ligaments, and static disorder of motor function.

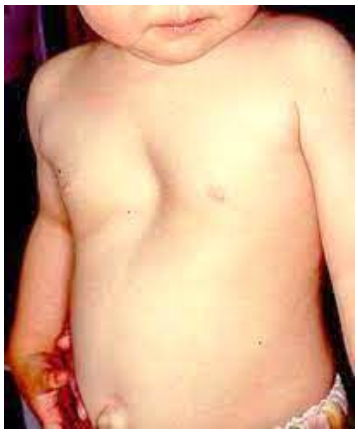


Fig. 6.7. “Chest cobbler”

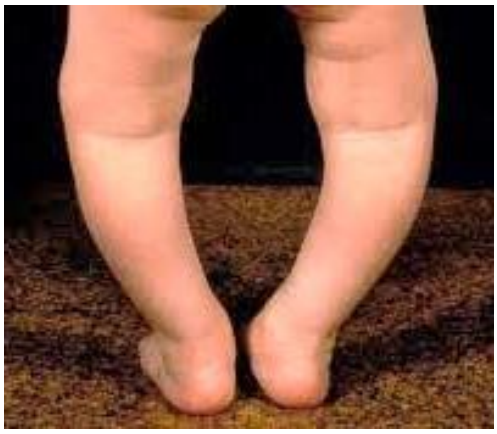


Fig. 6.8. O-like bending the legs

Enlargement of the liver and spleen in rickets is associated with metabolic disorders, anemia and congestion in the portal and splenic veins. Heart and diaphragmatic muscles hypotonia, degenerative changes in the myocardium and electrolyte disturbances lead to a weakening of the heart, decreased BP, tachycardia, moderate expansion of the heart borders, soft systolic murmur. Due to severe hypotension of intercostal muscles, diaphragm and muscles of the bronchi hypoventilation develops what together with acidosis creates a predisposition to develop pneumonia. Changes in immunobiological properties of the organism get children sick easily with infectious diseases which occur for a long time and in a more severe form. Decrease in activity of gastrointestinal enzymes leads to poor appetite and malabsorption of nutrients from intestine which together with abdominal muscles hypotension causes an increase of the abdomen volume ("frog belly") and slow bowel movement (constipation). A change in the blood (decrease of Hb and red blood cell count) is associated with dysfunction of the bone marrow.

Acute course is observed mainly in children in the first 6 months of life, mostly in preterm and overweight, who did not receive vitamin D as a prophylactic measure.

Subacute course is characterized by a slow development of symptoms, mild neurological and autonomic disorders, prevalence of osteoid hyperplasia on osteomalacia and deviations of biochemical parameters. This usually occurs in children older than 6 months.

Relapsing course is observed in frequently ill children with inappropriate diet when you stop to give vitamin D after the treatment of rickets. This type of course is characterized by periods of exacerbation followed by periods of remission. Bone X-ray reflects the formation of new bands of calcification in the metaphysis.

Ca-penic version of rickets is characterized by severe disorders of the autonomic nervous system (sweating, red dermographism, tachycardia), increased neuro-reflex excitability (hand tremor, sleep disturbances, unwarranted anxiety, vomiting, bowel dysfunction). There is an acute variant. There is a significant reduction in ionized Ca^{2+}, high levels of PTH, decreased calcitonin in the blood. *P-penic version* of rickets is associated with significant bone deformities: a distinct thickening of the metaphyseal regions of long bones of hands, sternal ribs and the presence of different strains of the skull. Motor retardation, severe hypotonia, abdominal enlargement, weak ligaments and articular apparatus, expressed hypophosphatemia, high levels of PTH and calcitonin, hyperfosfaturia also are typical. *Without Ca and P abnormalities version* is characterized by the severity of the frontal and parietal mounds in the absence of distinct changes in the nervous and muscular systems. In blood there is a moderate increase in the level of PTH at normal calcitonin. Ambiguous indicators of the level of Ca^{2+} and P^{3+} in the blood during the period of significant clinical signs are explained by multidirectional calcitonin concentration in the serum.

Diagnostics of rickets. There are 2 groups of diagnostic methods.

1. *Main methods*:

a) blood analysis (could be anemia);

b) urine (normal);

c) blood biochemistry: Ca^{2+} and ionized ones, P^{3+} (normal 1.3–1.8 mmol/l), alkaline phosphates (normal 140–320 U/l);

d) Sulkovich's analysis (weekly positive or negative).

2. *Additional methods:*

a) blood pH;

b) 24 hours urinary excretion of Ca, P (elevated);

c) active vitamin D metabolites ($25(OH)D_3$ in blood serum 15–25 ng/ml);

d) serum level of PTH (increased).

Changes in indicators depend on the stage of rickets and are presented in the Table 6.1.

Table 6.1

Dynamics of biochemistry parameters

Stage of the disease	**Serum Ca^{2+}**	**Serum P^{3+}**	**Alkiline phosphates**	**pH blood**	**pH urine**
Initial	N	N or moderate↓	↑	Metabolic acidosis	↑
Clinical signs	↓	↓	↑	Metabolic acidosis	N or ↑
Recovery/residual signs	Moderate ↓ or N	N or ↑	N	Metabolic acidosis	N

Instrumental methods, e.x. X-ray bones, also can be used for diagnostics of rickets. X-ray signs of rickets are presented in Table 6.2.

Table 6.2

X-ray signs of rickets

Stage of the disease	**X-ray changes**
Initial	Absent
Clinical signs	Osteoporosis, goblet metaphyseal extension, blurred and fuzzy zones prior to (preliminary) calcification, the epiphysis becomes saucer-shape, the nucleus of ossification identified indistinctly
Recovery/residual signs	Uneven sealing growth zones (fringed), the appearance of lines prior to (preliminary) ossification

Differential diagnosis of rickets. Rickets is manifested by quite vivid clinical symptoms and specialists are well acquainted with this disease that allows in most cases to timely and correctly verify the diagnosis. But there are diseases with phenotypic similarity to rickets which require differential diagnosis:

– vitamin D-resistant rickets;

– vitamin D-dependent rickets;

– renal tubular acidosis;

– Fanconi syndrome;

– hyper- and hypophosphatasia;
– chondrodystrophy;
– Blount's disease;
– hypothyroidism.

Treatment. Treatment of rickets should be comprehensive, timely, long-term and individually selected. Today, various schemes for the treatment of rickets are used in the world. But there isn't a single and internationally recognized program of treatment. An integrated approach to the treatment of rickets includes the elimination of vit D deficiency, the normalization of P-Ca metabolism, the elimination of metabolic disorders and the correction of vegetative disorders.

Specific therapy: vit D at dose 2000–5000 IU daily during 30–45 days. Treatment starts with 2000 IU for 3–5 days and after if tolerated, increase the dose to an individual aspect under the supervision of medical Sulkovich's test. Test is carried out before treatment and then every 7–10 days. Dose of 5000 IU is administered only when significant bone changes occurred.

When results are good (normalization of muscle tonus and vegetative nervous system, levels of alkaline phosphatase, Ca and P in the serum, disappearance of craniotabes) treatment is discontinued and the dose is reduced to preventive. Antirecurrent treatment is carried out at risk children (vit D_3 at dose of 2000–5000 IU for 3–4 weeks) 3 months after the end of the first course, except for the summer months. Medications of vit D which can be used for therapy of rickets are presented in Table 6.3.

Table 6.3

Medications of vitamin D

Name and form of medication	The content of D
Aqvadetrim Vitamin D3 (cholecalciferol), aqueous solution (Medana Pharma Terpol group, Poland)	1 ml (30 drops) — 15 000 IU, flacon — 10 ml, 1 drop — 500 IU
Videchol (D3 oleosum solution) 0.125 % (Russia)	1 drop — 500 IU, 1 ml — 25 000 IU
Ergocalciferoli oleosum solution (vit D2) 0.0625 %	1 drop — 625 IU, 1 ml — 25 000 IU
Ergocalciferoli oleosum solution (vit D2) in capsules	1 caps. — 500 IU
Vit D2 oleos 0.125 %	1 drop — 1 250 IU, 1 ml — 50 000 IU
Vigantol (cholecalciferol), oleos (Merck KGaA, Germany)	1 ml — 20 drops (20 000 IU)
Oxidevit (synthetic analogue, 1.25 $(OH)_2D_3$)	1 caps. — 500 IU

Non-specific therapy:

• For children older than 6 months in the complex of therapeutic interventions should be included therapeutic baths (alternate day, 10–15 procedures on the course).

• Pasty, sedentary children are recommended salt baths (2 big spoons of see salt per 10 liters of water, the temperature of water 35–36 °C duration 5 min), for irritable — conifers (1 tea spoon of extract for 10 liters of water, temperature of water 36 °C duration 10 min).

• At remission process in bone but not earlier than 3 weeks after the start of therapy with vitamin D massage is recommended.

• Magnesium in order to normalize the function of the parathyroid glands and reduce vegetative disorders (Asparkam, Pananginum).

• Antioxidants to normalize the process of lipid peroxidation (vit E and A, Vetoron, Qudesan).

• Medications for improving metabolic processes (Potassium orotate, Carnitine chloride) during 4–5 weeks.

• Premature babies require the concomitant use of Ca^{2+} supplements in dose 55–60 mg/kg/day for 2–3 weeks, for children of the 2nd year of life a diet rich in calcium is recommended.

• Citrate mixture (acidi citrici 2.1; natrii citrici 3.5; aquae destillatae ad 100) 1 tea spoon 3 times per day for 10–14 days.

Prevention of rickets. Prevention of rickets can be antenatal (non-specific and specific) and postnatal (non-specific and specific).

Antenatal non-specific prevention includes observation of pregnant women in antenatal clinics, correct day regimen enough (at least 2–3 hours a day) stay of a pregnant woman on the fresh air, proper nutrition with adequate dietary vitamins, calcium, protein and etc. *Antenatal specific* prevention inserts prescription for women with 28–32 weeks of pregnancy vit D (in normal pregnancy 500 IU). When a woman has extragenital or obstetric pathology she must take 1000–1500 IU of vit D per day for 8 weeks regardless of the time of year. Prescription of vit D for pregnant women at an earlier date is impractical because it may contribute to damage of the placenta.

Postnatal non-specific prevention includes breast feeding or adapted formulas (only in breast milk ratio of Ca : P is optimal 2 to 1), prescribtion for the whole lactation period multivitamin medications (Pregnavit, Materna), introduction of complementary foods in time, active movements (massage, gymnastics), sufficient exposure to the fresh air, day regimen, adequate dressing baby, tempering. *Postnatal specific* prevention in term infants is held till 3 years of life. Vit D is prescribed for full-term children who are breast-fed from 3–4 weeks of age at a dose of 500–1000 IU daily. Children at risk for rickets are recommended daily prescription of vit D 1000 IU in the autumn-winter-spring period during the first 3 years of life. In case of artificial feeding daily prophylactic dose is prescribed considering vitamin D, contained in the formula (1 liter of a formula contains 10 micrograms of vit D which is equivalent to 400 IU).

Spasmophilia. Spasmophilia/rickets or infantile tetany (from Greek "spasmos" — convulsions and "philia" — predisposition) — a pathological condition that occurs in patients with rickets in the first 6–18 months of life. It's a special form of disorders of Ca^{2+} and P^{3+} characterized by signs of increased neuromuscular excitability with a predisposition for spasms and convulsions (seizures).

Pathogenesis. The main reason of spasmophilia is the decreased level of ionized Ca^{2+} on the background of hyperphosphatemia and alkalosis that leads to seizures.

Seizures can be provoked by:

– any infectious process, high fever;

– hyperventilation (a shift to the alkalosis);

– repeated vomiting due to non-infectious and infectious diseases of the gastrointestinal tract;

– strong crying, irritation, fear and other factors that reduce the level of ionized Ca^{2+} in the blood.

Classification and clinical symptoms. There are two clinical forms of spasmophilia: asimptomatic and obvious.

Asimptomatic spasmophilia usually precedes obvious ones so it must be diagnosed on time. Chvostek's, Erb's, Trousseau's, Maslov's and Lust's symptoms are the most common symptoms of asimptomatic spasmophilia.

• Chvostek's symptom — a contraction of the facial muscles appears when tapping between the zygomatic arch and the corner of the mouth (Fig. 6.9).

• Erb's symptom — a muscle contraction when the cathode applied to the area of the median nerve is opened.

• Trousseau's symptom — a convulsive contraction of the fingers occurs in the form of an "obstetrician's hand" when the neurovascular plexus on the shoulder is compressed (Fig. 6.10).

• Maslov's symptom — a respiratory arrest is noted at the height of inspiration with a slight prick of the skin.

• Lust's symptom — a rapid abduction of the foot outward with its dorsiflexion when tapping below the head of the fibula (Fig. 6.10).

Fig. 6.9. Chvostek's symptom

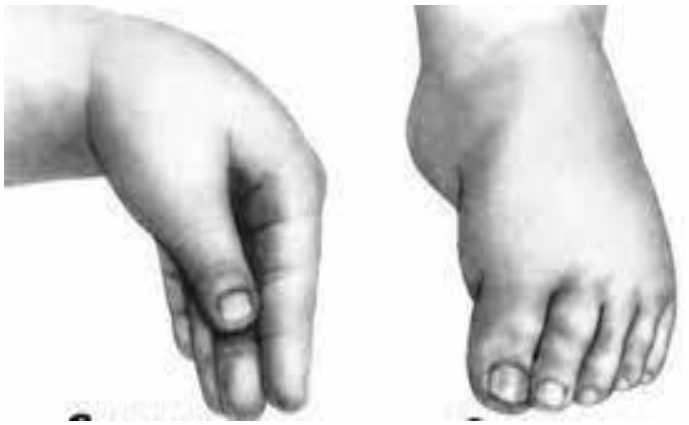


Fig. 6.10. Trousseau's and Lust's symptoms

Obvious spasmophilia, as a rule, manifests in the form of laryngospasm, carpopedal spasm and eclampsia (sometimes in combination with each other).

• Laryngospasm — a convulsive spasm of the glottis on inspiration, accompanied by a "cock's cry" and cyanosis.

• Carpopedal spasm — a tonic contraction of limb muscles mainly in the hands ("obstetrician's hand" and "horse's foot").

• Eclampsia — tonic and clonic convulsions with loss of consciousness that occur when the temperature rises or in a healthy condition.

Differential diagnostics is carried out with convulsions of another etiology: febrile convulsions, hypoglycemia, hypoparathyroidism (congenital or acquired), pseudohypoparathyreosis, hypomagnesemia, epilepsy.

Treatment of spasmophilia:

– Diazepam (0.5 % 0.1 ml/kg (no more than 2 ml per injection);

– Oxybutiric acid (IV or IM 20 % at dose 0.25–0.5 ml/kg);

– Phenobarbitali per os or per rectum at single dose 0.005–0.015 g;

– Immediately determination of Ca^{2+} level in the serum and after IV slowly 10 % Calcium gluconate 0.5 ml/kg;

– after 10 % Calcium gluconate per os 1 tea spoon 3 times daily after meal 7–10 days;

– therapeutic dose of vitamin D when the Ca level in blood came to normal;

– in laryngospasm provide access to fresh air and create a dominant focus of excitation by irritating the nasal mucosa, skin, vestibular apparatus and changing body position.

Hypervitaminosis D. *Pediatricians say: "It is better to have a major (large) rickets than little hypervitaminosis D".*

Hypervitaminosis D is a multi-organ disease resulting from both the direct toxic effect of the vitamin on cell membranes and the consequences of hypercalcemia. Hypervitaminosis D occurs when Vit D overdosed or individual hyper sensitivity to it happened. Intoxication of Vit D is not a common case in pediatrics. Vit D supplements are sold as over-the-counter drugs (medications that can be purchased without a prescription from a healthcare provider); however, there is a lack of public education about the permissible limits of Vit D intake which may lead to vitamin D toxicity. Vit D toxicity refers to serum 25(OH)D levels when the level exceeds 100 ng/mL (250 nmol/L) or is defined as hypervitaminosis D.

Pathogenesis. Due to a significant increase in Ca^{2+} absorption in the intestine hypercalcemia and hypercalciuria developed. They are accompanied by deposition of Ca^{2+} in the vessel wall with irreversible calcification of internal organs. Under the influence of the active metabolites of vit D Ca^{2+} and P^{3+} leached from the bones and formed osteoporosis (activates osteoclasts). The accumulation of salts in the newly formed bone, cortical thickening and new nuclei of ossification is enhanced since excess vit D inhibits the activity of parathyroid glands.

Vit D in high dose has a direct toxic effect on cells, enhancing lipid peroxidation and free radical formation which gives the instability of cell membranes including lysosomal and mitochondrial ones. Both processes — a direct toxic effect on the cells of the endocrine glands and growing hypercalcemia — lead to the involution of thymus and all lymphatic system and later to the gradual development of pluriglandulas failure. It causes a sharp decrease in the body's defenses and joining a variety of secondary infections.

Classification. *Stages of the disease:*

– initial;

– clinical sings;

– recovery;

– residual sings.

Grade of severity: I grade — mild, II grade — moderate, III grade — severe.

Course: acute (up to 6 months), chronic (more 6 months).

Clinical syptoms. *Acute intoxication* with vit D is more frequent in children of the first 6 months of life with an overdose of vit D in a relatively short period of time (2–3 weeks) or individual hypersensitivity to vit D. There are signs of neurotoxicity or exicosis: reduced appetite, thirst, vomiting, severe dehydration and rapidly decreased body weight, toxycosis, constipation (possible unstable and loose stools). Tonic-clonic seizures also can be.

Chronic intoxication with vit D occurs on the background of long-term (6–8 months or more) of vit D usage in moderate doses. The clinical picture includes increased irritability, poor sleeping, fatigue, joint pain, poor weight gain, premature closure of the large fontanelle and changes in the cardiovascular and urinary systems.

Treatment.

• Treatment of hypervitaminosis D is carried out in a hospital.

• Stop vitamin D, administered vitamins A (5000–10 000 IU/per day) and E (5–10 mg 1–2 time per day) 10–12 days.

• Infusion IV therapy in combination with diuretics (furosemide 0.5–1 mg/kg per day).

• In severe cases a short course of prednisolone can be used (5 mg/kg IV slowly until the patient's condition improves, then 1–2 mg/kg per day per os).

Outcome is serious: blood vessels calcification, development of nephrocalcinosis, chronic pyelonephritis with subsequent chronic renal failure.

CHAPTER 7
ALLERGIC DISEASES

7.1. FOOD ALLERGY

Etiology. Pathogenesis. Food hypersensitivity reactions are defined as adverse reactions caused by the intake and ingestion of a dietary substance and can be caused by a wide range of mechanisms. They are commonly reported; 20–25 % of adults have reactions to food. With symptoms that affect both children and adults from mild itching, stomach pain, and rash to severe anaphylaxis, it leads to anxiety and food restrictions for many patients and families.

While some hypersensitivity reactions are found more commonly in young children, such as reactions due to milk and egg allergy, and are usually outgrown, others accelerate in adulthood, such as decreased activity of the lactase enzyme and reactions to biogenic amines. Dose, timing of intake, co-existing factors such as pollen, infections, and exercise might aggravate allergic IgE antibody (IgE-ab)-mediated reactions. The origin and mechanisms behind food hypersensitivity and food allergy are identified to a varying extent, and both types can be co-existing. Food reactions can be categorized in different ways, but most commonly divided into toxic and nontoxic reactions, where the nontoxic can be divided into immunologic and nonimmunologic reactions (Fig. 7.1). Immunologic reactions can be further divided depending on the type of reaction. A thorough patient history, food diaries, food challenges, food elimination, blood sampling for specific IgE-ab, and skin prick test (SPT) are commonly used as diagnostic tools.

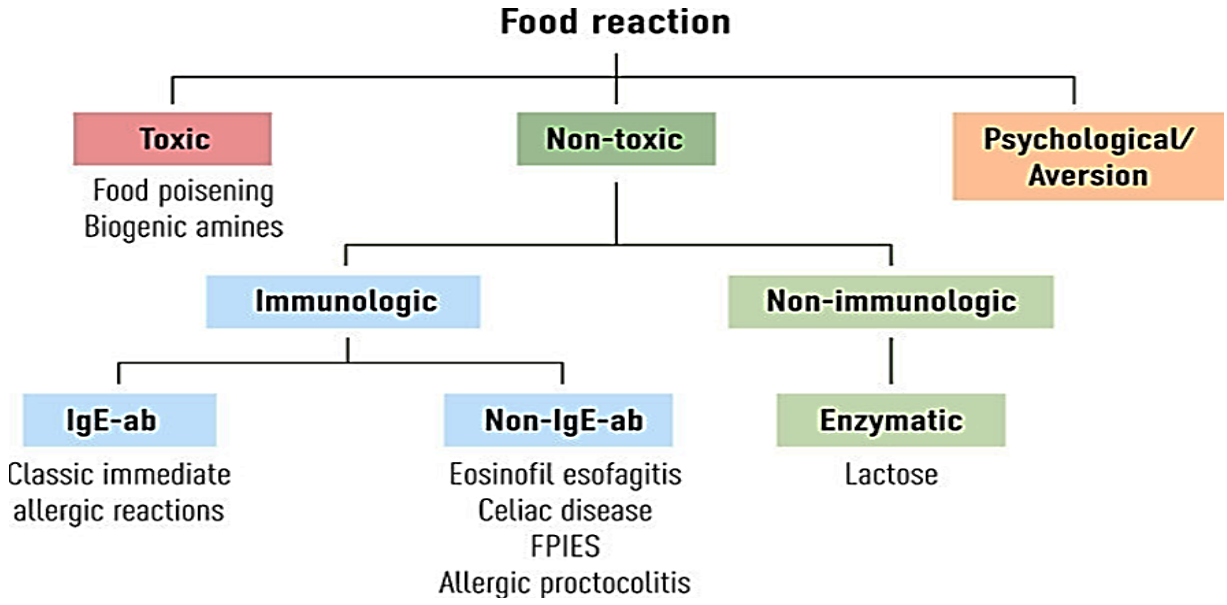


Fig. 7.1. Food reaction

Several theories behind food allergy development have been discussed; one of the most mentioned and studied is the hygiene hypothesis, established in 1989 by Strachan, UK. He found that children in families with many older siblings expressed atopic diseases to a lower extent than those living in smaller families

did, proposing that the shift from the earlier rural living conditions with many children to a more clean, dry, dust-free environment caused less exposure to microbes and allergens through the air, food, and water, thus leading to less stimulation of the immune system and thereby promoting development of atopic diseases. Other factors than older siblings e.g., being born vaginally, being exposed to viruses and infections, for example, through day care, and having furry pets at home — have been discussed as being protective.

Another proposed mechanism is the dual barrier hypothesis, where an infant with dry skin and eczema has an impaired skin barrier, enabling allergens to more easily penetrate the skin and exposing the immune system to food allergens in another way than the preferred oral introduction, facilitating the development of food sensitization and further on, food allergy. One third of infants with eczema are found to have a food allergy at the age of 1 year and they have also been found to have an increased prevalence of filaggrin gene mutations.

An additional theory that has been discussed is the fact that food allergies tend to be more prone in areas further from the equator and thus less exposed to sunlight, leading to lower levels of Vit D, a factor found in some studies to be associated with food allergy, as well as birth season. Studies from Australia, a country with a high incidence of food allergy and where low Vit D levels are common possibly due to sun avoidance, have found that there is a difference in parts of the country that have higher temperature and the incidence of peanut and egg allergy, and that this was even more common in children with low Vit D levels.

Eczema and atopic diseases are linked to an immune system more prone to express inflammatory markers such as interleukin (IL) 4, 5, and 13, shifting the immune response to a more T helper cell type 2 (Th2) responses. This facilitates the development of sensitization, while in patients with fewer allergies the response is more prone to be the expression of Th type 1 (Th1) and T-regulatory (T-reg) cell memory, factors that are found to be important to develop tolerance against an allergen.

Today, there is no known prevention for allergic disease in general, and studies regarding breast feeding, probiotics, preventive skin emollients, and Vit D substitution have been inconclusive. Some evidence has been found that early rather than late food introduction is beneficial and decreases the risk of food allergy. There are promising studies ongoing regarding oral immunotherapy (OIT) in children.

Immunologic reactions. IgE mediated allergy. Pathophysiology. Individuals with food allergy have a lack of immunologic and clinical tolerance to food, which is manifested as IgE-ab or non-IgE-ab mediated diseases. IgE-ab sensitization to food allergens is possible through the GI tract, defect in the skin barrier or the airway mucosa. The immune system in healthy individuals perceives food antigens as nonpathogenic, and following passage through the intestinal epithelium, these Ag are presented with CD103 dendritic cells in the mesenteric lymph node, where the production of T-reg are induced. In patients

with food allergy, the production of T-reg is replaced by the production of Ag-specific Th2 cells, which subsequently drive the IgE-ab switching in plasma cells, from IgG4 to IgE-ab production and development of mast cells. IgE-ab binds receptors on mast and basophil cells, and upon re-exposure, the food-allergen binds to the IgE-ab on mast and basophil cells surfaces, leading to the release of cell mediators, e.g. histamine (Fig. 7.2). The mediator release causes increased mucus production, vasodilatation, and increased vascular permeability with acute onset of allergic symptoms such as edema, stomach pain, vomiting, diarrhea, urticaria, bronchial obstruction and anaphylaxis. The risk for severe reactions is increased in patients with asthma that suffer from poor asthma control. There is still a lack of detailed knowledge regarding the immunopathogenic mechanisms related to non-IgE-ab-mediated and cell-mediated food allergies.

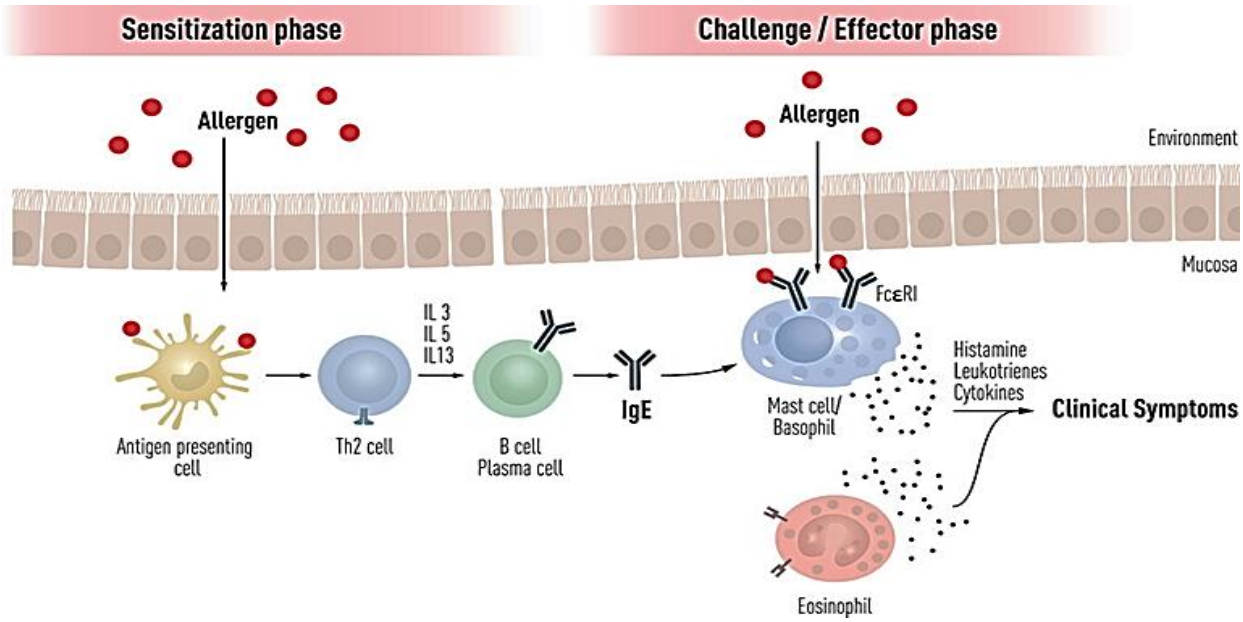


Fig. 7.2. Immunologic reactions

Immunologic reactions:

• *Type I immediate hypersensitivity reactions* involve IgE antibodies bound to mast cell and basophil cell surfaces. Upon binding of Ag to IgE, chemical mediators such as histamine, tryptase, leukotrienes, and prostaglandins are released, resulting in allergic symptoms (e.g. Anaphylaxis).

• *Type II cytotoxic antibody reactions* occur when antibodies (IgM, IgG or IgA) bind to cell surface Ag causing complement activation and ultimately, cell lysis, or release of anaphylatoxins (hemolytic anemia, Goodpasture syndrome etc).

• *Type III immune complex reactions* result when Ag-AB complexes are formed causing injury to vasculature and organs such as liver, spleen, and kidney (classic eg. is serum sickness).

• *Type IV delayed type hypersensitivity reactions* result when T cells recognize Ag in the context of MHC class II, which activates cytokine release, e.g. contact dermatitis to poison ivy.

The history, family history, and physical examination may indicate existing atopic disease in patients. Allergic rhinitis, allergic asthma, and food allergies are examples of atopic disease involving IgE antibodies. Of the two methods for assessing Ag-specific IgE AB, in vivo skin testing (via prick or intradermal testing) is the most sensitive method. Serum-based testing with quantitative fluorescent immunoassay proves to be useful in those patients unable to have skin testing performed such as dermatographism or extensive dermatitis. The presence of specific IgE does not equate to diagnosis of allergic disease. Rather, positive results must be correlated with the history. Therefore, obtaining screening tests of multiple allergens is not recommended.

7.2. ATOPIC DERMATITIS

Atopic Dermatitis (Eczema) is a chronic relapsing skin condition characterized by pruritus and skin inflammation, usually first appears between ages 3 and 6 months. The pathogenesis is complex and multifactorial. Restoring the skin barrier is an important treatment modality as is control of pruritus, reduction of inflammation, and minimizing exposure to known triggers. In severe atopic dermatitis, 30 % of patients may have a food allergy trigger; for moderate eczema, 15 %; for mild, less than 10 %. The exact cause of atopic dermatitis is not known, some things are linked to it:

– genes (this skin problem can be passed on from parents to a child);

– immune system (an immune system that isn’t fully developed may affect how much protection the skin can give);

– external factors (winter weather, using hot water for bathing, using soap, and being in dry, hot temperatures.

A child has a greater chance of having atopic dermatitis if he or she has family members with atopic dermatitis and/or allergies. Symptoms may come and go, or occur most or all of the time. Any area of the body may be affected. In babies, symptoms usually affect the face, neck, scalp, elbows, and knees, in children — skin inside the elbows, on the back of the knees, the sides of the neck, around the mouth, and on the wrists, ankles, and hands. Symptoms can include: dry, scaly skin; severe itching; redness and swelling; thickened skin; pale skin on the face; small, raised bumps that may become crusty and leak fluid if scratched; rough bumps on the face, upper arms, and thighs; darkened skin of eyelids or around the eyes; skin changes around the mouth, eyes, or ears; raised, red areas (hives).

There is no specific test for atopic dermatitis. Testing is usually not needed, but it may be done and include:

– Blood tests: check for levels of IgE (high in most children with allergies and with atopic dermatitis);

– Skin tests for allergies or other skin conditions.

The goals of treatment are to ease itching and inflammations, add moisture, and prevent infection. Treatment includes: staying away from irritants; bathing with a gentle cleaner or body wash; keeping child's fingernails short, to help

prevent scratching that can cause skin irritation and infection; using moisturizing lotion; corticosteroid cream or ointment to help ease itching and swelling. Medicines: antihistamine to help ease itching and improve sleep, calcineurin inhibitor skin cream or ointment to help ease itching and swelling. Phototherapy (light therapy). Antibiotic in case of infection. Immunomodulatory medicines. Biologic medicines in severe cases (dupilumab).

Complications: thickened skin, bacterial skin infection, and other allergy-related skin inflammation (allergic dermatitis): poor sleep because of intense itching. Overuse of steroid creams can lead to thinning of the skin and tissue beneath the skin.

7.3. ALLERGIC RHINITIS

Allergic rhinitis and conjunctivitis are IgE-mediated atopic diseases in response to relevant aeroallergens in a perennial and/or seasonal fashion. Symptoms include nasal pruritus, sneezing, clear rhinorrhea, nasal obstruction, lacrimation, ocular pruritus, and conjunctival injection. Like asthma, treatment for allergic rhinitis and conjunctivitis employs numerous modalities: education, avoidance of triggers, pharmacologic therapy, and immunotherapy. The most effective medications for the treatment are intranasal corticosteroids. When used properly, these sprays are efficacious and have no effects on the hypothalamic-pituitary-adrenal axis. Other treatments include oral and nasal antihistamines, oral decongestants, and leukotriene modifiers.

7.4. URTICARIA, ANGIOEDEMA AND ANAPHYLAXIS

The pathophysiology of urticaria involves swelling of the dermis due to inflammatory mediators released from skin mast cells. Angioedema is swelling below the dermis. Acute urticaria refers to urticaria occurring less than 6 weeks duration and chronic urticaria occurs 6 weeks or more. A causal agent is more likely to be found in acute urticaria such as a food, medication, insect sting, infection, blood transfusion, or contact agent. In chronic urticaria, an etiology is less likely to be found and most cases are idiopathic. Physical urticaria refers to lesions due to physical stimuli like dermatographia, cold, heat, and/or exercise and pressure.

There are two types of hereditary angioedema, and both are inherited in an autosomal dominant fashion. Type I accounts for the majority of cases and is due to decreased production of C1-esterase inhibitor. Patients with type II have normal levels of C1-esterase inhibitor, but function is reduced. Patients with hereditary angioedema with normal C1 inhibitor experience angioedema like Type I and II hereditary angioedema but have normal levels and function of C1-esterase inhibitor.

Anaphylaxis refers to a syndrome of symptoms (usually involving two or more organ systems) due to type I immediate hypersensitivity. Causative agents are numerous. Anaphylactoid reactions result from direct, nonspecific mast cell and basophil activation but are not immune mediated. Examples include reactions to radiocontrast media and opiates.

Serum sickness. Serum sickness is the prototypical type III reaction where AB binds to Ag forming immune complexes that can cause vascular injury or end-organ damage. Symptoms are fever, arthralgias, lymphadenopathy, and rash.

Insect allergies. Stinging insect hypersensitivity refers to allergic reactions to Hymenoptera, which include bees, yellow jackets, wasps, hornets, and fire ants. Biting insects such as the kissing bug, bed bugs, blackflies, and deerflies have also caused cases of anaphylaxis. Patients of any age who suffer from anaphylaxis due to Hymenoptera stings with positive specific IgE testing benefit from immunotherapy and should have an auto-injector of epinephrine. However, patients less than 16 years of age who experience only cutaneous symptoms do not require testing, immunotherapy, or epinephrine since their risk of life-threatening reaction is low.

Adverse reactions to foods:

• Cow's milk, egg, soy, wheat, peanut, tree nut, finned fish, and shellfish account for 90 % of IgE-mediated food allergies in children.

• Positive food skin and/or serum specific IgE testing alone does not equate to clinical reactivity and must be interpreted in the context of the history. In fact, the clinical history should dictate what food allergens should be tested; testing to many different foods as a screening tool has very little clinical value and is strongly discouraged.

• Neither skin nor serum testing for food allergies can predict severity of allergy nor the amount required to elicit a reaction. Only risk for an allergic reaction can be inferred from a positive allergy test to a food.

• Currently, treatment of food allergies is avoidance and the use of auto-injectable epinephrine in the case of accidental ingestion resulting in symptoms. There are other novel treatment modalities in clinical trials.

• Studies indicate that even for high-risk infants, early introduction of peanut into the diet decreased the development of peanut allergy.

Adverse reaction to drugs. Predictable adverse drug reactions are classified as either immunologic or nonimmunologic with the former being less common. Standardized allergy skin testing for reactions due to IgE is available for penicillin determinants but unavailable for most other medications. Drug challenges and drug desensitizations may be an appropriate approach in this setting.

Cow's milk allergy. Estimated prevalence of 0.5–1 % in infants younger than 6 months, much less common in older. Typical symptoms are fussiness, frequent mucoid stools with blood streaks. Family history of atopy is common. Usually a clinical diagnosis confirmed by resolution of symptoms on milk protein-free diet. Sigmoidoscopy shows mild superficial colitis. In older children, milk allergy may cause a celiac-like syndrome with protein-losing enteropathy, occult intestinal blood loss, edema, anemia, and failure to thrive. Anaphylactic shock after milk ingestion is rare but can be life threatening.

Differential diagnosis. Low-volume blood loss due to anal stenosis, anal fissure, hemorrhoid, juvenile polyp does not respond to a milk protein-free diet.

Celiac disease. Crohn disease. Severe diaper dermatitis may produce very similar symptoms of fussiness and small-volume rectal bleeding. Perianal streptococcal infection produces small volume rectal bleeding and fussiness. The infant with anal stenosis is fussy, has mucoid stools with blood streaks, and is often thought to be milk allergic. A careful rectal exam ination will differentiate this common problem from allergy.

Treatment. Milk protein-free diet for infants is helpful. If symptoms are minor in infants with rectal bleeding, no therapy is required as the problem will resolve spontaneously.

Anaphylaxis. Anaphylaxis is a severe allergic reaction characterized by an acute onset of cardiovascular (eg hypotension) or respiratory (eg bronchospasm) symptoms. It may be associated with typical skin features (urticarial rash or erythema/flushing and/or angioedema) and/or persistent severe gastrointestinal symptoms. Most reactions occur within 30 minutes of exposure to a trigger but can occur up to 4 hours later.

Causes of anaphylaxis in children include:

– foods: peanut, tree nuts, cow milk, eggs, soy, shellfish, fish, wheat;

– bites/stings: bee, wasp, jack jumper ants, ticks;

– medications: beta-lactams, NSAIDs;

– other: exercise, idiopathic, rubber latex (bottle nipples, pacifiers, toys). Newer monoclonal antibody therapies may produce delayed anaphylactic reactions and rebound symptoms that occur more than 12 hours after the initial reaction.

Pathophysiology. IgE- and non-IgE-mediated reactions.

Both IgE and non-IgE activation of mast cells and basophils ignites a cascade that results in the release and production of several inflammatory and vasoactive substances like histamine, tryptase, heparin, prostaglandins (PGD2, PGF2), leukotrienes (LTC4, LTD4, and LTE4), cytokines (TNF-α), and platelet activating factor (PAF). In anaphylaxis, these substances most commonly involve the skin, respiratory, cardiovascular, and gastrointestinal systems. As a result, urticaria, angioedema, bronchospasm, bronchorrhea, laryngospasm, increased vascular permeability and decreased vascular tone, and bloody diarrhea can develop. Many of the clinical presentations seen in anaphylaxis are due to activation of multiple histamine receptors, e.g., acute bronchospasm (wheezing, dyspnea) is a result of the interaction between H1 and H2 receptor activity. PGDs, leukotriene's, and PAF all contribute to the bronchoconstriction, vascular changes, and changes in vascular capacitance (increased vascular permeability and vasodilatation).

Anaphylaxis is a clinical diagnosis made in the setting of the acute onset of either criteria. *Typical skin features (urticaria, flushing and/or angioedema) plus involvement of:*

– Respiratory system and/or

– Cardiovascular system and/or

– Persistent severe GI symptoms (especially after exposure to non-food allergens eg insect sting) OR

– Hypotension, bronchospasm or upper airway obstruction where anaphylaxis is possible, even if typical skin features are not present.

Clinical features (Fig. 7.3):

1. Respiratory system (most common in children): persistent cough; wheeze, stridor, hoarse voice, difficulty talking or change in character of cry; tongue swelling; chest pain or dyspnea; subjective feeling of swelling, tightness or tingling the throat or mouth.

2. Cardiovascular system: pale and floppy (infant); palpitations, tachycardia, bradycardia; hypotension, pallor; collapse with or without unconsciousness; cardiac arrest.

3. Neurological system: dizziness; altered consciousness, confusion, sudden behaviour change.

4. Gastrointestinal system: nausea, vomiting, dysphagia; diarrhoea; abdominal or pelvic pain.

5. Dermatological system: urticarial rash; erythema, flushing, tearing; angioedema; pruritus (skin, eyes, nose, throat, mouth).

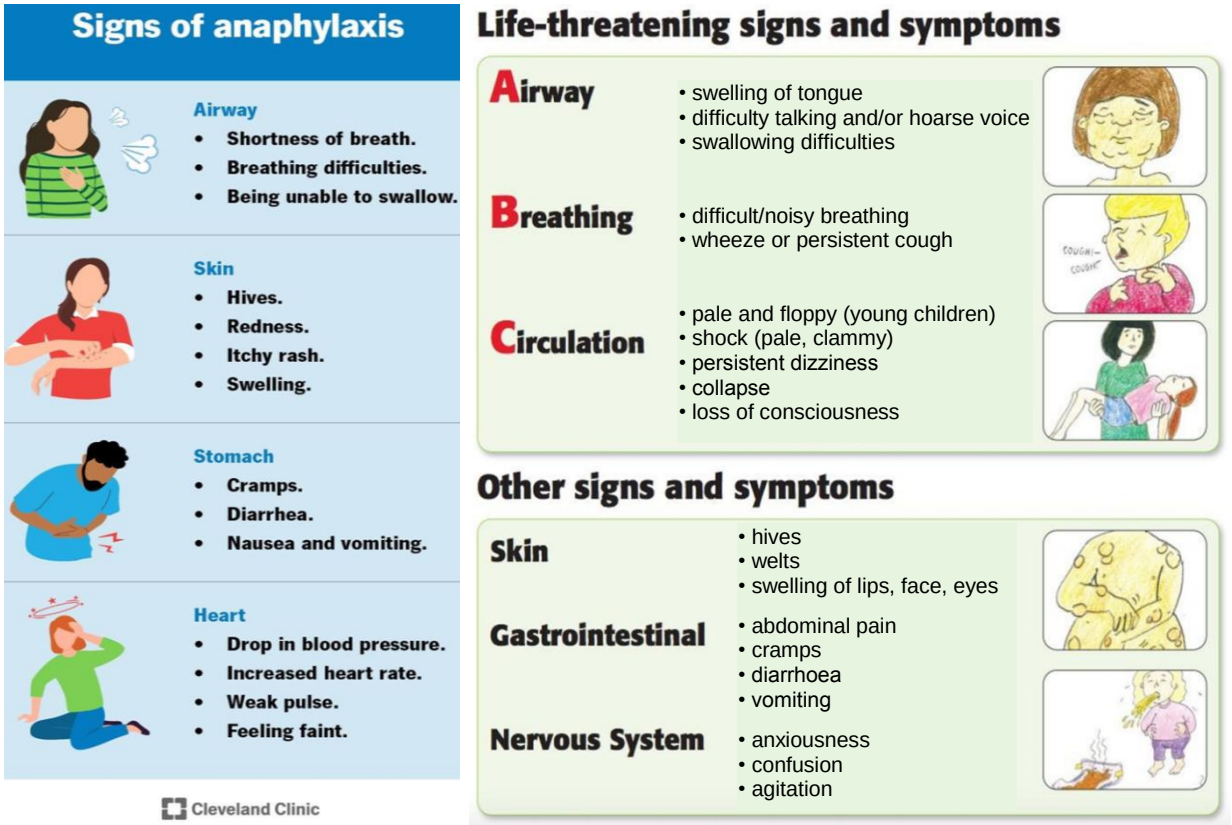


Fig. 7.3. Signs of anaphylaxis. Adopted

Diagnosis. The diagnosis of anaphylaxis is principally a clinical one. However, measurements of serum tryptase may be helpful in confirming the diagnosis. Levels may increase as soon as 15 minutes after onset of symptoms and can peak in up to 3 hours. Levels return to baseline in about 6–8 hours after onset of symptoms. A normal value does not rule out anaphylaxis, as tryptase levels tend not to increase in children with food-induced anaphylaxis. Other tests

that may be useful in distinguishing anaphylaxis from the differential diagnosis include C1 inhibitor functional assay (hereditary angioedema) and urine vanillylmandelic acid and serum serotonin levels (carcinoid syndrome).

Management:

• Remove allergen if still present (eg insect stinger, food debris in mouth).

• Lay patient flat. Do not allow the child to stand or walk. Fatality can occur within seconds if the child stands or sits suddenly. Treat the child in the supine position or lying on their side. If a vomiting child is sat upright, monitor for hypotension.

• Intramuscular adrenaline 10 microgram/kg or 0.01 mL/kg of 1 : 1000 (maximum 0.5 mL), into lateral thigh which should be repeated after 5 minutes if the child is not improving.

• Do not use SC adrenaline, as absorption is less reliable than the IM route.

• Do not use IV bolus adrenaline unless cardiac arrest is imminent.

• Use an adrenaline autoinjector if unable to calculate exact dose or to avoid delay, including in children < 1 year old (Fig. 7.4).

• Give oxygen.

• If not improving, give a second dose of adrenaline, consider adrenaline infusion (0.05–0.5 microgram/kg/min).

• Continue giving IM adrenaline every 5 minutes until IV access is obtained.

Other treatments to consider. Repeated doses of IM adrenaline together with:

• Nebulised or MDI salbutamol is recommended if the child has respiratory distress with wheezing. Also consider other anti-asthma medications.

• Antihistamines may be given for symptomatic relief of pruritus. 2nd generation antihistamines are preferred (eg cetirizine).

• Corticosteroids and leukotriene antagonists have no proven benefit in anaphylaxis.

• Avoid NSAIDs.

Observation and admission. All children with anaphylaxis should be observed for at least 4 hours in a supervised setting with facilities to manage deterioration. Admission for a minimum 12-hour period of observation is recommended if:

– further treatment is required within 4 hours of last adrenaline administration (biphasic or prolonged reaction);

– previous history of biphasic reaction;

– poorly controlled asthma;

– the child lives in an isolated location with delay to emergency services;

– anaphylaxis to monoclonal antibody.

Peripheral IV adrenaline infusion:

• Mix 1 mL of 1 : 1000 adrenaline in 1000 mL of fluid (glucose 5 % or glucose 10 %, NaCl 0.9 % saline and glucose with sodium chloride combinations).

• Start infusion at 0.1 microgram/kg/minute (6 mL/kg/hr); titrate dose according to response and side-effects.

• Monitor continuously (all vitals, 12-lead ECG and conscious state).

• Insert a second IV as fluid boluses may be needed.

• If hypotensive, resuscitate with fluid; use boluses of 20 mL/kg of NaCl 0.9 % for shock.

• Nebulised adrenaline is not recommended as first-line therapy, but may be a useful adjunct after IM adrenaline if upper airway obstruction or bronchospasm is present.

• If airway oedema is not responding to parenteral (IM, IV) and nebulised adrenaline, early intubation is indicated.

Adrenaline (epinephrine) dosages chart			
Age (years)	**Weight (kg)**	**Vol. adrenaline 1:1000**	**Adrenaline autoinjector**
<1	5-10	0.05-0.1 mL	
1-2	10	0.1 mL	10-20 kg (~1-5yrs) 0.15mg (green labelled device)
2-3	15	0.15 mL	
4-6	20	0.2 mL	
7-10	30	0.3 mL	>20kg (~>5yrs) 0.3mg (yellow labelled device)
10-12	40	0.4 mL	
>12 and adults*	>50	0.5 mL	

* For pregnant women, a dose of 0.3mg should be used.

Fig. 7.4. Adrenaline autoinjector usage. Adopted

7.5. Bronchial Asthma

Asthma is a heterogeneous disease, characterized by chronic airway inflammation. Asthma is hyperresponsiveness disorder, reversible air flow obstruction. Airway inflammation may cause recurrent or persistent bronchospasm with *wheezing, breathlessness, chest tightness, cough, particularly at night (early morning hours) or after exercise*.

Asthma is the most frequent chronic disease in children. Before puberty, the prevalence of asthma is 3 times higher in boys than in girls, during adolescence the prevalence is equal, adult-onset asthma is more common in women. In most children, asthma develops before age of 5 years, and, in more than half, asthma develops before age of 3 years.

Risk factors. Internal factors: genetic predisposition; atopy (genetic tendency to produce IgE in response to common environmental proteins); bronchial hyperresponsiveness (the inherent tendency of the airways to narrow in response to various stimuli); gender and ethnicity.

External factors: domestic allergens (house dust, animal's allergens); external allergens (mold, pollen, fungi); smoking (passive and active); air pollutants; respiratory infections; exercise and hyperventilation; weather conditions; stress; parasitic infections.

Pathogenesis. Interactions between environmental and genetic factors result in airway inflammation, which limits airflow and leads to functional and structural changes in the airways in the form of bronchospasm, mucosal edema, and mucus plugs. Asthma involves many different cells, chemical mediators, and chemotactic factors resulting in airway chronic inflammation, narrowing and hyperresponsiveness.

When allergens enter the low airways, dendritic cells (DCs) present the allergens to Th2 cells, which secrete Th2 cytokines, including IL-5, IL-4, and IL-13. IL-4 and IL-13 activate B cells, which produce IgE. IgE subsequently binds to surface of mast cells. When the same allergens enter the airways, they interact with IgE, which induces mast cells to release mediators, such as leukotrienes (LTs), histamine, and ILs. These mediators irritate airway smooth muscle and induce bronchoconstriction. In addition, IL-5 facilitates eosinophil recruitment to the lungs. Eosinophils also release mediators, including major basic protein (MBP), which stimulates mast cells to release histamines and LTs. MBP also inhibits M2 receptor and promotes acetylcholine release from cholinergic nerves and induces bronchospasm. IL-13 directly sensitizes airway smooth muscle contraction, stimulates epithelial cells to secret mucins, and induces fibrosis. Th9 cells can secrete IL-9, which activates Th2 cells and promotes mast cell accumulation. Lastly, epithelium injury by infection and pollutants induces release of cytokines, including thymic stromal lymphopoietin (TSLP), IL-25, and IL-33, which activate type 2 innate lymphoid cells (ILC2) and produce Th2 cytokines, such as IL-5 and IL-13 (Fig. 7.5).

Typical symptoms included cough, wheeze, shortness of breath, and chest tightness. Coughing, chest tightness, dyspnea, difficulty breathing, wheezing, whistling during expiration (Fig. 7.6). Curschmann spirals in sputum. Spiral-shaped mucus plugs, casts from small bronchi. Blocks air exchange, inhaled medications from reaching inflammation. Charcot–Leyden crystals in sputum. Needle-shaped, formed from breakdown of eosinophils.

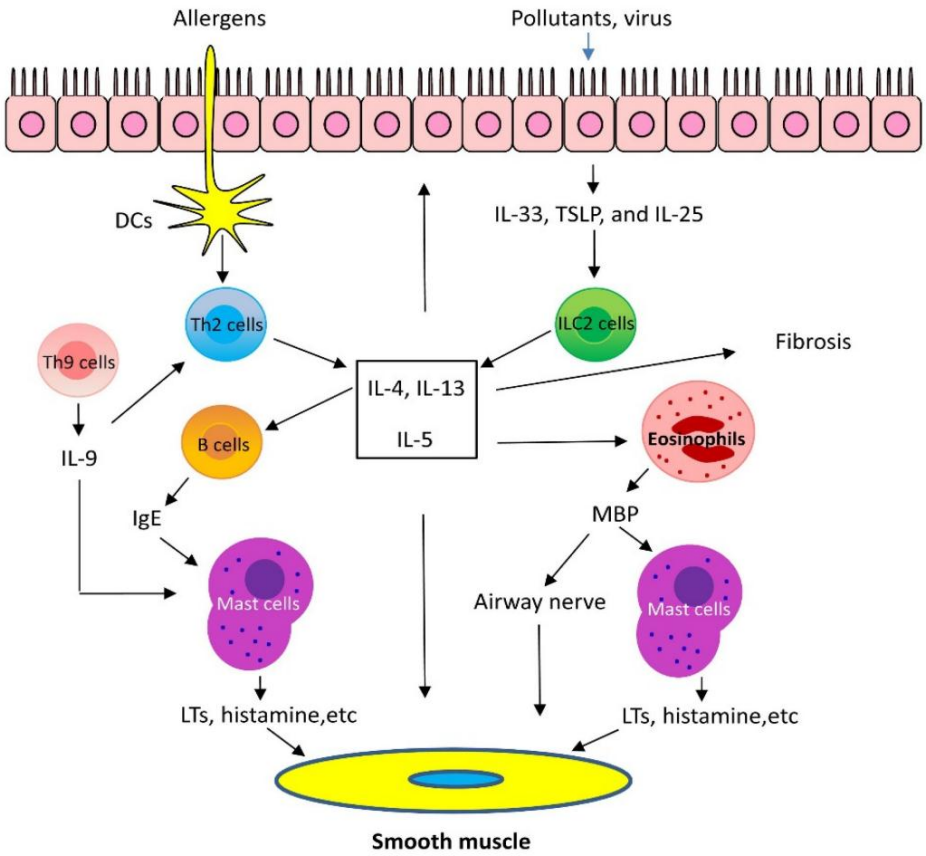


Fig. 7.5. Bronchial asthma pathogenesis. Adopted

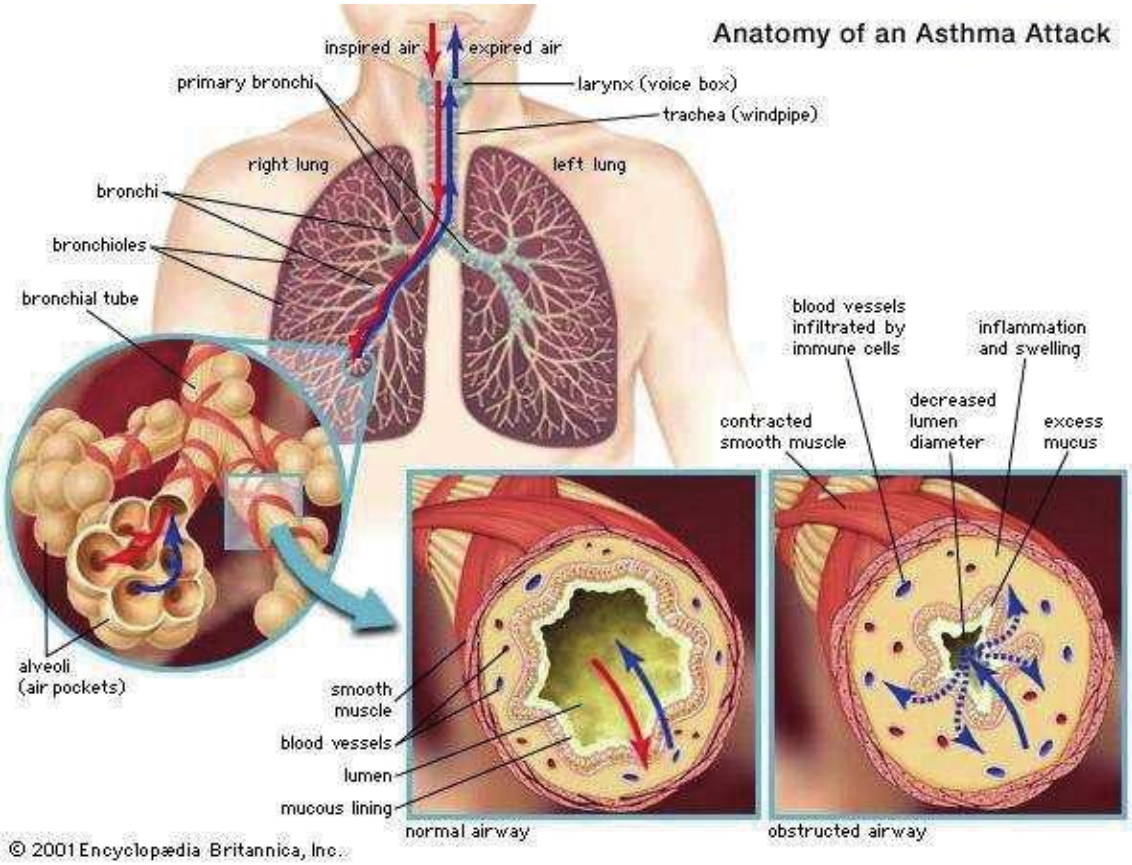


Fig. 7.6. Anatomy of an Asthma attack

The GINA (global strategy for asthma management and prevention) is presented in its strategy documents, which are freely available on the GINA Website. Annual update of the *Global Strategy for Asthma Management and Prevention* incorporates new scientific information about asthma based on a review of recent scientific literature by an international panel of experts on the GINA Science Committee. This comprehensive and practical resource about one of the most common chronic lung diseases worldwide contains extensive citations from the scientific literature and forms the basis for other GINA documents and programs.

Classification. Classifications are based *on frequency of symptoms* (esp. Night/morning), forced expiratory volume in one second (FEV1), peak expiratory flow rate (PEFR), frequency of medication use: intermittent, mild persistent, moderate persistent, severe persistent;

Asthma form: allergic, non-allergic, mixed.

Period: exacerbation; remission.

Complications: atelectasis, emphysema, pneumothorax.

Asthma is considered ***intermittent*** if without treatment **any** of the following are true:

– symptoms (difficulty breathing, wheezing, chest tightness, and coughing) occur on fewer than 2 days a week;

– attacs do not interfere with normal activities;

– nighttime symptoms occur on fewer than 2 days a month;

– lung function tests (spirometry and peak expiratory flow rate (PEFR)) are normal when the person is not having an asthma attack. The results of these tests are 80 % or more of the expected value and vary little (PEF varies less than 20 %) from morning to afternoon.

Asthma is considered ***mild persistent*** if without treatment **any** of the following are true:

– symptoms occur on more than 2 days a week but do not occur every day;

– attacks interfere with daily activities;

– nighttime symptoms occur 3 to 4 times a month;

– lung function tests are normal when the person is not having an asthma attack. The tests results are 80 % or more of the expected value and may vary a small amount (PEF varies 20 % to 30 %) from morning to afternoon.

Asthma is considered ***moderate persistent*** if without treatment **any** of the following are true:

– symptoms occur daily;

– inhaled short-acting asthma medication is used every day;

– symptoms interfere with daily activities;

– nighttime symptoms occur more than 1 time a week, but do not happen every day;

– lung function tests are abnormal (more than 60 % to less than 80 % of the expected value), and PEF varies more than 30 % from morning to afternoon.

Asthma is considered ***severe persistent*** if without treatment **any** of the following are true:

– symptoms occur throughout each day;

– severely limit daily physical activities;

– nighttime symptoms occur often, sometimes every night;

– lung function tests are abnormal (60 % or less of expected value), and PEF varies more than 30 % from morning to afternoon.

The diagnosis of asthma should be based on:

• A history of characteristic symptom patterns.

• Evidence of variable airflow limitation, from bronchodilator reversibility testing or other tests.

• Document evidence for the diagnosis in the patient's notes, preferably before starting controller treatment;

It is often more difficult to confirm the diagnosis after treatment has started.

Asthma is usually characterized by airway inflammation and airway hyperresponsiveness, but these are not necessary or sufficient to make the diagnosis of asthma.

Increased probability that symptoms are due to asthma if:

– more than one type of symptom (wheeze, shortness of breath, cough, chest tightness);

– symptoms are often worse at night or in the early morning;

– symptoms vary over time and in intensity;

– symptoms are triggered by viral infections, exercise, allergen exposure, changes in weather, laughter, irritants such as car exhaust fumes, smoke, or strong smells.

Wheezing: a musical, high-pitched whistling sound produced by airflow turbulence usually during exhalation, is one of the most common symptoms of asthma.

Cough: usually, the cough is nonproductive and nonparoxysmal; coughing may be present with wheezing. Cough at night or with exercise: coughing may be the only symptom of asthma, especially in cases of exercise-induced or nocturnal asthma; children with nocturnal asthma tend to cough after midnight, during the early hours of morning.

Decreased probability that symptoms are due to asthma if:

– isolated cough with no other respiratory symptoms;

– chronic production of sputum;

– shortness of breath associated with dizziness, lightheadedness or peripheral tingling;

– chest pain;

– exercise-induced dyspnea with noisy inspiration (stridor).

Statute asthmaticus is acute severe asthma or a severe asthma exacerbation (asthma attack that doesn't improve with traditional treatments, such as inhaled bronchodilators). These attacks can last for several minutes or even hours. It's

a major cause of acute illness in children and one of the top indications for admission to an intensive care unit (ICU). Mortality is rare after a child arrives at medical attention, but morbidity can be high with some children requiring days or weeks of hospitalization and recovery. Even children with mild or intermittent baseline asthma can have severe exacerbations requiring ICU, so predicting who will progress to a more severe attack is challenging. Several risk factors have been identified, but no combination can sufficiently predict the likelihood of a particular child developing a more severe exacerbation. Status asthmaticus include: difficulty breathing; heavy sweating; fatigue and weakness; abdominal, back, or neck muscle pain; panic or confusion; blue-tinted lips or skin; loss of consciousness. Life threatening symptoms: prior history of life-threatening exacerbation; previous ICU admission; previous endotracheal intubation; older age; inability to recognize; airflow obstruction; poor asthma control.

Differential diagnosis: allergic bronchopulmonary aspergillosis; aspiration syndromes; bronchiectasis; bronchiolitis; chronic bronchitis; chronic obstructive pulmonary disease (COPD); eosinophilic granulomatosis with polyangiitis; croup; cystic fibrosis; emphysema; foreign bodies of the airway; gastroesophageal reflux disease; heart failure; idiopathic pulmonary arterial hypertension; inhalation injury; pulmonary artery stenosis; sling vocal cord dysfunction.

Evaluation of patients with asthma should include history, response to treatment, spirometry (> 5 years of age), allergy testing, and chest radiograph, if warranted, trigger test, spirometry, peak airflowmetry.

Lung function tests: spirometry and plethysmography.

• Exercise challenge: involves baseline spirometry followed by exercise on a treadmill or bicycle to a heart rate greater than 60 % of the predicted maximum, with monitoring of the ECG and oxyhemoglobin saturation.

• Fraction of exhaled nitric oxide (FeNO) testing: Noninvasive marker of airway inflammation.

• Radiography: Reveals hyperinflation and increased bronchial markings; radiography may also show evidence of parenchymal disease, atelectasis, pneumonia, congenital anomaly, or a foreign body.

• Allergy testing: Can identify allergic factors that may significantly contribute to asthma.

• Histologic evaluation of the airways: infiltration with inflammatory cells, narrowing of airway lumina, bronchial and bronchiolar epithelial denudation, and mucus plugs.

Measurement of lung volumes and airflow rates using ***spirometry*** are important in assessing pulmonary disease. Most children above 5–6 years of age can perform spirometry. The patient inhales to TLC 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 forced expiratory *flow (FEF)* rates are measured. These are compared to predicted values based on patient age, gender, and race, but rely mostly on height. Severity

of disease is quantified by calculated percentage of predicted values. The ***peak expiratory flow rate (PEFR)*** can be obtained with a simple hand-held device 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. Measurement *of TLC, FRC, and RV* require *body plethysmography*. Helium dilution can also measure TLC and RV by determining the magnitude of dilution of inhaled helium in the air within the lung, but may underestimate air trapping.

Abnormal results on pulmonary function testing can be used to categorize ***obstructive*** (low flow rates and/or increased RV) or a ***restrictive lung disease*** (low FVC and TLC, with relative preservation of flow rates). When the FEV1 is decreased to a greater extent than the FVC (***FEV1/FVC ratio*** < 80 %), obstructive lung disease is diagnosed. The mean midexpiratory flow rate (***FEF 25–75 %***) is a more sensitive measure of small airways disease than the FEV1, but is also more variable. Spirometry can detect reversible airway obstruction characteristics of asthma when a significant improvement in FEV1 (> 12 %) or in FEF 25–75 % (> 25 %) following inhalation of a bronchodilator is measured. *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 only be performed in a pulmonary function laboratory with experienced technicians.

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 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.

Flexible bronchoscopy is useful in identifying dynamic or static airway abnormalities (stenosis, malacia, endobronchial lesions, and excessive secretions) and to obtain airway samples for culture (*bronchoalveolar lavage*). *Rigid bronchoscopy* is the method of choice for removing foreign bodies from the airways and performing other interventions, such as airway dilation. Transbronchial biopsies are rarely performed in children.

Treatment of asthma involves numerous interventions: environmental control of potential allergens, patient and care giver education, reduction of exposure to nonspecific irritants such as secondhand tobacco smoke, pharmacologic therapy, and yearly influenza vaccination.

The goals for therapy are as follows:

• Control asthma by reducing impairment through prevention of chronic and troublesome symptoms (e.g., coughing or breathlessness in the daytime, in the night, or after exertion).

• Reduce the need for a short-acting β2-agonist (SABA) for quick relief of symptoms (not including prevention of exercise-induced bronchospasm).

• Maintain near-normal pulmonary function.

• Maintain normal activity levels (including exercise and other physical activity and attendance at work or school).

• Satisfy patients' and families' expectations for asthma care.

To relieve smooth muscle airway bronchoconstriction, SABA should be employed on an as-needed basis and/or prior to physical activity.

The most effective antiinflammatory pharmacologic therapy for persistent asthma is *inhaled corticosteroids*, emphasizing finding the minimum dose that is able to achieve control and minimize risk and impairment from the disease. All metered-dose inhalers need to be administered with the use of an aerochamber to maximize lung deposition of the medication.

For patients with more severe asthma, additional therapies may be required to achieve treatment goals:

– combination therapy with long-acting β2agonists (LABA);

– leukotriene modifiers;

– theophylline;

– omalizumab and other biologic agents;

– anticholinergic agents;

– allergen immunotherapy;

– oral corticosteroids.

Use of peak flow monitoring and written asthma action plans may assist patients and their parents with at-home monitoring and adherence to medical therapy.

Asthma exacerbations may be treated with frequent administration of SABA and a course of systemic corticosteroids. Despite these interventions, status asthmaticus may ensue, requiring supplemental oxygen, continuous bronchodilation, IV corticosteroids, blood gas monitoring, magnesium sulfate, and hospitalization.

Treatment of status asthmaticus:

• β2-agonists — the 1st line of therapy.

• Anticholinergic (work centrally by suppressing conduction in vestibular cerebellar pathways).

• Glucocorticosteroids — among other therapeutic activities, can decrease mucus production, improve oxygenation, reduce β-agonist or theophylline requirements, and activate properties that may prevent late bronchoconstrictive responses to allergies and provocation.

• Bronchodilators — methylxanthines are weaker bronchodilators than β-agonists and have many adverse effects.

• IV Mg sulfate can relax smooth muscle and hence cause bronchodilation by competing with calcium at calcium-mediated smooth muscle binding sites.

• Fluid replacement: hydration, with IV normal saline at a reasonable rate, is essential. Special attention to the patient's electrolyte status is important. Hypokalemia may result from either corticosteroid use or β-agonist use. Correcting hypokalemia may help to wean an intubated patient with asthma from

mechanical ventilation. Hypophosphatemia may result from poor oral intake and is also an important consideration when weaning such patients.

• Antibiotics — only in case of evidence of infection (pneumonia, sinusitis).

• Oxygen monitoring and therapy (via a nasal canula or mask).

Upper airway obstruction. ***Etiology.*** Upper airway obstruction is defined as blockage of any part of the airway located above the thoracic inlet, ranges from nasal obstruction due to the common cold to life-threatening obstruction of the larynx or upper trachea. In children, nasal obstruction is usually more of a nuisance than a danger because the mouth can serve as an airway, but it may be a serious problem for neonates, who breathe predominantly through their noses. The differential diagnosis of airway obstruction varies with patient age and can also be subdivided into *supraglottic, glottic, and subglottic* causes.

Age-related differential diagnosis of sub-acute upper airway obstruction. ***Newborn:*** choanal atresia; rhinitis neonatorum; micrognathia (Pierre Robin syndrome, Treacher Collins syndrome, DiGeorge syndrome); macroglossia (Beckwith–Wiedemann syndrome, hypothyroidism, pompe disease, trisomy 21); pharyngeal collapse; laryngeal web; vocal cord paralysis/paresis (idiopathic, birth trauma or central nervous system pathology); congenital subglottic stenosis; nasal encephalocele.

Infancy: chronic or recurrent rhinitis (infection, acid reflux, irritant); laryngomalacia (most common); subglottic stenosis (congenital or acquired, e.g., after intubation); laryngeal web or cyst; laryngeal papillomatosis; airway hemangioma; vascular rings/slings.

Toddlers: chronic or recurrent rhinitis (infection, allergy, irritant); hypertrophied tonsils and adenoids (most common); spasmodic croup; laryngeal papillomatosis; vascular rings/slings.

Older children: chronic or recurrent rhinitis (infection, allergic, irritants); hypertrophied tonsils and adenoids (most common); paradoxical vocal fold movement; Infectious mononucleosis.

Differential diagnosis:

1. ***Acute stenosing laryngitis (Croup).*** Viral croup — inflammation of the larynx and upper airway structures causes sudden-onset barking cough, stridor, congestion, ± fever. Usually is self-limited, common in children < 5 years.

• Viral organisms causing croup: parainfluenza, respiratory syncytial virus (RSV), influenza, rubeola, adenovirus; other organisms Mycoplasma pneumonia.

• Bacterial infection of epiglottitis or trachea causes life-threatening stridor.

• Spasmodic croup — recurrent episodes of stridor with/without viral infection, may be allergic in origin.

• Viral croup is a clinical diagnosis. Evaluation for other causes of stridor is important and may require imaging, bronchoscopy.

Differential diagnosis:

• Laryngomalacia — common cause of stridor in newborns. Immaturity of cartilage supporting epiglottis and other supraglottic structures improves with time.

• Laryngeal cleft — failure of posterior cricoid fusion causes stridor and recurrent aspiration.

• Angioedema — histamine-mediated acute swelling of skin and/or multiple other systems may involve the larynx and trachea. Caused by allergy, C1 esterase deficiency, medications (ACE inhibitors), and cold exposure.

• Laryngeal/esophageal foreign body.

• Retropharyngeal abscess or tumor, mediastinal tumor.

• Subglottic stenosis — congenital or secondary to endotracheal intubation.

Treatment. Most viral croup is self-limited; stridor usually lasts 3–5 days. Use humidified air especially at night; maintain good hydration and food intake. Stridor at rest or hypoxia should be treated with oxygen; inhale nebulized racemic epinephrine or budesonide. Dexamethasone (single dose 6 mg/kg intramuscularly or 15 mg/kg orally) improves symptoms and reduces frequency of intubation. Severe dyspnea/hypoxia, exhaustion, and respiratory failure require endotracheal intubation.

Pearl: *The younger the child, the smaller diameter of the trachea, the higher the chance that swelling of the airway caused by viral infection may produce respiratory obstruction. Monitor the young child with croup carefully!*

2. *Bronchiolitis.*

• Acute respiratory infection of young infants producing cough, tachypnea, dyspnea, expiratory wheeze, rhinorrhea, ± fever.

• Other symptoms include irritability, hypoxia, anorexia, vomiting (often post-tussive).

• Most common cause is RSV, other organisms — parainfluenza, influenza, adenovirus, Mycoplasma, Chlamydia, Ureaplasma, and Pneumocystis.

• Nasal washing for RSV and other respiratory pathogens confirms etiology.

• Chest x-ray typically shows hyperinflation, peribronchial cuffing, increased interstitial markings, and subsegmental atelectasis.

Differential diagnosis: reactive airways disease; acute bacterial or viral pneumonitis; atelectasis; heart failure with pulmonary edema; airway foreign body.

Treatment. Supportive treatment suffices in most infants — humidity, fluids, removal of secretions. Respiratory distress may require oxygen, IV fluids, frequent suctioning of secretions. Bronchodilators and corticosteroids used in severely distressed infants. In at-risk patients (immunocompromised, cardiac disease, organ transplant, chronic lung disease), monoclonal RSV antibody prophylaxis reduces hospitalization rate and morbidity. Antiviral agents sometimes used in immunocompromised patients.

Pearl: *Chronic airway hyper-reactivity (asthma) may be a long-term result of RSV infection. RSV infection is also a significant cause of morbidity in infants with underlying lung and heart disease.*

3. *Epiglottitis* (*Streptococcus pneumoniae*, *Haemophilus influenza*; respiratory viruses): typical for 2–6 yr age children; high fever, rapid onset, no

cough, unable to swallow, toxic, agitated, tripod sitting, drooling, stridor Thumb sign, leukocytosis. Treatment: intubation, antibiotics.

4. *Bacterial tracheitis:* any age; high fever, toxic, anxious, ± ragged tracheal intubation, (*Staphylococcus aureus*, *Moraxella catarrhalis*) rapid onset, no URI symptoms stridor, ± cough. Treatment: leukocytosis, antibiotics.

5. *Retropharyngeal abscess* (*S. aureus*, *Group A streptococci*, *oral anaerobes*) age less than 6 yr; fever, insidious onset, sore throat, no URI/cough; moderately toxic, drooling, arched neck, inflamed pharynx, thickened retropharyngeal space, leukocytosis. Treatment: antibiotics, surgical drainage.

6. *Peritonsillar abscess* (*Group A strep.*, *oral anaerobes*) older than 8 yr; fever, sudden worsening, sore throat, trismus, moderately toxic, "hot potato" voice, drooling, asymmetric tonsil swelling. Imaging not needed; leukocytosis. Treatment: antibiotics, surgical drainage.

Noninfections:

1. *Angioedema*: any age; no fever, sudden onset, urticarial, facial swelling, ± allergen exposure; nontoxic (unless anaphylaxis), ± stridor, hoarse, facial edema, Steeple sign. Treatment: Aerosolized or intradermal epinephrine, systemic steroids, antihistamines.

2. *Spasmodic croup*: 6 months — 6 yr; sudden onset, no fever/URI, recurrent, often nocturnal; nontoxic, ± stridor, hoarse, barky cough. Treatment: aerosolized epinephrine, antihistamines, antacids, systemic steroids.

3. *Foreign body*: 6 months — 5 yr; sudden onset, cough and choke, nontoxic, anxious, stridor, aphonic, brassy cough. Radiopaque object may be seen rigid bronchoscopy.

CHAPTER 8
RESPIRATORY DISEASES

8.1. BRONCHITIS

Bronchitis is a lower respiratory tract inflammatory infectious disease which involves the large airways — the bronchi of all lobes of both lungs, without evidence of pneumonia that occurs in the absence of a chronic obstructive pulmonary disease. In the majority of cases it is a sign or complication of the acute respiratory infections.

Acute obstructive bronchitis is an acute inflammation of the bronchi, accompanied by the excessive secretion of mucus, inflammatory infiltration, edema of mucous membrane, thickening of the bronchial wall, and the spasm of the bronchi.

Etiology:

• Viruses: parainfluenza I and III, Respiratory-Syncytial virus, Adenovirus etc.

• Atypical microflora: *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Bordetella pertussis* infection.

• Bacterial infection: *Hemophilus influenzae*, *Pneumococcus*, *Staphylococcus*, *Streptococcus spp*., Gram-negative bacteria.

• Viral-bacterial associations.

Classification.

1. Forms: primary (only the bronchi are involved in the pathological process); secondary (as a sign or complication of respiratory or other systems diseases).

2. Course: acute bronchitis; acute obstructive bronchitis; recurrent bronchitis; chronic bronchitis.

Predisposing factors: different forms of dystrophy; foreign body, food aspiration; mucoviscidosis, immunodeficiency; air pollutant; predisposition to allergic reactions; selective IgA deficiency; connective tissue dysplasia signs; passive and active smoking.

Pathogenesis. Etiological agents lead to the inflammatory damage of the bronchial tree: cytolysis, degeneration, desquamation, local hyperemia, stasis, multiply microthrombosis, and innervation disturbances lead to the inflamma tion progress. In cases of viral-bacterial association, viruses, which have tropism to bronchial mucosa, decrease its protective functions due to the dam age, and bacteria can multiply in this place.

Clinical symptoms:

1. Symptoms of a common cold: running nose, sore throat, fatigue, and chilliness. Can be accompanied by conjunctivitis, pharyngitis and laryngitis.

2. Back and muscle aches.

3. Fever depends on the etiological agent and severity of the disease. In the majority of cases the body temperature is subfebrile or even normal.

4. Cough: dry at onset, in 2–3 days becomes productive, and small amounts of white mucus are often coughed up. The character and tin quantity of sputum can be different depending on many factors. This mucus often changes from white

to green or yellow. The color change does not mean the presence of bacterial infection. It means only that the cells associated with inflammation have moved into the airway and are coloring the sputum. Cough is the last symptom to subside and often takes 2 to 3 weeks or even longer. Viruses can damage the epithelial cells lining the bronchi, and the body needs time to repair the damage.

5. Airway hyperreactivity, which is a short-term narrowing of the airways with the impairment or limitation of the amount of the air I lowing into and out of the lungs.

The impairment of the airflow may be triggered by the common exposures, such as inhaling mild irritants (for example, perfume, strong odors, or exhaust fumes) or cold air.

6. A headache due to the intoxication.

7. Weakness due to the poisoning by viral or bacterial poisons.

8. Mild intoxication, night sweats.

Diagnostics. Anamnesis of the disease and presence of predisposing factors. Percussion: pulmonary sound. Auscultation: rough breath sounds, diffuse dry and/or different diameter moist rales, which can change after cough. Sometimes whistling and wheezing are present. X-Ray: an increased lung pattern due to the increased blood supply. CBC: WBC in normal or even mild leukopenia with lymphocytosis, monocytosis or mild neutrophilic leukocytosis depends on causative agent, normal or a little increased ESR.

Differential diagnosis:

1. Acute pneumonia (chest X-ray).

2. Broncho-pulmonary diseases, exacerbation of which is accompanied by the acute bronchitis signs (mucoviscidosis, bronchoectatic disease); broncho-pulmonary dysplasia.

3. Foreign body aspiraion.

4. Whooping cough.

5. Bronchial asthma (IgE test, pulmonary function test, allergy tests).

6. Tuberculosis (detecting mycobacteria/chest X-rays).

7. Pseudocroup (hoarseness, strong stridor).

8. Chronic bronchitis (patients history, pulmonary lung function).

Acute obstructive bronchitis. Acute obstructive bronchitis is the bronchitis accompanied by a bronchial obstruction syndrome.

Etiology. Respiratory viruses: coronavirus, rhinovirus, respiratory syncytial virus, parainfluenza type III virus, and adenovirus; atypical bacteria's Chlamydia pneumoniae and Mycoplasma pneumoniae. However, these pathogens have been identified in just a minority of patients with the acute bronchitis, and it is unclear if these agents are involved in causing the symptoms.

Pathogenesis. There are three main pathogenetic syndromes:

– bronchial mucous membrane hypertrophy due to the inflammation (infectious, allergic), which leads to edema and cellular infiltration of mucous and submucous membranes;

– hypersecretion and bronchial secret properties changes (ciliary dyskinesia syndrome leads to bronchial secret evacuation disorders);

– spasm of smooth bronchial muscles.

Children with catarrhal and lymphohypoplastic types of diathesis are more predisposed to hypersecretion due to the bronchial hyperreactivity, which means bronchial overreaction with usual triggers. The secondary bronchial hyperreactivity develops due to the infectious, allergic, irritant respiratory tract damage as a result of bronchopulmonary dysplasia, congenital hypoplasia, etc.

Clinical symptoms. Cough: productive, spasmodic, compulsive with viscous sputum. Dyspnea, long expiration. Intoxication: weakness, loss of appetite, malaise, dizziness. Fever of different severity.

The favorable course of the disease is typical. The signs of obstruction decrease in 2–4 days, but the expiration elongation can persist up to 7–10 days.

Diagnostics. Hoarseness, stridor, long expiration. Distant rales, the auxiliary muscles take part in the respiration, emphysematous lung sounds. Auscultation: multiple diffuse dry and different in diameter moist rales predominantly on expiration, changing in cough (after cough the quantity of rales decreases), signs of mild respiratory failure. CBC: WBC is normal or decreased, lymphocytosis, monocytosis, increased or normal ESR, neutrophilic shift in case of bacterial infection. X-Ray: emphysema signs, increased lung pattern, peribronchial and perivascular infiltration, shadows are absent.

Differential diagnosis:

1. Foreign body aspiration: cough appears to be abrupt, without other signs of the respiratory disease; parents usually know the real time of the cough appearance; signs of viral infection are absent; severity of symptoms varies with the change of the body position.

2. Bronchial asthma attack: the obstructive bronchitis episode appears in case of the acute respiratory viral infection, accompanied by the fever.

3. Pneumonia: severe infectious toxicosis; persistent fever; local changes in the lungs: local dullness of sounds, local moist rales.

4. Thymomegaly.

5. Intrathoracic lymph nodes enlargement.

6. Congenital lobar emphysema.

7. Diaphragmatic hernia.

8. Thoracic tumors.

Bronchiolitis. Bronchiolitis is an inflammatory disease of the lower respiratory passages, with severe obstruction at the level of the bronchioles. Infants under 2 years of age could be affected. The peak of incidence is at the age of 6 months. The disease usually occurs in winter or spring months.

Etiology. Viral infections: Respiratory Syncytial virus, Parainfluenza type III virus, Adenovirus, Influenza viruses. Rare: Mycoplasma pneumoniae, Chlamydia pneumoniae.

Pathogenesis. The inflammation of the bronchial mucosa leads to edema, thickening, formation of mucus plugs and cellular debris. A bronchiolar spasm occurs in some cases. The bronchial lumen, which is still narrow in infants, is further reduced. In infants even a slight further narrowing of the bronchiolar lumen causes a marked increase in the airway resistance and the reduction of the airflow. Resistance to the airflow is increased both with inspiration and expiration. At the expiration, the bronchioles are partially collapsed and, therefore, the egress of the air from the lungs is severely restricted at this phase. This leads to trapping the air inside the alveoli, causing emphysematous changes. When the obstruction becomes complete, the trapped air in the lungs may be absorbed causing atelectasis. Due to the diminished ventilation and diffusion, hypoxemia appears in almost all infants. In severely hypoxemic infants, retention of carbon dioxide leads to respiratory acidosis. In the milder cases, compensation occurs due to the hyperventilation of the normal alveoli.

An earlier sensitizing virus infection by the same virus precedes an episode of bronchiolitis. The presence of eosinophils in the blood and respiratory secretions suggests that the virus infection initiates the wheezing attack in a child who has already been sensitized.

Clinical symptoms:

1. The first clinical sign is the infection of the upper respiratory tract; usually, another family member is ill with a respiratory infection.
2. After 1–2 days of mild rhinitis, nasopharyngitis or tracheitis, an infant develops increasing spasmodic cough, dyspnea, tachypnea (till 70–90 bpm).
3. The retraction of the lower intercostal spaces and suprasternal notch soon becomes evident.
4. Wheezing, cough.
5. Nasal flaring (in babies).
6. Bluish appearance of the skin, perioral and generalized cyanosis.
7. Tachycardia.
8. Loss of appetite, vomiting.
9. Irritability, fatigue.
10. Fever is moderately high.

Diagnostics:

1. Anamnesis: a typical step-by-step onset of the disease, spasmodic cough.
2. The auxiliary muscles of respiration are working.
3. Both inspiration and expiration are prolonged.
4. There are emphysematous sounds on percussion.
5. Auscultation: rough or diminished breath sounds; in most severe cases they can be barely audible (Bronchiolitis obliterans).
6. Rales: abudance of moist little diameter diffuse rales, changing at the time of ough; dry rales and wheezing in expiration.
7. Percussion note is hyper-resonant.
8. Muffled heart sounds.

9. The liver and spleen are pushed down (as a result of the depression of the diaphragm due to emphysema);

10. CBC: WBC is usually normal or decreased, rare — leukcytosis; lymphocytosis, normal or increased ESR.

11. Chest X-ray: hyperinflation and mild infiltrates are noted on chest X-ray especially in the lateral views. The diaphragm is pushed down; the lung fields appear abnormally translucent.

Differential diagnosis:

1. Bronchial asthma: asthma is unusual below the age of 1 year; often a family history of asthma; several attacks occur in the same patient; asthma may occur without a preceding respiratory infection; patients with asthma respond to the injection of adrenaline.

2. Congestive heart failure: is suggested in the child with cardiomegaly; tachycardia; hepatomegaly; edema and rales in the bases of the lungs.

3. Foreign bodies in the trachea or bronchi: are diagnosed by the history of the foreign body aspiration, localized wheeze; signs of collapse or localized obstructive emphysema.

4. Pneumonia: the signs of the obstruction are pronounced; high fever; it's important to remember that though the illness appears to be severe, the mortality is generally low.

5. Pertussis: attacks of spasmodic cough are typical; anamnesis of vaccinations.

6. Cystic fibrosis: genetic disease, the first clinical signs appear soon after the birth. Accompanied by lungs disorders, pancreas and intestine, and sometimes liver and kidney disorders; recurrent character of the inflammation; children of the early age may have pneumonia, with a severe course and predisposition to the abscess formation; older children may have prolonged bronchitis with severe bronchospasms; pneumosclerosis with bronchiectasis development is typical; fingers remind of "drum sticks"; signs of digestive tract disorders, such as abdominal pain, swelling, borborygmus, flatulence, profuse fat stool with putrefactive odor; malnutrition; steatorrhea (large amount of neutral fat); the estimation of electrolytes amount (Cl– and Na+) secreted by sweat glands (pylocarpine test). In healthy children their concentration is less than 40 mmol/1. Cystic fibrosis is diagnosed in the majority of cases, when Cl– concentration exceeds 60 mmol/1, and in all cases when Cl– exceeds 100 mmol/1. DNA diagnostics: detection of the mutation type.

Obliterative bronchiolitis is a disease that results in the obstruction of the smallest airways of the lungs (bronchioles) due to the inflammation.

Etiology: Adenovirus (3, 7 and 21 types); Parainfluenza virus; measles; RS virus; Cytomegalovirus; Pneumocystis carinii; non-infectious reasons: systemic diseases of the connective tissue, post-transplantat reactions, broncho-pulmonary dysplasia.

Pathogenesis. There are bronchiole and little bronchi damages, when endarteritis with the narrowing of the lung and bronchial arteries are developed in

the affected area. The outcome of the pathological process is lobar or part of lobe sclerosis. But more often there is bronchiole and arteriole obliteration with air in non-ventilated, dystrophic lung tissue.

Clinical symptoms: febrile fever; dry cough; shortness of breath, wheezing; tiredness; cyanosis.

Diagnostics. Marked respiratory disorders: hypoxemia, hypercapnia, cyanosis. Auscultation: a large amount of little diameter moist rales, and long expiration. CBC: moderate leukocytosis, left shift of neutrophils, increased ESR; X-Ray: diffuse shadows without obvious contours.

If the obstructive signs continue to be present after the temperatures normalization, it indicates constant changes in the lungs (a chronic process), and unfavorable prognosis.

Bronchiolitis Obliterans with Organizing Pneumonia (BOOP). Obstruction of bronchi and bronchioles by fibrous tissue following damage to the lower respiratory tract. *Causes* include inhalation of toxic gases, infections, connective tissue diseases, AIDS, organ transplantation, aspiration, Stevens Johnson syndrome, idiopathic. Persistent cough, wheezing, sputum production after an episode of acute pneumonia. Digital clubbing rare. Restrictive abnormalities test of pulmonary function. Chest x-ray findings nonspecific. Diagnosis confirmed by lung biopsy.

Differential diagnosis: reactive airways disease, CF; bronchopulmonary dysplasia; severe pneumonia due to bacteria, fungi, or TB.

Treatment:

– supplemental oxygen if needed;

– antibiotics for documented bacterial infection;

– prevent further airway damage from aspiration, environmental toxins, infection;

– bronchodilators may be helpful if there is a reactive component;

– corticosteroids may be used.

Pearl: Prognosis depends upon underlying cause and age of onset. The course may progress to end-stage lung disease despite therapy.

Treatment of bronchitis. Indications for hospitalization:

– the first year age patients;

– absence of therapy efficiency;

– severe course of the disease.

1. Bed regimen in case of fever.

2. Diet. Because anorexia is a characteristic of acute infections, urging food at the time of the illness may precipitate vomiting or diarrhea, aversion to the feeding situation may arise and delay convalescence. The outcome of brief, acute infections does not depend on a normal dietary intake. In minor illnesses and especially when the child retains a good appetite, a regular diet may be offered. Milk and vegetable diet is reccommended. It is generally preferable to restrict the diet to favorite soft drinks in frequent small amounts, soup, toast, custard cooked cereals, etc.

3. Fluids. Maintenance of fluid intake is important because of the tendency to dehydration, caused by fever, anorexia, vomitting and diarrhea. In most cases the intake of small sips of fluids at frequent intervals is preferable, rather than large amounts less frequently. The increase of the liquid intake 1.5–2 times is recommended.

4. Control of fever. Fever is a protective reaction of the body, which provides activation of the immune factors, neutrophils and macrophages movement to the locus of infection, microbe's opsonization, complete phagocytosis etc. But hyperpyrexia leads to increased energy consumption and direct heart and brain damage, and can be harmful.

Fever of variable degrees accompanies the most acute infections in childhood. Frequently it is mild that it needs no treatment. High temperature increases restlessness, accentuates an insensible fluid loss from the skin and the lungs, and may produce meningismus or febrile convulsions. The control of fever is advisable when it upsets a child's condition. Although the opinions differ, measures are usually taken to reduce the temperature when it exceeds 38.5 °C. It is unnecessary to decrease a fever till a normal level, decrease to a non-dangerous level is recommended.

Antipyretics:

• Acetaminophen 0.2 g (0.5 g) (Paracetamol, Panadol) reduces fever with direct acting on hypothalamic heat-regulating centers, increasing dissipation of the body heat via vasodilatation and sweating. Dose: 10–15 mg/kg per day orally, divided into 4–6 times. When the child is vomiting, Acetaminofen may be given rectally in the form of suppositories.

• Ibuprofen (Ibufen, Nurofen etc.) 5–10 mg/kg per dose P.O. every 6–8 hours inhibits prostaglandin formation. Daily dose is 20–30 mg/kg.

• Contraindications: hypersensitivity; peptic ulcer disease; high risk of bleeding; renal insufficiency.

5. Local therapy includes evacuation of mucopurulent nasal secretion.

Nasal decongestants in case of associated rhinosinusitis. The proper use of vasoconstrictor nose drops, isotonic with nasal secretions, may be of benefit. Such drops may be instilled 3 times a day for no longer than 5 days. More frequent or prolonged administration may lead to the persistent congestion of the nasal membrane. The technique of instillation should be discussed carefully; it is useful to give printed instructions to ensure proper administration. Unless adequately instructed, parents tend to hold the child's head in the crook of the elbow, tilt the head backward, instill drops into both nostrils, and then hold the child up to comfort him immediately thereafter when he or she cries and struggles. In this case the drops run out of the nose and are of little or no effect.

Phenylephrine (Neo-synephrine) nasal drops: 0.125 %, 0.25 %, 0.5 %, 1 %; nasal spray: 0.25 %, 0.5 %, 1 %. Discontinue the use after 3 days to avoid rebound congestion.

Dose:

– 1–5 years old: use 1–2 drops/spray of 0.125 % in each nostril every 3–4 hours;

– 6–12 years: use 2–3 drops of 0.25 % or 1 spray of 0.25 % in each nostril every 3–4 hours;

– more than 12 years: use 2–3 drops of 0.25–0.5 % or 1–2 sprays of 0.25–0.5 % in each nostril every 3–4 hours.

Physiological solutions: 0.65 % NaCl — there are no contraindications. Usually it is used for 7–10 days.

6. Antiviral drugs: interferons and interferons inductors. Interferon leukocyte 2.0 ml — use for the first 3 days every 4–6 hours. Isoprinosine 0.5 in dose 50 mg/kg per day twice a day.

7. In case of bacterial infection antibiotics should be administered (see Treatment of pneumonia). Indications for antibacterial therapy: purulent sputum; leukocytosis, neutrophilic shift, increased ESR; patients with associated diseases: malnutrition, severe immaturity, immunodeficiency, anemia, rickets, other congenital or acquired chronic diseases.

8. Antitussive and mucolytic drugs characteristics is shown on Table 8.1.

Table 8.1

Antitussive and mucolytic drugs characteristics

Pharmacological group	International medicine title	Dosage
Antitussive	Butamiratum	2 months – 1 year: 2.5 mg every 6 hours; 1–3 years: 2.5–5 mg every 6 hours; 3–6 years: 7.5 mg every 8 hours; 6–12 years: 15 mg every 8 hours; > 12 years: 22.5 mg every 8 hours
	Glaucine (Glauvent)	1–2 mg/year of life every 8–12 hours. Max 1 time dose for children till 4 years is 10 mg
	Oxeladinum (Tusuprex)	More than 2 years — 5–10 mg every 6–8 hours
	Pentoxyverinum (Sedotussin)	1–3 years — 1.5–3 mg/kg per day; 4–10 years — 15 mg every 8 hours; 10–14 years — 22.5 mg every 6–8 hours
	Prenoxdiazinum (Libexin)	25–50 mg every 6–8 hours
Mucolytics	Ambroxol hydrochloridum	2–5 years — 7.5 mg every 8 hours; 6–12 years — 15 mg every 8–12 hours
	Acetylcysteinum	2–5 years — 100 mg every 8–12 hours; 6–14 years — 200 mg every 12 hours
	Bromhexinum	2–5 years — 2–4 mg every 8 hours; 6–10 years — 4–8 mg every 8 hours; > 10 years — 8–16 mg every 8 hours
	Carbocysteinum	2–5 years — 62.5–125 mg every 6 hours; 6–12 years — 250 mg every 6 hours

9. Infusion IV therapy in case of severe toxicosis, exicosis, electrolytes disorders.

10. In cases of ***obstructive bronchitis*** it is necessary to use: inhalation and oral (β_2-adrenergetic agonists (Berotec, Salbutamol, Terbutalin, etc); cholynolitics (Atrovent), combined drugs (Berodual, Duovent), inhalational corticoids (Inhacort, Budesonid, Flixotid).

11. Vibrating massage and postural drainage.

8.2. PNEUMONIA

Pneumonia causes substantial morbidity in children worldwide and is a leading factor of mortality in resource-limited countries. Pneumonia can occur at any age, but it is more common in younger children. The WHO estimates that more than 150 million cases of pneumonia occur each year among children younger than 5 years worldwide, accounting for 10–20 million hospitalizations. Pneumonia is a leading cause of morbidity and mortality in this population, resulting in 1.4 million deaths annually. Pneumonia is diagnosed in 20 out of 1,000 children of the 1st year of life, 40 out of 1,000 in preschool age, in schoolchildren and adolescents in approximately 10 out of 1,000. Most cases occur in India, China and Pakistan, with additional high numbers in Bangladesh, Indonesia and Nigeria. Substantial evidence revealed that the leading risk factors contributing to pneumonia incidence are lack of exclusive breastfeeding, undernutrition, indoor air pollution, crowding, low birth weight and lack of measles immunization. Most children are treated as outpatients and fully recover. However, in infants and immunocompromised individuals, mortality is much higher.

Community-acquired pneumonia (CAP) refers to pneumonia (any of several lung diseases) contracted by a person outside of the healthcare system. Hospital-acquired pneumonia (HAP) is seen in patients who have recently visited a hospital or who live in long-term care facilities. CAP is the most common type of pneumonia. Of all community cases, 7–13 % is severe enough to be life-threatening and require hospitalization.

Pneumonia can be generally defined as an infection of the lung parenchyma, in which consolidation of the affected part and a filling of the alveolar air spaces with exudate, inflammatory cells, and fibrin is characteristic. Although most cases of pneumonia are caused by microorganisms, noninfectious causes include aspiration of food or gastric acid, foreign bodies, hydrocarbons, and lipoid substances, hypersensitivity reactions, and drug- or radiation-induced pneumonitis.

Pneumonia can be classified in several ways.

By location acquired:

• *Community-acquired pneumonia* (CAP) refers to a pneumonia in a previously healthy person who acquired the infection outside a hospital. CAP is the most common type of pneumonia.

• *Hospital-acquired pneumonia* (HAP) also called nosocomial pneumonia, is acquired during or after hospitalization for another illness or procedure with onset at least 48–72 hrs after admission. HAP includes ventilator-associated pneumonia (VAP) which occurs after at least 48 hours of intubation and mechanical ventilation, postoperative pneumonia, and pneumonia that develops in unventilated hospitalized inpatients.

The causes, microbiology, treatment and prognosis are different from those of community-acquired pneumonia. Up to 5 % of patients admitted to a hospital for other causes subsequently develop pneumonia. Hospitalized patients may have many risk factors for pneumonia, including mechanical ventilation, prolonged

malnutrition, underlying heart and lung diseases, decreased amounts of stomach acid, and immune disturbances. Additionally, the microorganisms a person is exposed to in a hospital are often different from those at home. Hospital-acquired microorganisms may include resistant bacteria such as *MRSA, Pseudomonas*, *Enterobacter*, and *Serratia*. Because individuals with hospital-acquired pneumonia usually have underlying illnesses and are exposed to more dangerous bacteria, it tends to be more deadly than community-acquired pneumonia.

• *Congenital pneumonia* presents within the first 72 hours after birth.

By cause:

• Pneumonia is characterized as either typical or atypical depending on the presenting symptoms and thus the presumed underlying organism.

• Aspiration pneumonia (or aspiration pneumonitis) is caused by aspirating foreign objects which are usually oral or gastric contents, either while eating, or after reflux or vomiting which results in bronchopneumonia. The resulting lung inflammation is not an infection but can contribute to one, since the material aspirated may contain anaerobic bacteria or other unusual causes of pneumonia. Aspiration is a leading cause of death among hospital and nursing home patients, since they often cannot adequately protect their airways and may have otherwise impaired defenses.

By area of lung affected:

• ***Lobar*** pneumonia is an infection that involves one or more lobes of lung. Lobar pneumonia is often due to *Streptococcus pneumoniae* (though *Klebsiella pneumoniae* is also possible).

• ***Segmental*** pneumonia involves one or more segments of lung.

• ***Multifocal*/*lobular*** pneumonia affects the lungs in patches around the tubes (bronchi or bronchioles).

• ***Interstitial*** pneumonia involves the areas (interstitial tissue) in between the alveoli. It is more likely to be caused by viruses or by atypical bacteria.

By severity: ***moderate*** and ***severe*** pneumonia.

By duration: ***acute*** pneumonia lasts for 6–8 weeks.

Slowly resolving pneumonia refers to the persistence of symptoms or radiographic abnormalities beyond the expected time course > 6–8 weeks and < 6 month.

Recurrent pneumonia is defined as 2 or more episodes in a single year or 3 or more episodes ever, with X-ray clearing between occurrences. Recurrent pneumonia should be differentiated from:

– *hereditary disorders:* cystic fibrosis, sickle cell disease;

– *disorders of immunity:* Bruton agammaglobulemia, selective IgG subclass deficiencies, common variable immunodeficiency syndrome, severe combined immunodeficiency syndrome;

– *disorders of leukocytes:* chronic granulomatous disease, hyper IgE syndrome, leukocyte adhesion defect;

– *disorders of cilia:* immotile cilia syndrome, Kartagener's syndrome;

– *anatomic disorder:* sequestration, lobar emphysema, tracheoesophageal fistula;

– bronchietasis; foreign body; gastroesophageal reflux; aspiration (oropharyngeal in coordination).

Community-acquired pneumonia. *Etiology and risk factors.* The term "community-acquired pneumonia" (CAP) refers to a pneumonia in a previously healthy person who acquired the infection outside a hospital. Determining the cause of pneumonia in children is often difficult, sputum from the lower respiratory tract can rarely be obtained. As with adults, culturing the upper respiratory tract is of little value, as the normal flora in this area may not be responsible for the pneumonia. Direct culture of lung tissue is invasive and rarely performed. Several investigations have explored the etiology of CAP. These studies vary considerably in their etiologic findings. The use of different evaluative laboratory tests between studies poses a challenge in comparing the causes of pneumonia. It is widely accepted that the most prominent pathogens responsible for CAP in children are viral and bacterial in nature. It is important to note that children often present with combined infections of multiple viruses, bacteria, or both.

Streptococcus pneumoniae, Haemophilus influenzae, and *Staphylococcus aureus* are the major causes of hospitalization and death from pneumonia among children in developing countries, although in children with HIV infection — *Mycobacterium tuberculosis*, atypical mycobacterium, *Salmonella*, *Escherichia coli,* and *Pneumocystis jirovecii (carinii).* Viral pathogens are a prominent cause of lower respiratory tract infections in infants and children < 5 yr of age. Viruses are responsible for 45 % of the episodes of pneumonia identified in hospitalized children. Unlike bronchiolitis, for which the peak incidence is in the 1st yr of life, the highest frequency of viral pneumonia occurs between the ages of 2 and 3 yr, decreasing slowly thereafter. Of the respiratory viruses, influenza virus and respiratory syncytial virus (RSV) are the major pathogens, especially in children < 3 yr of age. Other common viruses causing pneumonia include parainfluenza viruses, adenoviruses, rhinoviruses, and metapneumovirus.

Pediatric CAP exhibits age-related causation because children may be exposed to different pathogens in various age-related settings (home, day care, school) and because, with the development of immunity, children become less likely to acquire certain infections and more likely to develop others. In children aged 3 months to 5 years, viruses are the most common cause of pneumonia, but *Streptococcus pneumonia* and atypical bacteria — particularly *Mycoplasma pneumoniae* and *Chlamydophila pneumonia* — are also common. In children aged > 5 years, *S. pneumoniae, M. pneumoniae,* and *C. pneumonia* are the most important causes of pneumonia. The microorganisms most frequently associated with pneumonia in children are listed in Table 8.2.

Immunization status is relevant because children fully immunized against *H. influenzae* type B and *S. pneumoniae* are less likely to be infected with these

pathogens. Children who are immunosuppressed or who have an underlying illness may be at risk for specific pathogens, such as *Pseudomonas spp*. in patients with cystic fibrosis.

Table 8.2

Causes of community-acquired pneumonia by age group

Age group	Frequent pathogens (in order of frequency)
Neonates (< 1 Mo)	Group B Streptococcus, *Escherichia coli,* other Gram-negative bacilli, *Streptococcus pneumoniae, Haemophilus influenzae* (type B, nontypable)
1–3 Mo	
Febrile Pneumonia	Respiratory syncytial virus, other respiratory viruses (Parainfluenza viruses, Influenza viruses, Adenoviruses), *S. pneumoniae, H. influenzae* (type B, nontypable)
Afebrile Pneumonia	*Chlamydia trachomatis, Mycoplasma hominis, Ureaplasma urealyticum,* Cytomegalovirus
3–12 Mo	Respiratory syncytial virus, other respiratory viruses (Parainfluenza viruses, Influenza viruses, Adenoviruses), *S. pneumoniae, H. influenzae* (type B, nontypable), *C. trachomatis, Mycoplasma pneumoniae*, Group A Streptococcus
2–5 Yr	Respiratory viruses (Parainfluenza viruses, Influenza viruses, Adenoviruses), *S. pneumoniae, H. influenzae* (type B, nontypable), *M. pneumoniae, Chlamydophila pneumoniae, S. aureus*, Group A Streptococcus
5–18 Yr	*M. pneumoniae, S. pneumoniae, C. pneumoniae, H. influenzae* (type B, nontypable), Influenza viruses, Adenoviruses, other respiratory viruses
≥ 18 Yr	*M. pneumoniae, S. pneumoniae, C. pneumoniae, H. influenzae* (type B, nontypable), Influenza viruses, Adenoviruses, *Legionella pneumophila*

There are *several factors that may increase a child's risk of acquiring CAP*. Immunologic disorders, hematologic disorders, cardiac conditions, and chronic pulmonary conditions are considered significant risk factors for pneumonia. Other factors include preexisting illnesses such as HIV infection and measles. In addition, malnourished children and infants who are not exclusively breastfed are more likely to have a weakened immune system, which increases their risk of acquiring pneumonia. Finally, environmental factors, including air pollution, living in a crowded home, and parental smoking, heighten a child's risk of infection.

Pathophysiology. Pneumonia results from the proliferation of microbial pathogens and the host's response to the offending microorganisms at the alveolar level of the lower respiratory tract. Microorganisms may gain access to the lower respiratory tract through *four different pathways*: inhalation of contaminated droplets, aspiration of oropharyngeal or gastrointestinal contents, hematogenous spread, and progressive extension from a contiguous site of infection. Pneumonia occurs after the host's immune and nonimmune defense systems are breached and manifests when the capacity of alveolar macrophages to ingest, kill, and clear microorganisms is exceeded by the number of pathogens.

The lower respiratory tract is normally kept sterile by physiologic defense mechanisms, including the mucociliary clearance, the properties of normal secretions such as secretory 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.

Viral pneumonia usually results from spread of infection along the airways, accompanied by direct injury of the respiratory epithelium, resulting in airway obstruction from swelling, abnormal secretions, and cellular debris. The small caliber of airways in young infants makes them 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.

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 exudate, 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 cavitation of the lung parenchyma, resulting in pneumatoceles, empyema, or, at times, bronchopulmonary fistulas.

Clinical presentation. The signs and symptoms of pneumonia are often nonspecific and widely vary based on the patient’s age and the infectious organisms involved (Fig. 8.1). Tachypnoea is the most sensitive finding in patients with diagnosed pneumonia.

Initial evaluation. Early in the physical examination, identifying and treating respiratory distress, hypoxemia, and hypercarbia is important. Visual inspection of the degree of respiratory effort and accessory muscle use should be performed to assess for the presence and severity of respiratory distress. The examiner should simply observe the patient's respiratory effort and count the respirations for a full minute. In infants, observation should include an attempt at feeding, unless the baby has extreme tachypnea.

Pulmonary findings in all age groups may include accessory respiratory muscle recruitment, such as nasal flaring and retractions at subcostal, intercostal,

or suprasternal sites. Retractions result from the effort to increase intrathoracic pressure to compensate for decreased compliance. Signs such as grunting, flaring, severe tachypnea, and retractions should prompt the clinician to provide immediate respiratory support.

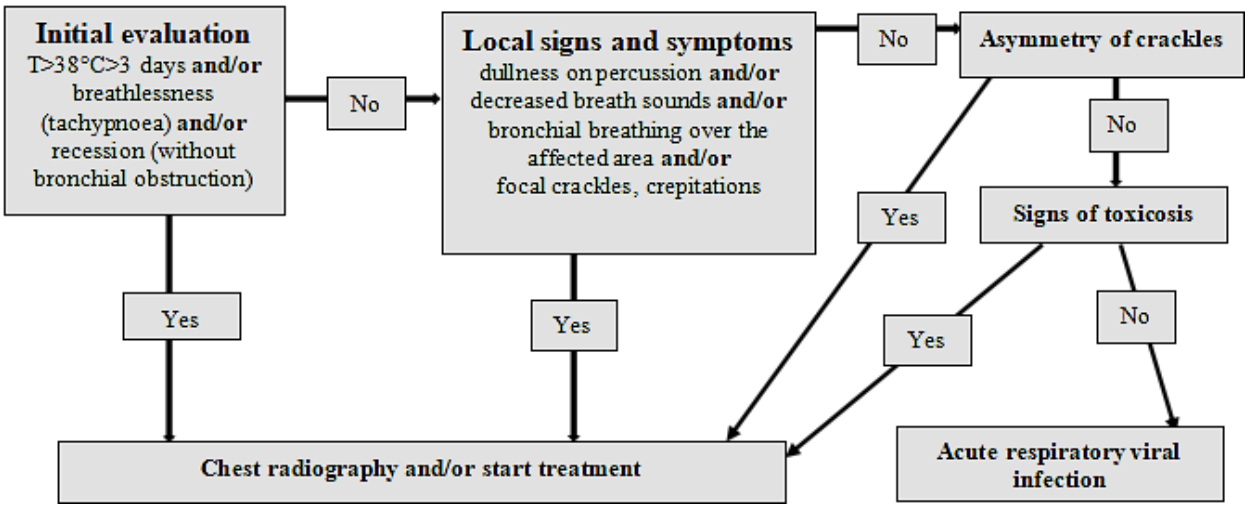


Fig. 8.1. Algorithm for the clinical diagnosis of pneumonia

An emergency department (ED) — based study conducted in the United States found that respiratory rate alone and subjective clinical impression of tachypnea did not discriminate children with and without radiographic pneumonia. The WHO clinical criteria for pneumonia has also been reported to demonstrate poor sensitivity (34.3 %) in diagnosing radiographic pneumonia in children presenting to a pediatric ED. However, children with tachypnea as defined by WHO respiratory rate thresholds were more likely to have pneumonia than children without tachypnea.

The WHO respiratory rate thresholds are as follows:

– children younger than 2 months — greater than or equal to 60 breaths/min;

– children aged 2–11 months — greater than or equal to 50 breaths/min;

– children aged 12 months – 59 months — greater than or equal to 40 breaths/min;

– children aged 5–11 years — greater than 35 breaths/min;

– children older than 12 years — greater than 30 breaths/min.

Airway secretions may vary substantially in quality and quantity but are most often profuse and progress from serosanguineous to a more purulent appearance. White, yellow, green, or hemorrhagic colors and creamy or chunky textures are not infrequent. If aspiration of meconium, blood, or other proinflammatory fluid is suspected, other colors and textures reflective of the aspirated material may be seen.

Infants may have external staining or discoloration of skin, hair, and nails with meconium, blood, or other materials when they are present in the amniotic fluid. The oral, nasal, and, especially, tracheal presence of such substances is particularly suggestive of aspiration.

An assessment of oxygen saturation by pulse oximetry should be performed early in the evaluation of all children with respiratory symptoms. Cyanosis may be present in severe cases. When appropriate and available, capnography may be useful in the evaluation of children with potential respiratory compromise.

Cyanosis of central tissues, such as the trunk, implies a deoxyHb concentration of approximately 5 g/dL or more and is consistent with severe derangement of gas exchange from severe pulmonary dysfunction as in pneumonia, although congenital structural heart disease, hemoglobinopathy, polycythemia, and pulmonary hypertension (with or without other associated parenchymal lung disease) must be considered.

Chest pain may be observed with inflammation of or near the pleura. Abdominal pain or tenderness is often seen in children with lower lobe pneumonia. The presence and degree of fever depends on the organism involved, but high temperature (38.4 °C) within 72 hours after admission and the presence of pleural effusion have been reported to be significantly associated with bacterial pneumonia.

Pneumonia may occur as a part of another generalized process. Therefore, signs and symptoms suggestive of other disease processes, such as rashes and pharyngitis, should be sought during the examination.

Auscultation. Auscultation is the most important part of the examination of the child with respiratory symptoms, is often very difficult in infants and young children. Babies and young children often cry during the physical examination making auscultation difficult. The best chance of success lies in prewarming hands and instruments and in using a pacifier to quiet the infant. The opportunity to listen to a sleeping infant should never be lost.

Older infants and toddlers may cry because they are ill or uncomfortable, but, most often, they have stranger anxiety. For these children, it is best to spend a few minutes with the parents in the child's presence. If the child sees that the parent trusts the examining physician, then he or she may be more willing to let the examiner approach. A small toy may help to gain the child's trust. Any part of the examination using instruments should be deferred as long as possible, because the child may find the medical equipment frightening. Occasionally, if the child is allowed to hold the stethoscope for a few minutes, it becomes less frightening. Even under the best of circumstances, examining a toddler is difficult. If the child is asleep when the physician begins the evaluation, auscultation should be performed early.

Children with respiratory symptoms may have a concomitant upper respiratory infection with copious upper airway secretions. This creates another potential problem, the transmission of upper airway sounds. In many cases, the sounds created by upper airway secretions can almost obscure true breath sounds and lead to erroneous diagnoses. If the etiology of sounds heard through the stethoscope is unclear, the examiner should listen to the lung fields and then hold the stethoscope near the child's nose. If the sounds from both locations are approximately the same, the likely source of the abnormal breath sounds is the upper airway.

Even when the infant or young child is quiet and has a clear upper airway, the child's normal physiology may make the examination difficult. The minute ventilation is the product of the respiratory rate and tidal volume. In young children, respiratory rate makes a very large contribution to the overall minute ventilation: babies take many shallow breaths as opposed to a few deep ones. Therefore, a subtle finding, particularly one at the pulmonary bases, can be missed.

The sine qua non for pneumonia has always been the presence of crackles or rales. Although often present, focal crackles as a stand-alone physical examination finding is neither sensitive nor specific for the diagnosis of pneumonia. Additionally, not all children with pneumonia have crackles.

Rales, rhonchi, and cough are all observed much less frequently in infants with pneumonia than in older individuals. If present, they may be caused by noninflammatory processes, such as congestive heart failure, condensation from humidified gas administered during mechanical ventilation, or endotracheal tube displacement. Although alternative explanations are possible, these findings should prompt careful consideration of pneumonia in the differential diagnosis.

Other examination findings suggestive of pneumonia include asymmetry of breath sounds in infants, such as focal wheezing or decreased breath sounds in one lung field, and asymmetry of chest excursions, which suggest air leak or emphysematous changes secondary to partial airway obstruction. Similarly, certain more diffuse lung infections (viral infections) may result in generalized crackles or wheezing.

In lobar pneumonia, fibrinous inflammation may extend into the pleural space, causing a rub heard by auscultation. Pericardial effusion in patients with lower lobe pneumonia due to *H. influenza* may also cause a rub. Other signs and/or findings in lobar pneumonia include abdominal pain or an ileus accompanied by emesis in patients with lower lobe pneumonia and nuchal rigidity in patients with right upper lobe pneumonia.

Percussion may reveal important information. Occasionally, a child presents with a high fever and cough but without auscultatory findings suggestive of pneumonia. In such cases, percussion may help to identify an area of consolidation.

Systemic and localized findings. Systemic findings in newborns with pneumonia may provide clues to the etiology. Rash or jaundice at birth may indicate congenital infection. Nonspecific findings such as tachycardia, glucose intolerance, abdominal distention, hypoperfusion, and oliguria are very common is moderately to severely ill newborns, and are not specific for a lung focus of infection. Localized findings include conjunctivitis (consider *C. trachomatis*), vesicles or other focal skin lesions (consider HSV), and unusual nasal secretions (consider congenital syphilis).

Adenopathy in older children suggests long-standing infection and should suggest a more chronic cause such as TB or a dimorphic fungal infection (histoplasmosis, blastomycosis). Hepatomegaly from infection may result from the presence of some chronic causative agents, cardiac impairment, or increased

intravascular volume. Apparent hepatomegaly may result if therapeutic airway pressures allow generous lung inflation and downward displacement of a healthy liver.

***Other considerations*.** Infants infected with organisms in utero or via the maternal genital tract commonly present within the first few hours after birth, but if infection is acquired during the delivery, the presentation may be delayed. The usual presenting symptoms include tachypnea, hypoxemia, and signs of respiratory distress. Auscultation may reveal diffuse fine crackles.

Early onset group B streptococci infection usually presents via ascending perinatal infection as sepsis or pneumonia within the first 24 hours of life. *C .trachomatis* pneumonia should be considered in infants aged 2–4 weeks. Pneumonia presents as an afebrile pneumonitis with congestion, wheezing, fine, diffuse crackles, a paroxysmal cough and is often associated with conjunctivitis. Infants infected with *C. pneumoniae*, *U. urealyticum*, *Mycoplasma hominis*, CMV, and *P. carinii* present between age 4 and 11 weeks with an afebrile pneumonia characterized by a staccato cough, tachypnea, and, occasionally, hypoxia.

Infants or toddlers with bacterial pneumonia may present with lethargy, irritability, acidosis, hypotonia, or hypoxia that is out of proportion to ausculatory findings; school-aged children and adolescents are often febrile and appear ill.

Mycoplasma pneumoniae is more common in school-aged children than toddlers. Mycoplasma infections are indolent, with gradual onset of malaise, low-grade fever, sore throat, hacking, dry cough (can be very persistent), headache, rashes (such as erythema multiforme, erythema nodosum and urticarial), myalgia and arthralgia. *C. pneumoniae* is also fairly common in children aged 5 years and presents in a similar fashion. In atypical pneumonia, wheeze is more often seen than in typical bacterial pneumonia.

Pneumonia caused by *B. pertussis* occurs predominantly in infants who have not completed their vaccinations or in children who did not receive vaccinations. Clinical presentation includes coryza, malaise, fever, paroxysms of cough occasionally accompanied by emesis, apnea, poor feeding, and cyanosis. Adolescents infected with pertussis present with a paroxysmal cough, which persists for more than 3 weeks and may last up to 3 months, unlike the whooping cough of younger children. Chest X-ray in this patients are almost always normal, despite the intensity of the cough.

Although infection with *H. capsulatum* is usually asymptomatic in older children and adolescents, infants and young children are at risk for symptomatic infection, which may cause respiratory distress and hypoxemia.

Pneumonia is the most common cause of acute chest syndrome, which occurs in 15–43 % of patients with sickle cell disease. This syndrome is characterized by fever, chest pain, dyspnea, cough, tachypnea, crackles.

Alternative diagnoses and missed diagnosis. There are a few other conditions that should be considered in children with this presentation. Bronchiolitis in babies' manifests with rhinorrhoea, fever and tachypnoea.

Bilateral crackles and/or wheeze may be evident. Children with upper respiratory tract infections have normal saturations and a clear chest on auscultation. Babies with HF often have a known history of congenital heart disease and may have bilateral chest signs without fever. UTI and bacteraemia should be considered in children with fever who have minimal respiratory symptoms or signs. Tachypnea alone may be a sign of underlying metabolic acidosis e.g. diabetic ketoacidosis. Lower lobe pneumonia may present with abdominal pain and fever. In these patients, the increased respiratory rate and low saturations may aid the diagnosis, however these signs can be absent or minimal. Children with pneumonia may also present with fever alone.

Diagnosis. *The chest radiograph* confirms the diagnosis of pneumonia and may 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. 8.2).

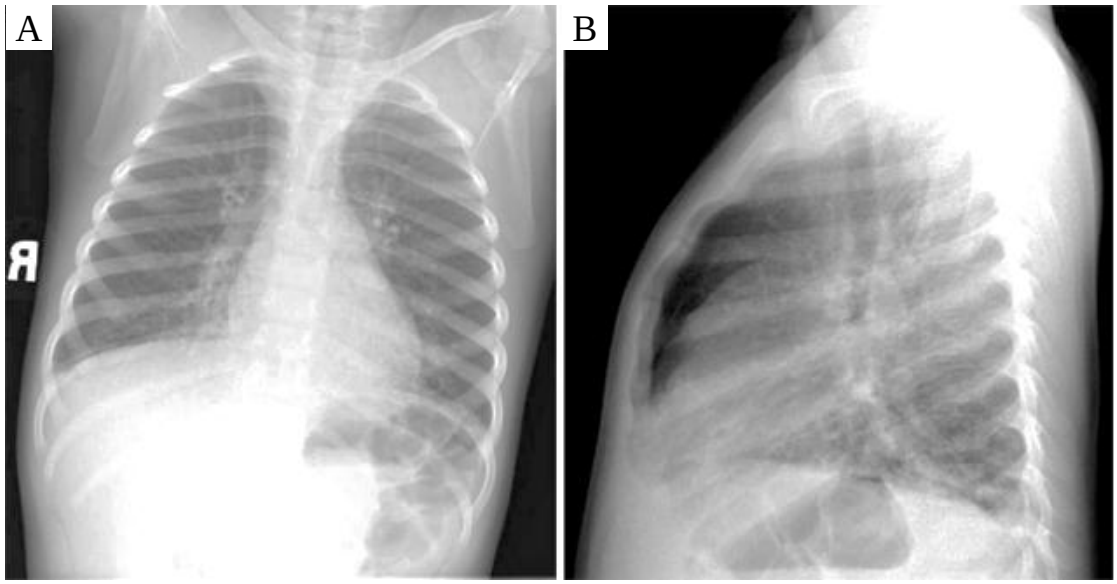


Fig. 8.2. Anteroposterior (A) and lateral (B) radiographs from a child with presumptive viral pneumonia

Chest X-ray shows hyperinflation with bilateral, symmetrical interstitial infiltrates in infants with pneumonia caused by *Chlamydia trachomatis* (Fig. 8.3).

Confluent lobar consolidation is typically seen with pneumococcal pneumonia (Fig. 8.4). X-ray appearance alone is not diagnostic and other clinical features must be considered. Repe at chest X-rays are not required for proof of cure for patients with uncomplicated pneumonia.

WBC count can be useful in differentiating viral from bacterial pneumonia. In viral pneumonia, the WBC count can be normal or elevated but is usually not higher than 20.000/mm^3, with a lymphocyte predominance. Bacterial pneumonia (occasionally, adenovirus pneumonia) is often associated with an elevated WBC count in the range of 15.000–40.000/mm^3 and a predominance of granulocytes. A large pleural effusion, lobar consolidation, and a high fever at the onset of the illness are also suggestive of a bacterial etiology.

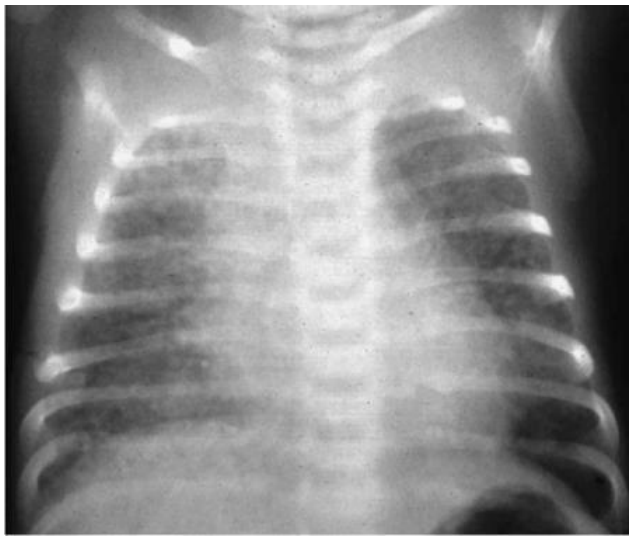


Fig. 8.3. Pneumonia caused by *Chlamydia trachomatis* in a 3-month-old infant with inclusion conjunctivitis

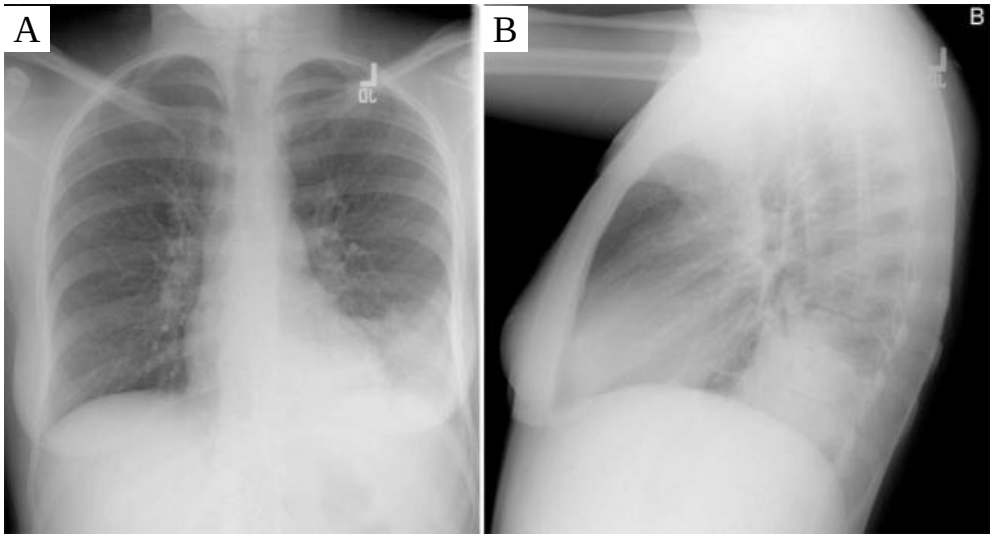


Fig. 8.4. Anteroposterior (A) and lateral (B) radiographs from a child with a left lower lobe infiltrate

Atypical pneumonia due to *C. pneumoniae* or *M. pneumoniae* is difficult to distinguish from pneumococcal pneumonia by X-ray and other labs, and although pneumococcal pneumonia is associated with a higher WBC count, ESR, and CRP, there is considerable overlap.

The definitive diagnosis of a viral infection rests on the isolation of a virus or detection of the viral genome or Ag in respiratory tract secretions. Growth of respiratory viruses in tissue culture usually requires 5–10 days. Reliable DNA or RNA tests for the rapid detection of RSV, parainfluenza, influenza, and adenoviruses are available and accurate. Serologic techniques can also be used to diagnose a recent respiratory viral infection but generally require testing of acute and convalescent serum samples for a rise in AB to a specific viral agent. This technique is laborious, slow, and not generally clinically useful because the infection usually resolves by the time it is confirmed serologically. Serologic

testing may be valuable as an epidemiologic tool to define the incidence and prevalence of the various respiratory viral pathogens.

The definitive diagnosis of a bacterial infection requires isolation of an organism from the blood, pleural fluid, or lung. Culture of sputum is of little value in the diagnosis of pneumonia in young children. Blood culture remains the non-invasive gold standard for determining the precise etiology of pneumonia. However, the sensitivity of this test is very low. Positive blood cultures are found only in 10–30 % of patients with pneumonia. Blood culture should be performed in severe pneumonia or when there is poor response to the first line antibiotics.

In *M. pneumoniae* infections, cold agglutinins at titers > 1 : 64 are found in the blood in ≈ 50 % of patients. Cold agglutinins are nonspecific, however, because other pathogens such as influenza viruses may also cause increases. Acute infection caused by *M. pneumoniae* can be diagnosed on the basis of a positive PCR test or seroconversion in an IgG assay. Serologic evidence such as the ASLO titer may be useful in the diagnosis of group A streptococcal pneumonia.

Severity assessment. Children with CAP may present with a range of symptoms and signs: fever, tachypnoea, breathlessness, difficulty in breathing, cough, wheeze, headache, abdominal pain and chest pain. The spectrum of severity of CAP can be mild to severe (Table 8.3).

Table 8.3

Severity assessment of pneumonia in children

	Mild to moderate	Severe
Infants	Temperature < 38.5 °C Respiratory rate < 50 breaths /min Mild recession Taking full feeds	Temperature > 38.5 °C Respiratory rate > 70 breaths/min Moderate to severe recession Nasal flaring Cyanosis Intermittent apnoea Grunting respiration Not feeding Tachycardia* Capillary refill time ≥ 2 s Chronic conditions
Older children	Temperature < 38.5 °C Respiratory rate < 50 breaths/min Mild breathlessness No vomiting	Temperature > 38.5 °C Respiratory rate > 50 breaths/min Severe difficulty in breathing Nasal flaring Cyanosis Grunting respiration Signs Tachycardia* Capillary refill time ≥ 2 s Signs of dehydration Chronic conditions**

* Values to define tachycardia vary with age and with temperature. Thorax 2011.

** Congenital heart disease, chronic lung disease of prematurity, chronic respiratory conditions leading to infection such as cystic fibrosis, bronchiectasis, immune deficiency.

Infants and children with mild to moderate respiratory symptoms can be managed safely in the community. The most important decision in the management of CAP is whether to treat the child in the community or refer and admit for hospital-based care. This decision is best informed by an accurate assessment of severity of illness at presentation and an assessment of likely prognosis. In previously well children there is a low risk of complications and treatment in the community is preferable. This has the potential to reduce inappropriate hospital admissions and the associated morbidity and costs. Management in these environments is dependent on an assessment of severity. Severity assessment will influence microbiological investigations, initial antimicrobial therapy, route of administration, duration of treatment and level of nursing and medical care.

A referral to hospital will usually take place when a general practitioner assesses a child and feels the clinical severity requires admission. In addition to assessing severity, the decision whether to refer to hospital or not should take account of any underlying risk factors the child may have together with the ability of the parents/carers to manage the illness in the community. This decision may be influenced by the level of parental anxiety.

Factors suggesting need for hospitalization of children with pneumonia:

– ***age < 6 mo;***
– ***sickle cell anemia with acute chest syndrome;***
– ***multiple lobe involvement;***
– ***immunocompromised state;***
– ***toxic appearance;***
– ***severe respiratory distress;***
– ***requirement for supplemental oxygen;***
– ***dehydration;***
– ***vomiting;***
– ***no response to appropriate oral antibiotic therapy;***
– ***noncompliant parents.***

Children with CAP may also access hospital services when the parents/carers bring the child directly to a hospital emergency department. In these circumstances hospital doctors may come across children with mild disease that can be managed in the community. Some with severe disease will require hospital admission for treatment. One key indication for admission to hospital is hypoxaemia. Children with low oxygen saturations were shown to be at greater risk of death than adequately oxygenated children. RR of > 70 breaths/min in infants aged < 1 year was a significant predictor of hypoxaemia.

There is no single validated severity scoring system to guide the decision on when to refer for hospital care. An emergency care-based study assessed vital signs as a tool for identifying children at risk from a severe infection: T > 39 °C, $SatO_2$ < 94 %, tachycardia and capillary refill time > 2 s were more likely to occur in severe infections. Auscultation revealing absent breath sounds with a dull percussion note should raise the possibility of a pneumonia complication by

effusion and should trigger a referral to hospital. There is some evidence that an additional useful assessment is the quality of a child's cry and response to their parent's stimulation; if these are felt to be abnormal and present with other worrying features, they may also strengthen the case for referral for admission to hospital. A global assessment of clinical severity and risk factors is crucial in identifying the child likely to require hospital admission.

Transfer to a ICU unit is warranted when the child cannot maintain an SatO2 level greater than 92 % despite a fraction of inspired oxygen greater than 0.6, the patient is in shock, the RR and pulse rate are rising, and the child shows evidence of severe respiratory distress and exhaustion (with or without a rise in partial arterial carbon dioxide tension), or when the child has recurrent episodes of apnea or slow, irregular breathing. The degree of respiratory failure severity is shown in Table 8.4.

Table 8.4

Severity assessment of respiratory failure in children

The degree of severity	Evidence	The partial pressure of oxygen, mm Hg. Art.	% of normal
First	**Symptoms are mild:** anxiety; irritability; a little shortness of breath; an increase in heart rate	60–80	less than 94
Second	Symptoms begin to grow, the child **it can be seen:** sunken area between the fins and jugular vein; noisy and pant; bluish skin or oral cavity during active movements; a large number of heartbeats	40–59	less than 90
Third	This stage is life threatening and requires immediate professional assistance. **The main symptoms are:** uneven and inconsistent breath; arrhythmia; permanent blue color of the skin or mucous membranes	less than 40	less than 74

Reassessment. For children with CAP, reassessment is important, whether in the community or in hospital.

In the community, after treatment for CAP has been initiated (e.g., oral antibiotics plus advice on antipyretics and hydration), parents/carers should be advised on what symptoms and signs to look for when reassessing their child. Looking for the features in the following three areas may be useful in identifying cases where the infection is not being adequately treated and reassessment by a doctor is required:

• Fever: a high swinging or persistent fever (the temperature should start to settle 48 h after treatment starts).

• Effort of breathing: the child seems to be working harder to breathe with a fast breathing rate and chest recession.

• Effect of breathing: the child is not comfortable and relaxed but is agitated and distressed.

In hospital, all the above should be assessed in addition to vital signs. Medical assessment should always look for signs of overwhelming infection and septicaemia, for pleural collections that may develop into empyema thoracis and for signs of dehydration. A prolonged fever is a useful pointer to empyema developing, and this may require drainage for successful treatment. Less common complications should also be considered. A child in hospital should be reassessed medically if there is persistence of fever 48 h after initiation of treatment, increased work of breathing or if the child is becoming distressed or agitated.

General management in the community and in hospital. The general management of a child who does not require hospital referral comprises advising parents and carers about:

– management of fever — use of antipyretics — avoidance of tepid sponging;
– preventing dehydration;
– identifying signs of deterioration;
– identifying signs of other serious illness;
– how to access further healthcare.

General management for children cared for in hospital:

1. *Oxygen therapy.* Hypoxic infants and children may not appear cyanosed. Agitation may be an indicator of hypoxia. Patients whose $SatO_2$ is < 92 % while breathing air should be treated with oxygen given by nasal cannulae, head box or face mask to maintain $SatO_2$ > 92 %.

2. *Fluid therapy.* Children who are unable to maintain their fluid intake due to breathlessness or fatigue need fluid therapy. Studies on preterm infants or infants weighing < 2000 g have shown that the presence of a nasogastric tube compromises respiratory status. Older children may be similarly affected, although potentially to a lesser extent because of their larger nasal passages so, although tube feeds offer nutritional benefits over intravenous fluids, they should be avoided in severely ill children. Where nasogastric tube feeds are used, the smallest tube should be passed down the smaller nostril. Patients who are vomiting or who are severely ill may require IV fluids and electrolyte monitoring.

3. ***Antibiotic treatment.*** The initial antibiotic treatment of CAP is empiric because the pathogen is rarely known at the time of diagnosis. Empiric antibiotic choices *should* be based on the presumptive cause, the patient's age and severity of illness, and local resistance patterns of common pathogens. Oral administration of antibiotics is preferred except when the patient cannot tolerate oral therapy or has severe CAP.

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*** (80–90 mg/kg/24 hr) should be prescribed. Therapeutic alternatives include ***cefuroxime axetil*** (30 mg/kg/day, in two divided doses, for 7 to 10 days) or ***amoxicillin/clavulanate***. Macrolides or cephalosporins can be used in patients with penicillin allergy.

For school-aged children and in those in whom infection with *M. pneumoniae* or *Cl. pneumoniae* (atypical pneumonia) is suggested, a macrolide antibiotic (***azithromycin:*** day 1 — 10 mg/kg, days 2 through 5 — 5 mg/kg/day; ***clarithromycin:*** 15 mg/kg/day, in two divided doses, for 7 to 10 days; ***erythromycin:*** 40 mg/kg/day, in four divided doses, for 7 to 10 days) is an appropriate choice. In adolescents, a respiratory fluoroquinolone (levofloxacin, gatifloxacin, moxifloxacin, gemifloxacin) may be considered for atypical pneumonias.

The empirical treatment of suspected bacterial pneumonia in a hospitalized child requires an approach based on the clinical manifestations at the time of presentation. Parenteral ***cefuroxime*** (150 mg/kg/ day IV, in divided doses, given every 8 hours for 10–14 days), ***cefotaxime*** (100 mg/kg/day IV, in divided doses, given every 8 hours for 10–14 days), or ***ceftriaxone*** (50–100 mg/kg/day IV/IM in 1–2 divided doses) is the mainstay of therapy when bacterial pneumonia is suggested. Patients receiving parenteral therapy may be switched to oral treatment once they are afebrile and improving clinically, can tolerate oral intake, and have no complications.

If clinical features suggest staphylococcal pneumonia — MRSA infection (pneumatoceles, empyema), initial antimicrobial therapy should also include ***vancomycin*** (40–60 mg/kg/day IV in 3–4 divided doses) or ***clindamycin*** (30–40 mg/kg/day IV in 3 divided doses). ***Linezolid*** is another alternative (10 mg/kg orally or IV every eight hours in children younger than 12 years, or 600 mg orally or IV twice per day in children 12 years and older).

If viral pneumonia is suspected, it is reasonable to withhold antibiotic therapy, especially for those 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 based on presumptive diagnosis of a viral infection, deterioration in clinical status should signal the possibility of superimposed bacterial infection and antibiotic therapy should be initiated.

Duration of therapy. No randomized controlled trials have established the optimal duration of therapy for children with uncomplicated CAP. In most cases, 7 to 10 days of empiric outpatient therapy is sufficient. Azithromycin should be continued for five days.

Patients should be reevaluated 24 to 48 hours after the initiation of empiric therapy. Ineffective empiric therapy may be the result of inappropriate drug selection, resistance to the initial agents, or development of complications.

Response to treatment. Typically, patients with uncomplicated community-acquired bacterial pneumonia respond to therapy with improvement in clinical symptoms (fever, cough, tachypnea, chest pain) within 48–96 hr of initiation of antibiotics. Radiographic evidence of improvement substantially lags behind clinical improvement.

A number of factors must be considered when a patient does not improve on appropriate antibiotic therapy ***(slowly resolving pneumonia)****:*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 (bronchiolitis obliterans, hypersensitivity pneumonitis, eosinophilic pneumonia, aspiration, and Wegener granulomatosis). A repeat chest X-ray is the 1st step in determining the reason for delay in response to treatment.

Supportive care. Children with pneumonia are usually febrile. They may have localized chest pain, referred pain to the abdomen, headache, or arthralgia. Pleural pain and abdominal pain may interfere with effective cough. These symptoms may be controlled with weight-appropriate doses of antipyretics and analgesics, such as acetaminophen (10–15 mg/kg) or ibuprofen (5–10 mg/kg). Aspirin is not recommended for children because of the risk of Reye syndrome.

Complications. ***Complications of pneumonia*** include:

1. Pulmonary functioning: respiratory distress; pulmonary failure including adult respiratory distress syndrome.
2. Primarily pulmonary parenchyma: necrotizing pneumonia; pulmonary abscess; pneumatocoele.
3. Primarily pleural space: pleural effusion with or without loculations; empyema; pneumothoraces; tension pneumothorax with diminished cardiac output.
4. Infectious disease: bacteremia and sepsis.

Complications of pneumonia are usually the result of direct spread of bacterial infection within the thoracic cavity (pleural effusion, empyema, pericarditis) or bacteremia and hematologic spread. Meningitis, suppurative arthritis, and osteomyelitis are rare complications of hematologic spread of pneumococcal or *H.°influenzae* type b infection.

Parapneumonic effusion is a collection of fluid in the pleural space in association with an underlying pneumonia. *Empyema* is the presence of pus in the pleural space. *S. aureus, S. pneumoniae,* and *S. pyogenes* are the most common causes of parapneumonic effusions and of empyema. A clinician should consider empyema when a child has a persistent fever beyond 7 days or a fever not settling after 48 h of antibiotics.

As the parapneumonic effusion develops pleuritic chest pain develops due to irritation of the parietal pleura; this complaint may become less prominent once the effusion grows larger because the pleura has separated. The child may lie on the affected side as a means of splinting and reducing pain. Hypoxia depends on the degree of consolidation and ventilation/perfusion mismatch. Findings on examination that are consistent with a pleural effusion include decreased breath sounds, decreased chest expansion and dullness to percussion of the affected side. A pleural rub may be discerned when the effusion is small.

The treatment of empyema is based on the stage (exudative, fibrinopurulent, organizing). Imaging studies including chest X-ray (Fig. 8.5), ultrasonography and CT are helpful in determining the stage of empyema. The amount of fluid is best estimated by ultrasound examination.

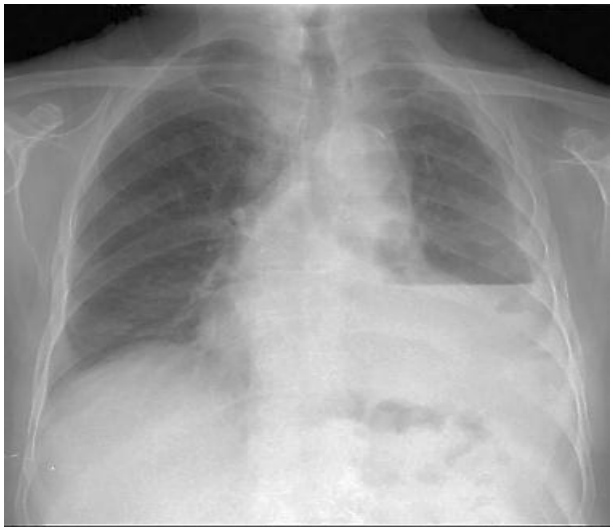


Fig. 8.5. Pleural empyema

CBC, glucose/protein, pH, LDH, gram stain and aerobic/anaerobic cultures, acid fast stain/mycobacterial cultures are routine pleural fluid studies (Appendix 2). Pleural fluid can also be sent for special microbiology, cytology, and biochemical analysis depending on the clinical suspicions. The mainstays of therapy include antibiotic therapy and drainage with tube thoracostomy. Additional approaches include the use of fibrinolytic therapy (urokinase, streptokinase, alteplase) and selected video-assisted thoracoscopy (VATS) to debride, lyse adhesions, and drain loculated areas of pus. Early diagnosis and intervention, particularly with VATS, may obviate the need for thoracotomy and open debridement.

Necrotising pneumonia. *Lung abscess* is a rare complication of CAP in children. Some children are predisposed to this more severe form of lung infection. The predisposing factors: congenital cysts, sequestrations, bronchiectasis, neurological disorders and immunodeficiency. There are also emerging data that certain serotypes of pneumococcal disease are more likely to lead to necrotising pneumonia and abscess formation than others, and that *S.°aureus* with Pantone–Valentine leukocidin toxin can lead to severe lung necrosis with a high risk of mortality. Suspicion of abscess/necrosis is often raised on the chest x-ray and diagnosis can be confirmed by CT scanning (Fig. 8.6, 8.7). Prolonged IV antibiotic courses may be required until the fever settles. Lung abscess with an associated empyema may be drained at decortication if the abscess is close to the parietal pleura and is large. Ultrasound- or CT-guided percutaneous drainage can be used.

In some cases, air may fill up the area between the pleural membranes, causing the lungs to collapse. This is called pneumothorax (Fig. 8.8). It may be a complication of pneumonia (particularly *Streptococcus pneumoniae*) or of the invasive procedures used to treat pleural effusion.

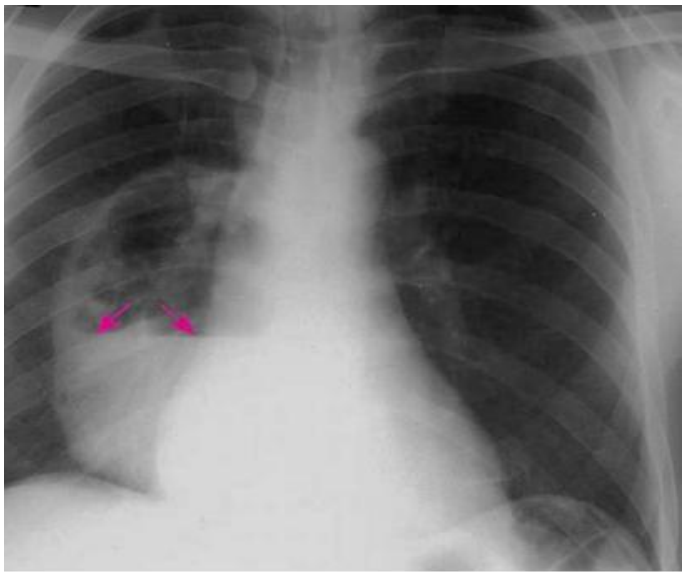


Fig. 8.6. Abscess in the lung. The arrows point to fluid that is surrounded by inflamed tissue

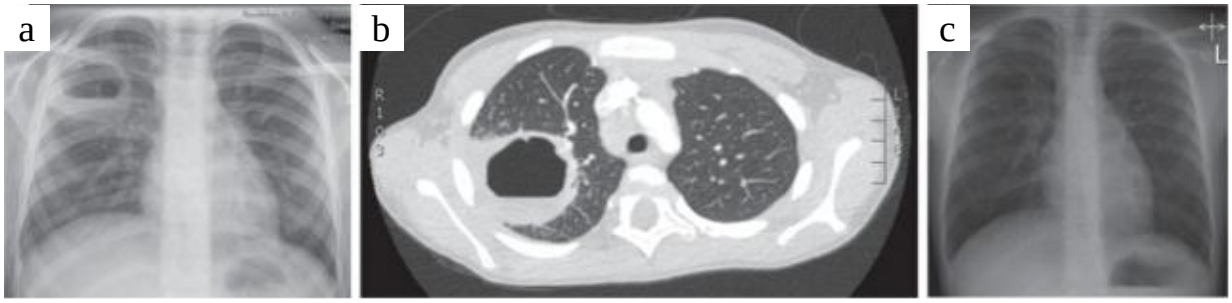


Fig. 8.7. Right upper lobe lung abscess on:
a — plain chest radiography; *b* — CT; *c* — good resolution in follow-up radiograph after 6 weeks of antibiotic therapy

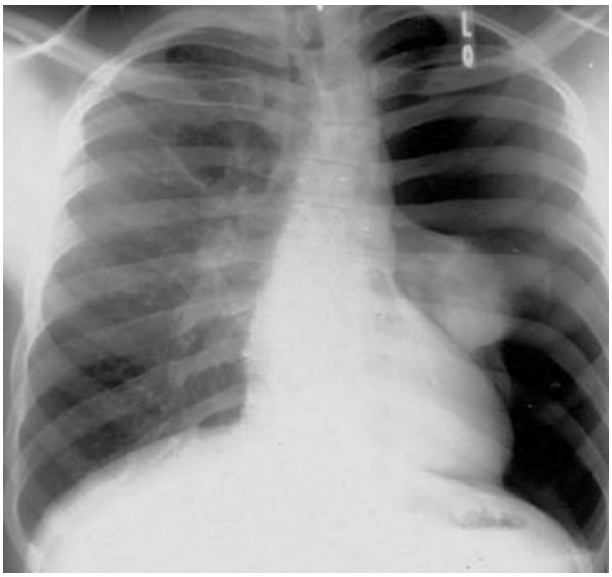


Fig. 8.8. Air appears dark on x-rays. In this x-ray showing a pneumothorax, one side of the chest is dark because there is only air where the now collapsed lung used to be

Acute Respiratory Distress Syndrome (ARDS):

• Acute respiratory failure with increases pulmonary capillary permeability, pulmonary edema, refractory hypoxemia, and decreased lung compliance.

• Tachypnea, respiratory alkalosis are early signs followed by tachy cardia, cyanosis, irritability, and dyspnea.

• Diagnosis requires absence of left ventricular failure and ratio of arterial oxygen (PaO_2) to inspired oxygen (FIO_2) concentration < 200.

• Bilateral diffuse alveolar infiltrates on chest X-ray. CT shows areas of collapse and overaeration.

• Direct precipitants are lung injury from aspiration, hydrocarbon, heat, contusion, infection, near drowning.

• Indirect precipitants — sepsis, shock, pancreatitis, burns, trauma, fat embolism, drug overdose, transfusion reaction.

Differential diagnosis:

• PaO_2 : FIO_2 between 200 and 300 with other ARDS criteria is usu ally called acute lung injury.

• Late phase of ARDS may be complicated by pulmonary fibrosis, pneumothorax, cor pulmonale, persistent infiltrates, all of which are characteristic of other chronic interstitial lung diseases.

Treatment:

• Precise identification of underlying cause is essential to effective therapy.

• Multiorgan system monitoring mandatory.

• Intensive cardiopulmonary and hemodynamic monitoring and support including pulmonary artery catheterization.

• Reduce intravascular volume to prevent pulmonary fluid accumulation.

• Ventilator strategies to recruit areas of dependent alveolar collapse and prevent overdistension of noncollapsed areas.

• Prone positioning may improve oxygenation.

• Inhaled nitric oxide reduces pulmonary artery pressure and improves ventilation/perfusion ratio.

• Surfactant replacement may improve lung compliance.

• Corticosteroids may reduce late-stage inflammation and fibrosis.

• Extracorporeal membrane oxygenation (ECMO) may not have any advantage over careful ventilator strategies.

Pearl: Nonpulmonary organ failures are the leading cause of death in pediatric and adult ARDS patients. Mortality is about 40 %.

Prevention. Current treatment guidelines suggest several interventions to prevent CAP. These include frequent handwashing, avoiding tobacco smoke, promoting breastfeeding, reducing exposure to other children, and immunization. The pneumococcal conjugate vaccine (Prevenar 13) is approved for the prevention of invasive pneumococcal disease in children six weeks to 71 months of age. Children should also be vaccinated against other potential causes of pneumonia, including influenza, *H. influenza* type B, pertussis, varicella, and measles.

CHAPTER 9
DISEASES OF THE DIGESTIVE SYSTEM IN CHILDREN

9.1. CHRONIC GASTRITIS, GASTRODUODENITIS

Gastritis (gastroduodenitis) is a chronic recurrent focal or diffuse inflammation of mucous membrane of the stomach (or/and the duodenum), characterized by physiological regeneration disorders, predisposed to progress, mucous membrane atrophy, and secretory insufficiency. In most patients it's associated with Helicobacter pylori infection.

Etiology, pathogenesis. Helicobacter pylori is a Gram-negative bacillus. Warren and Marshall first cultured and identified it as Campylobacter pylori in 1982, in 1989 it was renamed and recognized to be associated with antral gastritis, in 1990 a link between chronic H. pylori associated gastritis and malignancy in adults (gastric lymphoma and adenocarcinoma) was found. H. pylori infection is usually acquired in childhood; most infected are asymptomatic.

H. pylori becomes established into the mucous layer of the stomach, and it can move and multiply, secrets virulence factors: enzymes mucinase, catalase, phospholipase A, urease, protease, and two toxins (vacuolar and ulcerogenic). The main virulence factor is urease, which separates the urea. As a result of urea hydrolysis, ammonia and carbon dioxide are formed. Ammonia damages the stomach epithelium and creates alkaline medium around the H. pylori. The increase of pH on the epithelium surface leads to membrane potential disorder, disorders of membrane enzymes activity, and H+ ions move from the stomach into the cells with cells damage. Alkaline medium leads to constant stimulation of G-cells and increases gastrin secretion. The level of the stomachs secretion increases. The inflammation of different degrees of activity is formed as a result of the stomach epithelium damages. Activation of phagocytosis is present; the secretion of specific IgA and IgG by the stomach mucous membrane is increased. Constant stimulation of the stomach secretion leads to the acidic medium in the duodenum and duodenal epithelium damages. Then compensatory metaplasia takes place and the stomach epithelium is formed in the duodenum. H. pylori can live in the duodenum, and H. pylori-associated duodenitis occurs.

In cases of autoimmune gastritis, the main glandules are damaged. These damages cause synthesis of parietal cell antibodies. ABs damage fundal glandules, and high differential stomach cells death. The reason of autoimmune gastritis is unknown.

Reactive gastritis is caused by reflux of bile and pancreatic secretions into the stomach, but it can be also caused by exogenous substances, including NSAIDs, acetylsalicylic acid, chemotherapeutic agents, and alcohol.

Classification:

A. *Forms:* 1) acute; 2) chronic; 3) particular forms: eosinophilic, lymphocytic, granulomatous, radiatic, ischemic.

B. ***Etiology:*** 1) Hp (+); 2) Hp (–); 3) autoimmune; 4) reactive or chemical: drug, radioactive, alcoholic, nicotinic, etc.; 5) essential.

C. ***By localization:*** 1) gastritis: antral, fundal, pangastritis; 2) duodenitis: bulbitis, post bulbar duodenitis, pan duodenitis; 3) gastroduodenitis.

D. ***Endoscopic changes:*** 1) erythematous (exudative); 2) nodular; 3) atrophic; 4) hemorrhagic; 5) erosive; 6) mixed;

E. ***Secretory function:*** 1) normal secretory; 2) hypersecretory; 3) hyposecretory.

F. ***Periods of the disease:*** 1) exacerbation; 2) subclinical remission (partial remission); 3) clinical remission (complete remission); 4) clinical and endoscopic remission; 5) clinical, endoscopic, and morphological remission.

G. ***By morphological appearances***: 1) superficial; 2) diffuse.

H. ***By the character of morphological changes:*** degree of activity, inflammation, atrophy, intestinal metaplasia.

Clinical symptoms:

1. Abdominal pain in epigastric or pyloro-duodenal area is of a different degree of severity, can appear in time of eating or 10–20 min after meal; sometimes with the empty stomach or in 1–1.5 hours after meal. The pain can irradiate to left hypochondrium, the left part of the chest or the left hand.
2. Fullness.
3. Nausea, vomiting.
4. Flatulence.
5. Malaise.
6. Sometimes fever.

Diagnostics:

1. Complaints.
2. Anamnesis (family history of gastritis and peptic ulcer disease or other GI disorders, abdominal pain (character, location, frequency, duration and severity of epigastric pain)).
3. Appetite assessment, diet analysis.
4. Weight changes.
5. Treatment of other diseases (NSAIDs): aspirinic ulcers, corticosteroids ulcers.
6. Endoscopy (esophagogastroduodenoscopy — EGDS) for detecting gastritis, duodenitis, and peptic ulcer disease (PUD). EGDS is used for the detection of H. pylori by means of biopsy, culture, and cytology analysis; and for DNA testing by using PCR. Endoscopic biopsy is indicated for the following: histologic examination of gastric tissue; rapid urease testing; culture of organisms; PCR testing to identify H. pylori DNA.
7. An express test based on detection of urease activity, which is the highly specific marker of H. pylori.
8. Intragastric pH-metria. Normal level of pH of fundal part is 1.7–2.5, and in pyloric part more than 5.

Treatment:

1. Diet No. 1.

2. Treatment of H. pylori infection.

3. Antisecretory agents — H2 receptor antagonists:

– Ranitidine (Ranisan) 0.075 (0.15; 0.3 g) in a dose 2–6 mg/kg per day every 8–12 hours;

– Famotidine (Famocid, Quamatel) 0.02 (0.04 g) in a dose 0.5–0.8 mg/kg per day twice a day;

– Nizatidine (Axid) in a dose 10 mg/kg per day;

4. Antacids which are not absorbed in the stomach (not used in the USA): Almagel (gel Al, MgO, Sorbitol); Phosphalugel (gel Al phosphate); Maalox (Al hydroxide + Mg hydroxide); Gastal (Mg hydroxide + Na carbonate).

5. Selective Ml-cholinolytics: Gastrozepin (Pirenzepin) 0.5–1 tablet 30 min before meal and at bedtime.

6. Cytoprotective agents: Sucralfate 1,000 mg tablets in a dose 40–80 mg/kg per day.

Treatment of Hp infection. ***Triple scheme*** is usually used for children of 5–15 years of age with normal or increased secretory function, duration of therapy is 14 days.

1. Colloidal Bismuth Subcitrate (De-Nol) 0.12 use 1 tab. every 6–8 hours (1 hour before meal and at bedtime, not eat or drink before and after administration) *OR*

Proton pomp inhibitors (PPIs): suppresses acid secretion by specific inhibition of the H+/K+-ATPase enzyme system on the secretory surface of parietal cells: Omeprazole 0.02 g in a dose 1–2 mg/kg per day 1 time per day in the morning before meal; Rabeprazole 0.03; Pantoprazole 0.04.

2. Penicillines: amoxicillin 30–50 mg/kg per day.

3. Macrolides: clarithromycin 7.5 mg/kg per day OR Metronidazol 0.25 (Imidazole ring-based antibiotic, active against various anaerobic bacteria and protozoa) — 40 mg/kg per day, OR Nifuratel — 15 mg/kg per day.

Quadruple scheme. Secretory function is normal or increased. Duration of therapy is 7–14 days: 1) colloidal bismuth subcitrate; 2) antibiotics; 3) furazolidone (Metronidazole); 4) PPIs.

9.2. PEPTIC ULCER DISEASE

Peptic ulcer disease (PUD) is a chronic recurrent disease, characterized by ulcer defect in the stomach or duodenum as a result of equilibrium disorders between protective and aggressive factors.

Pathogenesis. By 3–4 years of age, gastric acid secretion approximates adult values. The pH of the stomach contents is 1–2. Excessive acid secretion is associated with a large parietal cell mass, hypersecretion by antral G-cells, and increased vagal tonicity, resulting in increased or sustained acid secretion in response to meals and increased secretion at night. Control of acid secretion is

achieved through multiple different feedback mechanisms involving endocrine, paracrine, and neural pathways. Factors which promote gastric acid production include acetylcholine released by the nerves vagus, histamine secreted by enterochromaffin cells, and gastrin released by the G-cells of the antrum. Mediators that decrease gastric acid secretion and enhance protective mucin production include prostaglandins.

A continuous layer of mucous gel that serves as a diffusion barrier to H+ ions and other chemicals covers the gastrointestinal mucosa. Mucus production and secretion are stimulated by prostaglandin E2. Another important function of epithelial cells is to secrete chemokines when threatened by microbial attack. Secretion of bicarbonate into the mucous coat, which is regulated by prostaglandins, is important for neutralization of H+. If mucosal injury occurs, active proliferation and migration of mucosal cells happens, driven by epithelial growth factor, TGFa, insulin-like growth factor, gastrin, and bombesin, and cover the area of epithelial damage. And equilibrium disorders between protective and aggressive factors result in ulcer defect formation.

Peptic ulcer is the end result of the inflammation due to an imbalance between cytoprotective and cytotoxic factors in the stomach and duodenum. It presents with varying degrees of gastritis or frank ulceration. The pathogenesis is multifactorial, but the final common pathway for the development of ulcers is the action of acid and pepsin-laden contents of the stomach on the gastric and duodenal mucosa, and the inability of mucosal defense mechanisms to allay those effects. Abnormalities in the gastric and duodenal mucosa can be visualized on endoscopy. Deep mucosal lesions that disrupt the muscular layer of the gastric or duodenal wall define peptic ulcers. Gastric ulcers are generally located on the lesser curvature of the stomach, and 90 % of duodenal ulcers are found in the duodenal bulb.

Etiology. Ulcers in children can be classified as primary peptic ulcers, which are chronic and more often duodenal, or secondary, which are usually more acute at onset and more often are gastric. Primary ulcers are most often associated with H. pylori infection; however, idiopathic account for up to 20 % of duodenal ulcers in children.

Primary peptic ulcers:

– associated with H. pylori;

– H. pylori negative (idiopathic).

Secondary peptic ulcers:

– physiological stress (decrease of the stomach blood circulation);

– burns, sepsis, shock, hypoglycemia, brain injury, uremia, physical overstrain;

– traumatic gastropathy: foreign body, recurrent severe vomiting, nasogastric probe;

– drugs: NSAIDs, Valproic acid, chemotherapy;

– immune-associated: celiac gastritis, allergic gastritis, eosinophilic gastritis;

– infections: CMV, Herpes Simplex, Influenza virus type A, Candida Albicans, Syphilis, Histoplasmosis, Mucormycosis, phlegmonous gastritis, emphysematous gastritis;

– corrosion gastropathy: overdosage of ion-drugs, acid intake;

– granulomatous gastritis: Crohn's disease, X histiocytosis, idiopathic, tuberculosis;

– autoimmune: diabetes mellitus, systemic connective tissue diseases;

– hypersecretory conditions: Zollinger–Ellison syndrome, G-cell hyperplasia, systemic mastocytosis, cystic fibrosis, short bowel syndrome, hyperparathyroidism;

– vascular insufficiency: sickle-cell anemia, Henoch-Schonlein IgA vasculitis;

– liver cirrhosis;

– radioactive gastropathy.

Classification:

A. *Localization:*

1. *PUD of the stomach:* PUD of cardial and sub cardial departments; mediogastral; pyloro-antral.

2. *PUD of the duodenum:* bulbar: anterior and posterior wall; postbulbar: proximal and distal parties of the duodenum.

3. *PUD of the stomach and duodenum.*

B. *Clinical periods:* 1) exacerbation; 2) remission (partial, complete).

C. *Endoscopic stage:* 1) fresh ulcer; 2) beginning of epithelization; 3) healing without scar and scar-ulcer deformation (phases of "red" and "white" scars).

D. *Severity of process:*

1. Mild: healing in 1 month, remission more than 1 year.

2. Moderate: healing more than 1 month, remission less than 1 year.

3. Severe: recurrences more than 2 times per year, multiple ulcers, complications, long healing.

E. *Diameter of ulcer (size):* 1) small — less than 0.5 cm; 2) moderate — 0.5–1.0 cm; 3) large — 1–2 cm; 4) gigantic — more than 2 cm.

F. *Complications:* 1) bleeding (hemorrhage) — 80 %; 2) perforation — 8 %; 3) penetration — 1.5 %; 4) pyloro-duodenal stenosis — 11 %.

Clinical symptoms:

1. Epigastric pain alleviated by the ingestion of food (in 30 % of cases).

2. The pain is dull or aching, rather than sharp or burning, as in adults. It can last from minutes to hours. Patients have frequent exacerbations and remissions lasting from weeks to months. Nocturnal pain is common in older children.

3. Nausea, vomiting.

4. Hematemesis or melena.

5. Feeding difficulty.

6. Occasionally, bright red blood per rectum may be seen if the rate of bleeding is brisk and the intestinal transit time is short.

7. Rarely, in patients with acute or chronic blood loss, penetration of the ulcer into the abdominal cavity or adjacent organs produces shock, anemia, peritonitis, or pancreatitis.

Treatment. Ulcer therapy has two goals: ulcer healing and elimination of the primary cause. Other important considerations are relief of symptoms and prevention of complications.

1. H2 receptor antagonists (ranitidine, famotidine, nizatidine) competitively inhibit the binding of histamine at the H2 subtype receptor of the gastric parietal cell.

2. PPIs are more potent in ulcer healing, which block the gastric parietal cell H+/K+-ATPase pump in a dose-dependent way, reducing basal and stimulating gastric acid secretion. At least 5 PPIs are available in the United States: omeprazole, lansoprazole, pantoprazole, esomeprazole, and rabeprazole, but not all are approved for children. PPIs are well tolerated with only minor adverse effects: diarrhea, headache, and nausea. All PPIs have comparable efficacy in treatment of PUD using standard doses, and are superior to H2-receptor antagonists. PPIs have their greatest effect when given before meals.

4. Cytoprotective agents can also be used as adjunct therapy if mucosal lesions are present.

5. Antibiotics in combination with a PPIs should be used for the treatment of H. pylori associated ulcers.

9.3. GASTROESOPHAGEAL REFLUX DISEASE

Reflux of gastric contents into the esophagus occurs occasionally in most people, especially post prandial. The lower esophageal sphincter and gravity provide the main antireflux forces, which must combat the tendency of intragastric pressure to cause gastroesophageal reflux (GER). Pathologic GER occurs as a result of presence of abnormalities in the lower esophageal sphincter, which leads to the increase of the intragastric pressure.

Rumination is effortless regurgitation of recently ingested food into the mouth. GER is the passage of gastric contents into the esophagus with or without regurgitation and/or vomiting. GER is considered to be pathologic, referred to as gastroesophageal reflux disease (GERD) when the reflux leads to troublesome symptoms and/or complications, such as esophagitis or stricturing.

Clinical symptoms:

1. Regurgitation: recurrent regurgitation with/without vomiting in the older child; rumination; wet pillow; halitosis; failure to thrive, malnutrition, weight loss; feeding refusal.

2. Esophagitis: heartburn; dysphagia; anemia, hematemesis, hemoccult positive stool; irritability; esophageal stricture; Barretts esophagus.

3. Pulmonary symptoms: recurrent pneumonia associated with aspiration; bronchitis; recurrent otitis media; asthma; cough; abscess; atelectasis; apnea, sudden infant death syndrome, laryngospasm, stridor.

4. Neuropsychological symptoms: “seizures”, “spells”, mouthing, staring; dystonia, Sandifer syndrome (dystonic neck posturing).

5. General: irritability; dental erosion.

“Red flag” symptoms and signs that suggest disorders other than GERD:

1. Weight loss, lethargy, fever, excessive irritability suggesting a variety of conditions, including systemic infections.

2. Dysuria suggests UTI, especially in infants and young children.

3. Bulging fontanelle/rapidly increasing head circumference, seizures, macro/microcephaly may suggest raised intracranial pressure due to meningitis, brain tumor or hydrocephalus.

4. Persistent forceful vomiting is typical for hypertrophic pyloric stenosis.

5. Nocturnal vomiting may suggest increased intracranial pressure.

6. Bilious vomiting: Hirschsprung disease, intestinal atresia, or midgut volvulus, or intussusception.

7. Hematemesis suggests a potentially serious bleed from the esophagus, stomach or upper gut, possibly GERD-associated, occurring from acid peptic disease, Mallory-Weiss tear or reflux-esophagitis.

8. Rectal bleeding: bacterial gastroenteritis, inflammatory bowel disease, acute surgical conditions and food protein-induced gastroenteropathy.

Diagnostics:

1. Careful history.

2. Observation of feeding (e.g., length of feeding period, volume of each feed, type of formula, quality of milk supply when breastfeeding, methods of mixing the formula, size of the feeds, additives to the feeds, restriction of allergens, time interval between feeding). A 2–4-week trial of extensively hydrolyzed protein-based (or amino acid based) formula in infants suspected of GERD.

3. The pattern of regurgitation/spitting/vomiting (e.g., nocturnal, immediately post prandial, long after meals, digested versus undigested).

4. A family medical history.

5. Possible environmental triggers, including family psychosocial history and factors such as tobacco use and second-hand tobacco smoke-exposure.

6. The patient’s growth chat.

7. Prior pharmacologic and dietary interventions (PPIs, etc.).

8. The presence of warning signs.

9. Esophageal pH probe evaluation.

10. Ultrasonography (to exclude anatomical abnormalities).

11. Scintigraphy should not be used for the diagnosis of GERD in children.

12. Barium contrast study (to exclude anatomical abnormalities).

13. 24-Hour esophageal pH testing.

14. Esophagogastroduodenoscopy (EGDS) with/without biopsy not to diagnose GERD, but to recognize erosive esophagitis, microscopic esophagitis, other conditions mimicking GERD (eosinophilic esophagitis, infectious esophagitis), to evaluate the mucosa in the presence of alarm symptoms

(hematemesis), to detect complications of GERD (strictures, Barrett esophagus), to diagnose conditions that predispose to GERD (hiatal hernia).

Differential diagnosis:

1. *Gastrointestinal obstruction*: pyloric stenosis; malrotation with volvulus; intussusception; Hirschsprung disease; antral/duodenal web; foreign body; incarcerated hernia; superior mesenteric artery (SMA) syndrome.

2. *Neurologic*: hydrocephalus; subdural hematoma; intracranial hemorrhage; intracranial mass.

3. *Other gastrointestinal disorders:* achalasia; gastroenteritis; peptic ulcer; eosinophilic esophagitis; food allergy/intolerance; inflammatory bowel disease; pancreatitis; appendicitis.

4. *Infectious:* sepsis/meningitis; UTI; respiratory infection; otitis media; hepatitis.

5. *Metabolic/endocrine:* galactosemia; hereditary fructose intolerance; urea cycle defects; amino and organic acidemias; fatty acid oxidation disorders; metabolic acidosis; congenital adrenal hyperplasia/adrenal crisis.

6. *Others:* heart failure; obstructive uropathy; renal failure; child neglect or abuse; self-induced vomiting; cyclic vomiting syndrome; rumination.

Treatment. ***Conservative therapy:***

1. Positioning: upright, elevation of head of bed, prone position.

2. Feeding modifications including formula or food thickeners, reduced feeding volumes or more frequent feedings, and extensively hydrolyzed or amino-acid based formula.

3. Meals: small portion (but frequent is detrimental); thickened; not before reclining.

4. Weight loss in obesity.

5. Loose clothing.

6. Avoid (because of detrimental effect on lower esophageal sphincter pressure): fatty products, chocolate, alcohol, nicotine, peppermint, spearmint, Theophylline, Isoproterenol, Sedatives, Irritants and acid food (citrus, tomato, coffee).

7. Ingest (because of beneficial effect on lower esophageal sphincter pressure): antacids, proteins.

Medicines:

1. Alginates and antacids are designed to neutralize acid and contain either sodium/potassium bicarbonate, or aluminum, magnesium or calcium salts, and are typically used to treat acid related disorders such as heartburn or dyspepsia.

2. Antacid therapy (antacids, H2-histamine blockers): Ranitidine 5–10 mg/kg per day; Nizatidine 10–20 mg/kg per day; Famotidine 1 mg/kg per day.

3. PPIs: Omeprazole 1–4 mg/kg per day; Lansoprazole 2 mg/kg per day for infants; Esomeprazole 10 mg/day (weight no more than 20 kg) or 20 mg/day (weight more than 20 kg); Pantoprazole 1–2 mg/kg per day. It's recommended a 4–8 week course of H2-receptor antagonists or PPIs for treatment of typical

symptoms (i.e., heartburn, retrosternal or epigastric pain) in children with GERD, and not recommended in patients with extra-esophageal symptoms (i.e., cough, wheezing, asthma), except in the presence of typical GERD symptoms and/or diagnostic testing suggestive of GERD.

4. Barrier: Alginic acid.

5. Lower esophageal sphincter pressure: Metoclopramide 0.4–0.9 mg/kg daily; Domperidone 0.8–0.9 mg/kg per day; Baclofen 0.5 mg/kg per day. Domperidone and metoclopramide are antidopaminergic agents that facilitate gastric emptying.

It is recommended to evaluate treatment efficacy and exclusion of alternative causes of symptoms in children not responding to 4–8 weeks of therapy for GERD.

Surgical therapy. 1) fundoplication (Nissen operation); 2) treatment of complications: stricture dilation; bowel interposition.

9.4. BILIARY SYSTEM DISEASES

Biliary system starts from biliary capillaries localized into the liver. These vessels connect and form interlobular bile ducts, then right and left hepatic ducts, and one common hepatic duct appears from the liver. At the lower border of the liver the gallbladder is located. The gallbladder is a reservoir for bile; regulates the pressure in the biliary system; participates in the the bile production; provides the reabsorption of proteins, inorganic substances; secrets of mucin, antiuric cholecystokinin hormone; plays enzymatic role.

Anatomic-physiological features of gallbladder and bile ducts in children. The liver is the largest gland in the human body. The size of the liver is relatively big, 4 % of the body weight in a newborn (versus 2 % in adults). The lower edge of the liver till 7 years of age is palpated below the edge of the right costal margin. In a newborn, the lobules of the liver are not expressed; it is formed by the age of 1 year of life. Histological structure of the liver corresponds to adult till 8 years of life. In children's bile there is less concentration of bile acids, cholesterol, lecithin, salts and alkali, but it is enriched by water, mucin, pigments and urea, increased concentration of taurocholic acid. Bile neutralizes the content of the duodenum, emulsifies fats, activates lipase of the pancreas, promotes the absorption of fat-soluble vitamins, and strengthens the peristalsis of the colon.

Bile ducts dyskinesia. The work of the biliary tract is regulated by centers of the brain and the vegetative nervous system. The impulse of inhibition is a function of the sympathetic, and impulses of excitation — of the parasympathetic nervous system. Bile ducts dyskinesia is a disease characterized by bile intake disorder in duodenum because of muscular apparatus of the biliary tract motility disorders.

Etiology: 1) vegetative nervous system disorders; 2) postponed acute viral hepatitis; 3) neuroses; 4) food allergy; 5) atopic dermatitis; 6) chronic gi tract diseases; 7) parasites (lambliasis); 8) chronic laryngitis; 9) poisons.

Classification. There are two types of bile ducts dyskinesia: 1) hypertonic (hypertonic-hyperkinetic); 2) hypotonic (hypotonic-hypokinetic).

Pathogenesis. Cholecystokinin is the principal factor controlling postprandial gallbladder contraction. There are several hormones, which influence gallbladder motility and modulate the effect of cholecystokinin, including vasoactive intestinal peptide (VIP), somatostatin, and substance P. In a physiologic condition cholecystokinin causes gallbladder contraction and relaxation of Oddi's sphincter. Abnormal biliary motility may be a primary disorder in which impairment of the motility of the bile ducts results from the process intrinsic to the bile duct muscle, or dyskinesia can develop to a variety of other disorders (celiac disease, parenteral nutrition, starvation, administration of somatostatin, diabetes mellitus). Primary dyskinesia may result from a decreased gallbladder activity due to chronic acalculous cholecystitis or from a deficiency of cholecystokinin receptors. Discoordinated gallbladder or cystic duct contractions could also impair gallbladder emptying into the common bile duct.

Clinical symptoms: 1) chronic right upper quadrant abdominal pain; 2) vomiting; 3) nausea; 4) fatty-food intolerance; 5) fatigue; 6) irritability, fearfulness; 7) headache; 8) heartbeat; 9) hyperhidrosis.

There are two types of bile ducts dyskinesia (Table 9.1).

Table 9.1

Differential signs of hypertonic and hypotonic types of biliary dyskinesia

Criteria	Hypertonic form	Hypotonic form
Anamnesis	Neurotic reactions, vegetative nervous system disorders	Negative emotions, physical activities
Hereditary predisposition	Typical	Typical
Seasonality of an exacerbation	Autumn and spring	Non typical
Duration of the disease	Till one year	1–1.5 year
Pain syndrome: • constant pain • association with a diet • attack pain • pain in the right hypochondrium	 Non typical In 30–40 min after cold food Typical Typical	 Typical In 1–1.5 hours after meal, especially fatty products Non typical Typical

Diagnostics:

1. Anamnesis. Abdominal pain (with or without nausea or fatty food intolerance), absence of gallstones, abnormally low cholecystokinin-stimulated gallbladder ejection fraction.
2. CBC.
3. Biochemical blood analysis: liver function tests, amylase, lipase, urea, creatinine, electrolytes.
4. Urine test.
5. Radiologic studies include an abdominal ultrasound to rule out gallstones or other structural disorders of the gallbladder and the biliary tract, and an upper gastrointestinal study.

Treatment. It's necessary to understand the exact mechanism of biliary dyskinesia, whether the problem is the contraction of the gallbladder or in

the sphincter of Oddi. General advice regarding the diet should be given, at least 4–5 meals a day. Fatty food should be avoided and loads of fruits and berries should be included in the diet. Food should be boiled and steamed (Table 9.2).

Table 9.2

Therapeutic measures in biliary dyskinesia

Therapeutic measures	Dyskinesia	
	Hypotonic-hypokinetic	Hypertonic-hyperkinetic
Diet	Products with choleretic properties contain cellulose	Fatty products, spices restriction
Neurotropic drugs	With stimulative activity: caffeine, Eleutherococcus, Ginseng, Aloe	With sedative activity: tranquilizers, Novocain
Spasmolytic agents	Are not used	Papaverinum, No-Spa, Ganglion Blockers
Thermal procedures	In the period of exacerbation	Used
Physical examinations	Toning type used	With sedative exercises
Physiotherapy	Galvanization, faradization, mud cure	Electrophoresis of Novocaine, Papaverine, Magnesium sulphate
Mineral waters	High and average mineralization, room temperature, sulfate sodium, sulfate magnesium every 8 hours	Hydrocarbonate-chloride-sodium, slow mineralization, warm temperature, 5–6 times per day

Cholelithiasis. Gallbladder calculi are more common in adults and remain relatively rare in children; however, the incidence of cholelithiasis in children has increased.

Etiology. Cholelithiasis in children can be divided into three groups: hemolytic, known other etiology, and idiopathic. Almost 20 % of all gallstones are due to hemolytic diseases such as sickle-cell disease, hereditary spherocytosis and thalassemia. In 50 % of cases gallstones are due to another known etiology such as total parenteral nutrition, prolonged fasting, iliac disease or ileal resection, furosemide therapy, congenital biliary diseases such as choledochal cyst, and chronic liver disease. Around 30 % of cases are idiopathic.

Pathogenesis. Cholesterol supersaturation of bile with stasis predisposes to cholesterol gallstone formation. Mixed cholesterol gallstones are the commonest stones in adults and in adolescent girls. Pigment stones are more common in children. Black pigment stones are formed due to supersaturation of bile with calcium bilirubinate and are seen in hemolytic disorders, in association with total parenteral nutrition. Brown pigment stones are associated with infection and biliary stasis. Biliary sludge is composed of mucin, calcium bilirubinate and cholesterol crystals. It is commonly associated with prolonged fasting, total parenteral nutrition, pregnancy, sickle-cell disease, treatment with ceftriaxone.

Clinical symptoms depends on the age of a child:

A. Infants (less than 2 years): cholestatic jaundice, transient acholic stools, abdominal pain, sepsis.

B. Children (2–14 years): typical biliary symptoms (40–50 %) (pain in the right upper quadrant or in epigastrium; nausea, vomiting and fat intolerance,

non-specific abdominal pain (20–30 %)), "Acute abdomen" (5–10 %): due to the acute cholecystitis, pancreatitis or cholangitis. In 20 % cholelithiasis can be asymptomatic.

C. Adolescents (14–18 years). The same as in children, but right upper quadrant pain and fatty food intolerance are more common in adolescents.

The most common symptom of gallstones is biliary colic — very specific type of pain, occurring as the primary or the only symptom in 70 % with gallstones who develop symptoms. Biliary colic occurs when the bile ducts (cystic, hepatic or common bile duct) are suddenly blocked by a gallstone. In case of hepatic duct or common bile duct obstruction, it's due to continued secretion of bile by the liver. In case of cystic duct obstruction, the wall of the gallbladder secretes fluid into the gallbladder, the distention of the ducts or gallbladder that causes biliary colic.

Diagnostics:

1. Ultrasound (US). Gallstones are usually mobile, single or multiple, can cast an acoustic shadow. Biliary sludge though appearing echogenic on US, does not cast an acoustic shadow. Small stone, as 1.5 mm, can be detected by US. The sensitivity and specificity of US exceeds 95 % for gallbladder cholelithiasis;
2. Cholescintigraphy, with Technetium-99m is the most accurate method of diagnosing acute cholecystitis;
3. Magnetic resonance cholangiopancreatography is increasingly used to investigate a complicated gallstone disease;
4. Endoscopic retrograde cholangiopancreatography offers the additional advantage of therapeutic intervention in common bile duct stones.

Treatment.

1. Diet. Frequency of feeding: 4–6 times. Exclude fat, fried, spicy, chocolate, carbonated drinks, smoked products, fat meat (mutton, pork), alcohol. Vegetable food, dairy products, wheat bran are recommended.
2. Dissolution of stones in a gallbladder by means of special medicines (ursodeoxycholic and chenodeoxycholic acids), applied only in case of single small (to 2 cm) cholesteric (X-ray negative) stones, in the absence of contraindications. Duration of treatment is 1–1.5 years.
3. Surgical methods.

9.5. CHRONIC INFLAMMATORY BOWEL DISEASES (IBD)

Functional gastrointestinal disorders (FGIDs) are common in children of all age groups. In the absence of biomarkers or specific tests to diagnose these disorders, the diagnosis is based on symptom-based criteria (current are called the Rome IV criteria 2016). Pediatric criteria divide FGIDs according to age groups (neonates and toddlers — 0 to 3 years old; children and adolescents — 4 to 18 years old). Within the children and adolescents' group of diagnoses, there are three diagnostic categories based on the most bothersome symptom according

to the patient's own report (or parental report in younger children): *disorders of nausea and vomiting, disorders of abdominal pain, and defecation disorders*.

Functional gastrointestinal disorders in neonates and toddlers: infant regurgitation; infant rumination syndrome; cyclic vomiting syndrome; infant colic; functional diarrhea; infant dyschezia; functional constipation.

Functional gastrointestinal disorders in children and adolescents.

Functional nausea and vomiting disorders: cyclic vomiting syndrome; functional nausea and functional vomiting; rumination syndrome; aerophagia.

Functional abdominal pain disorders: functional dyspepsia (postprandial distress syndrome; epigastric pain syndrome); irritable bowel syndrome (IBS): predominant constipation; predominant diarrhea; mixed bowel habits: unclassified.

Abdominal migraine; functional abdominal pain-not otherwise specified.

Functional defecation disorders: functional constipation; nonretentive fecal incontinence.

Crohn disease and ulcerative colitis are the two main types of inflammatory bowel disease. High rates of these conditions are seen in Australasian children — furthermore, increasing rates have been evident in recent years. Children can present with typical symptoms of abdominal pain, diarrhoea, haematochezia and/or weight loss. Atypical presentations (such as skin lesions or isolated short stature) can also occur: these may be associated with delays in the consideration and diagnosis of IBD. Initial steps in establishing a diagnosis of IBD include delineation of inflammatory markers exclusion of any other likely aetiology. Definitive diagnosis relies upon key endoscopic, histologic and radiological findings. Overall management of IBD encompasses care within a team-based, child and family-focused, multi-disciplinary setting.

Crohn's disease (CD) can cause inflammation anywhere in the GI tract from the mouth to the anus. ***Ulcerative colitis*** can cause inflammation and ulceration in the large intestine (colon and rectum). The cause and cure of IBD are currently unknown.

Crohn's disease is characterized by transmural inflammation involving any part of the GI tract. The most common symptoms during a flare are: abdominal pain, frequent diarrhoea (sometimes mixed with mucus and blood), tiredness, fatigue, raised temperature, fever, loss of appetite, weight loss, malnutrition, anaemia. *Diagnostics.* Blood tests, stool tests, imaging studies such as CT and magnetic resonance enterography, endoscopic studies such as colonoscopy and EGDS with multiple biopsies obtained along the GI tract. Small bowel imaging has been recommended to rule out stricturing and fistulae. Video capsule endoscopy is a non-invasive technique to visualize the small intestine.

Differential diagnosis with an infection, irritable bowel syndrome.

The Pediatric Rome IV criteria for the diagnosis of ***irritable bowel syndrome:*** four subtypes have been defined. The classification allows differentiation of treatments for patients with different subtypes of IBS. The subtypes are based on the predominant stooling pattern according to

the Bristol Stool Scale: IBS with constipation (IBS-C), diarrhea (IBS-D), mixed bowel habits (IBS-M), and an unclassified group for those who do not fit in these subtypes. IBS-C seems to be the most common subtype in children and adolescents; however, it is not uncommon for patients to change subtype over time. The committee recommends that patients with abdominal pain and constipation should first be treated for constipation. When symptoms of abdominal pain persist despite adequate treatment of constipation, the patient is to be diagnosed with IBS-C and treated according to evidence-based guidelines.

For the treatment of IBS, education, establishing a therapeutic alliance and providing reassurance, may be sufficient. In other cases, additional therapeutic strategies can be applied. There is increasing evidence for a non-pharmacological treatment approach, including biopsychosocial modifying therapies and dietary interventions. In patients who prefer a pharmacological approach, the Rome IV Interactive Clinical Decision Toolkit recommends antispasmodics as 1st line and the use of tricyclic antidepressants in recalcitrant cases. The treatment of the patient's stool problems may require additional medications. Laxatives can be used in cases of constipation and medications that decrease motility and secretions can be used in cases of diarrhea. Common medications used in IBS-D are loperamide and cholestyramine. Studies in adults have shown significant benefit from the use of lubiprostone, prucalopride, and linaclotide over placebo in IBS-C. For adults with IBS-D, the use of bile acid sequestrants may be beneficial, as up to 50 % of adults with functional diarrhea and IBS-D have bile acid malabsorption. Rifaximin, eluxadoline, and alosetron have been shown to be beneficial in the treatment of IBS-D in adults but no trials have been conducted in children.

Treatment of inflammatory bowel disease. *Medications* are mainly used to reduce inflammation: aminosalicylates, corticosteroids, immunosuppressants, biologics, antibiotics. *Diet* including treating active disease, managing symptoms, ensuring nutritional adequacy and complications of Crohn's disease: exclusive enteral nutrition, Crohn's disease exclusion diet, low or moderate FODMAP diet, moderate, low fibre or low residue diet, high energy and protein diet, oral vitamin and mineral supplementation.

Surgery. Sometimes parts of the bowel are too damaged to be healed by medications and the best option is operation. The goal of surgery is to keep as much of the bowel as possible while restoring quality of life. Common types of surgery include: resection, stricturoplasty, creating a stoma.

Clinically, Crohn's disease differs from ***ulcerative colitis*** in that it may result in inflammation deeper within the entire colonic walls (mucosa, submucosa, muscularis and serosa, (trammeller) (colon, and rectum). Furthermore, Crohn's disease may also affect other systemic organs outside the colon tract through fistulation (in up to 28 % of pediatric patients exhibit extraintestinal manifestations).

Ulcerative colitis typically involves superficial inflammation of the rectum with extension into adjacent mucosa in a continuous fashion. Ulcers (sores) also develop on the surface of the intestines inner lining which may bleed and produce

mucus. The inflammation almost always involves the rectum and may extend up the large intestine, either when it first develops or sometimes extend over time.

Symptoms can be different for each person and may be serious or mild, depend on how much of the large intestine has become inflamed and how strong the inflammation is. The most common symptoms during a flare are: abdominal pain, frequent diarrhoea (sometimes mixed with mucus and blood), tiredness, fatigue, raised temperature, fever, loss of appetite, weight loss, malnutrition, anaemia. The Pediatric Ulcerative Colitis Activity Index (PUCAI) is a non-invasive tool for assessment of UC disease severity consisting of six clinical items: daily abdominal pain, rectal bleeding, stool consistency, number of stools, nocturnal stools, and activity level for a maximum score of 85. Scores under 10 represent remission while a score $\geq$ 65 signifies severe disease activity.

Diagnosis of ulcerative colitis include: blood tests, stool tests, endoscopy, bowel imagine and scans.

Treatment of ulcerative colitis.

Medications for ulcerative colitis are mainly used to reduce inflammation. The main types include: aminosalicylates, corticosteroids, immunosuppressants, biologics, Janus kinase inhibators.

Diet has an important role to play in of many aspects of ulcerative colitis, including symptom management, ensuring nutritional adequacy and potentially treating active disease or supporting remission: high energy and protein diet, oral vitamin and mineral supplementation, low or moderate FODMAP diet, supplementary treatment.

Surgery. The goal of surgery is to keep as much of the bowel as possible while restoring quality of life. The most common types of surgery for ulcerative colitis are ileostomies and pouch surgery, often called a j-pouch.

CHAPTER 10
HELMINTHIC DISEASES

Helminthiases are parasitic diseases caused by worms (helminths). In total, more than 250 species of helminths parasitizing humans have been registered. There are 2 types of helminths causing infestations in humans: *Roundworms* (nematodes) and *Flatworms* (tapeworms (cestodes) and flukes (trematodes)). The most important in childhood are helminthiases caused by roundworms (nematodosis). Helminthiasis caused by flatworms (cestodiasis, trematodiasis) is a rare pathology, usually with natural foci.

Ascariasis (Ascaris Lumbricoides).

Etiology. Ascariasis is caused by nematodes Ascaris lumbricoides. Adult worms of A. lumbricoides inhabit the lumen of the small intestine and have a life span of 10–24 months. The reproductive potential of Ascaris is prodigious — a gravid female worm produces 200,000 eggs/day. After passage in the feces, the eggs embryonate and become infective in 5–10 days under favorable environmental conditions. Adult worms can live for 12–18 months.

Epidemiology:

1. Ascariasis occurs globally and is the most prevalent human helminthiasis in the world.
2. It is most common in tropical areas of the world where environmental conditions are optimal for maturation of ova in the soil.
3. The highest rate of infection is in children of preschool or early school age.
4. Transmission is primarily "hand-to-mouth", but it may also involve ingestion of contaminated raw fruits and vegetables.
5. Ascaris eggs can remain viable at 5–10 °C for as long as 2 years.

Pathogenesis. Ascaris live in the human small intestine. Larvae are released, then penetrate into the intestinal wall, and migrate to the lungs along the way of the venous circulation. The parasites cause pulmonary ascariasis as they enter into the alveoli and migrate through the bronchi and trachea. They are subsequently swallowed and return to the intestines, where they mature into adult worms. Female Ascaris begin depositing eggs in 8–10 weeks (Fig. 10.1)

Clinical symptoms. The most common clinical problems are due to pulmonary diseases and obstruction of the intestinal or biliary tract.

1. Allergic symptoms, urticaria due to larvae migration.
2. Fever.
3. Transient respiratory symptoms (cough and dyspnea, pulmonary infiltrates).
4. Vomiting and abdominal distention.
5. Signs of acute bowel obstruction.

Ascaris lumbricoides occasionally migrate into the biliary and pancreatic ducts, where they cause cholecystitis or pancreatitis. Children with recurrent infection are at risk of protein-energy malnutrition.

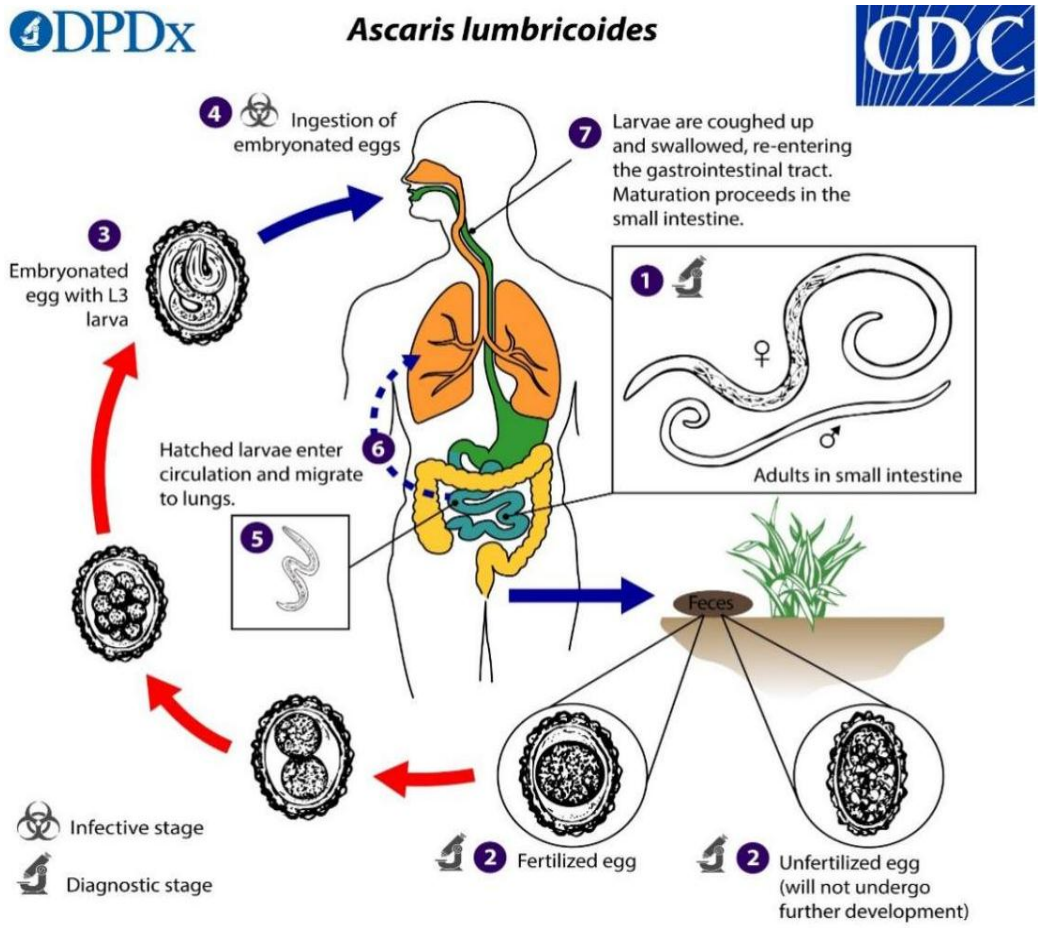


Fig. 10.1. Ascaris lumbricoides life circle

Diagnostics:

• Anamnesis.

• CBC shows eosinophilia.

• Presence of larvae in the sputum.

• Microscopic examination of fecal smears — a high number of eggs excreted by adult female worms.

Treatment. Although several chemotherapeutic agents are effective against ascariasis, none have documented utility during the pulmonary phase of infection:

– Albendazole (400 mg P.O. once, for all ages); or

– Mebendazole (100 mg bid P.O. for 3 days or 500 mg P.O. once for all ages); or

– Pyrantel pamoate (11 mg/kg P.O. once, maximum 1 g).

Surgery may be required in case of severe obstruction.

Prevention. Although ascariasis is the most prevalent worm infection in the world, little attention has been given to its control due to controversy concerning its significance for public health and the likelihood of recurrent infections in epidemiologic situation, when transmission rates are high. Short-term preventive measures include chemotherapy. Improving sanitary conditions and sewage facilities, discontinuing the practice of using human feces as fertilizer, and educating are the most effective long-term preventive measures.

Enterobiasis (Enterobius Vermicularis).

Etiology. The cause of enterobiasis, or pinworm infection, is Enterobius vermicularis. It is a small (1.0 cm in length), white, threadlike nematode, roundworm, that typically inhabits the cecum and appendix. Gravid females migrate at night to the perianal and perineal regions, where they deposit up to 15.000 eggs. Eggs remain viable for 20 days. Human infection occurs by the fecal-oral route, typically by ingestion of embryonated eggs that are carried on fingernails, clothing or n house dust. After ingestion, the larvae mature into adult worm's in 36–53 days.

Epidemiology:

1. Enterobiasis infection occurs in individuals of all ages and socioeconomic levels, infects 30 % of children worldwide.

2. The infection occurs primarily in family surroundings where children are present.

3. The prevalence of the pinworm infection is the highest in children 5–14 years of age. It is common in areas where children live, play, and sleep close together, thus facilitating egg transmission.

4. As the lifespan of the adult worm is short, chronic parasitism is likely caused by repeated cycles of reinfection (Fig. 10.2). Autoinoculation can occur in individuals who habitually put their fingers into the mouth.

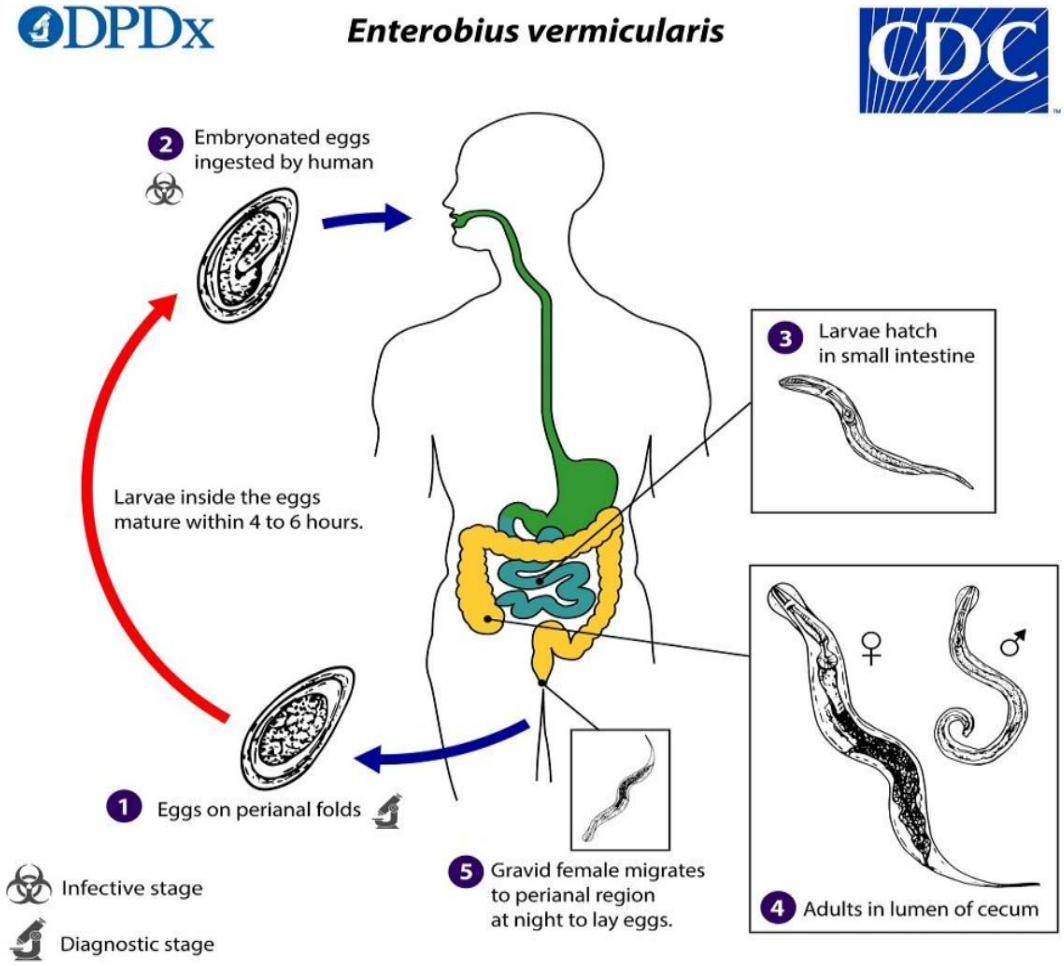


Fig. 10.2. Enterobius vermicularis life circle

Clinical symptoms. Pinworm infection is innocuous and rarely causes serious medical problems.

1. Itching.

2. Restless sleep secondary to nocturnal perianal or perineal pruritus. The precise cause and incidence of pruritus are unknown and depend on the intensity of the infection, psychological profile of the infected child and his or her family, or allergic reactions to the parasite.

4. Aberrant migration to ectopic sites occasionally may lead to appendicitis, chronic salpingitis, pelvic inflammatory disease, peritonitis, hepatitis, and ulcerative lesions in the large or small bowel.

Diagnostics:

1. A history of nocturnal perianal pruritus in children.

2. Eosinophilia is not observed in most cases, because tissue invasion does not occur.

3. Diagnosis is made by identification of parasites' eggs or worms. Microscopic examination of adhesive cellophane tape pressed against the perianal region early in the morning frequently demonstrates eggs. Repeated examinations increase the chance of detecting ova; a single examination detects 50 % of infections, 3 examinations — 90 %, and 5 examinations — 99 %. Worms seen in the perianal region should be removed and preserved in 75 % ethyl alcohol until microscopic examination can be performed.

5. Routine stool samples rarely demonstrate Enterobius ova.

Treatment. Anthelmintic drugs should be administered to infected individuals and their family members:

– a single oral dose of Mebendazole (100 mg RO. for all ages) repeated in 2 week results in cure rates of 90–100 %;

– alternative regimens include a single oral dose of Albendazole (400 mg P.O. for all ages) repeated in 2 weeks, *or*

– a single dose of pyrantel pamoate (11 mg/kg P.O., maximum 1 g).

Morning bathing removes a large portion of eggs.

Frequent changing of underclothes, bed clothes, and bed sheets decreases environmental egg contamination and may decrease the risk for autoinfection.

Prevention. Family members of the infected child must receive treatment as well. Repeated treatments every 3–4 months may be required in case of repeated exposure. Proper hands hygiene is the most effective method of illness prevention.

Trichocephalosis. Trichocephalosis is an intestinal nematodosis characterized by a chronic course with the development of dyspeptic, asthenic and anemic syndromes. Trichocephalosis is almost universal; it is more common in tropical and subtropical climates, where infestation is detected in 40–50 % of the local population. In endemic regions, it's the second most common helminthiasis after ascariasis.

The etiological agent causing trichocephalosis is the round helminth Trichocephalis trichiuris (whipworm) — a brownish nematode with a thin thread-

like front part and a rounded thickened rear end. Adult helminths parasitize in the cecum, but with massive infestation they can live in the entire large intestine, including the rectum. Infection with trichuriasis occurs through the fecal-oral mechanism when mature eggs are placed in the mouth with contaminated hands or by ingestion. In the gastrointestinal tract, the larvae invade the wall of the small intestine. After 5–10 days, they descend to the cecum, where they are reintroduced into the mucosa and turn into adults within 1–1.5 months. The duration of helminth parasitism in the human intestine reaches 5–7 years (Fig. 10.3).

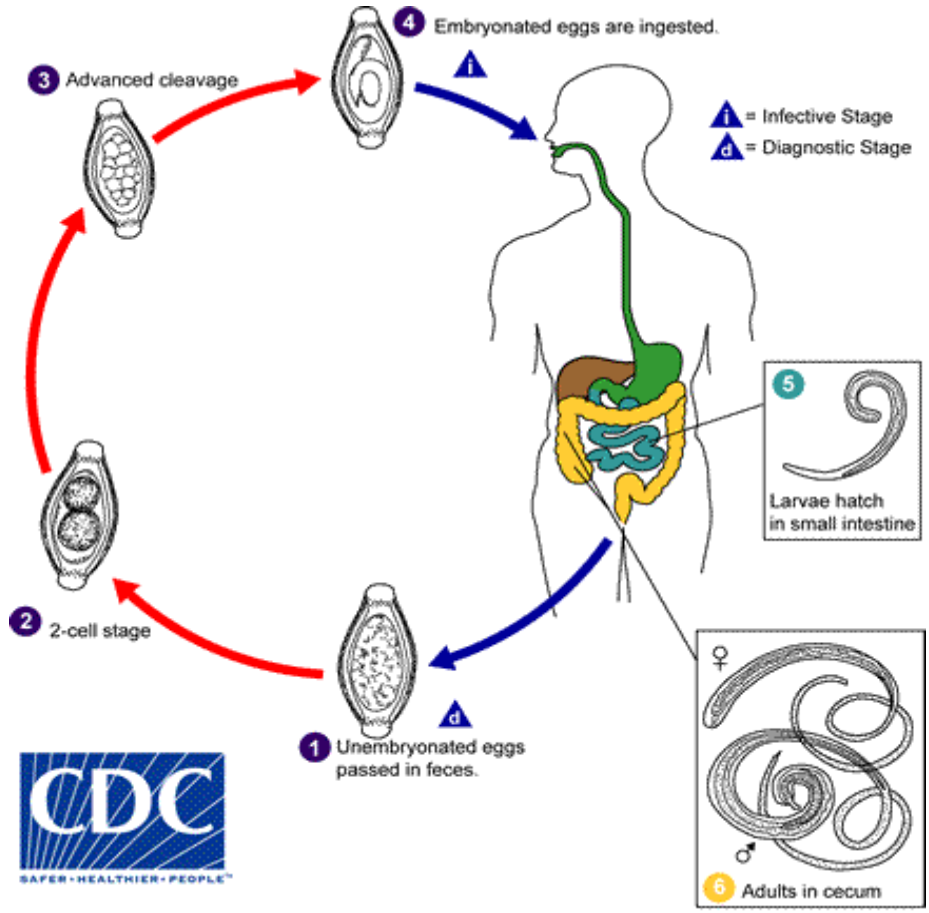


Fig. 10.3. Trichocephalis trichiuris life circle

Clinical signs of damage to the GI tract and central nervous system. The main symptoms are associated with digestive disorders and include lack of appetite, drooling, nausea, vomiting, flatulence, unstable stool (diarrhea alternating with constipation). With highly intense helminth infestation, severe colitis with intractable diarrhea mixed with blood, tenesmus, and rectal prolapse can develop. Abdominal pain may be focused in the epigastrium, right iliac region, or may not have a clear localization. Pain in the epigastrium with trichuriasis often simulates the clinical picture of a peptic ulcer of the stomach and duodenum, and pain in the lower abdomen — chronic appendicitis. Changes in the CNS include weakness, poor sleep, irritability, dizziness, headaches, fainting, convulsive syndrome, retardation in physical development.

The diagnosis of trichuriasis is beyond doubt when whipworm eggs are detected in feces using enrichment methods.

Antihelminthic therapy albendazole, mebendazole, carbendacim, etc. If necessary, a second course of antiparasitic therapy is repeated with another drug. Concomitant treatment includes group B vitamins, enzymes, probiotics, and iron supplements.

Prevention is similar to that for other intestinal helminthiases, maintaining hygiene (boiling water, washing hands, vegetables and fruits), protecting the soil from fecal pollution, and increasing the level of hygienic education of the population.

Teniidosis. *Etiology:* Cestodes — Taenia saginata, Taenia solium.

Essentials of diagnosis: Beef tapeworm (Taenia saginata) cysts in muscle transmitted to beef-eating humans cause taeniasis. T. saginata cysts mature in the GI tract to adult tapeworms. Proglottids of mature worms shed in feces. Taeniasis may cause chronic abdominal pain and weight loss. Large parasite load may obstruct the intestine. Humans can be the intermediate host for Taenia solium. Larvae released from eggs ingested by humans encyst in human muscle, brain, and eye (cysticercosis). Most cysts cause no symptoms. In cysticercosis, cysts cause late-appearing brain mass, seizures, headache hydrocephalus, meningitis, retinal detachment, and uveitis.

Diagnosis to taeniasis rests on finding T. saginataeggs or proglottids in feces or perianal skin. In cysticercosis, CT scan of the brain may reveal cysts. ELISA antibody titers to T soliumpositive in 98 % of patient sera and 75 % of patient. T. saginata used to be recognized as a cause of human vitamin B12 deficiency. The organisms compete with the host for dietary B12 and if the parasites load is big enough it can deprive the host.

Taenia saginata life circle is shown on the Fig. 10.4.

Differential diagnosis:

– seizure disorder;

– bacterial or viral meningitis/encephalitis;

– brain tumor;

– chronic headache;

– chronic abdominal pain;

– failure to thrive.

Treatment:

• Beef and pork inspection, proper cooking of meat, washing of vegetables and fruits, treatment of carriers, and prohibition of “night soil” as fertilizer has almost eliminated cestode infestation in the United States.

• Prognosis for T. saginata infestation good. Praziquantel and albendazole are both effective.

• Treat cysticercal meningitis or encephalitis with praziquantel or albendazole to eliminate cysts and ameliorate symptoms.

• Death of T solium larvae during antibiotic treatment may cause edema and exacerbate cerebral symptoms. Dexamethasone helps with this complication.

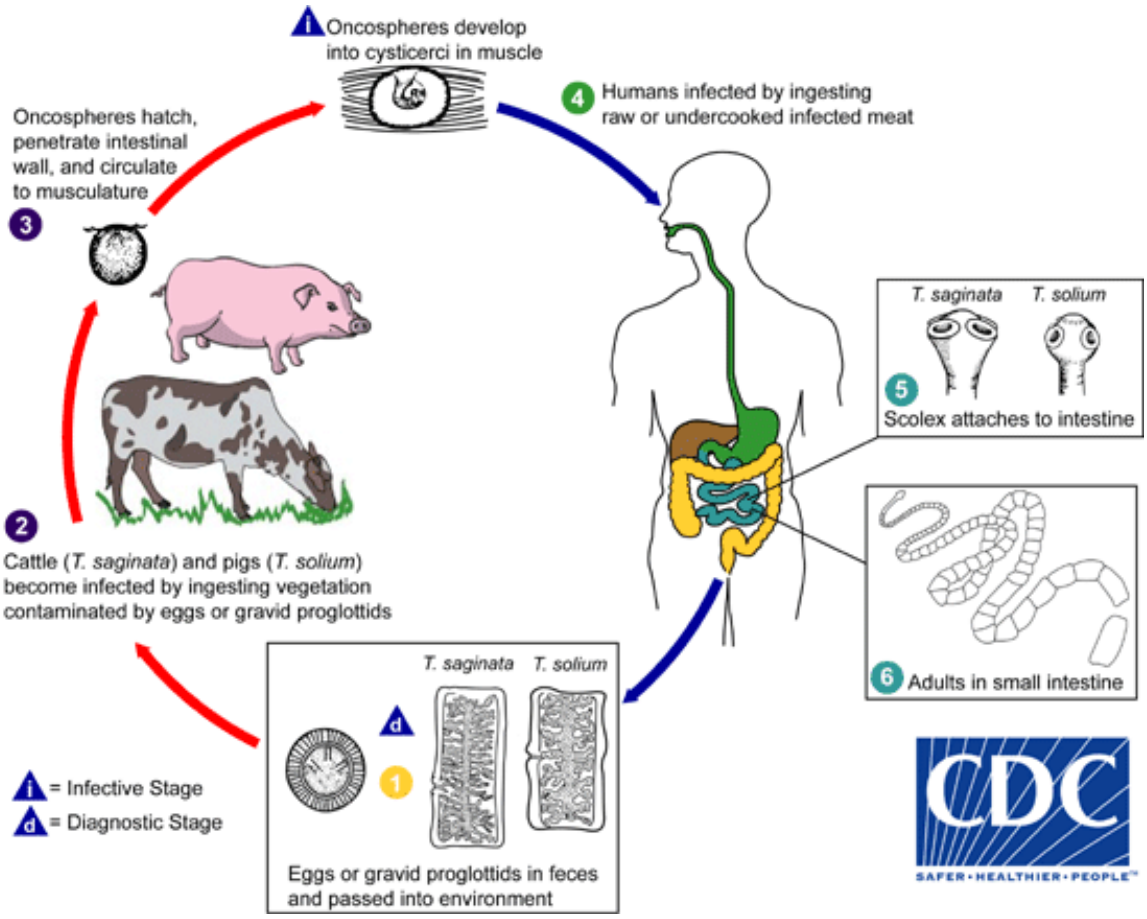


Fig. 10.4. Taenia saginata life circle

Hymenolepiasis is the most common intestinal tapeworm infection of humans caused by worm of family cestoda (tapeworm) species Hymenolepis nana (the dwarf tapeworm, mostly causes human infections, adults measuring 15 to 40 mm in length) and Hymenolepis diminuta (rat tapeworm, exclusively infects rats and rarely humans, adults measuring 20 to 60 cm). This infection does not require an intermediate host and infection can occur directly from one infected person to another by fecal-oral transmission.

Most people who are infected do not have any symptoms. Symptoms may experience nausea, weakness, loss of appetite, diarrhea, and abdominal pain. Young children, especially those with a heavy infection, may develop a headache, itchy bottom, or have difficulty sleeping.

Hymenolepiasis is diagnosed by the finding of eggs in wet mounts of stool. Because the proglottids usually disintegrate while in the lumen of the small intestine, they are rarely seen in clinical specimens.

Praziquantel is the drug of choice for treatment of Hymenolepiasis.

The risk factors of infection with H. nana include absence of proper sanitation, contact with environments contaminated with human feces, inadequate treatment of excreta and waste, consumption of untreated water, presence of infected person in the household, and bathing in contaminated irrigation canals.

Life circle of Hymenolepis nana is shown on Fig. 10.5.

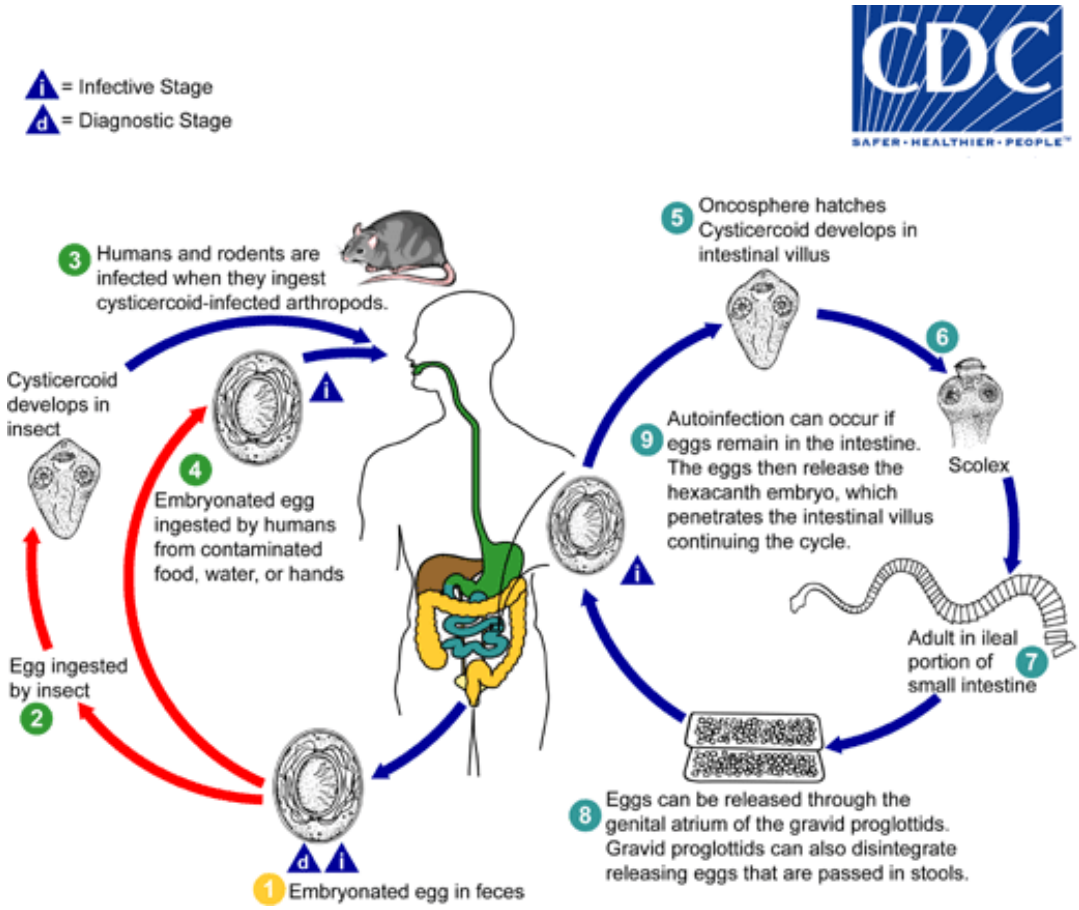


Fig. 10.5. Hymenolepis nana life circle

Toxocariasis (Visceral Larva Migrans — Toxocara canis, Toxocara cati).

Life circle of Toxocara spp. is shown on the Fig. 10.6:

• Dogs or cats infected with ascarids shed eggs in feces.

• Ingestion of eggs does not always cause disease.

• Disease occurs when larvae penetrate the intestine and migrate to liver, lungs, or eyes where they incite a granulomatous reaction as they die.

Symptoms:

• Anorexia, fever, fatigue, pallor, abdominal distension, hepatomegaly, seizures, myocarditis, encephalitis. Laboratory — dramatic eosinophilia up to 60–70 %; positive Toxocara ELISA is diagnostic.

• Ocular larva migrans — Toxocara causes unilateral posterior or peripheral inflammatory mass in older children. Presents with strabismus. Ocular larva migrans usually does not have eosinophilia. Antibody titers low in serum but high in ocular vitreous and aqueous fluid.

Differential diagnosis:

– other diseases with eosinophilia — trichinosis, eosinophilic leukemia, collagen vascular disease, strongyloidiasis, ascariasis, tropical eosinophilia, allergies;

– other diseases causing seizures, enlarged liver, pneumonitis, and cough — the tip-off is eosinophilia.

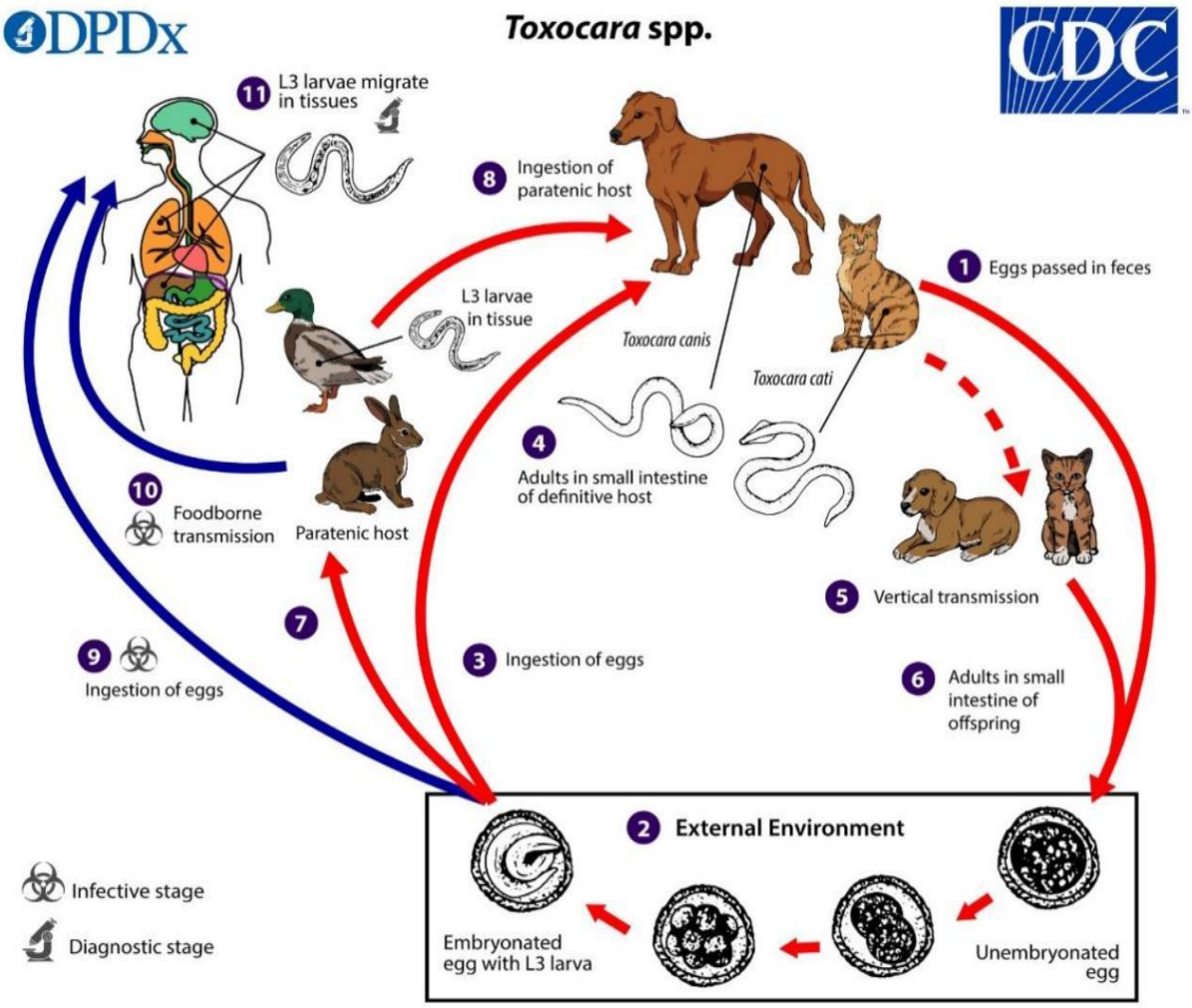


Fig. 10.6. Toxocara spp. life circle

Treatment:

• Prevent pica. It is the most common cause of this infection.

• Hand washing after handling soil frequented by dogs and cats.

• De-worm dogs and cats with Toxocara.

• Most patients recover spontaneously, but disease can last 6 months.

• In patients with brain, heart, eye, or lung disease — thiabendazole, diethylcarbmazine, albendazole, or mebendazole are used.

• Corticosteroids used to treat marked inflammation especially of lung and eye.

CHAPTER 11
CONGENITAL HEART DISEASES

Prevalence. Congenital heart diseases (CHD) are the most common group of structural malformations in children which occurs in 0.5–0.8 % of live births. The incidence is higher in stillborns (3–4 %), abortuses (10–25 %), and premature infants (about 2 % excluding patent ductus arteriosus (PDA)). This overall incidence does not include mitral valve prolapse, PDA of preterm infants, and bicuspid aortic valves (present in 1–2 % of adults). CHD have a wide spectrum of severity in infants: about 2–3 in 1,000 newborns will be symptomatic in the 1st yr of life. The diagnosis is established by 1 wk of age in 40–50 % of patients with CHD and by 1 month (mo) of age in 50–60 %. With advances in both palliative and corrective surgery in the last 20 years (yrs), the number of children with CHD surviving to adulthood has increased dramatically. Despite these advances, CHD remains the leading cause of death in children with congenital malformations.

Relative frequency of the most common CHD:

1. Ventricular septal defect (VSD) 25–30 %.
2. Atrial septal defect (secundum) 6–8 %.
3. Patent ductus arteriosus 6–8 %.
4. Coarctation of aorta 5–7 %.
5. Tetralogy of Fallot 5–7 %.
6. Transposition of great arteries 3–5 %.
7. Others 5–10 %.

Most CHD are well tolerated in the fetus because of the parallel nature of the fetal circulation. Even the most severe CHD (hypoplastic left heart syndrome) can usually be well compensated by the fetal circulation. The entire fetal cardiac output would be ejected by the RV via the ductus arteriosus into both the descending and ascending aortae (the latter filling in a retrograde fashion). It is only after birth when the fetal pathways (ductus arteriosus and foramen ovale) are closed that the full hemodynamic impact of an anatomic abnormality becomes apparent. One notable exception is the case of severe regurgitant lesions, most commonly of the tricuspid valve. In these lesions (Ebstein anomaly), the parallel fetal circulation cannot compensate for the volume load imposed on the right side of the heart. In utero HF, often with fetal pleural and pericardial effusions and generalized ascites (nonimmune hydrops fetalis) may occur.

Although the most significant transitions in circulation occur in the immediate perinatal period, the circulation continues to undergo changes after birth, and these later changes may also have a hemodynamic impact on cardiac lesions and their apparent incidence. As pulmonary vascular resistance falls over the 1st several weeks of life, left-to-right shunting through intracardiac defects increases and symptoms become more apparent. Thus, in patients with a VSD, heart failure is often manifested between 1 and 3 mo of age. The severity of various defects can also change dramatically with growth; some VSDs may become smaller and

even close as the child ages. Alternatively, stenosis of the aortic or pulmonary valve, which may be mild in the newborn period, may become worse if valve orifice growth does not keep pace with patient growth. The physician should always be alert for associated congenital malformations, which can adversely affect the patient's prognosis.

Etiology. The cause of most CHD is unknown, but rapid progress is being made in identifying the genetic basis of many congenital heart lesions. ***Most cases of CHD*** were thought to be ***multifactorial*** and result from ***a combination of genetic predisposition and environmental stimulus.*** A small percentage of CHD were related to chromosomal abnormalities, in particular, trisomy 21, 13, and 18 and Turner syndrome: heart disease is found in more than 90 % with trisomy 18, 50 % of patients with trisomy 21, and 40 % of those with Turner syndrome. Other genetic factors were suspected to play a role in CHD; for example, certain types of VSDs (supracristal) are more common in Asian children. The risk of recurrence of CHD increases if a 1st-degree relative (parent or sibling) is affected.

A growing list of CHD have been associated with ***specific chromosomal abnormalities***, and several have even been linked to specific gene defects. A well-characterized genetic cause of CHD is the deletion of a large region of chromosome 22q11, known as the DiGeorge critical region. The estimated prevalence of 22q11 deletions is 1 in 4.000 live births. Cardiac lesions associated with 22q11 deletions are most often seen in association with either the DiGeorge syndrome or the Shprintzen (velocardiofacial) syndrome. The acronym CATCH22 has been used to summarize the major components of these syndromes (*c*ardiac defects, *a*bnormal facies, *t*hymic aplasia, *c*left palate, and *h*ypocalcemia). The specific cardiac anomalies are conotruncal defects (tetralogy of Fallot, truncus arteriosus, double-outlet RV, subarterial VSD) and branchial arch defects (coarctation of the aorta, interrupted aortic arch, right aortic arch). Congenital airway anomalies such as tracheomalacia and bronchomalacia are sometimes present. Although the risk of recurrence is extremely low in the absence of a parental 22q11 deletion, it is 50 % if one of the parents carries the deletion.

Two to 4 % of cases of CHD are associated with known ***environmental or adverse maternal conditions and teratogenic influences***: maternal diabetes mellitus, phenylketonuria, or SLE; congenital rubella syndrome or other viruses; and maternal ingestion of drugs (lithium, ethanol, warfarin, thalidomide, antimetabolites, anticonvulsant agents).

Parents who have a child with CHD require genetic counseling regarding the probability of a cardiac malformation occurring in subsequent children. With the exception of syndromes known to be due to mutation of a single gene, most CHD is still relegated to a multifactorial inheritance pattern, which should result in a low risk of recurrence. The incidence of CHD in the normal population is approximately 0.8 %, and this incidence increases to 2–6 % for a 2nd pregnancy after the birth of a child with CHD or if a parent is affected. This recurrence risk is highly dependent on the type of lesion in the 1st child. When two 1st-degree relatives have CHD the risk for a subsequent child may reach 20–30 %.

Fetal EchoCG improves the rate of detection of CHD in high-risk patients. The resolution and accuracy of fetal EchoCG are not perfect, and families should be counseled that a normal fetal EchoCG does not guarantee the absence of CHD. CHD may also evolve during the course of the pregnancy; e.g., moderate aortic stenosis with a normal-sized LV at 18 wk of gestation may evolve into aortic atresia with a hypoplastic LV by 34 wk because of decreased flow through the atria, ventricle, and aorta during the latter half of gestation.

When structural abnormalities of other systems are present, consider EchoCG for associated cardiac disorders.

Evaluation of the infant or child with CHD. *The initial evaluation* for suspected CHD involves a systematic approach ***with 3 major components***.

1. CHD can be divided into 2 major groups based on the presence or absence of cyanosis, which can be determined by physical examination aided by pulse oximetry.

2. These 2 groups can be further subdivided according to whether the chest X-ray shows evidence of increased, normal, or decreased pulmonary vascular markings.

3. The ECG can be used to determine whether right, left, or biventricular hypertrophy exists. The character of the heart sounds and the presence and character of any murmurs further narrow the differential diagnosis. The final diagnosis is then confirmed by EchoCG or cardiac catheterization, or by both.

The most common CHD:

1. ***Acyanotic*** — ventricular septal defect (VSD), PDA, atrial septal defect (ASD).

2. ***Outflow obstruction*** — pulmonary stenosis, aortic stenosis, coarctation of the aorta.

3. ***Cyanotic*** — tetralogy of Fallot, transposition of the great vessels, AV septal defect complete.

Acyanotic congenital heart disease: the left-to-right shunt lesions.

1. ***Patent ductus arteriosus: postnatal persistence of the ductus arteriosus connecting pulmonary artery and aorta during fetal life.*** In a fetus most of the pulmonary arterial blood is shunted through the ductus arteriosus into the aorta. Functional closure of the ductus normally occurs soon after birth, but if the ductus remains patent when pulmonary vascular resistance falls, aortic blood is shunted into the pulmonary artery. The aortic end of the ductus is just distal to the origin of the left subclavian artery, and the ductus enters the pulmonary artery at its bifurcation. Female with PDA outnumber males 2 : 1. PDA is also associated with maternal rubella infection during early pregnancy. It is a common problem in premature babies, where it can cause severe hemodynamic derangements and major sequelae.

In a term infant with PDA the wall of the ductus is deficient in both the mucoid endothelial layer and the muscular media. In a premature the PDA usually has a normal structure; patency is the result of hypoxia and immaturity.

PDA persisting beyond the 1st few weeks of life in a term infant rarely closes spontaneously or with pharmacologic intervention, whereas if early pharmacologic or surgical intervention is not required in a premature infant, spontaneous closure occurs in most instances. A PDA is seen in 10 % of patients with other CHD and often plays a critical role in providing pulmonary blood flow when the RV outflow tract is stenotic or atretic or in providing systemic blood flow in the presence of aortic coarctation or interruption.

Pathophysiology. As a result of the higher aortic pressure, blood shunts left to right through the ductus, from the aorta to the pulmonary artery. The extent of the shunt depends on the size of the ductus and on the ratio of pulmonary to systemic vascular resistance. In extreme cases, 70 % of the LV output may be shunted through the ductus to the pulmonary circulation. If the PDA is small, pressure within the pulmonary artery, the RV, and the RA is normal. However, if the PDA is large, pulmonary artery pressure may be elevated to systemic levels during both systole and diastole. Patients with a large PDA are at extremely high risk for the development of pulmonary vascular disease if left unoperated. Pulse pressure is wide because of runoff of blood into the pulmonary artery during diastole.

Clinical manifestations. A small PDA does not usually have any symptoms. A large PDA will result in HF similar to that encountered in infants with a large VSD. *Retardation of physical growth may be a major manifestation in infants with large shunts*. A large PDA will result in striking physical signs attributable to the wide pulse pressure, most prominently, bounding peripheral arterial pulses. The heart is normal in size when the ductus is small but moderately or grossly enlarged in cases with a large communication. The apical impulse is prominent and, with cardiac enlargement, is heaving. A thrill, maximal in the 2nd left interspace, is often present and may radiate toward the left clavicle, down the left sternal border, or toward the apex, usually systolic but may also be palpated throughout the cardiac cycle. The classic continuous murmur is described as being like machinery or rolling thunder in quality. It begins soon after onset of the 1st sound, reaches maximal intensity at the end of systole, and wanes in late diastole. It may be localized to the 2nd left intercostal space or radiate down the left sternal border or to the left clavicle. When pulmonary vascular resistance is increased, the diastolic component of the murmur may be less prominent or absent. In patients with a large left-to-right shunt, a low-pitched mitral mid-diastolic murmur may be audible at the apex as a result of the increased volume of blood flow across the mitral valve.

Diagnosis. If the left-to-right shunt is small, the *ECG* is normal; if the ductus is large, left ventricular or biventricular hypertrophy is present. The diagnosis of an isolated, uncomplicated PDA is untenable when RV hypertrophy is noted.

Radiographic studies in patients with a large PDA show a prominent pulmonary artery with increased intrapulmonary vascular markings. Cardiac size depends on the degree of left-to-right shunting; it may be normal or moderately to markedly enlarged. The chambers involved are the left atrium and ventricle. The aortic knob is normal or prominent.

The *EchoCG* of the cardiac chambers is normal if the ductus is small. With large shunts, LA and LV are increased. The size of the LA is usually quantitated by comparison to the size of the aortic root, known as the LA:Ao ratio. Scanning from the suprasternal notch allows direct visualization of the ductus. Doppler demonstrates systolic or diastolic (or both) retrograde turbulent flow in the pulmonary artery and aortic retrograde flow in diastole.

The clinical pattern is sufficiently distinctive to allow an accurate diagnosis by noninvasive methods in most patients. In patients with atypical findings or when associated cardiac lesions are suspected, *cardiac catheterization* may be indicated. It demonstrates normal or increased pressure in the RV and pulmonary artery, depending on the size of the ductus. The presence of oxygenated blood shunting into the pulmonary artery confirms a left-to-right shunt. The catheter may pass from the pulmonary artery through the ductus into the descending aorta. Injection of contrast medium into the ascending aorta shows opacification of the pulmonary artery from the aorta and identifies the ductus.

Prognosis and complications. Patients with a small PDA may live a normal span with few or no cardiac symptoms, but late manifestations may occur. Spontaneous closure of the ductus after infancy is extremely rare.

Heart failure most often occurs in early infancy in the presence of a large ductus but may occur late in life even with a moderate-sized communication. The chronic LV volume load is less well tolerated with aging. *Infective endarteritis* may be seen at any age. Pulmonary or systemic emboli may occur. Rare complications: aneurysmal dilatation of the pulmonary artery or the ductus, calcification of the ductus, noninfective thrombosis of the ductus with embolization, and paradoxical emboli. Pulmonary hypertension (Eisenmenger syndrome) usually develops in patients with a large PDA who do not undergo surgical treatment.

Treatment. Spontaneous closure occurs in term neonates at 3–5 days of age. Hypoxia retards spontaneous closure. Medical closure with indomethacin or ibuprofen is 80–90 % effective in infants > 1000 g. Irrespective of age, PDA require surgical or catheter closure. In small PDA, the rationale for closure is prevention of bacterial endarteritis or other late complications. In moderate to large PDA, closure is accomplished to treat HF or prevent the development of pulmonary vascular disease, or both. Once the diagnosis of a moderate to large PDA is made, treatment should not be unduly postponed after adequate medical therapy for cardiac failure has been instituted. Surgical closure of PDA can be accomplished by thoracoscopic techniques to minimize scarring and reduce postoperative discomfort. Because the case fatality rate with surgical treatment is considerably less than 1 % and the risk without it is greater, ligation and division of the ductus are indicated in asymptomatic patients, preferably before 1 yr of age. Pulmonary hypertension is not a contraindication to surgery at any age if it can be demonstrated at cardiac catheterization that the shunt flow is still predominantly left to right and that severe pulmonary vascular disease is not present. After closure, symptoms of frank or incipient cardiac failure rapidly disappear.

Infants who had failed to thrive usually have immediate improvement in physical development. The pulse and blood pressure return to normal, and the machinery-like murmur disappears. The radiographic signs of cardiac enlargement and pulmonary overcirculation disappear over a period of several months, and the ECG becomes normal. Transcatheter PDA closure is routinely performed. Small PDAs are generally closed with intravascular coils. Moderate to large PDAs may be closed with a catheter-introduced sac into which several coils are released or with an umbrella-like device.

Differential diagnosis: ASD and VSD in neonates may have similar findings.

2. *Atrial Septal Defects (ASDs.)*: *congenital opening in the interatrial septum*. ASDs can occur in any portion of the atrial septum (secundum, primum, or sinus venosus), depending on which embryonic septal structure has failed to develop normally. Less commonly, the atrial septum may be nearly absent, with the creation of a functional single atrium. Isolated secundum ASDs account for ~ 7 % of CHD. The majority of cases are sporadic; however, autosomal dominant inheritance does occur as part of the Holt-Oram syndrome (hypoplastic or absent radii, 1st-degree heart block, ASD).

An isolated valve-incompetent *patent foramen ovale (PFO)* is a common EchoCG finding during infancy. It is usually of no hemodynamic significance and is not considered an ASD; however, a PFO may play an important role if other structural heart defects are present. If another cardiac anomaly is causing increased RA pressure (e.g., pulmonary stenosis or atresia, tricuspid valve abnormalities, RV dysfunction), venous blood may shunt across the PFO into the LA with resultant cyanosis. Because of the anatomic structure of the PFO, left-to-right shunting is unusual outside the immediate newborn period. In the presence of a large volume load or a hypertensive LA (e.g., secondary to mitral stenosis), the foramen ovale may be sufficiently dilated to result in a significant atrial left-to-right shunt. A valve-competent but probe-PFO may be present in 15–30 % of adults. An isolated PFO does not require surgical treatment, although it may be a risk for paradoxical (right to left) systemic embolization.

Atrioventricular septal defects (ostium primum and atrioventricular canal or endocardial cushion defects). AV septal defects are grouped together because they represent a spectrum of a basic embryologic abnormality, a deficiency of the AV septum. An *ostium primum defect* is situated in the lower portion of the atrial septum and overlies the mitral and tricuspid valves. In most instances, a cleft in the anterior leaflet of the mitral valve is also noted. The tricuspid valve is usually functionally normal, although some anatomic abnormality of the septal leaflet is generally present. The ventricular septum is intact.

An *AV septal defect* (AV canal defect) consists of contiguous atrial and ventricular septal defects with markedly abnormal AV valves. The severity of the valve abnormalities varies; in the complete form of AV septal defect, a single AV valve is common to both ventricles and consists of an anterior and a posterior bridging leaflet related to the ventricular septum, with a lateral leaflet in each

ventricle. The lesion is common in children with Down syndrome and may occasionally occur with pulmonary stenosis.

Pathophysiology. The basic abnormality in *ostium primum defects* is the combination of a left-to-right shunt across the atrial defect and mitral insufficiency. The shunt is usually moderate to large, the degree of mitral insufficiency is generally mild to moderate, and pulmonary arterial pressure is typically normal or only mildly increased. The physiology of this lesion is therefore similar to that of an ostium secundum ASD.

In *AV septal defects*, the left-to-right shunt occurs at both the atrial and ventricular levels. Additional shunting may occur directly from the LV to the RA because of absence of the AV septum. Pulmonary hypertension and an early tendency to increase pulmonary vascular resistance are common. AV valvular insufficiency increases the volume load on one or both ventricles. Some right-to-left shunting may also occur at both the atrial and ventricular levels and lead to mild but significant arterial desaturation. With time, progressive pulmonary vascular disease increases the right-to-left shunt so that clinical cyanosis develops (Eisenmenger physiology).

Clinical manifestations. Many children with ostium primum *defects* are asymptomatic, and the anomaly is discovered during a general physical examination. In moderate shunts and mild mitral insufficiency, the physical signs are similar to those of the secundum ASD, but with an additional apical murmur caused by mitral insufficiency. A history of exercise intolerance, easy fatigability, and recurrent pneumonia may be obtained, especially in infants with large left-to-right shunts and severe mitral insufficiency. Cardiac enlargement is moderate or marked, and the precordium is hyperdynamic.

Auscultatory signs produced by the left-to-right shunt include a normal or accentuated 1st sound; wide, fixed splitting of the 2nd sound; a pulmonary systolic ejection murmur sometimes preceded by a click; and a low-pitched, mid-diastolic rumbling murmur at the lower left sternal edge or apex, or both, as a result of increased flow through the AV valves. Mitral insufficiency may be manifested by an apical harsh (occasionally very high pitched) holosystolic murmur that radiates to the left axilla.

With *complete AV septal defects*, congestive HF and intercurrent pulmonary infection usually appear in infancy. During these episodes, minimal cyanosis may be evident. The liver is enlarged and the infant shows signs of failure to thrive. Cardiac enlargement is moderate to marked, and a systolic thrill is frequently palpable at the lower left sternal border. A precordial bulge and lift may be present as well. The 1st heart sound is normal or accentuated. The 2nd heart sound is widely split if the pulmonary flow is massive. A low-pitched, mid-diastolic rumbling murmur is audible at the lower left sternal border, and a pulmonary systolic ejection murmur is produced by the large pulmonary flow. The harsh apical holosystolic murmur of mitral insufficiency may also be present.

Diagnosis. Chest *X-ray* in complete AV septal defects shows marked cardiac enlargement caused by the prominence of both ventricles and atria. The pulmonary artery is large, and pulmonary vascularity is increased.

The *ECG* in a complete AV septal defect is distinctive. The principal abnormalities are: 1) superior orientation of the mean frontal QRS axis with left axis deviation to the left upper or right upper quadrant; 2) counterclockwise inscription of the superiorly oriented QRS vector loop; 3) signs of biventricular hypertrophy or isolated RV hypertrophy; 4) RV conduction delay (RSR' pattern in leads V_3R and V_1); 5) normal or tall P waves; 6) occasional prolongation of the P-R.

The *EchoCG* shows signs of RV enlargement with encroachment of the mitral valve echo on the LV outflow tract; the abnormally low position of the AV valves results in a "gooseneck" deformity of the LV outflow tract on both EchoCG and angiography. In normal hearts, the tricuspid valve inserts slightly more toward the apex than the mitral valve does. In AV septal defects, both valves insert at the same level because of absence of the AV septum. In complete AV septal defects, the ventricular septal echo is also deficient and the common AV valve is readily appreciated. *Doppler EchoCG* demonstrates left-to-right shunting at the atrial, ventricular, or ventricular-to-atrial levels and semiquantitate the degree of AV valve insufficiency.

Cardiac catheterization and *angiocardiography* may be required to confirm the diagnosis, although most patients can be operated on without catheterization. It demonstrates the magnitude of the left-to-right shunt, the severity of pulmonary hypertension, the degree of elevation of pulmonary vascular resistance, and the severity of insufficiency of the common AV valve. Children with ostium primum defects generally have normal or only moderately elevated pulmonary arterial pressure. Conversely, complete AV septal defects are associated with RV and pulmonary hypertension and, in older patients, with increased pulmonary vascular resistance.

Prognosis and complications. The prognosis for complete AV septal defects depends on the magnitude of the left-to-right shunt, the degree of elevation of pulmonary vascular resistance, and the severity of AV valve insufficiency. Death from HF during infancy used to be frequent before the advent of early surgery. In patients who survived without surgery, pulmonary vascular obstructive disease or, more rarely, pulmonic stenosis usually developed. Most patients with ostium primum defects and minimal AV valve involvement are asymptomatic or have only minor, nonprogressive symptoms until they reach the 3rd – 4th decade of life, similar to the course of patients with secundum ASDs.

Treatment. Many ASDs close spontaneously. Ostium secundum ASDs < 4 mm diameter usually close spontaneously. In symptomatic children 1–3 yrs old, close ASD surgically or place occluding device during cardiac catheterization

Ostium primum defects are approached surgically from an incision in the RA. The cleft in the mitral valve is located through the atrial defect and is repaired by direct suture. The defect in the atrial septum is usually closed by insertion of

patch prosthesis, the surgical mortality rate is low. Surgery of complete AV septal defects is more difficult, especially in infants with HF and pulmonary hypertension. Because of the risk of pulmonary vascular disease developing as early as 6–12 mo of age, surgery must be performed during infancy. Correction of these defects can be accomplished in infancy, and palliation with pulmonary arterial banding is reserved for the subset of patients who are either too small or have other associated lesions that make early corrective surgery too risky. The atrial and ventricular defects are patched and the AV valves reconstructed. Complications: surgically induced heart block requiring placement of a permanent pacemaker, excessive narrowing of the LV outflow tract requiring surgical revision, and worsening of mitral regurgitation requires replacement with a prosthetic valve.

Differential DS: Holt-Oram syndrome, partial anomalous pulmonary venous return, Ebstein anomaly of the tricuspid valve.

3. *Ventricular septal defect: hole in the wall between two ventricles.* VSD is the most common cardiac malformation and accounts for 35 % of CHD. Defects may occur in any portion of the ventricular septum, but most are of the membranous type. These defects are in a posteroinferior position, anterior to the septal leaflet of the tricuspid valve. VSDs between the crista supraventricularis and the papillary muscle of the conus may be associated with pulmonary stenosis and other manifestations of the tetralogy of Fallot. VSDs superior to the crista supraventricularis (supracristal) are less common; they are found just beneath the pulmonary valve and may impinge on an aortic sinus and cause aortic insufficiency. VSDs in the midportion or apical region of the ventricular septum are muscular in type and may be single or multiple (Swiss cheese septum).

Pathophysiology. The physical size of the VSD is a major, but not the only determinant of the size of the left-to-right shunt. The level of pulmonary vascular resistance in relation to systemic vascular resistance also determines the shunt's magnitude. In small communication (< 0.5 cm^2), the VSD is called *restrictive* and RV pressure is normal. The higher pressure in the LV drives the shunt left to right; the size of the defect limits the magnitude of the shunt. In large *nonrestrictive* VSDs (> 1.0 cm^2), right and left ventricular pressure is equalized. In these defects, the direction of shunting and shunt magnitude are determined by the ratio of pulmonary to systemic vascular resistance.

After birth in a large VSD, pulmonary vascular resistance may remain higher than normal, and thus the size of the left-to-right shunt may initially be limited. As pulmonary vascular resistance continues to fall in the 1st few weeks after birth because of normal involution of the media of small pulmonary arterioles, the size of the left-to-right shunt increases. A large left-to-right shunt develops, and clinical symptoms become apparent. In most cases during infancy, pulmonary vascular resistance is only slightly elevated, and the major contribution to pulmonary hypertension is the extremely in large pulmonary blood flow. In some infants with a large VSD, pulmonary arteriolar medial thickness never decreases. With continued exposure of the pulmonary vascular bed to high systolic pressure and high flow,

pulmonary vascular obstructive disease develops. When the ratio of pulmonary to systemic resistance approaches 1 : 1, the shunt becomes bidirectional, the signs of HF abate, and the patient becomes cyanotic (Eisenmenger physiology).

Clinical manifestations. Vary according to the size of the defect and pulmonary blood flow and pressure. *Small VSDs* with trivial left-to-right shunts and normal pulmonary arterial pressure are the most common. These patients are asymptomatic, and the cardiac lesion is usually found during routine physical examination. A loud, harsh, or blowing holosystolic murmur is present and heard best over the lower left sternal border, and it is frequently accompanied by a thrill. A short, harsh systolic murmur localized to the apex in a neonate is often a sign of a tiny muscular VSD. In neonatal period, the left-to-right shunt may be minimal because of higher right-sided pressure, and therefore the systolic murmur may not be audible during the 1st few days of life. In premature infants, the murmur may be heard early because pulmonary vascular resistance decreases more rapidly.

Large VSDs with excessive pulmonary blood flow and pulmonary hypertension are responsible for dyspnea, feeding difficulties, poor growth, profuse perspiration, recurrent pulmonary infections, and HF in infancy. Cyanosis is usually absent, but duskiness is sometimes noted during infections or crying. Prominence of the left precordium is common, as are a palpable parasternal lift, a laterally displaced apical impulse and apical thrust, and a systolic thrill. The holosystolic murmur of a large VSD is generally less harsh than that of a small VSD and more blowing in nature because of the absence of a significant pressure gradient across the defect. The pulmonic component of the 2nd sound may be increased as a result of pulmonary hypertension.

Diagnosis. In small VSDs, the *chest X-ray* is usually normal, although minimal cardiomegaly and a borderline increase in pulmonary vasculature may be observed. The *ECG* is generally normal but may suggest left ventricular hypertrophy. The presence of RV hypertrophy is a warning that the defect is not small and that the patient has pulmonary hypertension or an associated lesion such as pulmonic stenosis. In large VSDs, the *chest X-ray* shows cardiomegaly with prominence of both ventricles, the LA, and the pulmonary artery. Pulmonary vascular markings are increased, and frank pulmonary edema, including pleural effusions, may be present. The *ECG* shows biventricular hypertrophy; P waves may be notched or peaked.

The *EchoCG* shows the position and size of the VSD. In small defects, especially in the muscular septum, the defect itself may be difficult to image and is visualized only by Doppler. In defects of the membranous septum, a thin membrane can partially cover the defect and limit the volume of the left-to-right shunt. Doppler shows whether the VSD is pressure restrictive by calculating the pressure gradient across the defect. Estimation of RV pressure helps determine whether the patient is at risk for the development of early pulmonary vascular disease.

Catheterization is usually performed only when the size of the shunt is uncertain after a comprehensive clinical evaluation, when laboratory data do not fit well with the clinical findings, or when pulmonary vascular disease is suspected.

Prognosis and complications. The course of a VSD depends on the size of the defect. A significant number (30–50 %) of small defects close spontaneously, most frequently during the 1st 2 yr of life. 85 % of VSDs are < 3 mm and close spontaneously. VSDs 3–5 mm rarely develop pulmonary hypertension. When left-to-right shunt ratio is > 2 : 1, HF may be severe enough to require VSD closure by surgical patching. Small muscular VSDs are more likely to close (up to 80 %) than membranous VSDs are (up to 35 %). The vast majority of defects that close do so before the age of 4 yr, although spontaneous closure has been reported in adults. These VSDs often have ventricular septal aneurysms limiting the magnitude of the shunt. Most children with small defects remain asymptomatic, without evidence of an increase in heart size, pulmonary arterial pressure, or resistance. Long-term risks are infective endocarditis, arrhythmia, subaortic stenosis, exercise intolerance. Small, hemodynamically insignificant VSD is not an indication for surgery.

VSDs > 6 mm always require surgery to prevent chronic left-to right shunt and pulmonary hypertension. Infants with large defects have repeated episodes of respiratory infection and HF despite medical management. HF may be manifested in many of these infants primarily as failure to thrive. Pulmonary hypertension occurs as a result of high pulmonary blood flow. Such patients are at risk for pulmonary vascular disease and the development of aortic valve regurgitation with time if the defect is not repaired, the greatest risk in supracristal VSD. A small number of patients an Eisenmenger physiology develops.

Treatment. In patients with small VSDs, parents should be reassured of the relatively benign nature of the lesion, and the child should be encouraged to live a normal life, with no restrictions on physical activity. Surgical repair is currently not recommended. As protection against infective endocarditis, the integrity of primary and permanent teeth should be carefully maintained; antibiotic prophylaxis should be provided for dental visits (including cleanings), tonsillectomy, adenoidectomy, and other oropharyngeal surgical procedures, as well as for instrumentation of the genitourinary and lower intestinal tracts. American Heart Association recommendation: no antibiotic prophylaxis for bacterial endocarditis in unrepaired or completely repaired VSD. Prophylaxis recommended for patients with residual VSD postsurgery.

The ECG is an excellent means of screening these patients for possible pulmonary hypertension or pulmonic stenosis as indicated by RV hypertrophy. EchoCG is used to screen for the development of LV outflow tract pathology (subaortic membrane or aortic regurgitation) and to confirm spontaneous closure.

In infants with a large VSD, medical management has two aims: to control HF and prevent the development of pulmonary vascular disease. If early treatment is successful, the shunt may diminish in size with spontaneous improvement,

especially during the 1st yr of life. The clinician must be alert to not confuse clinical improvement caused by a decrease in defect size with clinical changes caused by the development of Eisenmenger physiology. Pulmonary vascular disease can be prevented when surgery is performed within the 1st yr of life.

Indications for surgical closure of a VSD include patients at any age with large defects in whom clinical symptoms and failure to thrive cannot be controlled medically; infants between 6 and 12 mo of age with large defects associated with pulmonary hypertension, even if the symptoms are controlled by medication; and patients older than 24 mo with a Qp : Qs ratio greater than 2 : 1. Severe pulmonary vascular disease is a contraindication to closure of a VSD.

The long-term prognosis after surgery is excellent. Most infants begin to thrive, and cardiac medications are no longer required. Catch-up growth occurs in most patients over the next 1–2 yr. Because surgery is now performed in young infants with VSD, Eisenmenger syndrome (suprasystemic pulmonary hypertension with right-to-left shunt) has almost disappeared.

Differential Diagnosis: VSD is often associated with more complex CHD such as transposition of the great arteries or tricuspid atresia.

4. *Coarctation of the aorta: narrowing of the segment of the aorta.* Constrictions of the aorta (CoA) of varying degrees may occur at any point from the transverse arch to the iliac bifurcation, but 98 % occur just below the origin of the left subclavian artery at the origin of the ductus arteriosus (juxtaductal coarctation). The anomaly occurs twice as often in males as in females. CoA may be a feature of Turner syndrome and is associated with a bicuspid aortic valve in more than 70 % of patients.

Pathophysiology. CoA can occur as a discrete juxtaductal obstruction or as tubular hypoplasia of the transverse aorta starting at one of the head or neck vessels and extending to the ductal area (preductal or infantile-type coarctation). Often, both components are present. CoA may be initiated in fetal life by the presence of a cardiac abnormality that results in decreased blood flow anterograde through the aortic valve (e.g., bicuspid aortic valve, VSD).

In discrete juxtaductal coarctation, ascending aortic blood flows through the narrowed segment to reach the descending aorta, although LV hypertension and hypertrophy result. In the 1st few days of life, the PDA may serve to widen the juxtaductal area of the aorta and provide temporary relief from the obstruction. Net left-to-right ductal shunting occurs in acyanotic infants. With more severe juxtaductal coarctation or in the presence of transverse arch hypoplasia, RV blood is ejected through the ductus to supply the descending aorta. Perfusion of the lower part of the body is then dependent on RV output, the femoral pulses are palpable, and differential blood pressures may not be helpful in diagnosis. The ductal right-to-left shunting is manifested as differential cyanosis, with the upper extremities being pink and the lower extremities blue. Such infants may have severe pulmonary hypertension, high pulmonary vascular resistance; signs of HF. CoA associated with arch hypoplasia were referred to as *infantile type*

because its severity usually led to recognition of the condition in early infancy. *Adult type* referred to isolated juxtaductal coarctation, which if mild, was not usually recognized until later childhood. These terms have been replaced with the more accurate anatomic terms describing the location and severity of the defect.

Blood pressure is elevated in the vessels that arise proximal to the CoA; BP as well as pulse pressure is lower below the constriction. CoA usually results in the development of an extensive collateral circulation, chiefly from branches of the subclavian, superior intercostal, and internal mammary arteries, to create channels for arterial blood to bypass the area of CoA. The vessels contributing to the collateral circulation may become markedly enlarged and tortuous by early adulthood.

Clinical manifestations. CoA recognized after infancy is rarely associated with significant symptoms. Some children or adolescents complain about weakness or pain (or both) in the legs after exercise, but in many instances, even patients with severe CoA are asymptomatic. Older children are frequently brought to the cardiologist's attention when they are found to be hypertensive on routine physical examination.

The classic sign of CoA is a disparity in pulsation and BP in the arms and legs. The femoral, popliteal, posterior tibial, and dorsalis pedis pulses are weak (or absent in up to 40 %), in contrast to the bounding pulses of the arms and carotid vessels. The radial and femoral pulses should always be palpated simultaneously for the presence of a radial-femoral delay. Normally, the femoral pulse occurs slightly before the radial pulse. A radial-femoral delay occurs when blood flow to the descending aorta is dependent on collaterals, in which case the femoral pulse is felt after the radial pulse. In normal persons, systolic BP in the legs obtained by the cuff method is 10–20 mm Hg higher than that in the arms. In CoA, BP in the legs is lower than that in the arms; frequently, it is difficult to obtain. It is important to determine the BP in each arm; a pressure higher in the right than the left arm suggests involvement of the left subclavian artery in the area of CoA. The right subclavian may arise anomalously from below the area of CoA and result in a left arm pressure that is higher than the right. With exercise, a more prominent rise in systemic BP occurs, and the upper-to-lower extremity pressure gradient will increase.

The precordial impulse and heart sounds are usually normal; the presence of a systolic ejection click or thrill in the suprasternal notch suggests a bicuspid aortic valve (present in 70 %). A short systolic murmur is often heard along the left sternal border at the 3rd and 4th intercostal spaces. The murmur is well transmitted to the left infrascapular area and occasionally to the neck. In older patients with well-developed collateral blood flow, systolic or continuous murmurs may be heard over the left and right sides of the chest laterally and posteriorly, a palpable thrill can occasionally be appreciated in the intercostal spaces on the back.

Neonates or infants with more severe CoA, usually including some degree of transverse arch hypoplasia, initially have signs of lower body hypoperfusion,

acidosis, and severe HF. These signs may be delayed days or weeks until after closure of the ductus arteriosus. If detected before ductal closure, patients may exhibit differential cyanosis, best demonstrated by simultaneous oximetry of the upper and lower extremities. The heart is large, and a systolic murmur is heard along the left sternal border with a loud 2nd heart sound.

Diagnosis. *X-ray* depends on the age of the patient and on the effects of hypertension and the collateral circulation. Cardiac enlargement and pulmonary congestion are noted in infants with severe CoA. During childhood, the findings are not striking until after the 1st decade, when the heart tends to be mildly or moderately enlarged because of LV prominence. The enlarged left subclavian artery commonly produces a prominent shadow in the left superior mediastinum. Notching of the inferior border of the ribs from pressure erosion by enlarged collateral vessels is common by late childhood. The descending aorta has an area of poststenotic dilatation.

ECG is usually normal in young children but reveals evidence of LV hypertrophy in older patients. Neonates and infants display right or biventricular hypertrophy. The segment of CoA can generally be visualized by *EchoCG;* associated anomalies of the mitral and aortic valve can also be. The descending aorta is hypopulsatile. Doppler is useful for demonstrating the specific site of the obstruction. Pulsed and continuous wave Doppler studies determine the pressure gradient directly at the area of CoA; in the presence of a PDA, however, the severity of the narrowing may be underestimated. *Cardiac catheterization* with selective left ventriculography and aortography is useful in certain patients with additional anomalies and as a means of visualizing collateral blood flow. In cases that are well defined by EchoCG, diagnostic catheterization is not usually required before surgery.

Prognosis and complications. Abnormalities of the aortic valve are present in most patients. Bicuspid aortic valves are common but do not generally produce clinical signs unless the stenosis is significant. The association of a PDA and CoA is also common. VSDs and ASDs may be suspected by signs of a left-to-right shunt; they are exacerbated by the increased resistance to flow through the left side of the heart. Mitral valve abnormalities are also seen, as is subvalvular aortic stenosis.

Severe neurologic damage or even death may rarely occur from associated cerebrovascular disease. Subarachnoid or intracerebral hemorrhage may result from rupture of congenital aneurysms in the circle of Willis, rupture of other vessels with defective elastic and medial tissue, or rupture of normal vessels; these accidents are secondary to hypertension.

Untreated, the great majority of older patients with CoA would succumb between the ages of 20–40 yr; some live well into middle life without serious disability. The common serious complications are related to systemic hypertension, which may result in premature coronary artery disease, HF, hypertensive encephalopathy, or intracranial hemorrhage. HF may be worsened by associated anomalies. Infective endocarditis or endarteritis is a significant

complication in adults. Aneurysms of the descending aorta or the enlarged collateral vessels may develop. In infants HF and hypoperfusion may be life threatening and require immediate medical intervention.

Treatment. In neonates with severe CoA, closure of the ductus often results in hypoperfusion, acidosis, and rapid deterioration. These patients should be given an infusion of prostaglandin E_1 to reopen the ductus and re-establish adequate lower extremity blood flow. Once a diagnosis has been confirmed and the patient stabilized, surgical repair should be performed. Older infants with HF but good perfusion should be managed with anticongestive measures to improve their clinical status before surgery.

Older children with significant CoA should be treated relatively soon after diagnosis. Delay is unwarranted, especially after the 2nd decade of life, when the operation may be less successful because of decreased LV function and degenerative changes in the aortic wall. Associated valvular lesions increase the hazards of late surgery.

The procedure of choice for isolated juxtaductal CoA is controversial. Surgery remains the treatment of choice, and several surgical techniques are used. The area of CoA can be excised and a primary re-anastomosis performed. Often, the transverse aorta is splayed open and an "extended end-to-end" anastomosis performed to increase the effective cross-sectional area of the repair. The subclavian flap procedure, which involves division of the left subclavian artery and incorporation of it into the wall of the repaired coarctation, is used by some, often in the younger age group. Others favor a patch aortoplasty, in which the area of CoA is enlarged with a roof of prosthetic material. The use of angioplasty for native coarctation remains controversial.

After surgery, a striking increase in the amplitude of pulsations in the lower extremities is noted. In the immediate postoperative course, "rebound" hypertension is common and requires medical management. This exaggerated acute hypertension gradually subsides, and in most patients, antihypertensive medications can be discontinued. Residual murmurs are common and may be due to associated cardiac anomalies, to a residual flow disturbance across the repaired area, or to collateral blood flow. Rare operative problems include spinal cord injury from aortic cross-clamping if the collaterals are poorly developed, chylothorax, diaphragm injury, and laryngeal nerve injury. If a left subclavian flap is used, the radial pulse and BP in the left arm are diminished or absent. Repair of CoA in the 2nd decade of life or beyond may be associated with a higher incidence of premature cardiovascular disease, even in the absence of residual cardiac abnormalities. Early onset of adult chronic hypertension may occur, even in patients with adequately resected CoA.

Although re-stenosis in older patients after coarctectomy is rare, a significant number of infants operated on before 1 yr of age require revision later in childhood. All patients should be monitored carefully for the development of recoarctation and aortic aneurysm. Should recoarctation occur, balloon

angioplasty is the procedure of choice. Scar tissue from previous surgery makes reoperation more difficult, yet makes balloon angioplasty safer because of the lower incidence of aneurysm formation. Relief of obstruction with this technique is usually excellent. Intravascular stents are now commonly used in many patients with generally excellent results.

6. ***Tetralogy of fallot.*** Most common cyanotic cardiac lesion. 10 % of all CHD, consists of: 1) obstruction to RV outflow (pulmonary stenosis); 2) VSD; 3) dextroposition of the aorta with septal override; 4) RV hypertrophy.

Pathophysiology. The pulmonary valve annulus may be of nearly normal size or quite small. The valve itself is often bicuspid and, occasionally, is the only site of stenosis. More commonly, the subpulmonic muscle, the crista supraventricularis, is hypertrophic, which contributes to the infundibular stenosis and results in an infundibular chamber of variable size and contour. When the RV outflow tract is completely obstructed (pulmonary atresia), the anatomy of the branch pulmonary arteries is extremely variable; a main pulmonary artery segment may be in continuity with RV outflow, separated by a fibrous but imperforate pulmonary valve, or the entire main pulmonary artery segment may be absent. The branch pulmonary arteries may be discontinuous. In these more severe cases, pulmonary blood flow may be supplied by a PDA and by *major aortopulmonary collateral arteries (MAPCAs)* arising from the aorta.

The VSD is usually nonrestrictive and large, is located just below the aortic valve, and is related to the posterior and right aortic cusps.

Systemic venous return to the RA and RV is normal. When the RV contracts in the presence of marked pulmonary stenosis, blood is shunted across the VSD into the aorta. Persistent arterial desaturation and cyanosis result. Pulmonary blood flow, when severely restricted by the obstruction to RV outflow, may be supplemented by the bronchial collateral circulation (MAPCAs) and, in the newborn, by a PDA. Peak systolic and diastolic pressures in each ventricle are similar as at the systemic level. A large pressure gradient occurs across the obstructed RV outflow tract, and pulmonary arterial pressure is normal or lower than normal. The degree RV outflow obstruction determines the timing of the onset of symptoms, the severity of cyanosis, and the degree of RV hypertrophy. When obstruction to RV outflow is mild to moderate and a balanced shunt is present across the VSD, the patient may not be visibly cyanotic *(acyanotic or "pink" tetralogy of Fallot)*.

Clinical manifestations. Infants with mild degrees of RV outflow obstruction may initially be seen with HF caused by a ventricular-level left-to-right shunt. Often, cyanosis is not present at birth, but with increasing hypertrophy of the RV infundibulum and patient growth, cyanosis occurs later in the 1st yr of life. It is most prominent in the mucous membranes of the lips and mouth and in the fingernails and toenails. In infants with severe RV outflow obstruction, neonatal cyanosis is noted immediately, pulmonary blood flow may be dependent on flow through the PDA. When the ductus begins to close in the 1st few hours or

days of life, severe cyanosis and circulatory collapse may occur. Older children with long-standing cyanosis who have not undergone surgery may have dusky blue skin, gray sclerae with engorged blood vessels, and marked *clubbing* of the fingers and toes.

Dyspnea occurs on exertion. Infants and toddlers play actively for a short time and then sit or lie down. Older children may be able to walk a block or so before stopping to rest. Children assume a *squatting* position for the relief of dyspnea caused by physical effort; the child is usually able to resume physical activity within a few minutes. These findings occur most often in patients with significant cyanosis at rest. *Hypoxic, "blue" or "tet" spells* are a particular problem during the first 2 yr of life. The infant becomes hyperpneic and restless, cyanosis increases, gasping respirations ensue, and syncope may follow. The spells occur most frequently in the morning on initially awakening or after episodes of vigorous crying. Temporary disappearance or a decrease in intensity of the systolic murmur is usual as flow across the RV outflow tract diminishes. The spells may last from a few minutes to a few hours but are rarely fatal. Short episodes are followed by generalized weakness and sleep. Severe spells may progress to unconsciousness, convulsions or hemiparesis. The onset is usually spontaneous and unpredictable. Spells are associated with reduction of an already compromised pulmonary blood flow, which when prolonged results in severe systemic hypoxia and metabolic acidosis. Infants who are only mildly cyanotic at rest are often more prone to the development of "tet" spells because they have not acquired the homeostatic mechanisms to tolerate rapid lowering of arterial oxygen saturation, such as polycythemia.

Immediate care:

1) placement of the infant on the abdomen in the knee-chest position while making certain that the infant's clothing is not constrictive;

2) administration of oxygen;

3) injection of morphine subcutaneously in a dose not in excess of 0.2 mg/kg. Calming and holding the infant in a knee-chest position may abort progression of an early spell;

4) rapid correction of metabolic acidosis with IV NaHCO3;

5) β-Adrenergic blockade — IV propranolol (0.1 mg/kg given slowly to a max of 0.2 mg/kg).

Growth and development may be delayed in severe untreated tetralogy of Fallot, particularly when $SatO_2$ is chronically less than 70 %. Puberty may also be delayed in patients who do not undergo surgery. The pulse is usually normal, as is venous and arterial pressure. The left anterior hemithorax may bulge anteriorly because of RV hypertrophy. The heart is generally normal in size, and a *substernal RV impulse* can be detected. In about half the cases, a *systolic thrill* is felt along the left sternal border in the 3rd and 4th parasternal spaces. The *systolic murmur* is usually loud and harsh; it may be transmitted widely, especially to the lungs, but is most intense at the left sternal border. The murmur is generally ejection in quality at the upper sternal border, but it may sound more holosystolic

toward the lower sternal border. It may be preceded by a click. The murmur is caused by turbulence through the RV outflow tract. It tends to become louder, longer, and harsher as the severity of pulmonary stenosis increases from mild to moderate; however, it can actually become less prominent with severe obstruction, especially during a "tet" spell. Either the 2nd heart sound is single, or the pulmonic component is soft. A continuous murmur may be audible, especially if prominent collaterals are present.

Diagnosis. The typical configuration as seen on the *X-ray*: anteroposterior view consists of a narrow base, concavity of the left heart border in the area usually occupied by the pulmonary artery, and normal heart size. The hypertrophied RV causes the rounded apical shadow to be up-tilted so that it is situated higher above the diaphragm than normal. The cardiac silhouette has been likened to that of a boot or wooden shoe. The hilar areas and lung fields are relatively clear because of diminished pulmonary blood flow or the small size of the pulmonary arteries, or both. The aorta is usually large, and in about 20 % of instances it arches to the right, which results in an indentation of the leftward-positioned air-filled tracheobronchial shadow in the anteroposterior view.

ECG right axis deviation and evidence of RV hypertrophy. A dominant R wave appears in the right precordial chest leads (Rs, R, qR, qRs). In some cases, the only sign of RV hypertrophy may initially be a positive T wave in leads V_3R and V_1. The P wave is tall and peaked or sometimes bifid. *EchoCG* establishes the diagnosis and provides information about the extent of aortic override of the septum, the location and degree of the RV outflow tract obstruction, the size of the proximal branch pulmonary arteries, and the side of the aortic arch.

Cardiac catheterization demonstrates a systolic pressure in the RV equal to systemic pressure. If the pulmonary artery is entered, the pressure is markedly decreased, although crossing the RV outflow tract, especially in severe cases. Pulmonary arterial pressure is usually lower than normal, in the range of 5–10 mm Hg. The level of arterial oxygen saturation depends on the magnitude of the right-to-left shunt; in "pink tets", systemic saturation may be normal, whereas in a moderately cyanotic patient at rest, it is usually 75–85 %.

Complete and accurate information regarding the anatomy of the vessels (*selective right ventriculography, left ventriculography, aortography* or *coronary arteriography)* is important when evaluating these children as surgical candidates.

Prognosis and complications. Before correction, patients are susceptible to several serious complications; most undergo palliation or repair in infancy, and these complications are rare. *Cerebral thromboses*, usually occurring in the cerebral veins or dural sinuses and occasionally in the cerebral arteries, are common in the presence of extreme polycythemia and dehydration. Thromboses occur most often in infants. They may have iron deficiency anemia, frequently with Hb and Hct levels in the normal range. Therapy consists of adequate hydration and supportive measures. Phlebotomy and volume replacement with fresh frozen plasma are indicated in extremely polycythemic patients. Heparin is

of little value and is contraindicated in hemorrhagic cerebral infarction. Physical therapy should be instituted as early as possible.

Brain abscess is less common than cerebral vascular events and extremely rare when most patients are repaired at much younger ages. Patients with a brain abscess are usually older than 2 yr. The onset is often insidious and consists of low-grade fever or a gradual change in behavior, or both. Some have an acute onset of symptoms that may develop after a recent history of headache, nausea, and vomiting. Seizures may occur; localized neurologic signs depend on the site and size of the abscess and the presence of increased intracranial pressure. CT or MRI confirms the diagnosis. Antibiotic may help keep the infection localized, but surgical drainage of the abscess is necessary.

Bacterial endocarditis may occur in the RV infundibulum or on the pulmonic, aortic, or rarely, the tricuspid valves. Endocarditis may complicate palliative shunts or, in patients with corrective surgery, any residual pulmonic stenosis or VSD. Antibiotic prophylaxis is essential before and after dental and certain surgical procedures associated with a high incidence of bacteremia.

Heart failure is not a usual feature in the tetralogy of Fallot. It may occur in infant with "pink" or acyanotic tetralogy of Fallot. As the degree of pulmonary obstruction worsens with age, the symptoms of HF resolve and eventually the patient experiences cyanosis, often by 6–12 mo of age. These patients are at increased risk for hypercyanotic spells at this time.

Treatment. Depends on the severity of the RV outflow tract obstruction. Infants with severe tetralogy require medical treatment and surgery in the neonatal period. Therapy is aimed at providing an immediate increase in pulmonary blood flow to prevent the sequelae of severe hypoxia. It is critical that oxygenation and normal body temperature be maintained during the transfer. Prolonged, severe hypoxia may lead to shock, respiratory failure, and intractable acidosis and will significantly reduce the chance of survival, even when surgically amenable lesions are present. Blood glucose levels should be monitored because hypoglycemia is more likely to develop in infants with cyanotic heart disease.

Infants with marked RV outflow tract obstruction may deteriorate rapidly because as the PDA begins to close, pulmonary blood flow is further compromised. The IV administration of prostaglandin E_1 (0.05–0.20 mg/kg/min), a potent and specific relaxant of ductal smooth muscle, causes dilatation of the PDA and usually provides adequate pulmonary blood flow until a surgery can be performed. Should be administered IV as soon as cyanotic CHD is clinically suspected and continued through the preoperative period and during cardiac catheterization. Postoperatively, the infusion may be continued briefly as a pulmonary vasodilator to augment flow through a palliative shunt or through a surgical valvulotomy.

Infants with less severe RV outflow tract obstruction who are stable and awaiting surgical intervention require careful observation. Prevention or prompt treatment of dehydration is important to avoid hemoconcentration and possible thrombotic episodes. "Tet" spells in infancy or early childhood may be precipitated

by a relative iron deficiency; iron therapy may decrease their frequency and also improve exercise tolerance and general well-being. RBC indices should be maintained in the normocytic range. Oral propranolol (0.5–1 mg/kg every 6 hr) may decrease the frequency and severity of hypercyanotic spells, but with the excellent surgery available, surgical treatment is indicated as soon as spells begin.

The modified *Blalock–Taussig shunt* is currently the most common aortopulmonary shunt procedure and consists of a Gore–Tex conduit anastomosed side to side from the subclavian artery to the homolateral branch of the pulmonary artery. Sometimes the conduit is brought directly from the ascending aorta to the main pulmonary artery and is called a *central shunt*. The Blalock–Taussig operation can be successfully performed in the newborn period with shunts 3–4 mm in diameter and has also been used successfully in premature infants. After a successful procedure, cyanosis diminishes. The development of a continuous murmur over the lung fields after the operation indicates a functioning anastomosis. A good shunt murmur may not be heard until several days after surgery. The duration of symptomatic relief is variable. As the child grows, more pulmonary blood flow is needed and the shunt eventually becomes inadequate. When increasing cyanosis develops, a corrective operation should be performed if the anatomy is favorable. If not possible (e.g., because of hypoplastic branch pulmonary arteries) or if the 1st shunt lasts only a brief period in a small infant, a second aortopulmonary anastomosis may be required on the opposite side. Several groups have reported successful palliation of the tetralogy of Fallot in infants by balloon pulmonary valvuloplasty.

Corrective surgical therapy consists of relief of the RV outflow tract obstruction by removing obstructive muscle bundles and patch closure of the VSD. The surgical risk of total correction is less than 5 %. A right ventriculotomy was the standard approach; however, a transatrial-transpulmonary approach can be used to reduce the long-term risks of a ventriculotomy.

After successful total correction, patients are generally asymptomatic and are able to lead unrestricted lives. Immediate postoperative problems include RV failure, transient heart block, residual VSD with left-to-right shunting, myocardial infarction from interruption of an aberrant coronary artery, and disproportionately increased left atrial pressure because of residual bronchial collaterals. Postoperative HF (particularly in transannular outflow patch) requires a positive inotropic agent such as digoxin. The majority of patients after tetralogy repair and all of those with transannular patch repairs have a to-and-fro murmur at the left sternal border, usually indicative of mild outflow obstruction and mild to moderate pulmonary insufficiency. Patients with more marked pulmonary valve insufficiency also have moderate to marked heart enlargement. Patients with a severe residual gradient across the RV outflow tract may require reoperation, but mild to moderate obstruction is virtually always present and does not require re-intervention.

CHAPTER 12
HEART DISEASES IN CHILDREN

12.1. ACUTE RHEUMATIC FEVER (ARF)

Systemic inflammatory disease of connective tissue with a predominant localization in the cardiovascular system, developed in connection with the infection of β-hemolytic Streptococcus Group A (GAS) in individuals with a genetic predisposition, manifested with arthritis, carditis, chorea and erythema of the skin, with a tendency to recurrence, progression, and the formation of acquired heart disease. According to the WHO data the prevalence ranges from 0.3 to 18.6 per 1,000 schoolchildren, in developing countries is higher. The incidence in Belarus is quite low, in Minsk about 2 cases per 100,000 children per year, more common between the ages of 7–15 yrs.

Epidemiology. Important in the epidemiology GAS strains (more than 80), different M-types. In families of patients with rheumatism its frequency is higher than in the population, and 4 times more likely to form heart defects. "Rheumatic diathesis" or predisposition to rheumatic fever is present in 1–3 % of children and adults, with tonsillitis and pharyngitis caused by GAS (changing the structure of the tonsils, carries of Streptococcus, and detected antibodies to Streptococci), possible association of GAS and virus. Streptococcal infection can get sick any, but not everyone gets an ARF, children under the 3–4 yrs old don't get sick ARF, because lymphatic tissue ring has no receptors for GAS fixation. Receptors appear later only in individuals with a hereditary predisposition and the presence of tonsillitis, adenoiditis.

GAS differs in epidemiology: rare in children which are sensitive to other infections — infants and young before 3–4 yrs. Flashes are observed only in those groups where GAS is capable enough to firmly lock onto the mucosal cells of the throat and cause quite a long inflammatory process (usually at least 9 or 10 days).

Election tropism of GAS to the mucosal epithelium of the nasopharynx. Specific features of the immune response to the localization of Streptococci infection in the nasopharynx. The direct connection of the mucous membranes of the upper respiratory tract and lymphoid ring, by lymphatic to the mediastinum and heart membranes, which leads to germs and the products of its life activity (enzymes, toxins, etc.). Genetic predisposition, prevalence of HLA A11, B35, DR4, DR5 and DR7, antigens HLA-B7; B35; Cw4; specific alloantigens of B-lymphocytes membrane D8/17 detected in 100 % people with rheumatism (in healthy — 6–15 %). In patients with mitral regurgitation — HLA-A2 and B7; in aortic valve insufficiency —HLA-B7. More common III (B) and II (A) blood group (ABO).

Pathology: 1) mucoid swelling; 2) fibrinoid changes; 3) granulomatosis (4–6-week development Aschoff–Talalaev's granulomas, cycle of 3 to 4 months); 4) sclerosis (8–12 months). Two last steps are irreversible. Full development of the granuloma occurs in 8–12 months.

Classification. ***Major Jones criteria:***

– carditis,

– polyarthritis,

– Sydenham chorea,

– erythema marginatum,

– subcutaneous nodules.

Minor Jones criteria: previous rheumatic fever, polyarthralgia, fever, high ESR, prolonged PR interval suggestive of carditis.

Diagnosis requires 2 major or 1 major and 2 minor Jones criteria plus evidence of GAS infection (antistreptolysin O, positive throat culture).

Carditis. Immune complexes cross-react with cardiac sarcolemma causing carditis, mitral and aortic insufficiency, and congestive heart failure.

Myocarditis (65–100 % of patients), the most common manifestation of cardiac pathology in ARF: severe diffuse (rare); moderate changes; manifested with tachy- or bradycardia, muted I tones; contractive function decreasing; prolongation of PQ interval; reduction of the T wave and ST segment (Fig. 12.1).

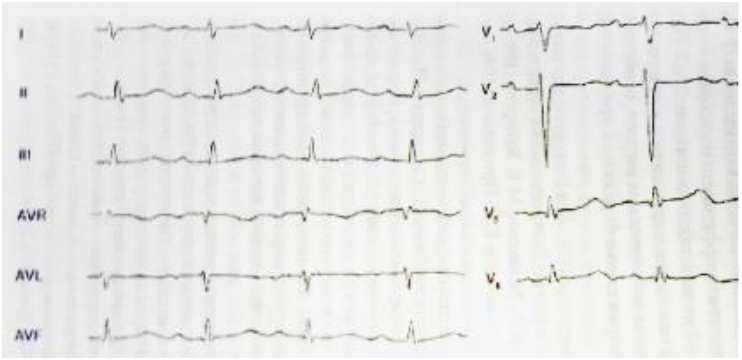


Fig. 12.1. Prolongation of PQ interval; Reduction of the T wave and ST segment

Endocarditis (in 70 % of patients) and 100 % (for re-ARF) parietal; valvular (appearance blowing systolic murmur, with chordal “squeak” at the top and V point); total (severe intoxication, significant inflammatory changes in laboratory parameters).

Pericarditis (10–15 % of patients): pericardial rub; cardiac enlargement during percussion and X-ray; reduction of QRS complex; ST interval change (rise in the acute phase); deformation of the T wave (Fig. 12.2.)

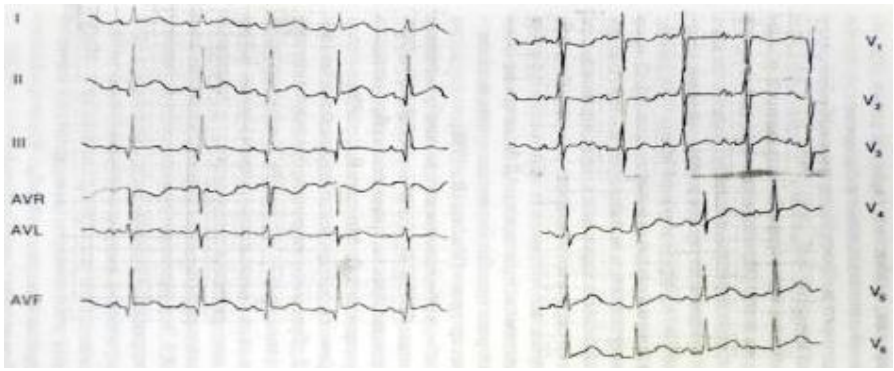


Fig. 12.2. Reduction of QRS complex; ST interval change (rise in the acute phase); deformation of the T wave

Cardiac enlargement due to severe myocarditis is shown on the Fig. 12.3.

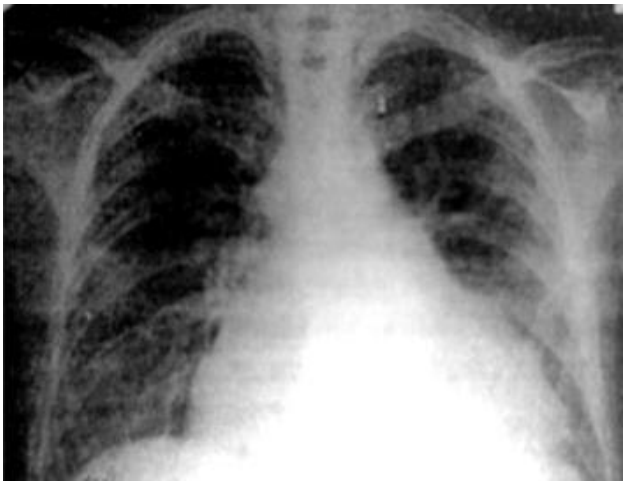


Fig. 12.3. Cardiomegaly due to severe myocarditis

Polyarthritis: large joints are swollen, red, and extremely tender.

Erythema marginatum (in 7–10 % of patients). Erythema confirms the presence of vasculitis and a high probability of carditis.

Sydenham Chorea (in 12–20 % of patients): involuntary movements (distal sweeping hyperkinesis); muscular hypotonia; ataxia, emotional lability, slurred speech, and weakness; sometimes onset is after acute stage of disease.

Rheumatic nodules (rarely observed). Subcutaneous nodules: nontender, moveable, present in severe disease.

ARF in adolescents: Most aggressive course. Higher rates of formation of acquired heart disease. High incidence of cerebral pathology (vasculitis and neuropsychiatric disorders), and recurrence (20 %).

Clinical signs. Mild degree of activity: can be without involvement of the heart, but with a minor manifestation of chorea; isolated myocarditis; latent course. X-ray and ECHO manifestations are quite different. ECG signs of myocardial damage (if myocarditis): reduced voltage of ECG peaks; AV block 1st degree; increase in the electrical activity of the LV; possible arrhythmias. Blood: ESR 20–30 mm/h, leukocytosis with neutrophilic shift, CRP 1–2 +; ASLO > 200 IU.

Moderate degree: damage of the myocardium and endocardium (endomyocarditis); heart failure I and IIA of degree. ECG signs of myocarditis, may be temporary prolongation of the QT interval. Blood: leukocytosis with neutrophilic shift, ESR > 30 mm/h; 1–3 +++ CRP, ASLO > 400 IU.

Severe grade: endomyocarditis with symptoms of HF IIB; pancarditis with HFII A and II B; severe cardiac disease; chorea with severe clinical symptoms. ECG signs: the same as in the 2nd degree of activity can be arrhythmia. Blood: leukocytosis, neutrophilic shift, ESR > 50 mm/h; 3–4 + CRP, fibrinogen high; ASLO above normal 3–5 times.

Differential diagnosis:

– other polyarthritis/arthralgia — juvenile rheumatoid arthritis, systemic lupus erythematosus, and other autoimmune disorders;

– pyogenic arthritis — Haemophilus influenza type B, Neisseria gonorrhoeae, Staphylococcus aureus, Streptococcus pyogenes, Kingella kingae;

– dystonia from medications, brain tumor;

– other myocarditis — Kawasaki disease, adenovirus, coxsackie A and B, echovirus, cytomegalovirus, parvovirus, influenza A virus, human immunodeficiency virus;

– mitral and aortic insufficiency due to bacterial endocarditis

Treatment:

– treat GAS infection with penicillin and arthritis with aspirin;

– treat heart failure with diuretics, ACE inhibitors;

– treat carditis with aspirin or corticosteroid until acute phase inflammatory tests resolve;

– prevent future GAS with monthly intramuscular benzathine penicillin. Erythromycin or sulfadiazine in children with penicillin allergy;

– lifelong GAS prophylaxis in patients with heart disease. Prophylaxis for 3–5 years with no residual heart disease;

– late development of mitral stenosis may require surgical replacement.

Primary prophylaxis: hygiene, vaccinations; proper treatment of Strept infection.

Secondary prophylaxis: every 3–4 weeks during 5 years after ARF, especially in case of genetic predisposition: benzylpenicillin; or Bicillin-5; or Retarpen; or Extencillin.

Outcome: in most cases favorable.

Heart disease is formed at the first attack of rheumatic fever in 15–20 % of children, in case of re-ARF (after the 2nd or 3rd attack) — 50–100 %. Some patients have only Sydenham chorea or idiopathic chronic carditis with no obvious ARF episode. These patients have rheumatic fever even without tests proving recent streptococcal infection.

12.2. CHRONIC RHEUMATIC DISEASE

Acquired heart disease (AHD) — acquired morphological changes of valve, leading to disruption of its function and hemodynamics. ICD-10 in category 08.I propose to use the term of "combine" with the defeat of several valves and "combined" — a combination of stenosis and insufficiency of one valve. In developed countries annually 1–2 cases of rheumatic heart diseases per 100 000 populations, while in developing countries (India) — 100–150 cases per 100 000 populations are recorded.

Mitral valve insufficiency — insufficient closure of the valve as a result of organic changes its wings and subvalvular structures (chords, papillary muscles). The most common acquired heart disease in children, up to 70 % of the AHD. MVI is detected in 1–4 % of the population, in 40–60 % of healthy people there is little (no more than I degree) mitral regurgitation.

Etiology: rheumatic endocarditis 50–75 %; infective endocarditis; congenital mitral valve insufficiency; systemic connective tissue disease, connective tissue

dysplasia syndrome (Marfan syndrome, Ehlers–Danlos syndrome, myxomatous transformation of the valve leaflets, etc); hypertrophic cardiomyopathy, injury, dilation of the LV of any etiology.

Hemodynamic. During ventricular systole, blood flows from it not only in the aorta, but partly back into the LA due to the incomplete closing of the AV-hole that leads to its dilation and hypertrophy. The volume of blood flowing into the LA depends on the grade of MVI and rate. Simultaneous intake of excessive amounts of blood during diastole leads to ventricular hypertrophy and promotes dilation. With a slight defect of mitral valve long-term compensation is possible. Circulation through dilatation and hypertrophy of the LV and the LA with no load on the right departments. When the LA loses its ability to cope with returning from the LV and the blood pressure increases in the minor circle which leads to Kitaevs reflex, increases the load on the RV. Increasing the load on the right heart eventually leads to the development of congestion in the major circle (enlargement of the liver, ascites, swelling of the legs). Severity of MVI is determined by the color Doppler (regurgitation).

At the stage of compensation children cannot complain. In severe MVI (regurgitation over 40–60 %) — tachypnea, palpitations, pain, and irregular heart beating. Pale skin, mild cyanosis of the lips and nose, "mitral" blush cheeks. In LV decompensation — shortness of breath at rest and cardiac asthma attacks. With the development of right HF jugular veins, acrocyanosis, ascites, edema of the legs etc. occur. A heart hump can form, apical impulse strengthened and shifted to the left and down. The border of relative cardiac dullness extended to the left and upward, weakening tone at the apex, strengthening II tone on pulmonary artery. Systolic murmur "blowing" the tone associated with the I tone decreasing with epicenter at the apex of the heart or in the V point, which is held to the base of the heart and the left axillary region (at least on the back). The murmur is amplified on the left side (back) position, after exercise.

Echo-CG: leaflets during systole cannot interlock, revealed enlargement of the LA and LV. Doppler reveals the turbulent flow of blood in the LA according to the degree of regurgitation. X-ray: mitral configuration of the heart (LV and atrial hypertrophy), in advanced cases — also the right heart, symptoms of pulmonary congestion. ECG revealed signs of hypertrophy of the LA (P-mitrale) and LV. There are signs of overload (diastolic — volume, isotonic) and metabolic abnormalities in the LV: offset ST interval and negative T waves in I, II, aVL, V5, V6 leads.

Diagnosis is based on clinical manifestations, ECG and X-ray, ECHO-CG data. Direct signs of MVI: systolic murmur at the apex; 1st weakening tone and presence of accent II tone of the PA. Indirect symptoms: increased LV; increased apical impulse, enlargement of the heart to the left; signs of hypertrophy and diastolic LV overload, detected on ECG, X-ray, ECHO.

Treatment: treatment of the underlying disease (rheumatism, SDCT et al.), prevention of relapse, treatment of the HF with ACE inhibitors, diuretics, glycosides, treatment and prevention of arrhythmia. Radical treatment for severe

MVI is surgery — mitral valve replacement or plastic. Indications for surgical treatment of MVI 3–4 grade with a volume of more than 30–50 % of regurgitation even with non-severe manifestations.

Mitral valve stenosis. MVS mostly occurs in girls (80 %). The formation of stenosis occurs very slowly — for 5–15 years after a first episode of ARF. Other reasons: infective endocarditis with large vegetations impedes blood flow, fibroid induration and calcification of the valve leaflets, fusion of them commissure, thickening and shortening of the chordae tendineae. Congenital mitral stenosis can manifest with heart failure in infancy and early childhood.

The pressure in the LA increases, develops its hypertrophy, accelerates blood flow to the LV due to narrowing of the mitral orifice to 1–1.5 cm^2 (normal area of the mitral orifice 4–6 cm^2, the pressure in the LA does not exceed 5 mm Hg). In severe MS (mitral orifice area < 1.0 sm^2), LA pressure greater than 25 mm Hg, which leads to pulmonary hypertension. Pulmonary hypertension leads to pulmonary vascular remodeling: development of proliferative and sclerotic processes in the vascular wall of pulmonary arterioles due to the production of cytokines. This contributes to chronic hypoxemia, leading to endothelial dysfunction (a decrease of endogenous relaxing factor, prostacyclin, prostaglandin E2, nitric oxide) and direct pulmonary vasoconstriction.

Pallor in combination with a peculiar face painting — cyanotic lips and cheeks blush ("facies mitralis"). Pulse in mitral stenosis usually small and on the left hand may be delayed (pulsus differens). Apical impulse weakened, diastolic tremor — "cat's purring." Loud and short ("slamming") I tone (caused by rapid reduction of insufficient blood filling of the LV and the increase of the amplitude of oscillations in sclerosed mitral valve). Diastolic murmur at the apex of the heart, which is often heard as presystolic, auscultated best with the patient on his left side, or after exercise; not conducted. Determined accent II tone on the pulmonary artery, often doubling or splitting it. After II tone on the apex of the heart is often recorded sound phenomenon, called "click" open or tone of mitral valve opening, characteristic only of mitral stenosis. Presystolic murmur flapping tone I, II tone and the tone of mitral valve opening make melody, given the picturesque name — "the rhythm of quail." In case of severe dilatation recurrent nerve compression and hoarseness (Ortner's syndrome) can happened and atrial fibrillation developed. Orthopnea and nocturnal cardiac asthma attacks occur when a long-term mitral stenosis leading to pulmonary hypertension and RV failure. Atrial fibrillation, infection and infective endocarditis in severe mitral stenosis can cause pulmonary edema.

ECG — signs of LA hypertrophy (P wave initially increased, expanded, and then becomes bimodal in I, II standard in V1–2 leads, often biphasic P wave + (–) and RV hypertrophy. X-ray — an increase of LA, RV dilatation and hypertrophy; pulmonary venous congestion.

Echo-CG — thickening of the valve leaflets, narrowing of the mitral orifice to 1–1.5 cm^2 or less (normal 4–6 cm^2) unidirectional movement of the leaflets expanding the cavity of the RV.

Treatment: suppression activity of inflammatory process and prevent relapse of the underlying disease (rheumatic fever and others.) Therapy and prevention of complications: heart rhythm disorders, thromboembolic complications, circulatory failure — diuretics, nitrates, β-blockers, pulmonary hypertension and others. Radical treatment for MS is a surgiry.

Aortic valve insufficiency (regurgitation). *Etiology:* rheumatic process with the development of aortic valve deformation at (almost always combined with a lesion of the mitral valve); infective endocarditis; myxomatous degeneration of the valve; hereditary connective tissue diseases; congenital bicuspid valve; trauma; syphilis; dilatation of the aortic root in hypertension, etc.

The inconsistency of the aortic valve leading to enter during diastole additional volume of blood from the aorta into the LV, and filling it with a conventional blood volume of the LA, resulting in an increased diastolic filling expansion cavity and ventricular hypertrophy, which initially are compensatory factors.

Clinical signs: often proceeds without symptoms and may be compensated long-term due to powerful LV. During decompensation: pain in the heart angina nature, dizziness, fainting, tachypnoe first at physical activity, then at rest, with the development of RV failure — edema, enlargement of the liver, pale skin, fast and high pulse, capillary Quincke pulse. Lower DBP at moderately elevated SBP, DBP reduction rate is proportional to the degree of aortic insufficiency, increased pulse pressure — enhanced pulsation of the carotid arteries ("dance of the carotid", symptom Musset (head rocking back and forth). Apical impulse palpation strengthened and shifted to the left and down, the heart enlarged to the left.

At the top I weakening tone; in III–IV intercostal space on the left of the sternum — protodiastolic murmur, more quiet, better auscultated while standing, tilt the torso forward. Systolic murmur (valve opening is narrowed relative expansion of the left ventricle and the aorta simultaneously can be heard. Diastolic murmur special tone (noise Flint) at the apex of the heart (regurgitation of the aortic lifts lowered into the LV mitral valve) can be auscultated. ECG — signs of diastolic LV overload, subsequently signs of hypertrophy of the LA. Echo-CG: aortic valve not closed, dilatation of the LV and hyperkinesis its wings. Doppler reveals aortic insufficiency and indirectly determines its severity (wide regurgitation and depth of its penetration into the LV at the time of reverse flow in the thoracic aorta and subclavian artery). On the X-ray heart has aortic configuration with emphatic "waist" — silhouette "sitting ducks" (Fig. 12.4).

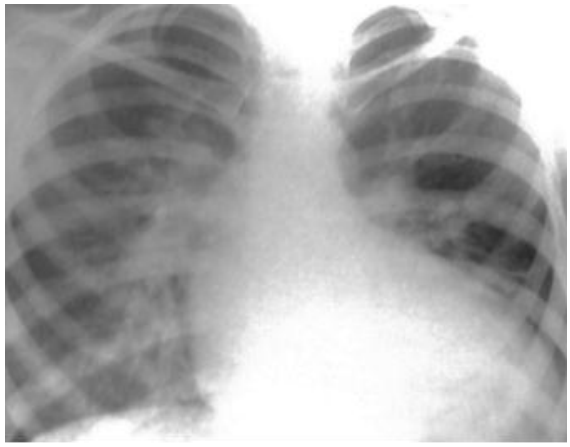


Fig. 12.4. Cardiac silhouette "sitting ducks"

Differential diagnosis: PDA, VSD with aortic valve prolapse in the area of the defect, acquired mitral stenosis.

Treatment aimed at relieving symptoms and improving quality of life, treatment of the underlying disease (rheumatic process et al.) and heart failure (ACE inhibitors, vasodilators (nifedipine), diuretics). At low and moderate regurgitation (I-II stage), 85–95 % of patients live more than 10 years after diagnosis, and in severe aortic insufficiency (III stage) — only 50 %. Surgery — prosthetic valve in case of resistant heart failure.

Aortic stenosis. *Etiology:* rheumatic process (almost always combined with a lesion of the mitral valve); other reasons: isolated aortic valve calcification. Deformation, fibrosis and calcification of bicuspid aortic valve (in population 2 % of cases, endothelial damage and collagen matrix flaps — deposition of calcium (calcification). Infective endocarditis with massive vegetations, injury. Rarely — CRF, carcinoid syndrome, diabetes, Paget's disease, SLE. The predominance of males (2.5 times more likely than female). In 10–15 % of all cases of aortic stenosis can be combined with other acquired valvular heart defects. Among children and adolescents congenital aortic stenosis is detected in 2–11.7 % of cases. By localizing obstruction aortic stenosis can be: valvular (75 %); subvalvular (20 %); supravalvular (10 %). Orifice area of the aortic valve: mild stenosis 1.2–2 sm^2; moderate stenosis — 0.75–1.2 sm^2; severe stenosis < 0.75 sm^2 (normal area is 2.5–3 sm^2).

Hemodynamics: due to the narrowing of the LV outflow tract, increase the load on the LV — LV systolic overload. This enables the compensatory mechanisms that contribute to long-term maintenance of normal cardiac output; LV hypertrophy develops, increasing the pressure in the cavity and its extension systole.

Clinical signs. At the stage of compensation for a long time AS can be without symptoms. Complaints usually appear when narrowing AO is less than 0.75 cm^2: manifestations of decreased cardiac output — fatigue, dizziness, syncope, especially during physical exercises, stress, headache, anginal pain in the heart, cardiac asthma attacks, low systolic blood pressure, slow small pulse, signs of valvular defect (systolic murmur, systolic jitter, II tone attenuation, valves changes on ECHO); signs of LV hypertrophy and dilatation; enhanced apical impulse, expanding the heart to the left, the signs of hypertrophy and dilatation of the LV on ECG and ECHO, X-ray (aortic configuration of the heart, Fig. 12.5).

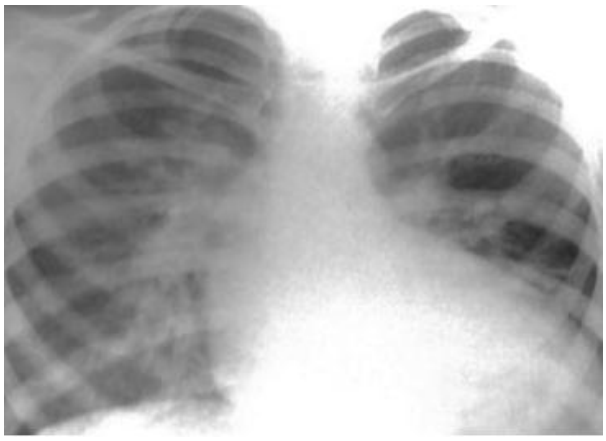


Fig. 12.5. Aortic configuration of the heart

Differential diagnosis: hypertrophic cardiomyopathy; stenosis of pulmonary artery valve; septal ventricular defects; heart failure; coarctation of the aorta.

Treatment is aimed at relieving symptoms and improving quality of life, prevention of sudden death, heart failure, prevention of IE; contraindicated competitions. Medications: ACE inhibitors, hydralazine, nitrates at the hospital — a short course to reduce afterload on the LV. Treatment of arrhythmias with antiarrhythmic drugs class III (amiodarone), electrical cardioversion may be performed staging cardioverter-defibrillator. In case of progression of heart failure, anginal pain, fainting surgical treatment is shown. The only effective treatment is prosthetic aortic valve.

Cardiomyopathy. *Dilated cardiomyopathy* is usually idiopathic but also caused by acute or chronic carditis, chronic tachyarrhythmia, left heart obstruction, coronary artery disease, anthracycline toxicity, mitochondrial and fatty acid oxidation defects. Early symptoms of dilated cardiomyopathy may resemble upper respiratory infection.

Hypertrophic myopathy: familial, leading cause of sudden cardiac death in children, mutations in several cardiac sarcomere proteins.

Restrictive myopathy: rare, presents with heart failure, prominent S4, jugular venous distension, may mimic constrictive pericarditis.

Echo-CG, ECG, and biopsy distinguish the three forms of cardiomyopathy.

Associated syndromes:

• Dilated cardiomyopathy: older children with Duchenne and Becker muscular dystrophy, carnitine deficiency, left-sided cardiac obstructive lesions, congenital coronary artery disease, fatty acid oxidation defects, mitochondrial oxidative phosphorylation defects.

• Hypertrophic cardiomyopathy: Noonan syndrome, Friedreich ataxia, mitochondrial disease, Pompe disease (type II glycogen storage), mitochondrial oxidation defects.

• Restrictive cardiomyopathy: endocardial fibroelastosis.

Treatment:

• Dilated myopathy with digoxin, diuretics, afterload reduction, anticoagulants, antiarrhythmics, supplemental carnitine.

• Treat hypertrophic myopathy with restricted physical activity, β-blockers, verapamil or disopyramide for LV outlet obstruction, surgical myectomy, implanted cardiac defibrillator.

• Cardiac transplantation is sometimes needed.

Ventricular tachycardia/fibrillation is the usual cause of death in hypertrophic cardiomyopathy.

Infective endocarditis and pericarditis. *Endocarditis:* underlying heart disease, fever, new or changing murmur, splenomegaly, septic emboli, dyspnea, and tachypnea, ↑ WBC, ↑ ESR, hematuria. Blood culture grows Str. viridans (50 %), S aureus (30 %), and fungus (10 %).

Pericarditis: retrosternal pain, fever, shortness of breath, pericardial friction rub, tachycardia, hepatomegaly, jugular vein distension, ECG with elevated ST segment, muffled heart sounds.

Endocarditis most common in persons with aortic valve disease, aorticopulmonary shunts, prosthetic valves. Dental procedure, nonsterile surgery, or cardiovascular surgery precedes onset in 30 %.

Pericarditis: effusion may cause cardiac tamponade and right heart failure.

Chest X-ray and echocardiography confirm diagnosis.

Differential diagnosis:

• Acute rheumatic fever — immune-mediated pancarditis.

• Pericarditis — occurs in rheumatoid arthritis, uremia, tuberculosis (TB), autoimmune disorders, infection with TB, Coxsackie B, influenza virus.

• Bacterial pericarditis — GAS, Streptococcus pneumoniae, S aureus, Haemophilus influenzae often cause severe disease with later restrictive pericardopathy.

• Postpericardiotomy — autoimmune pericarditis 1–2 weeks after open heart surgery with fever, friction rub, chest pain, elevated ST segments.

• Bacterial endocarditis in the normal heart — immunodeficiency, indwelling central venous catheters, drug abuse.

Treatment:

• Endocarditis — empiric therapy is indicated in an at-risk setting even when cultures are negative. Use specific antibiotics based on culture results obtained.

• Monitor with ultrasound for valve damage and valvular vegetations.

• Pericarditis: treatment depends on the cause. Cardiac tamponade requires immediate pericardiocentesis.

• Postpericardiotomy syndrome: aspirin or corticosteroids.

• Endocarditis: antibiotic prophylaxis is required for some types of congenital heart defects in high-risk situations, especially dental work and surgery. The most common agent of bacterial endocarditis in IV drug users is Staphylococcus aureus.

CHAPTER 13
CARDIAC ARRHYTHMIAS

Anatomy and physiology of the heart. The cardiovascular system exists to provide tissue perfusion, to ensure the body's cells are provided with oxygen and nutrients at the same time as removing metabolic wastes. The heart can be described as a hollow organ located centrally in the chest directly behind the sternum, between the lungs, and it is a component of the mediastinum. It is supported at its base (which is at the top) by the great vessels and it rests on the diaphragm with its apex (which is at the bottom) directed anteriorly and to the left. Two-thirds of the mass of the heart lies to the left of the body's midline (Fig. 13.1). The heart provides the impetus to drive blood flow throughout the body. The function of the heart is to circulate blood and therefore oxygen and nutrients to the tissues; the blood then removes metabolic wastes from the tissues. It is a four-chambered double-pump. The atria receive returning blood and direct it to the ventricles. The ventricles provide the impetus to circulate the blood through the systemic and pulmonary circulations. The systemic and pulmonary circulations are illustrated in Fig. 13.2.

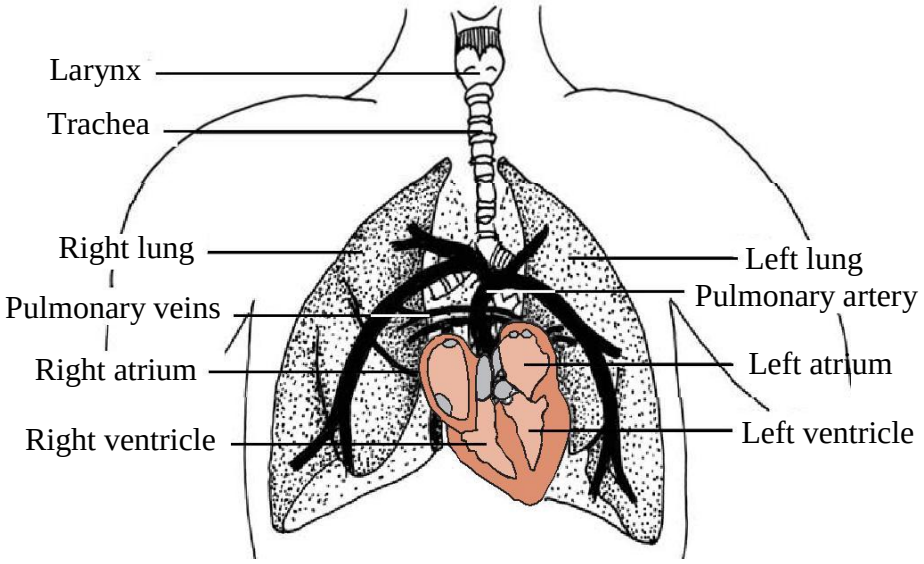


Fig. 13.1. The heart in situ

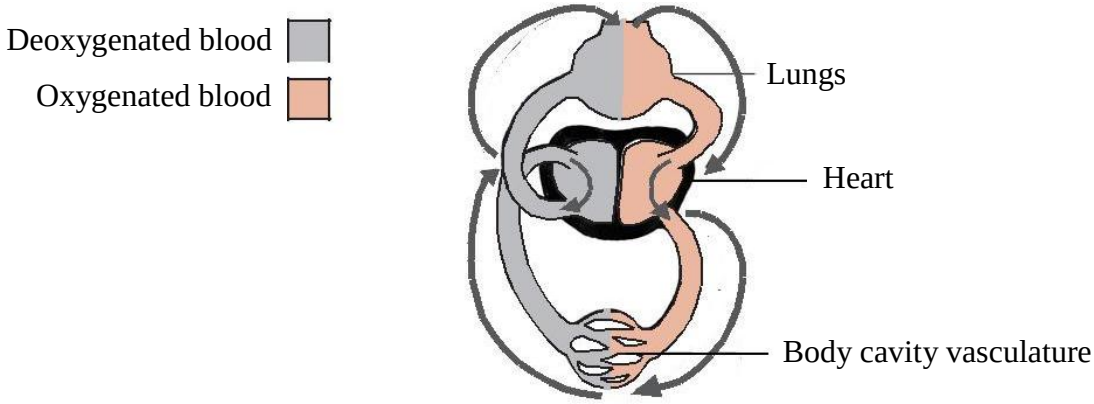


Fig. 13.2. The systemic and pulmonary circulations

The two sides of the heart are divided by the atrial and ventricular septa. The atrial septum is largely muscular tissue, and the ventricular septum is divided into two distinct parts — the membranous septum (the small, superior portion that borders the right atrium) and the larger muscular portion (which forms the true division between the left and right ventricles) as well as forming the wall of the left ventricle and functioning as part of the left ventricle.

The heart consists of three distinct layers: the epicardium, myocardium and endocardium. Epicardium is the thin, transparent layer of the heart wall. It also forms the visceral layer of the pericardium, which is made up of two sacks, an outer one consisting of fibrous tissue, and an inner one consisting of mucous membrane. Myocardium is the middle layer and it is made of specialized cardiac muscle cells called myocytes. Cardiac muscle fibres (Fig. 13.3) are involuntary, striated and branched, arranged as interlacing bundles of fibres. They are responsible for cardiac contraction. Each cell has branches that lie in close relation to the next cell, forming junctions known as intercalated discs. These fibres facilitate the passage of nervous impulses from one cell to the next; therefore, each individual cell does not need its own nerve supply. Endocardium is the inner layer, a membrane consisting of flattened squamous epithelial cells lining the inside of the myocardium and covering the heart valves and tendons.

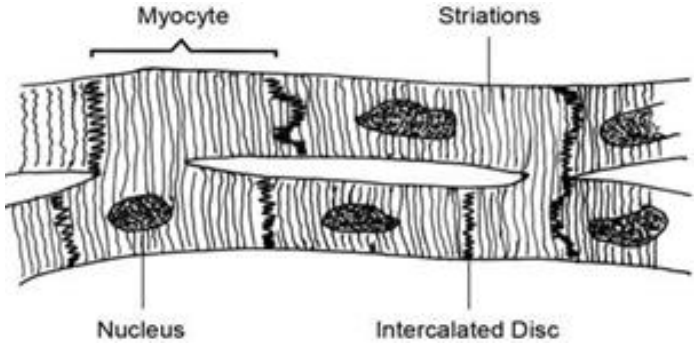


Fig. 13.3. Cardiac muscle fibres

The blood flow through the heart is described below.

1. Superior and inferior venae caves return deoxygenated blood from the systemic circulation to the right atrium (RA) from all areas of the body.
2. Blood passes from the RA to the right ventricle (RV) via the tricuspid valve.
3. Blood passes into the pulmonary artery via the pulmonary valve to the lungs where it picks up oxygen and releases carbon dioxide.
4. Oxygenated blood returns to left side of the heart via the four pulmonary veins.
5. Blood from the left atrium (LA) passes into the left ventricle (LV) via the mitral valve.
6. Blood passes from the LV into the aorta via the aortic valve to be distributed around the systemic circulation.

Conduction system of the heart. The heart's conduction system relies on the sinoatrial node (the pacemaker of the heart) and the atrioventricular (AV) node,

which are small groups of specialized neuromuscular cells in the myocardium that initiate and then conduct electrical impulses over the heart muscle, causing it to contract. These specialized cells have the ability to discharge electrical impulses automatically that is without the influence of a nerve supply. This is known as automaticity; even if there is no stimulation from the CNS, the heart will continue to beat automatically. However, the system can be stimulated or depressed by nerve impulses initiated from the brain. The lower down the conducting system the impulse is triggered, the slower the rate will be.

There are two nodes that are central to the conduction process.

First is the sinoatrial (SA) node. This small mass of specialized neuromuscular cells is located in the wall of the RA near the opening of the superior vena cava. The SA node is often described as the pacemaker of the heart because each heart beat is normally triggered by the impulses initiated by the SA node. The SA node normally discharges at 60–100 beats per minute (b.p.m.).

The second is the AV node. This mass of specialized neuromuscular cells is situated in the wall of the atrial septum near the AV valves. Normally the AV node is stimulated by the wave of electrical impulses initiated by the SA node, sweeping over the atrial myocardium via internodal tracts or pathways. The AV node normally discharges at 40–60 b.p.m.

However, it is also capable of initiating electrical impulses if there is no stimulation from the SA node or the CNS. The bundle of His (AV bundle) consists of a mass of specialized neuromuscular fibers originating from the AV node and passing downwards in the septum that separates the LV and RV. This bundle of fibres then divides into 2 branches, one feeding each ventricle — these are the left and right bundle branches. Within the myocardium of the ventricles, the branches further divide into a network of fine filaments called the Purkinje fibres. The bundle of His and the Purkinje fibres (together referred to as the His–Purkinje fibres) convey electrical impulses from the AV node to the myocardium of the ventricles. The His–Purkinje fibres normally discharge at 20–40 b.p.m.

The electrical impulses initiated by the SA node stimulate the atrial myocardium to contract. This first wave of impulses and contraction stimulate the AV node to continue the wave of contraction to the apex of the heart via the His–Purkinje fibres and then upward over the myocardium. In this way, the ventricular wave of contraction begins at the apex of the heart (at the bottom) and blood is forced upward into the pulmonary artery and aorta to leave the heart at its base (at the top). The function of the bundle branches is to conduct unified electrical impulses throughout the ventricles, thus causing brief, powerful and unified contraction of the ventricles (Fig. 13.4).

Electrophysiology of depolarisation and repolarization. Without an electrical stimulus, the heart would not beat. The heart has specialized cells with 4 characteristics that ensure the heart continues to pump with or without stimulation from the CNS, these are:

1. Automaticity (spontaneous initiation of an electrical impulse).

2. Excitability (the cells respond to an electrical stimulus as a result of electrolyte shifts).

3. Conductivity (the electrical impulse is transmitted from one cell to the next).

4. Contractility (the cell contracts as a result of an electrical stimulus).

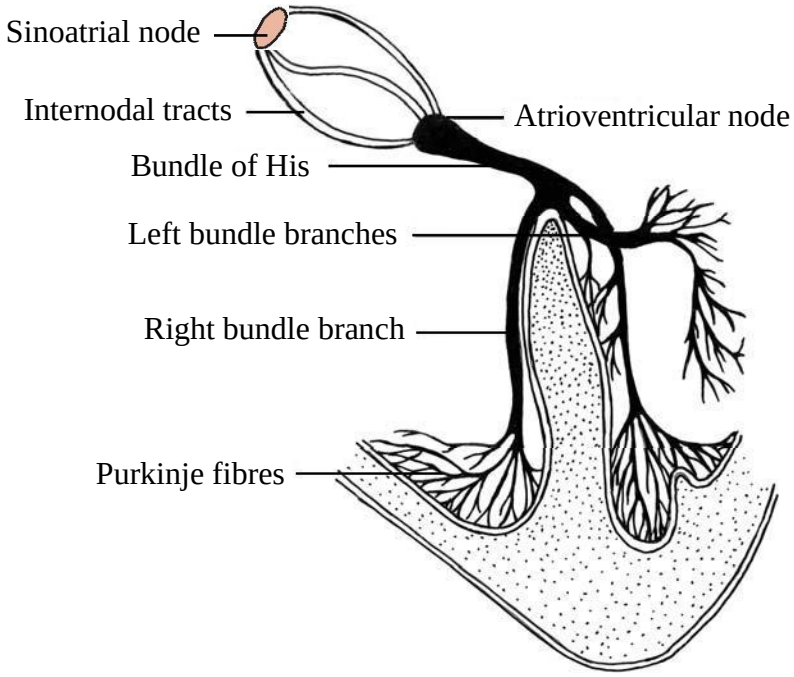


Fig. 13.4. The conduction system of the heart

There are two types of cardiac muscle cells — contractile and non-contractile. The contractile cells make up 99 % of all cardiac muscle cells and provide the powerful contraction that propels blood around the body. The conducting system, which initiates and controls those contractions, is made up of non-contractile cells. The human body contains various electrolytes in solution through which electrical currents will flow. In the heart, each cardiac cell contains such electrolyte fluids and is also surrounded by them. The main electrolytes responsible for electrical activity within the heart are sodium (Na+), potassium (K+) and calcium (Ca++). In resting (or polarised) cardiac cells, the inside of the cell is relatively negatively charged in comparison to the outside of the cell, which is positively charged; this creates what is known as the resting potential.

When myocardial cells are stimulated by an electrical impulse, a change takes place in the cell membrane's permeability and various electrolytes move across the cell membrane by diffusion or active transport so that the inside of the cell becomes positively charged.

The process by which the inside of a cell becomes more positive in relation to the outside is called depolarisation and it is this movement of electrolytes that generates the electrical flow, which is picked up by the ECG. This is known as the action potential (Fig. 13.5).

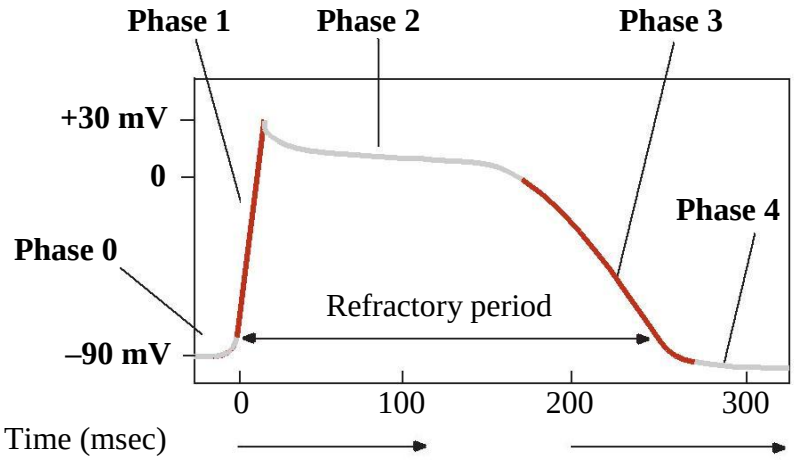


Fig. 13.5. The action potential

There are five phases of the action potential.

Phase 0 — rapid depolarization: positively charged Na+ and Ca++ move into the cell. Na+ moves in rapidly and Ca++ more slowly, through slow calcium channels. The inside of the cell therefore becomes more positively charged.

Phase 1 — early repolarization. The sodium channels close so no more Na+ can enter the cell, therefore the inside of the cell cannot become any more positively charged.

Phase 2 — plateau phase. Ca++ continues to flow in slowly, whilst positively charged K+ starts to flow out of the cell, so the overall charge starts to become more negative.

Phase 3 — rapid repolarization. The calcium channels close, so no more Ca++ enters the cell and K+ flows out rapidly, so the inside of the cell becomes more negative more quickly.

Phase 4 — resting phase. The Na+, K+ and Ca++ return to their original state.

A depolarised cell is electrically negative on the outside compared with any of its neighbouring non-stimulated cells. A potential difference therefore exists between the cells and current flows between them until they have all been depolarised. When the cell is depolarised it becomes excited and ready for action. It also stimulates the cell or cells next to it so there is a smooth wave of depolarisation all the way down the conducting tissue of the heart. The refractory period is how long it takes for an excitable membrane that has returned to its resting state following excitation to be ready for a second stimulus. During the so-called relative refractory period, it is possible for a very strong electrical impulse to depolarise the cell early. During the absolute refractory period, the cells cannot be stimulated at all.

A single heartbeat. Each beat of the heart is initiated by the SA node. On the ECG trace it is made up of a normal P wave, a QRS complex and a T wave (Fig. 13.6).

The rhythm should be regular with a rate of approximately 72 b.p.m. (in adult). When this is the case, the heart is said to be in sinus rhythm, which is

the normal rhythm of the heart (Fig. 13.7). If there is any deviation from this sinus rhythm, an arrhythmia is present. You will not be able to recognise an arrhythmia if you cannot first recognize normal sinus rhythm, as this is the rhythm against which all other rhythms are compared.

R

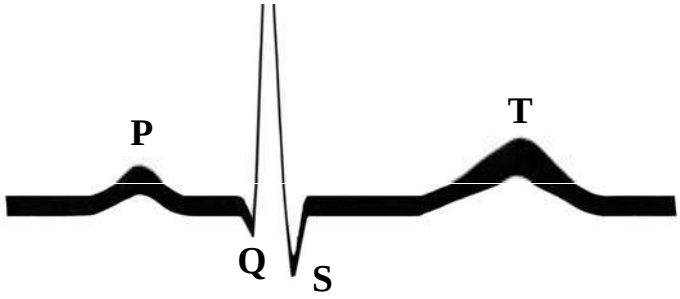


Fig. 13.6. One heart beat

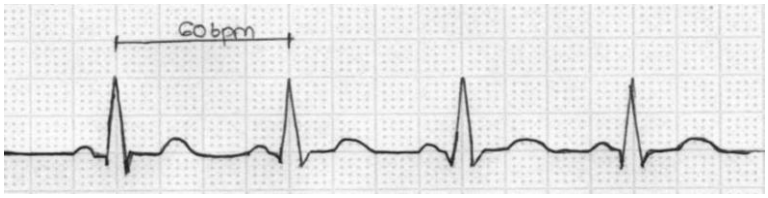


Fig. 13.7. Sinus rhytm

Waveforms. There are 4 stages within each heart beat and each is represented in terms of waves, namely the P, Q, R, S and T waves.

Stage 1 — sinoatrial node impulse. The SA node fires an electrical impulse, which spreads over the atria via the internodal tracts, resulting in atrial depolarisation. This is denoted by the P wave. Depolarisation causes the atria to contract. The P wave is 0.06–0.12 seconds in duration.

Stage 2 — atrial repolarization (i.e. the atria relax). The wave of repolarisation is usually not seen as it is hidden by the more powerful QRS complex.

Stage 3 — ventricular depolarization occurs next as the wave of depolarization passes down the bundle of His, the right and left bundle branches and the Purkinje fibres. It is represented by the QRS complex. Ventricular depolarization causes the ventricles to contract. The QRS complex should last for less than 0.12 seconds and is measured from the beginning of the Q wave to the end of the S wave. All three waves (Q, R and S) may not be present because of the speed of contraction, but the heart's activity can still be normal.

Stage 4 — ventricular repolarization is represented by the T wave as the myocardial cells return to their resting charge.

Intervals and segments of ECG. Intervals contain waves. Segments are the lines between the waves where there is no electrical activity and the trace does not deflect either above or below the baseline (i.e. they are isoelectric). The intervals and segments in one heart beat are shown in Fig. 13.8.

PR interval: is the time from the beginning of the P wave to the beginning of the QRS complex. It indicates the time taken for the impulse to pass from the SA

node to the ventricle. It reflects atrial depolarisation and is between 0.12 and 0.2 seconds in duration. A long PR interval may indicate that there is a conduction delay through the atria or AV node. A short PR interval suggests the impulse originated away from the SA node.

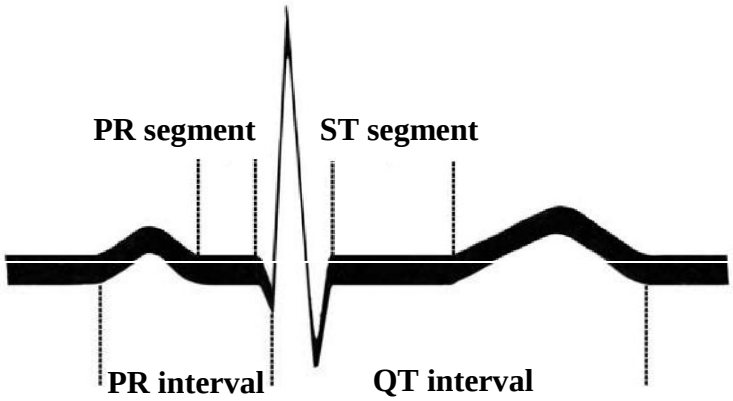


Fig. 13.8. Intervals and segments in one heart beat

PR segment: indicates the time between the end of the P wave and the beginning of the QRS complex.

ST segment: indicates the time between the end of the S wave and the beginning of the T wave and represents the beginning of ventricular repolarisation. The beginning of the ST segment is known as the J point. The ST segment should be isoelectric and if it is raised or depressed it may indicate the presence of myocardial ischaemia.

QT interval: represents the time from the beginning of the Q wave to the end of the T wave and therefore reflects the time taken for the ventricles to depolarise and repolarise. It usually lasts for 0.36–0.44 seconds.

Cardiac arrhythmias are very common and produce symptoms such as dizziness, palpitations and syncope. They are generally benign although, in a critically ill patient they can create further complications with an already compromised cardiovascular system. But there are arrhythmias that are dangerous for the patient if they are left untreated and there are arrhythmias that bring about sudden death. The cardiac monitor can give you prior warning of problems that may lie ahead, many of which can be resolved or abated to some degree.

Classification of arrhythmias. *Arrhythmias* generally classified by their site of origin: SA node (sinus rhythms), atrial (supraventricular), junctional or ventricular arrhythmias. These arrhythmias result from a disturbance in impulse formation. However, heart blocks result from a disturbance in impulse conduction. Cardiac arrhythmias may arise for several reasons:

1. From abnormal electrical conduction within the heart.
2. Through re-entry circuits whereby an impulse travels where it has already been.
3. From enhanced automaticity (an irritable focus within the conducting system firing an impulse when it shouldn’t).

Sinus node arrhythmias. The heart rate stays within normal limits but it is irregular. The rhythm generally corresponds to the respiratory cycle, increasing during inspiration and decreasing during expiration, because of the effect breathing has on the vagus nerve (Fig. 13.9). The P wave, QRS complex and T wave are normal but the RR intervals are irregular. It is usually insignificant and requires no treatment but it may be indicative of a more serious problem.

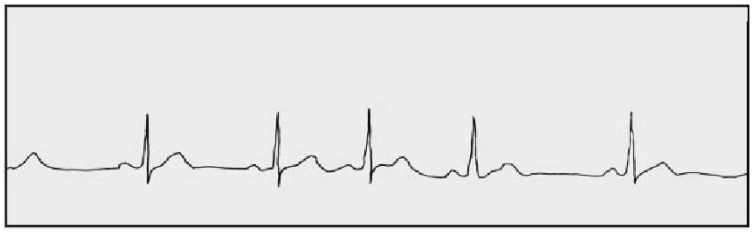


Fig. 13.9. Sinus arrhythmia

Causes: sick sinus syndrome, digoxin toxicity, myocardial infarction, raised intracranial pressure.

Management. Sinus arrhythmia often occurs naturally in children and athletes. Unless the patient is symptomatic, it is no cause for concern and requires no treatment. If sinus arrhythmia has an underlying cause it should be closely monitored and corrected.

Sinus bradycardia. Sinus bradycardia (Fig. 13.10) has a regular rhythm and a rate of less than 60 b. p. m. The P wave, QRS complex and T wave are normal. It often occurs in athletes and during relaxation and sleep when the body's metabolic demands are reduced. There is no cause for concern. However, if the patient has an underlying condition, a decrease in cardiac output may occur — resulting in hypotension — and the patient may be predisposed to further serious arrhythmias. A bradycardia of less than 45 b.p.m. is not well tolerated and will produce symptoms of reduced cardiac output.

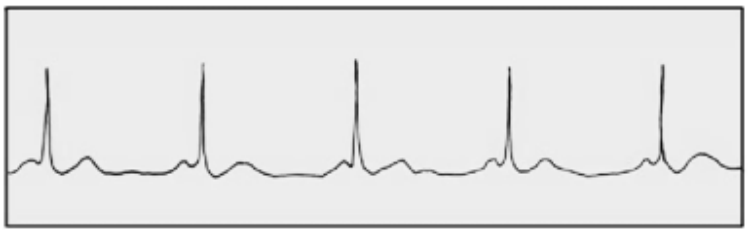


Fig. 13.10. Sinus bradycardia

Causes. Increased vagal stimulation caused e.g. by sleep, vomiting, carotid sinus massage, inferior, myocardial infarction, pneumothorax, raised intracranial pressure, hypothermia, hypovolaemia, hypoxia, acidosis, electrolyte disturbances, some drugs (e.g. digoxin, calcium-channel blockers, beta-blockers).

Management. For as long as the patient is asymptomatic, no treatment is necessary. However, if the patient is compromised by the bradycardia, swift treatment is necessary. A heart rate of less than 60 b.p.m. may cause collapse or symptoms of inadequate perfusion, particularly if there is a sudden bradycardia —

in which case the adult bradycardia Resuscitation algorithm should be used. Assess airway, breathing and circulation (ABC), ensure the patient's airway is clear, and give oxygen and respiratory assistance if required. Transcutaneous or transvenous pacing may be required with drug intervention to support the patient's circulation prior to pacing (e.g. using atropine and/or inotropic agents).

Sinus tachycardia. Sinus tachycardia has a regular rhythm. The P waves, QRS complexes and T waves are normal and regular with a rate of 100–160 b.p.m. (Fig. 13.11). The P waves may increase in amplitude or be superimposed on the preceding T wave, sometimes making identification difficult.

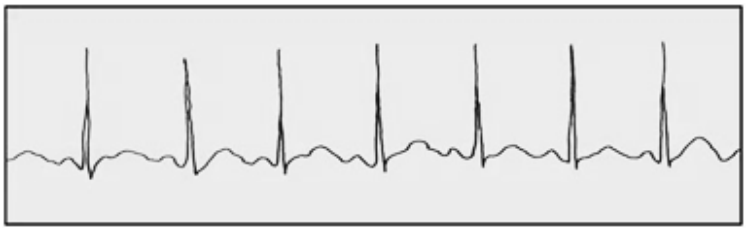


Fig. 13.11. Sinus tachycardia

Causes: strenuous exercise, anxiety, haemorrhage, hypovolaemia, pain, acute myocardial infarction, initial stage of cardiogenic shock. Sinus tachycardia is of little or no significance when there is no underlying cause or it occurs as a response to strenuous exercise or a high-anxiety state. In the critically ill patient, it may be caused by pain and/or hypovolaemia for which treatment should be given swiftly. Sinus tachycardia can have serious consequences as it increases cardiac work and therefore oxygen consumption and can therefore lead to heart failure. In patients with underlying heart disease, it can be an ominous prognostic sign.

Management. If there is no underlying cause, the tachycardia is transient, and the patient is asymptomatic, no treatment is necessary, only observation. With a sustained sinus tachycardia, however, even if the patient is asymptomatic, the cause should be determined and treated. Sinus tachycardia can severely reduce cardiac output because of the reduction in ventricular filling time, so there is less blood in the ventricles to pump into the circulation. The heart has to work harder as it tries to maintain the circulation and therefore it needs more oxygen (which it cannot get because of the reduction in cardiac output) which is why this chain of events can lead to HF. Symptoms of reduced cardiac output are produced and treatment should be instigated to slow the heart rate and increase the power of ventricular contraction. Treatment:

1. For tachycardia caused by haemorrhage or hypovolaemia — stop the bleeding and replace fluid.
2. For tachycardia with another cause, give β-blockers and/or calcium-channel blockers.

In the critically ill patient it may also be necessary to support the circulation with inotropic agents to increase cardiac contractility, which will increase blood pressure and improve oxygen delivery to the tissues.

Atrial (supraventricular) arrhythmias.

Premature atrial contractions (PACs). Premature atrial contractions are also known as atrial premature beats or atrial ectopic beats. They are simply beats that occur sooner than the expected beat. They occur because an irritable focus outside of the SA node fires, causing the heart to contract. It takes a little time for the SA node to reset itself so there is a slight pause before the next beat, although this is not long enough to be a full compensatory pause. PACs occur in patients with underlying heart disease but they also occur quite normally and cause no problems in healthy people (Fig. 13.12).

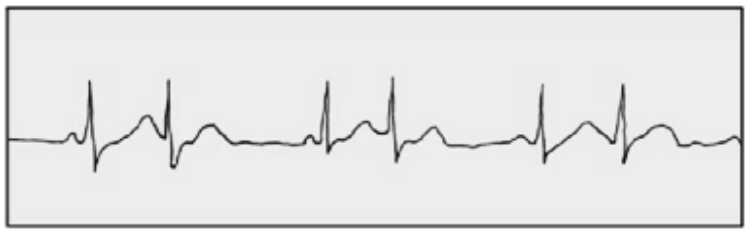


Fig. 13.12. Premature atrial contractions

Causes: smoking, alcohol consumption, exhaustion, caffeine consumption, pyrexia, infection, coronary heart disease, valves disease, lung disease, hypoxia, respiratory failure. In patients with an underlying cardiac problem they can lead to further arrhythmias or HF or to symptoms of a reduced cardiac output (if the PACs are frequent). They therefore need to be closely monitored and treatment should be instigated where necessary.

Management. If the patient has no cardiac disease and is asymptomatic, treatment is rarely necessary. If the PACs are caused by a removable cause such as caffeine, alcohol or other such irritants, then the patient should be advised to reduce intake of such substances. In patients who have an underlying disease with symptoms resuling from the PACs, drug treatment may be commenced to increase the atrial refractory period (e.g. digoxin).

Atrial flutter. Atrial flutter is a form of supraventricular tachycardia (Fig. 13.13). It is present when there is an irritable focus within the atria firing at a rate of approximately 300 b.p.m. Not all of these impulses pass through the AV node but when one does, the ventricles contract. So the atrial rate is much higher than the ventricular rate. P waves are not distinguishable and it is recognised by a typical so-called saw-toothed appearance, caused by the flutter waves. The flutter originates from a single focus within the atria. If it takes two impulses (flutter waves) to stimulate ventricular contraction; the conduction ratio is 2 : 1 three flutter waves; 3 : 1 four flutter waves; 4 : 1 and so on. A 2 : 1 block is most common and you will see an atrial rate of approximately 300 b.p.m. with a ventricular rate of approximately 150 b.p.m.

Causes: hypoxia, acute myocardial infarction, cardiac surgery, valvular disease, chronic obstructive pulmonary disease, infection, hypovolaemia.

Fig. 13.13. Atrial flutter

Management. If the ventricular rate is normal, the patient may be asymptomatic, but if the ventricular rate is badly affected and is too slow or too high, symptoms of reduced cardiac output and perfusion disturbances will be seen. The goals of treatment are:

1. To control the ventricular rate.
2. To restore sinus rhythm.
3. To prevent recurrences of atrial flutter.

If the patient is unstable, synchronous direct-current (DC) cardioversion is commonly the initial treatment of choice. An antiarrhythmic agent, beta-blocker or calcium-channel blocker may be used if the symptoms are less severe. If the heart rate is high, it may be necessary to terminate the arrhythmia by the use of a temporary pacing wire.

Atrial fibrillation. It is a very common arrhythmia, occurs when there are many foci in the atria all firing through re-entry circuits, in a chaotic fashion. The atria lose their kick and cardiac output can be reduced by up to 25 %. There is no electrical synchronisation within the atria and therefore no P waves are present. The foci in the atria may fire at up to 600 times each minute and thus they quiver instead of contracting. Instead of P waves, there are f waves, which show as an erratic baseline waveform. The rate is very irregular and may be very rapid.

Causes: smoking, caffeine, alcohol, anxiety and stress, hypoxia, hypotension, electrolyte disturbances, acute myocardial infarction, pulmonary embolism, chronic obstructive pulmonary disease. Atrial fibrillation can be a sustained arrhythmia or can occur paroxismaly. The ventricular rate can vary. It depends how many of the impulses pass through the AV node to stimulate ventricular contraction. The QRS complexes are described as irregularly irregular and T waves are unidentifiable (Fig. 13.14).

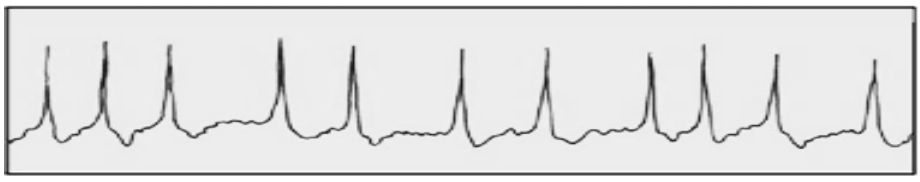


Fig. 13.14. Atrial fibrillation

Management. If the patient is unstable and the arrhythmia has been present for less than 48 hours, the treatment of choice is electrical cardioversion. If the ventricular rate is very rapid, carotid sinus massage may be useful for slowing

the heart rate. If cardioversion does not convert the heart back to sinus rhythm, or if AF is persistent, the decision to perform pharmacologic conversion may be made. In this case, an IV antiarrhythmic agent will be used. In the absence of structural heart disease (coronary artery disease or left ventricular dysfunction), a class Ic drug such as flecainide or propafenone is used. In the presence of structural heart disease, amiodarone should be the drug of choice. Anticoagulation is also necessary because when the atria are fibrillating they do not empty correctly so there is an increased chance of clot formation.

Atrial tachycardia. Atrial tachycardia is often referred to as supraventricular tachycardia (SVT). It is indeed a type of SVT but so are all types of tachycardia that originate above the ventricles (i.e. they are supraventricular). Atrial tachycardia is caused by an abnormal focus in the atria which fires at a rate in excess of 150 b.p.m. (can reach 250 b.p.m.). It is often associated with stress and/or stimulants but usually manifests in digoxin toxicity and primary or secondary heart conditions and it can lead to more serious arrhythmias. P waves are often superimposed on the T waves of the preceding beats and thus the T wave may appear distorted. The P waves are usually followed by a normal QRS complex (Fig. 13.15). The rhythm is often regular but it may be irregular if there is an AV block present and it can occur as paroxysmal atrial tachycardia. Multifocal atrial tachycardia (MAT) occurs when there are several foci that intermittently fire.

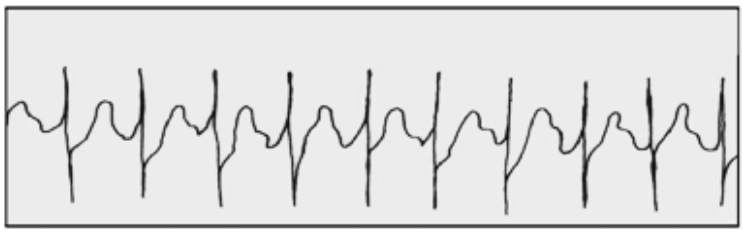


Fig. 13.15. Atrial tachycardia

Causes: smoking, caffeine, stress, primary or secondary cardiac disease, digoxin toxicity (most common cause).

Management. If there is no underlying cause, the tachycardia is transient and the patient is asymptomatic, no treatment is necessary — but the patient should be observed. However, with a sustained atrial tachycardia, even if the patient is asymptomatic, the cause should be determined and treated.

Sustained atrial tachycardia, as with sinus tachycardia, can severely reduce cardiac output because of the reduction in ventricular filling time (so there is less blood in the ventricles to pump into the circulation). In addition to this, the heart is working harder in an attempt to maintain the circulation and therefore needs more oxygen, which it cannot get because of the reduction in cardiac output — this chain of events can lead to heart failure. Symptoms of reduced cardiac output are produced and treatment should be instigated to slow the heart rate and increase the power of ventricular contraction. Depending on how unstable the patient is as a result of the arrhythmia, the condition is treated with adenosine

or amiodarone or electrical cardioversion. Carotid sinus massage can sometimes be successful in slowing the heart rate in the first instance; can be used either to diagnose or to treat atrial tachycardia but it is to be avoided in older patients. When the carotid sinus is massaged, the vagus nerve is stimulated and therefore the firing of the SA node is inhibited, slowing the heart rate down. However, a number of complications are associated with carotid sinus massage — bradycardia, asystole, reduced blood pressure as a result of vasodilation, ventricular arrhythmias and cerebral vascular accident. Therefore, it should only be carried out by experienced healthcare professionals when resuscitation equipment is to hand.

ECG of patient with Wolff–Parkinson–White (WPW) with the accessory pathway located in the inferoseptal heart wall and atrial fibrillation episode and supraventricular paroxysmal tachycardia in the same patient are presented on Fig. 13.16 and 13.17. Patient with WPW syndrome that presents a very fast AF triggering a ventricular fibrillation (arrow).

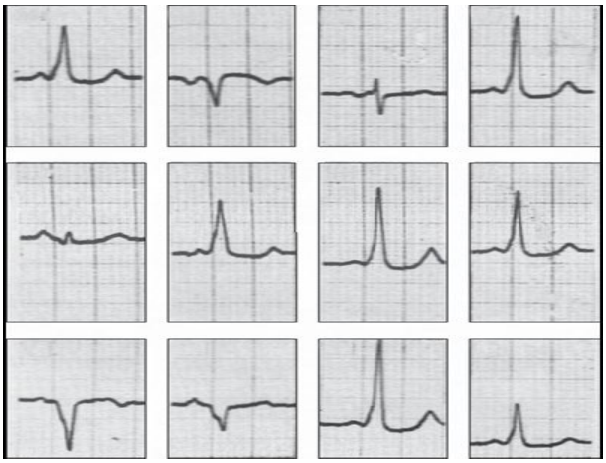


Fig. 13.16. Wolff–Parkinson–White (WPW) patient with the accessory pathway located in the inferoseptal heart wall (Type III WPW)

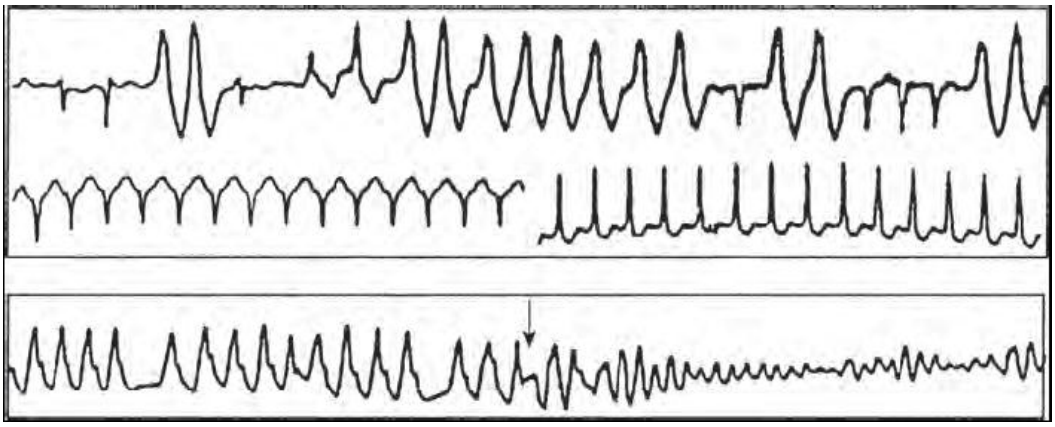


Fig. 13.17. Atrial fibrillation episode and supraventricular paroxysmal tachycardia in a patient with WPW syndrome

Arrhythmias arising at the AV junction. In critical and acute care areas, the most common arrhythmias seen (that arise at the AV junction, i.e. around the area of the AV node and bundle of His) are junctional escape rhythm and AV block.

Junctional escape rhythms. If the SA node fails to initiate impulses and another focus within the atria does not take over as pacemaker, the AV node may take over. This causes abnormal conduction as the impulse spreads upwards over the atria (instead of downwards). The rate is slower than normal because, the lower down the conducting system the impulses are generated, the slower the rate will be. When monitoring in lead II, a junctional escape rhythm can be determined by a rate of 60 b.p.m. or less, with inverted P waves. The P waves may be inverted because the positive deflection denotes the downward wave of depolarisation; as the impulse originates in the AV node the wave of depolarisation passes in an upward direction over the atria and will therefore be seen as a negative deflection on the ECG (Fig. 13.18). P waves may be absent if atrial and ventricular depolarisation occurs simultaneously because the P wave will be hidden within the more powerful QRS complex. It is possible to see inverted P waves when the rhythm arises low in the atria; inverted P waves do not automatically demonstrate nodal rhythm. If the PR interval is less than 0.12 seconds, it is nodal rhythm, but if there is a normal PR interval, the rhythm originated in the atria and it something other than junctional escape rhythm.

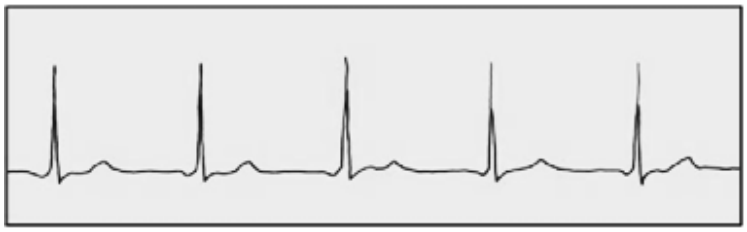


Fig. 13.18. Junctional escape rhythms

Causes: hypoxia, digoxin toxicity, cardiac disease, sick sinus syndrome, myocardial infarction, cardiac surgery, drugs that may cause bradycardia, complete heart block.

Management. If the patient is asymptomatic, generally the arrhythmia itself is not treated but, if necessary, the underlying cause is. Junctional escape rhythm, as the name suggests, serves as an 'escape' mechanism to maintain the heart rate during periods of bradycardia or asystole and it should not be suppressed. In complete heart block, or symptomatic sick sinus syndrome, a permanent pacemaker may be needed. An anticholinergic agent such as atropine may be required if symptomatic bradycardia is present. An accelerated junctional escape rhythm will result in tachycardia.

First-degree AV block. Generally, not dangerous in itself and the arrhythmia is not treated as it does not usually affect cardiac output. Recognised by an extended PR interval of greater than 0.2 seconds. There is a delay at the AV junction before the impulse passes into the bundle of His. The P wave will be followed by a normal QRS complex and T wave and the rate will not be affected. First-degree AV block may occur normally in a healthy patient (Fig. 13.19).

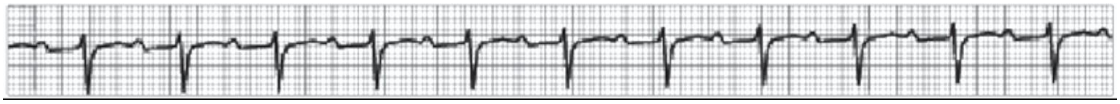


Fig. 13.19. First-degree AV block

Causes: myocardial infarction, degenerative cardiac disease, most commonly caused by drugs that depress AV conduction: (e.g. β-blockers, digoxin, calcium-channel blockers).

Management. If the patient is asymptomatic, the arrhythmia is not treated. However, a delay in conduction means there is a problem in the conducting system and therefore should be monitored. The underlying cause should be treated, if necessary, because first-degree block can progress to more serious forms of heart block.

Second-degree AV block. There are two types of second-degree heart block Mobitz type I and Mobitz type II. Mobitz type I is also known as Wenckebach phenomenon.

Mobitz type I (Wenckebach phenomenon). This is a cyclical rhythm recognised by a progressively increasing PR interval. It continues to increase until eventually the impulse is blocked and cannot stimulate ventricular depolarisation so the next QRS complex is dropped. The sequence then begins again (Fig. 13.20).

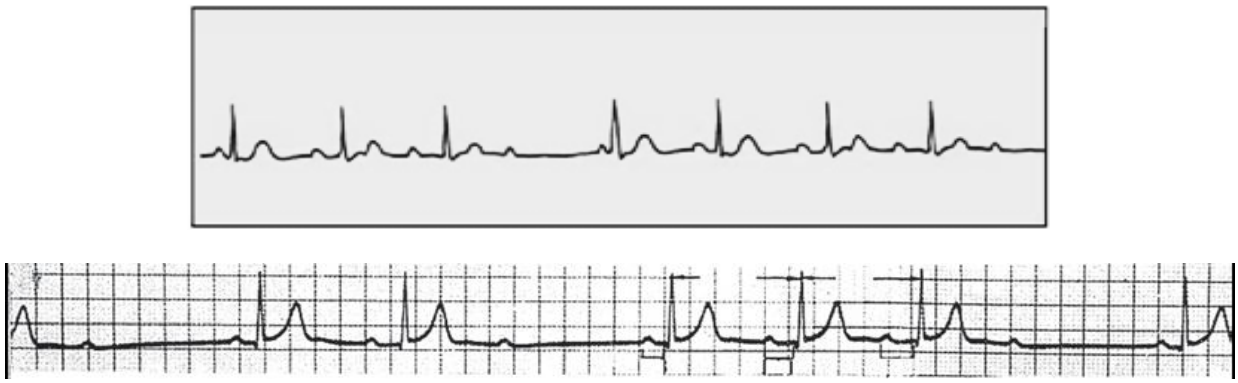


Fig. 13.20. Second-degree AV block — Mobitz type I

Causes: myocardial infarction, degenerative cardiac disease, drugs that depress AV conduction (β-blockers, digoxin, calcium-channel blockers).

Management. If asymptomatic, the arrhythmia is not treated as it is usually transient. However, a delay in conduction means there is a problem in the conducting system and this should be monitored. The underlying cause should be treated, because Mobitz I can progress to more serious forms of heart block. If the rhythm is prolonged and causes a reduction in cardiac output, it may be necessary to give atropine. A temporary transvenous pacing wire may be required to support the patient until the arrhythmia has resolved.

Mobitz type II. A Mobitz type II second-degree AV block is more serious than a type I block but is less common. This arrhythmia usually requires intervention because it frequently progresses to high-grade block or complete heart block. It is easily recognised as frequent impulses fail to pass through

the AV node and are seen as missed beats (no QRS complex) or it takes two P waves to stimulate a QRS complex. This is known as a 2 : 1 block, meaning every other QRS complex is dropped (Fig. 13.21).

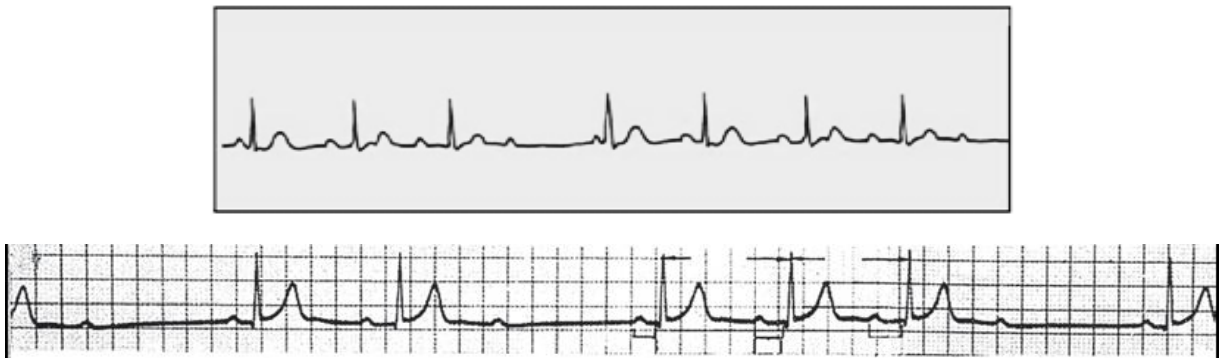


Fig. 13.21. Second-degree AV block — Mobitz type II

Causes: myocardial infarction, degenerative heart disease, digoxin toxicity. A high-grade AV block exists if there is a 3 : 1 or higher ratio of P waves to QRS complexes. This will result in a drastic reduction in cardiac output and rapidly progresses to complete heart block.

Management. Transcutaneous pacing or a temporary transvenous pacing wire is indicated for all, including asymptomatic, as patients with Mobitz II second-degree usually progress to complete heart block. An anticholinergic drug such as atropine may also be required.

Third-degree AV block (complete heart block) is potentially life-threatening and requires immediate intervention. The atria depolarise normally but the impulse cannot pass through the AV node, so no impulses are passed from the atria to the ventricles. A focus in the ventricles may take over but the ventricles beat at a slower rate than the atria and the atria and ventricles depolarise and contract independently of one another. A focus in the His–Purkinje system may take over as the pacemaker, causing ventricular depolarisation. The ventricular rate will be slow and the patient will immediately suffer symptoms of a reduced cardiac output (Fig. 13.22).

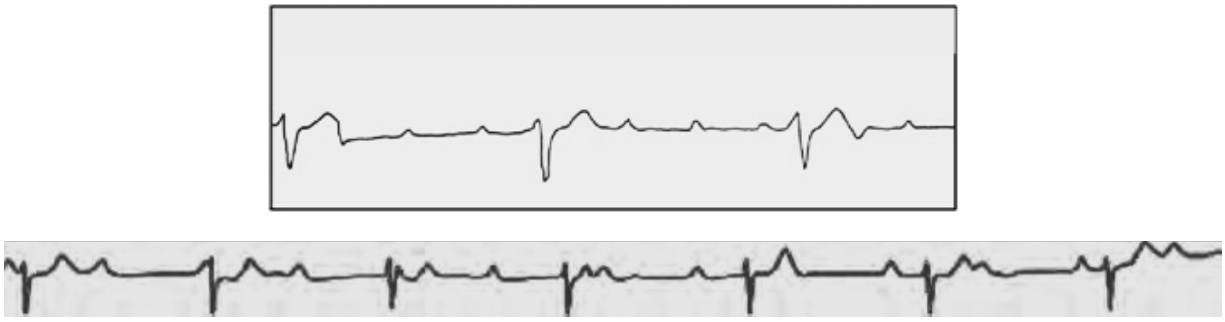


Fig. 13.22. Third-degree AV block. A complete AV dissociation is observed

A normal and regular atrial rate will be seen, usually with normal P waves which do not relate to the QRS complexes. P waves can sometimes be disguised by a QRS complex or T wave. The ventricular rate is also regular but much

slower than the atrial rate and the QRS complexes are widened because they are initiated lower down the conducting system than normal. If a ventricular focus does not take over as pacemaker, ventricular "standstill" will follow which is seen as a row of P waves with no QRS complexes.

Causes: myocardial infarction, degenerative cardiac disease, digoxin toxicity, drugs that depress AV conduction (β-blockers and calcium-channel blockers).

Management. In a critically ill patient, this arrhythmia will usually drastically reduce cardiac output. It is a medical emergency and it requires immediate drug therapy in order to improve the ventricular rate. Atropine is usually given and inotropic agents may be required to support the patient's circulation. The insertion of a temporary transvenous pacing wire is often necessary until the cause of the block has been resolved. If the block is permanent, a permanent pacemaker will subsequently be required.

Ventricular arrhythmias.

Ventricular extrasystoles. Also known as ventricular ectopic beats or premature ventricular contractions, arise from an irritable focus within the ventricles, firing randomly, very common and can occur in healthy. They do not necessarily cause any symptoms or problems, easily recognised (wide and bizarre QRS complexes). During a ventricular extrasystole, there is a reduced (or no) cardiac output and if they don't occur frequently, they are usually of no importance and are left untreated. If they are very frequent or occur in salvos (i.e. two or more together), or occur in a repeating pattern (such as in bigeminy or trigeminy), or occur in a patient with cardiac disease, then they can cause a reduction in cardiac output or lead to more serious ventricular arrhythmias, in which case treatment will be necessary. There are various types of ventricular extrasystoles that result in various arrhythmias.

Causes: use of substances such as alcohol, caffeine, tobacco and cocaine, electrolyte imbalance, hypoxia, hypothermia, myocardial infarction, metabolic acidosis, digoxin toxicity.

Unifocal ventricular extrasystoles. Unifocal ventricular extrasystoles are all the same shape and size and are caused by an irritable ectopic focus in the ventricles firing before it should. Conduction through the myocardium is abnormal and ventricular depolarisation is delayed, resulting in a wide QRS complex. Occurring infrequently, these arrhythmias are of little or no consequence but if there is a salvo of three or more then this is — by definition — ventricular tachycardia (Hand, 2002) and this indicates an irritable or unstable myocardium (Fig. 13.23).

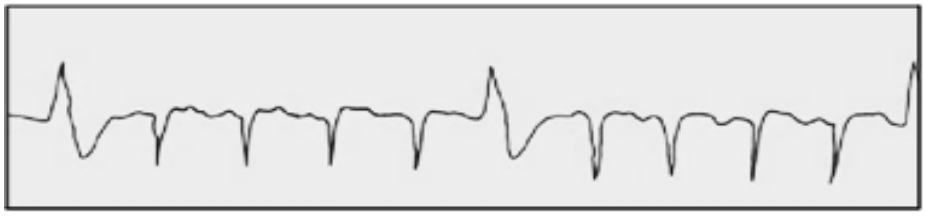


Fig. 13.23. Uniifocal ventricular extrasystoles

Multifocal ventricular extrasystoles are more dangerous than unifocal ventricular extrasystoles because there is more than one irritable focus in the ventricular muscle. They can be easily recognised by their differing shapes and sizes, and lead to more serious arrhythmias, or even lethal arrhythmias such as ventricular fibrillation (Fig. 13.24).

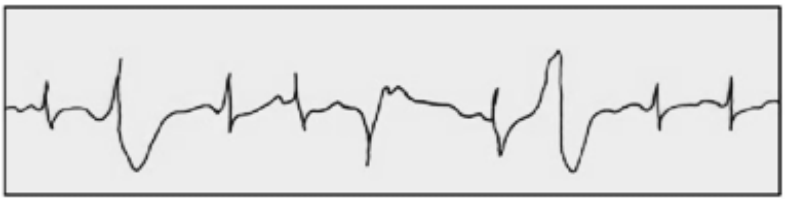


Fig. 13.24. Multifocal ventricular extrasystoles

Bigeminy is caused by an abnormal focus in the ventricular muscle and is recognised by a unifocal ventricular ectopic beat after each normal sinus beat. If this is prolonged, it causes reduced cardiac output and hypotension and will require intervention (Fig. 13.25).

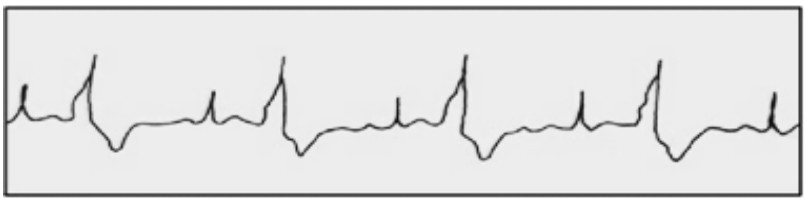


Fig. 13.25. Bigeminy

R-on-T phenomenon. Occurs when a ventricular extrasystole occurs at the peak of the T wave of the preceding beat (i.e. during ventricular repolarisation, when the heart is resting). This is very dangerous and can lead to ventricular tachycardia or ventricular fibrillation (Fig. 13.26).

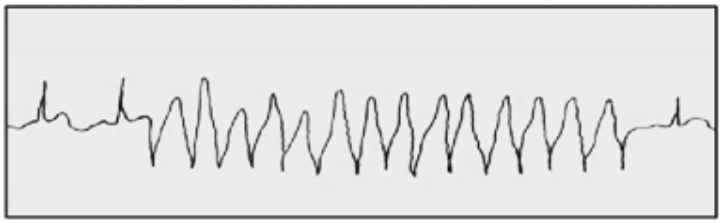


Fig. 13.26. R- on T-phenomen, ventricular tachycardia

Management of ventricular extrasystoles and related rhythms. If ventricular extrasystoles are infrequent and the patient is asymptomatic, no treatment is necessary. However, if they are frequent and/or produce symptoms of reduced cardiac output, treatment will need to be instigated. The treatment depends upon the cause of the problem.

– If caused by hypoxia, oxygen administration is required.

– If caused by acidosis, correct the acidosis.

– If caused by hypokalaemia, hypocalcaemia or hypomagnesaemia — IV supplementation.

– If they are frequent and/or dangerous, give antiarrhythmic drugs. However, antiarrhythmic agents may worsen existing arrhythmias or cause new rhythm disturbances; this is known as the proarrhythmic effect. IV amiodarone is used for the acute treatment of ventricular extrasystoles, and beta-blockers and calcium-channel blockers may also be used.

Ventricular tachycardia (VT), also known as broad complex tachycardia, is present if a focus in the ventricular muscle fires at high frequency and more than three ventricular ectopic beats occur in a row at a rate of 100–250 b.p.m. It causes rapidly repeated ventricular extrasystoles. There are no P waves present, the QRS complexes are wide and slightly irregular and may vary slightly in shape. It may occur paroxysmally and cause no symptoms, but sustained VT is very dangerous and is usually a life-threatening arrhythmia that often precedes ventricular fibrillation and requires immediate intervention. VT can be monomorphic or polymorphic and either can be pulseless.

Monomorphic ventricular tachycardia is caused by a single ectopic focus firing rapidly and all the complexes look the same (Fig. 13.27).

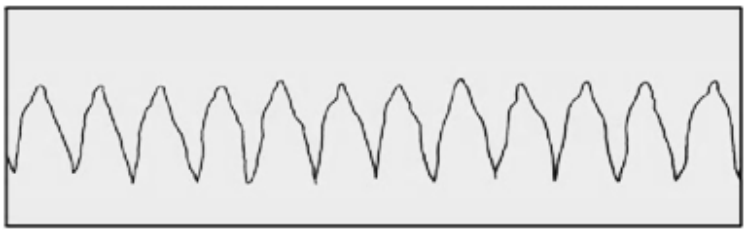


Fig. 13.27. Monomorphic ventricular tachycardia

Polymorphic ventricular tachycardia occurs when there are more than one ectopic foci firing and the complexes therefore change in shape and size (Fig. 13.28). An example of this is **torsades de pointes**, which may be paroxysmal and is often caused by drugs. The patient often becomes pulseless and will collapse as a result because ventricular filling time is severely reduced, as is the force of contraction. Cardiac output is reduced, so is the blood pressure. The condition may degenerate into ventricular fibrillation, causing immediate cardiac arrest. Immediate action is therefore necessary.

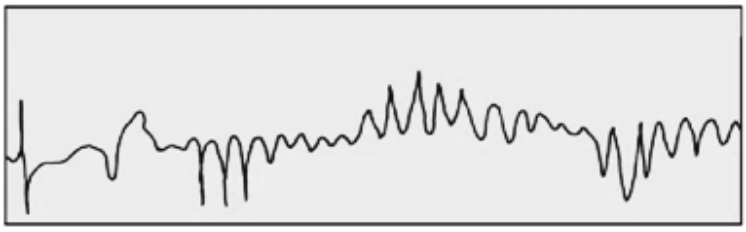


Fig. 13.28. Monomorphic ventricular tachycardia “torsades de pointes”

Causes: myocardial infarction, proarrhythmic effects of some antiarrhythmic agents, electrolyte imbalance, heart failure, valvular disease.

Management. Depends on the symptoms produced.

– If the patient is pulseless, it is treated in the same way as ventricular fibrillation, namely by defibrillation and cardiopulmonary resuscitation (Resuscitation algorithm).

– If the pulse is present but the patient is unstable, DC synchronised cardioversion is needed immediately.

– A stable patient will be treated with amiodarone and the cause corrected. If amiodarone is ineffective, DC synchronised cardioversion will be needed.

Ventricular fibrillation (VF) is caused by numerous irritable foci within the myocardium firing rapidly and chaotically (Fig. 13.29). The effect of this is that the ventricles quiver rather than contract and thus there is no cardiac output; the physiological effects are the same as asystole. There is a greater chance of survival as there is still some electrical activity. The finer the trace, the less chance there is of survival. Untreated VF will usually cause sudden death.

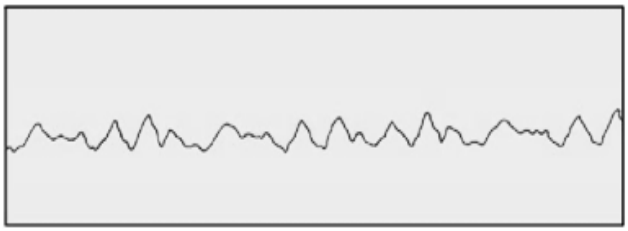


Fig. 13.29. Ventricular fibrillation

Causes: Hypoxia, Electrolyte imbalances, Acid-base disturbances, ventricular tachycardia and other arrhythmias, Digoxin toxicity, Hypothermia, Heart disease.

Management. Immediately check the patient (VF can be mimicked by external electrical interference). If the patient is unresponsive, defibrillation must be instigated immediately following the Resuscitation algorithm, as the patient is in cardiac arrest. If there is any doubt about whether the rhythm is asystole or fine VF do not attempt defibrillation. Continue chest compression and ventilation. Consider giving a single precordial thump (a sharp blow to the lower third of the sternum) when cardiac arrest is confirmed rapidly after a witnessed and monitored sudden collapse and there is no defibrillator immediately to hand. A precordial thump should be undertaken immediately after confirmation of cardiac arrest but only by healthcare professionals. Cardiopulmonary resuscitation must be initiated if defibrillation is delayed for any reason to ensure oxygen delivery. IV epinephrine is administered if defibrillation does not immediately revert the rhythm to sinus rhythm.

Asystole. Asystole literally means ‘no systole’ and there is no electrical activity and no mechanical contraction of the heart (this is ventricular “standstill”). Without immediate treatment, asystole is rapidly irreversible and death ensues. The ECG trace is seen as a flat line (Fig. 13.30).

Causes: untreated ventricular fibrillation, severe hypoxia, severe electrolyte imbalances, severe acid-base disturbances, myocardial infarction, hypothermia.

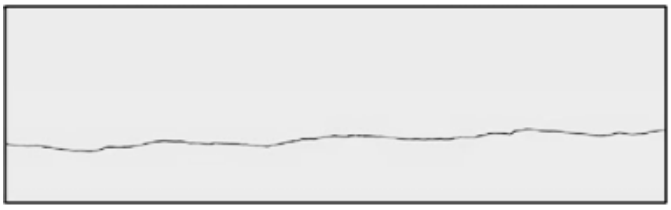


Fig. 13.30. Asystole

Management. Check the patient immediately. Asystole can be mimicked by something as simple as electrode detachment. Ensure that fine VF is excluded by turning up the gain on the monitor. If the patient is pulseless and unresponsive, cardiopulmonary resuscitation must be instigated immediately, together with a single dose of IV atropine and repeated doses of epinephrine, following the Resuscitation algorithm. It should be noted that treatment for a patient in asystole (particularly sustained asystole) is unlikely to be successful.

Many of the arrhythmias discussed within this chapter require no treatment, because they will not affect cardiac output, however, many arrhythmias may compromise cardiovascular system and some of them are even life-threatening. It is important to remember that what may appear to be a benign arrhythmia may lead to a more serious arrhythmia, particularly in already critically ill. Appropriate management requires precise diagnosis and treatment of the underlying cause.

When an arrhythmia is detected:

– check ABCs (airway, breathing, circulation);

– cardiopulmonary resuscitation without delay if necessary;

– if the patient is asymptomatic then often no treatment is required;

– if cardiac output is affected, then treatment is necessary.

Table 13.1 summarizes appropriate interventions for the differrant arrhythmias.

Table 13.1

Specific interventions for arrhythmias

Arrhythmia	Non-drug intervention	Drug intervention
Sinus arrhythmia	Treat cause if symptomatic	Treat cause if symptomatic
Sinus bradycardia	Transcutaneous or transvenous pacing	Atropine
Sinus tachycardia	If caused by haemorrhage, stop bleeding and replace fluid	Beta-blockers Calcium-channel blockers
Premature atrial contractions	Treat cause if symptomatic	Digoxin (if problematic)
Atrial flutter	Direct-current synchronised cardioversion (if tachycardia, use transcutaneous or transvenous pacing)	Beta-blockers Verapamil
Atrial fibrillation	Direct-current synchronised cardioversion (if less than 48 hours from onset of arrhythmia) Carotid sinus massage	Flecainide or propafenone (if no structural heart disease) Amiodarone (if structural heart disease) Anticoagulant drugs
Atrial tachycardia	Carotid sinus massage Direct-current synchronised cardioversion	Adenosine Amiodarone

End of Table 13.31

Arrhythmia	Non-drug intervention	Drug intervention
Junctional escape rhythm	Treat cause if symptomatic	Atropine (if arrhythmia causes symptomatic bradycardia)
First-degree AV block	Treat underlying cause	Treat underlying cause
Mobitz type I second-degree heart block	Transcutaneous pacing Transvenous pacing	Atropine
Mobitz type II second-degree heart block*	Transcutaneous pacing Transvenous pacing	Atropine
Third-degree AV block*	Transcutaneous pacing Transvenous pacing	Atropine
Unifocal ventricular extrasystoles	Treat underlying cause	Amiodarone Beta-blockers Calcium-channel blockers Lidocaine
Multifocal ventricular extrasystoles	Treat underlying cause	Amiodarone Beta-blockers Calcium-channel blockers Lidocaine
Bigiminy	Treat underlying cause	Amiodarone Beta-blockers Calcium-channel blockers Lidocaine
R- on T-phenomenon*	Treat underlying cause	Amiodarone Beta-blockers Calcium-channel blockers Lidocaine
Monomorphic ventricular tachycardia*	If pulseless: defibrillation and/or cardiopulmonary resuscitation If pulse present: (patient unstable) DC synchronised cardioversion; (patient stable, amiodarone ineffective) DC synchronised cardioversion	Epinephrine Amiodarone
Polymorphic ventricular tachycardia*	If pulseless: defibrillation and/or cardiopulmonary resuscitation If pulse present: (patient unstable) DC synchronised cardioversion; (patient stable, amiodarone ineffective) DC synchronised cardioversion	Epinephrine Amiodarone
Ventricular fibrillation*	Defibrillation and/or cardiopulmonary resuscitation	Epinephrine
Acystole*	Cardiopulmonary resuscitation	Epinephrine Atropine

* Require treatment regardless of symptoms.

Drug and non-drug interventions. The interventions listed in Table 13.1 are instigated if the patient is demonstrating symptoms of reduced cardiac output.

Where no symptoms are apparent, or are unlikely, treatment is usually not necessary. Arrhythmias marked with an asterisk (*) require the treatment stated, regardless of the symptoms.

Drugs used for arrhythmia treatment. Table 13.2 lists the drugs used for arrhythmia treatment, according to the Vaughan–Williams classification of antiarrhythmic drugs (Anaesthesia UK, 2008; British Medical Association and Royal Pharmaceutical Society of Great Britain, 2009).

Table 13.2

Drugs used for arrhythmia treatment

Class	Mechanism	Drug(s)	Uses
I	Sodium-channel blockers that prolong the action potential	Quinidine Procainamide Disopyramide	Supraventricular arrhythmias
Ib	Sodium-channel blockers that shorten the action potential	Lidocaine	Ventricular extrasystoles
Ic	Sodium-channel blockers that don't affect action potential	Flecainide Propafenone	Ventricular extrasystoles
II	Beta-blockers	Atenolol Esmolol Propanalol	Sinus tachycardia Atrial fibrillation Atrial tachycardia Ventricular extrasystoles
III	Potassium-channel blockers	Amiodarone	Atrial fibrillation Ventricular extrasystoles Stable ventricular tachycardia
IV	Calcium-channel blockers	Verapamil Diltiazam	Sinus tachycardia Atrial flutter Atrial fibrillation Atrial tachycardia Ventricular extrasystoles
V	Other mechanisms	Digoxin Atropine Epinephrine	Premature atrial contractions Atrial fibrillation Atrial tachycardia Sinus bradycardia Junctional escape rhythm Second-degree heart block (Mobitz I and II) Third-degree heart block Asystole Ventricular fibrillation Asystole

Defibrillation. The delivery of a direct electrical current through the heart depolarises the myocardium allowing the sinoatrial node to resume its normal pacemaker function.

Automatic external defibrillators (AED) should be used wherever possible. All healthcare professionals should consider the use of an AED to be an integral component of basic life support as sophisticated, reliable, safe, computerised

devices that deliver defibrillatory shocks to victims of cardiac arrest by giving visual and voice prompts to rescuers.

Manual defibrillator — self-adhesive defibrillator pads, attached to the defibrillator through an interface cable, rather than paddles because this will reduce the risk of sparks and the operator will not have to lean over the patient. Water-based gel pads should be placed between the paddles and the patient's skin. The paddles should be placed in the appropriate position: the right (sternal) electrode is placed below the clavicle to the right of the sternum. The apical paddle is placed vertically in the mid-axillary line, level with the V6 ECG electrode's position. The paddles should be pressed firmly to the chest wall with an optimal force of 8 kg A shock of between 150–360 Joules is delivered when the patient is in ventricular fibrillation.

Safety considerations. Turn off oxygen supplementation or remove the oxygen mask or nasal cannulae and move them at least 1 meter away before the shock is delivered. Sparks from poorly applied paddles may cause a fire in an oxygen-rich environment. Remove any transdermal drug patches before a shock is delivered. This is particularly important for GTN (glyceryl trinitrate) patches because they may explode.

Cardioversion. Cardioversion is carried out in the same manner as defibrillation but the direct-current (DC) shock is delivered in synchrony with the peak of the R wave. The defibrillator has a "synchronise" switch which is utilised for cardioversion. The other major differences are that the conscious patient will usually require sedation, and the intensity of the shock is usually less. Current evidence suggests that the majority of patients will be successfully cardioverted by shocks of 200 Joules, and it appears that only a very small percentage of patients benefit from stronger shocks. Antero-posterior electrode placement may be more effective than the traditional antero-apical position in cardioversion of atrial fibrillation, although either position is acceptable.

Pacing. Temporary pacing. A pacemaker is a device that generates an electrical impulse from a pulse generator, which is then transmitted through the heart causing depolarisation. This in turn brings about contraction of the myocardium. Temporary pacemakers are used in emergency and acute situations until the arrhythmia has resolved or until a permanent pacemaker can be fitted if necessary.

Transcutaneous pacing is used in an emergency situation and is a simple, non-invasive process of applying external electrodes to the anterior chest wall, or on the patient's anterior chest wall and one on the patient's back. Electrical impulses are generated and these pass through the skin to the myocardium and thus pace the heart.

Putting it all together. When considering a rhythm strip, it is helpful to approach diagnosis with a systematic evaluation that will help you to determine the rhythm. The following 6 steps can be applied systematically to each arrhythmia you deal with.

1 — consider whether the rhythm is life-threatening. If it is life-threatening, summon help and instigate the appropriate Resuscitation algorithm.

2 — consider the heart rate (bradycardia — less than 60 b.p.m., normal rate — 60–100 b.p.m., tachycardia — more than 100).

3 — consider the P waves. If P waves are present: are they normal in appearance? Does one P wave occur before each QRS complex?

4 — consider the PR interval:

– Is the PR interval of normal duration (0.12–0.2 seconds)?

– Is the interval prolonged?

– Is the interval shortened?

– Is it consistent?

5 — Consider the QRS complex:

– Is the QRS complex normal in duration (0.06–0.12 seconds)?

– Is the QRS consistent in duration?

– Are the complexes of normal shape and configuration?

– Is the QRS consistent in form?

6 — Consider the RR interval:

– Is the RR interval consistent?

– If it is inconsistent, is there some pattern in the variation?

Now, bearing these six steps in mind, we can work out with arrhythmias.

CHAPTER 14
HEART FAILURE

Heart failure (HF) is referred to the condition, when the heart fails to ensure proper supply of organs and tissues with blood in order to meet metabolic demands.

HF develops when the cardiac output is insufficient metabolic demands of the organism or when the heart cannot successfully manage the venous return. These lead to pulmonary congestion and plethora (in case of left ventricular (LV) HF (LVHF)), peripheral edema (in case of right ventricular HF (RVHF)), or both in case of total HF.

According to **ICD-10** HF is classified in section I — cardiovascular diseases: I50.0 — congestive HF; I50.1 — LVHF; I50.9 — HF non-specified.

New **ICD-11** classification encodes Heart Failure in the class 11 — Diseases of the circulatory system, 12 subclasses which includes 8 clarifying diagnoses:

BD10 — Congestive heart failure.

BD11 — Left ventricular failure (it contains 4 clarifying diagnoses).

BD12 — High output syndromes.

BD13 — Right ventricular failure.

BD14 — Biventricular failure.

KB40 — Neonatal cardiac failure (it contains 4 clarifying diagnoses).

BD1Y — Other specified heart failure.

BD1Z — Heart failure, unspecified.

Epidemiology. Clinically manifested chronic HF in adult is diagnosed in not less than in 1.5–2 %, among children the data vary a lot and in general prevalence is estimated to be 0.87–3.0 cases per 100 000. According to British heart association 34 % of children with acute HF due to the myocardial disease need transplantation or die within one year from manifestation. According to the cause prevalence of HF may vary a lot as well: it is 8–14 per 1000 children with congenital heart disease (CHD), diagnosed at the first year life, 10–20 per 1000 children with cardiac arrythmias (AV-block, chronic tachycardia, etc), 0.65–4.0 per 100 000 children with cardiomyopathies.

Etiology. Causes of HF are divided in two major groups: cardiac and non-cardiac.

1. Cardiac:

– infants: nearly 80 % of cases of HF are due to CHD. More rarely cardiac arrhythmias and myocarditis;

– 1 to 3 years of life: CHD, infectious myocarditis, cardiac arrhythmias or problems with conduction system;

– preschoolers and school-aged children: CHD, infectious or toxic myocarditis (i.e. anthracycline toxicity), cardiomyopathies, cardiac arrhythmias or problems with conduction system;

– Adolescents: myocarditis (infectious, toxic, immune-mediated in systemic connective tissue or autoimmune diseases), pericarditis, congenital or acquired heart defects, cardiac arrythmias or problems with conduction system, infective endocarditis, cardiomyopathies.

2. Non-cardiac (to fulfill the HF criteria there should be evidence of cardiac dysfunction together with non-cardiac problem):

– sepsis, respiratory diseases, chronic severe anemia, hyperhydration caused by non-cardiac issues (kidney disease), thyrotoxicosis, genetic diseases (inborn errors of metabolism, neuro-muscular diseases).

Pathogenesis. HF is referred to the pathophysiological syndrome when due to the various cardiovascular diseases and/or imbalance of vasoconstrictive and vasodilating neuro-humoral systems the ability of heart to maintain proper cardiac output decreases which leads to discrepancy between hemodynamical needs and ability to maintain them.

According to the initial mechanism types of HF are:

– with **primary impairment of myocardial metabolism** (hypoxia, myocarditis, inborn errors of metabolism and storage diseases);

– with **volume or pressure overload** or their **combination (**congenital or acquired cardiac defects, hyperhydration, severe arterial hypertension);

– **combination** of two types given above (with progression of HF any type becomes mixed).

According to the predominant type of dysfunction. **Systolic dysfunction** — heart failure with reduced ejection fraction (HFrEF) — significantly reduced ejection fraction (EF) of LV < 40 % or heart failure with mildly reduced ejection fraction (HFmrEF) — EF of LV 41–50 %.

Diastolic dysfunction — heart failure with preserved EF (HFpEF), diagnosed in patients with symptoms of HF, evidence of structural or functional abnormalities and elevated natriuretic peptides, in case the EF is found to be within normal range or slightly reduced.

Along with reduction of contractility the compensatory mechanisms are activated to maintain adequate perfusion. They include:

1. Sympathetic system activation (which has positive inotropic and chronotropic action on myocardium). As cardiac output (CO) linearly depends on stroke volume (SV) and heart rate (HR) (CO = SV × HR) in tachycardia CO can be maintained nearly normal even if the contractility is reduced.

2. RAAS activation in response to reduction of renal perfusion which via vasoconstriction and higher peripheral vascular resistance helps to maintain systemic pressure within normal range.

4. Frank-Starling mechanism (strength of contraction of cardiomyocytes increases with the stretching (i.e., with the rise of end-diastolic volume) which leads to rise of SV and CO.

5. Hypertrophy of myocardium (allows to an increase the strength of contractions in pressure overload).

6. Sodium and water retention (which results from activation of RAAS) helps to maintain systemic pressure in case of reduced CO.

All the mechanisms listed above allow to tolerate myocardial dysfunction and are beneficial if short standing. However, if they persist for a long period of time they become the factors which further damage the myocardium and account for the HF progression.

Thus, sympathetic system activation leads to rise in peripheral vascular resistance which in its turn defines elevated afterload and results in hypertrophy of myocardium. Also higher intensity of catabolic processes and higher demand in oxygen might be seen in prolonged hyperactivation of sympathetic system. Diaphoresis, one more consequence of adrenergic stimulation, can cause dehydration in severe cases. Finally, due to constant stimulation the density of β-adrenoreceptors on cardiomyocytes might lower and the loss of positive inotropic effect of catecholamines can occur.

RAAS activation leads to vasoconstriction and activation of sympathetic nervous system, enhances peripheral noradrenergic activity, stimulates aldosterone and vasopressin synthesis, myocardial remodeling and hypertrophy, proliferation of smooth muscle cells within vessels' wall. Retention of water and sodium mediated by aldosterone increases blood volume and heart preload.

Diastolic HF results from rigidity of myocardium and decreased relaxation, valvular heart defects or pericarditis. Elevated end-diastolic pressure (EDP) is seen in this case but end-diastolic volume (EDV) remains normal and contractility of myocardium is not affected. In severe cases (cardiac tamponade, hypertrophic cardiomyopathy) CO decreases significantly.

Respiratory changes in HF. In HF with LV systolic disfunction or severe diastolic disfunction elevated left ventricle EDP is noted. If HF develops acutely resistance of LA walls is rather high which leads to rise of EDP in LA. This pressure is transferred on pulmonary veins and might lead to the transudation of fluid into the interstitial space. The younger the child the higher the permeability of pulmonary vessels and interstitial edema is. Thus, interstitial and peribronchial edema occur both resulting in ventilation/perfusion (V/Q) mismatch and stimulation of respiratory drive (tachypnea). Pulmonary resistance is increased as well which contributes to restrictive changes (limited ability to expand) and bronchial obstruction develops due to peribronchial edema. Therefore, both phases of breathing are getting affected in HF. The work of breathing rises significantly increasing the oxygen demand and at the same time the ventilatory cost of CO_2 eliminating.

Under normal conditions excess of fluid should be eliminated from lungs by increasing the lymphatic drainage but in HF compensatory mechanisms are overloaded and alveolar edema occurs. Thus, alveoli are becoming poorly ventilated which affects V/Q and PaO_2 decreases. Systemic hypoxemia stimulates respiratory drive and the vicious cycle of dyspnea, high demand in oxygen and V/Q mismatch is being initiated.

One of the important mechanisms for protection from pulmonary edema in pulmonary venous hypertension is Kitaevs' effect. Due to this effect reflectory spasm of pulmonary arteries occurs in pulmonary venous hypertension to prevent alveolar capillaries from excessive pressure. If this effect is being activated for a prolonged period, resistance of pulmonary arteries increases significantly resulting in right ventricle afterload rise and subsequent hypertrophy.

Summarizing all the above mentioned, all the compensatory mechanisms activated in HF at the same time increase the work of heart and its oxygen demand. Resulting from combination of both underlying problems and adaptation mechanisms structural remodeling of myocardium occurs — hypertrophy activation of collagen production, dystrophy, necrosis and apoptosis of cardiomyocytes. Dilation of heart chambers and decrease in contractility are observed then contributing to relative insufficiency of mitral and tricuspid valves. Congestion, ischemia and systemic inflammatory response due to immune imbalance cause dystrophic changes in target organs (liver, kidneys, brain etc.).

Classification. In school-aged children the classification of HF by Strazhesko–Vasilenko can be used (Table 14.1). It is based on structural changes in the heart and degree of physical activity limitations. Similar criteria are used in the American College of Cardiology/American Heart Association (ACC/AHA) classification and New-York Heart Association (NYHA).

Table 14.1

HF classification by Strazhenko–Vasilenko and NYHA

HF classification by Strazhesko–Vasilenko		**Functional classes of HF according to NYHA**	
I	Initial stage of cardiac disease. Hemodynamics is normal. Hidden HF	I	Physical activity is normal. Intensive physical activity is tolerated but dyspnea and/or fatigue may be observed
IIA	Clinically manifested stage of cardiac disease. Hemodynamical changes are moderate and predominantly affect one of the blood circuits	II	Mild limitation of physical activity: no symptoms at rest, daily physical activity is tolerated but causes fatigue, dyspnea and tachycardia
IIB	Severe cardiac disease. Moderate changes of hemodynamics in both blood circuits	III	Significant limitation of physical activity: mild symptoms at rest, even mild physical activity can cause worsening of general condition
III	End stage of heart disease. Pronounced changes of hemodynamics and severe irreversible changes of target organs (lungs, liver, kidneys, brain, vessels)	IV	Physical activity total intolerance; symptoms of HF are present at rest, minimal efforts cause significant worsening

In children of first years of life it is not always possible to assess their complaints. Classifications, which are based on objective signes and symptoms, are worked out — HF classification modyfied by N. A. Belokon; functional classes (FC) classification (NYHA) were modyfied by R. D. Ross (Table 14.2).

Table 14.2

Modified classifications of HF in children (by N. A. Belokon and R. D. Ross)

HF stages by N. A. Belokon			Functional classes by R. D. Ross	
Stage	**Left ventricular HF**	**Right ventricular HF**	**Class**	
I	Symptoms are absent at rest and only appear following hard physical activity (tachycardia, dyspnea)		I	No symptoms, physical activity is not limited
IIA	Heart rate (HR) is elevated by 15–30 %, breath rate (BR) is elevated by 30–50 % from normal for age	Liver is enlarged, palpated 2–3 cm below costal margin	II	Mild tachypnea or diaphoresis while feeding in babies. Dyspnea while physical activity in older children
IIB	HR is elevated by 30–50 %, BR by 50–70 % above normal. Acrocyanosis +/–, obsessive cough, crackles on lung auscultation	Liver is enlarged, palpated 3–5 cm below costal margin, pastosity, neck veins bulging	III	Significant tachypnea or diaphoresis while feeding in babies which causes prolonged feeding and leads to malnutrition. Severe dyspnea while physical activity in older children
III	HR is elevated by 50–60 %, BR is elevated by 70–100 %. Clinical signs of pulmonary congestion	Hepatomegaly, peripheral edema, generalized edema (hydropericardium, ascites)	IV	At rest tachypnea, diaphoresis and grunting are observed

Clinical manifestation.

I stage: exertional dyspnea and tachycardia. In babies — irritability or sleepiness, transient perioral cyanosis while breastfeeding. Investigations reveal decreased cardiac output on functional tests (signs of decreased compensatory capacities of myocardium). According to presence of clinical manifestations *stage I* is now used to be devided into two subgroups: pre-clinical (IA) and clinical (IB).

IIA stage: tachypnea and tachycardia are at rest, marked fatigue and mild to moderate decrease of BP. In predominantly right ventricular HF pastosity or transient peripheral edema can be observed, mild to moderate hepatomegaly. In left ventricular HF tachypnea and tachycardia, transient wet crackles at lung bases, periodical coughing are observed.

IIB stage: marked tachycardia and dyspnea are at rest, perioral cyanosis, pallor or marble skin, decreased BP (both systolic and diastolyc), cardiomegaly, muffled heart tones, liver and kidney function impairment.

At *stage IIB* HF usually involves both systemic and pulmonary circuits even though initially was either left ventricular or right ventricular. Venous congestion signs are observed in:

1) systemic circuit — jugular vein distention, cyanosis, hepatomegaly, stable peripheral edema, ascitis, hydrothorax, decreased diuresis;

2) pulmonary circuit — obsessive cough, dyspnea, intercostal retractions, diffuse wet crackles over lung fields, signs of pulmonary edema.

IIIA stage (end-stage) severe congestion in both pulmonary and sytemic circuits (marked signes of pulmonary edema, abrupt progression of hepatomegaly and generalised edema), cyanosis, abrupt decrease of BP, significant cardiomegaly, encephalopathy and signs of dystrophy in target organs (liver, kidney, brain etc).

IIIB stage — irreversible dystrophy of organs and systems.

Factors which precipitate congestion signs and symptoms in children with compensated HF:

I. Conditions which lead to activation of metabolic processes and increase the demand to cardiac output: fewer, infections, anemia, tachycardia, hyperthyroidism, Increased circulating blood volume (rise in pre-load), Excessive intake of salt and fluid, Renal insufficience.

II. Conditions which lead to increased afterload: Poor management of arterial hypertension, Pulmonary embolism (right ventricular overload).

III. Conditions which lead to decreased contractivity of myocardium: Medicines with negative inotropic effect (high doses of beta-adrenoblockers), Ischemia or myocardial infarction.

IV. Severe bradycardia.

Diagnostics. Two major goals:

1. To diagnose HF and its stage.
2. To determine the cause of HF.

HF diagnosis is based on:

1. *History* (cardiac diseases, sudden death among relatives, presence of risk factors, preceding illnesses, pregnancy course and growth parameters during the first years of life — often failure to thrive, sudden rise in body weight may be due to progression of edema) and *complaints* (difficulty breathing, skipped, irregular or fast heart beats, physical excersie intolerance, paroxismal nocturnal dyspnea or cough, fatigue, decreased appetite, in infants and babies — difficulties with feeding, prolonged feeding).

2. *Physical examination* — skin (cyanosis, marble skin, pallor in syndrome of low cardiac output, capillary refill time greater than 3 sec.); edema (ankles, scrotum, coccyx), arrythmias, tachycardia, arterial hyper/hypotension, tachypnea, diffuse apex beat size, cardiac borders shift, muffled heart tones, pathological S3 (gallop rhythm), hepatomegaly, hepatojugular reflux (jugular veins bulging when pressure over the right upper quadrant is applied), decreased diuresis.

3. *Laboratory data:*

• CBC.

• Urine test.

• Blood biochemistry (urea, creatinine, electrolytes, glucose, bilirubin, ALT, AST, LDH and myocardial fraction (HBDH), creatinkinase and myocardial fraction, troponin, iron, ferritin, transferrin, lipids).

• Hormonal studies (thyroid gland function).

• Coagulation tests, INR, D-dimers — hypercoagulation is possible, especially in policytemia.

• Acid-base studies and blood gases (metabolic lactate acidosis as the result of tissue hypoxia).

• Natriuretic peptides:

– NT-proBNP < 125 pg/ml — HF is unlikely;

– NT-proBNP 200–400 pg/ml HF stage I;

– NT-proBNP 400–1000 pg/ml HF stage IIA;

– NT-proBNP > 1000 pg/ml HF stage II B–III.

• If acute myocarditis is suspected — additionally test for viral DNA, RNA, serology tests; complement components C3, C4; IgA, IgM, IgG; antinuclear antibodies.

4. *Instrumental studies:*

• ECG (arrythmias, blockades, LV hypertrophy, wide and deformed QRS, ST segment depression and T wave changes — ischemic changes in myocardium).

• Echocardiogram (EF, End-diastolic pressure and volume, pulmonary artery pressure, structural abnormalities, hypokinesis).

• Chest X-ray (cardiomegaly, pulmonary congestion).

• Functional tests (6-minute walk — distance is assessed when walking in comfortable regimen) — additional method used in school aged children:

– FC I: from 426 m to 550 m;

– FC II: from 300m to 425 m;

– FC III: from 150 m to 300 m;

– FC IV: < 150 m.

• MRI (structural and functional characteristics of myocardium to diagnose storage diseases (Fabry, hemochromatoses, glycogen storage diseases), non-compact myocardium, cardyomyopathies). Additional method of EF assessment if EchoCG is not informative (poor acoustic window); MRI with contrast (gadolinium) — detects fibrose changes in myocardium.

• Coronary angiography if coronary arteries anomalies are suspected.

• Cardiac catheterization.

• PET CT scan, cardiac scintigraphy with 99mTc-labelled diphosphonates.

Management. Major goals of treatment are:

– to relieve symptoms;

– to protect target organs (brain, kidneys, vessels, liver);

– to improve quality of life;

– to reduce the number of hospital admissions;

– to improve the prognosis and to reduce the rate of progression.

Diet. Reduced amounts of salt, sugars, caffeinated drinks, fried, smoked foods or those rich in saturated fats are recommended depending on the stage. Patients should be encouraged to have more food rich in potassium (dried fruits, bananas), polyunsaturated fats, and overall more homemade than processed food in their diet.

In advanced stages dietary salt intake should be limited up to 1–1.5 g/day for 5 to 7 days to stabilyze the patient. These strict limitations should not be

prolonged because of risk of electrolyte imbalance. In children of the first years of life there is no need to limit salt in diet as specialised milk formulas use allow to control its intake.

Daily need in calories is higher in HF patients compared to healthy pears. Children of the first year of life should get **150 kcal/kg/day**. If breast feeding is possible bottle breast feeding is preferred to prevent tiredness, prolonged feeding and failure to thrive. Number of feedings should be increased and the volume of each feeding decreased. Nutritional status and growth should be regularly monitored. If malnutrition is observed breast milk fortifiers or energy dense formulas with partial or complete hydrolysis of protein can be used. If failure to thrive persists, it is possible to use partial (at night) or full tube feeding.

In children over one-year-old, the daily calorie requirement is **125–130 kcal/kg/day**, decreasing at school age to 80–100 kcal/kg/day. If there are signs of malnutrition or decreased appetite, partial (up to $^1/_2$ daily calorie requirement) or full enteral nutrition with isocaloric or hypercaloric (when fluid restrictions are needed) formulas is recommended.

Water balance. Fluid restriction depends on the degree of heart failure, the severity of edema and decreased diuresis. As a rule, with HF stage I fluid intake restrictions are not required. Starting from stage IIA, diuresis, water balance (the difference between the volume of fluid intake and excretion), body weight changes are assessed. If there are signs of fluid retention, it is necessary to limit its intake to amounts no more than the volume of urine excreted the day before. Daily morning weighing allows to identify hidden swelling in the early stages and timely correct therapy.

Physical activity appropriate to the severity of heart failure is encouraged in all patients. Light exercise is recommended (for example, walking at a calm pace), as well as exercise therapy. In case of decompensation of heart failure, any exercise is contraindicated; physical rest is necessary. As the condition improves in the hospital, physical rehabilitation is prescribed which may include individually selected exercises, subject to regular monitoring of the ECG and the patient's condition.

Etiotropic treatment. In the presence of a correctable cause of HF (CHD, coronary vessels anomalies, myocarditis, etc.) etiotropic treatment is possible and is subject to a particular etiology.

Conservative therapy is prescribed long-term (often lifelong) and based on following principles:

– reducing the requirements for cardiac output (by limiting physical activity, providing thermal comfort, reducing peripheral vascular resistance);

– prevention of myocardial dystrophy and remodeling (by decreasing afterload and preload (regulation of blood volume);

– maintaining of adequate cardiac output (by use of inotropic agents);

– correction of homeostasis disorders and prevention/treatment of complications (correction of electrolyte balance and acid-base balance, prevention and treatment of hypercoagulation and thromboembolism).

The major groups of medications used in the treatment of heart failure include:

1) drugs that improve the patient's condition (diuretics, cardiac glycosides);

2) means to reduce the frequency of hospitalizations and improve survival:

– angiotensin-converting enzyme inhibitors (ACEIs);

– angiotensin II receptor blockers (ARBs) (if intolerant to ACEIs);

– angiotensin receptor-neprilysin inhibitor (ARNI);

– aldosterone receptor antagonists;

– beta blockers.

Treatments to reduce hospitalizations and improve survival. All patients, in the absence of contraindications (renal artery stenosis, angioedema, hyperkalemia, GFR less than 30 ml/min), should be prescribed an **ACEIs** at an initial dose of 20–25 % of the target (*enalapril* 0.05–0.08 mg/kg) followed by a gradual increase to the maximum tolerated over 4–8 weeks while monitoring blood potassium levels and renal function. ACEIs reduce the synthesis of angiotensin II and the breakdown of bradykinin, mediators that affect the sympathetic nervous system, endothelial function, vascular tone and myocardial functioning. Hemodynamic effects include dilation of arteries and veins, a sustained decrease in LV filling pressure during rest and exercise, a decrease in systemic vascular resistance and a direct beneficial effect on ventricular remodeling.

If side effects occur (obsessive dry cough, angioedema), it is possible to use an **ARBs** (*losartan* for children 6–16 years old weighing 20–50 kg, 25 mg per day once orally, maximum dose 50 mg per day once). In some cases, when using ACEIs in the maximal dosages the improvement is not achieved, it is possible to use a combination of ACEIs with ARBs but in this case the risk of side effects (ex. hyperkalemia) increases.

A new group of drugs is **ARNI**, a combination drug containing an *angiotensin II receptor blocker and a neprilysin inhibitor* (sacubitril). Neprilysin is an enzyme involved in the breakdown of natriuretic peptides. By inhibiting the activity of neprilysin, ARNI increase natriuretic peptides concentration. Effects include decreased blood pressure, decreased afterload and increased natriuresis. ARNI can be prescribed to children aged 1 year and older, yet in the Republic of Belarus using of ARNI in children is limited.

Beta blockers can be used in addition to ACEIs in all patients with stable mild, moderate, severe congestive HF, with reduced EF. In case of tachycardia, negative chronotropic and inotropic effects have a beneficial effect on the myocardium reducing the need for oxygen. However, when initiating treatment the manifestations of HF may worsen due to a decrease in CO. Therefore, the initial dose should be low and increased gradually over 8 weeks or more to the target or maximum tolerated while monitoring HR, BP and ejection fraction of LV, diuresis and body weight. Beta blocker therapy is not started in decompensated HF. The preferred drug is *carvedilol* (for children 0–14 years old, the initial dose is 0.03 mg/kg/day in 2 divided doses (maximum dose 0.2 mg/kg/day), for adolescents the initial dose is 1.5 mg/day in 2 divided doses (maximum dose 18.75 mg/day)).

Diuretics are an integral part of the complex treatment of children with HF stages IIB and III. They can be prescribed for stage IIA in the presence of edema.

Aldosterone receptor antagonists (*spironolactone, eplerenone*) are often used in patients with HF, especially those with moderate to severe symptoms, including those taking ACEIs or ARBs, since aldosterone can be synthesized independently of the RAAS. The greatest effect is observed in patients with severe right ventricular HF and congestive changes in the liver, since in this case the metabolism of aldosterone decreases and its concentration in the blood increases significantly. Serum potassium and creatinine levels should be regularly monitored because of the risk of hyperkalemia and renal dysfunction which increases when used concomitantly with ACEIs or ARBs. In patients with HF, when ACEIs are insufficiently effective, it is preferable to use them in a combination with aldosterone receptor antagonists rather than with ARBs. Spironolactone is prescribed to adolescents at an initial dose of 25 mg once a day, max dose is 50 mg per day once. Contraindications: serum potassium level > 5.0 mmol/l, creatinine > 220 μmol/l, simultaneous administration of ACEIs and ARBs.

In the presence of volume overload, loop **diuretics** should initially be used (most often *furosemide* 1–3 mg/kg per day) due to their rapid effect (10–15 minutes after IV administration of furosemide). *Thiazide diuretics* can be prescribed to children with HF IIA when patients have mild fluid retention and no signs of pulmonary congestion (*hydrochlorothiazide* starting at a dose of 1 mg/kg/day, max 2.5 mg/kg/day, maintenance dose 12.5 mg per day once for school-age children). Patients with low BP and a tendency to collapse should not be prescribed thiazide diuretics since they have the most powerful hypotensive effect. With long-term use of loop diuretics, especially when combined with thiazide diuretics, hypokalemia and alkalosis, hyponatremia and hypomagnesemia, hypovolemia with arterial hypotension can occur. Therefore, as the patient's condition improves the dose of diuretics should be reduced to a minimum up to complete withdrawal if other drugs allow to control the symptoms of HF.

Inotropic drugs. This group includes *glycoside and non-glycoside drugs*. Non-glycoside inotropic agents include adrenergic (adrenaline, norepinephrine, dopamine, dobutamine) and non-adrenergic (milrinone, enoxymone — phosphodiesterase inhibitors) agents. Despite the improvement in myocardial contractility, non-glycoside drugs, when used long-term in the treatment of chronic HF, lead to an increase in mortality. Currently recommended for use only in case of acute decompensation to stabilize the condition of the patient, including as a bridge to heart transplantation.

Dobutamine, a β1-adrenergic agonist, increases SV and CO, reduces both systemic and pulmonary perifferal vascular resistance if given at medium and high doses (7.5–10 mcg/kg/min), increases HR and systemic BP, reduces the filling pressure of the ventricles, at low doses (2–4 mcg/kg/min) increases renal and coronary blood flow, improves oxygen supply to the myocardium.

Dopamine at a dose of 5 to 10 mcg/kg/min is used in the case of decompensated refractory HF to increase cardiac output, stabilize systemic BP and

increase diuresis. The effect occurs within 5 minutes from the start of the infusion with peak effect after 5–7 minutes. It has a tachycardic and arrhythmogenic effect.

Milrinone is used at a loading dose of 25–50 mcg/kg/min, maintenance dose of 0.25–1 mcg/kg/min. Milrinone should be used with caution in patients with hypotension because of the risk of peripheral vasodilation.

Cardiac glycosides are used in patients with systolic HF when ACEIs and diuretics do not allow to control symptoms. Currently, low doses of digoxin are recommended for treatment of HF in children (weighing more than 55 kg up to 0.25 mg/day, weighing less than 55 kg up to 0.125 mg/day). At such a dose extracardiac neuromodulatory effect of glycosides is fully manifested but no proarrhythmic effect is present. In HF due to CHD the saturation dose is administered first (40–50 mcg/kg in infants, 30–40 mcg/kg in children greater than one year, administered over 2–3 days three times per day). In case of DCMP a maintenance dose of digoxin is given without saturation (infants — 10–12 mcg/kg/day; older than one year — 8–10 mcg/kg/day).

Treatment of cardiac arrhythmias. As most antiarrhythmic drugs decrease myocardial contractility the potential risks and benefits of their use should be considered before initiation of treatment. Antiarrhythmic therapy is prescribed to selected patients with arrhythmias that persist after correction of conditions that could contribute to their occurrence (electrolyte or metabolic disorders, hypoxia), subject to poor tolerance.

Class III antiarrhythmic drugs (amiodarone, sotalol) are preferred. **Amiodarone** (10 mg/kg/day for 10 days followed by 5 mg/kg/day 5 days a week), which is effective against both supraventricular and ventricular arrhythmias, does not affect myocardial contractility and has a mild peripheral vasodilator action. It is possible to use **sotalol** starting with minimal doses (initial dose 0.3 mg/kg/day 2 times a day to 2 mg/kg/day in 2–3 doses), given its pronounced beta-blocking properties.

Treatment and profylaxis of thromboembolism. Routine administration of antiplatelet agents is not recommended for children with chronic HF. Indications for anticoagulants use in children with HF include:

– artificial mechanical heart valves;

– primary pulmonary hypertension (PH) or stage 4 secondary PH in heart disease;

– significant dilatation of the heart chambers, abrupt decrease in myocardial contractility;

– atrial fibrillation;

– history of thromboembolism with EF less than 25 % (shortening fraction less than 15 %);

– signs of blood clots in the cavities of the heart according to ECHO-CG;

– infective endocarditis.

Heparin is used at a dose of 100–150 units/kg/day subcutaneously every 12 hours, from 1.5 to 4 weeks, under the control of activated partial thromboplastin time (with an extension of 1.5 times compared to the original).

Warfarin is given at initial dose 0.1–0.2 mg/kg/day, followed by INR control on days 2–4 and dose adjustment to maintain the target INR value of 2.0–3.0. Before initiation of treatment conditions associated with a high risk of bleeding (coagulopathies, ulcerative lesions of the gastrointestinal tract, etc.) should be ruled out. When a maintenance dose is determined continuous use of **warfarin** with regular monitoring of INR every 10–14 days is recommended. Typically, the maintenance dose is 0.09–0.33 mg/kg/day.

Low molecular weight heparins can also be used.

Treatment of anemia. When diagnosing HF and during subsequent follow-up, evaluation for anemia is recommended (hemoglobin, hematocrit, serum iron, ferritin, transferrin). If anemia is detected, iron supplements can be prescribed; if there is a significant deficiency, iron supplements are administered intravenously. If anemia persists after replenishing iron depot, erythropoietin medications are recommended. Main groups of drugs for the treatment of chronic HF with reduced and normal ejection fraction in children showed at Table 14.3.

Table 14.3

Main groups of drugs for the treatment of CHF with reduced and normal ejection fraction in children

Drug family	HF with reduced EF	HF with preserved or mildly decreased EF
Diuretics	Recommended for all patients with stages IIB–III HF, in case of congestion	Can be used for normalisation of volemic status (under the close monitoring of kidney function and BP). As antihypertensives
ACEIs	Indicated for all patients with grade IIa or higher chronic HF in the absence of specific contraindications	Routinely not indicated. Used in hypertension (under the close monitoring of kidney function and BP: risk of hypotension, renal dysfunction)
β-adrenergic agonist	Indicated for all patients with symptomatic and asymptomatic HF with LV systolic dysfunction in combination with ACEIs in the absence of contraindications	Routinely not indicated. Can be prescribed if necessary to control the ventricular rhythm in atrial fibrillation
Mineralocorticoid receptor antagonists	Indicated for systemic LV dysfunction	Not indicated
ARBs	In case of ACEIs intolerance	Can be used in patients in which ACEIs indicated but poorly tolerated
Digoxin	In patients with congestive HF (IIB and higher), stage HF IIA with persistence of symptoms despite sufficient pharmacotherapy	Not recommended if not otherwise specifically indicated (arrythmias, which need to controle the atrial rhythm)
Non-glycoside inotropic agents	Can be used as palliative treatment to relieve symptoms in patients with advanced HF, if transplantation not possible or as a bridge to transplantation	Not indicated. Phosphodiesterase inhibitors (milrinone) can be used if specific indications are present (pulmonary hypertension)

Surgical treatment:

1. Artificial pacemaker implantation — in 2nd or 3rd grade AV block associated with ventricular dysfunction.

2. Cardiac resynchronization therapy:

• In patients with EF < 35 %, complete left bundle branch block, in QRS>normal upper range, medication-resistent HF grades IIA and higher.

• Systemic right ventricle with EF < 35 %, complete right bundle branch block, in QRS > normal upper range, medication-resistent HF grades IIA and higher.

3. Implantable cardioverter/defibrillator:

• Children with HF who had cardiac arrest if the potentially correctable cause has not been identified.

• Children with DCMP and unexplained syncope and at least moderate LV dysfunction, EF < 35 %.

• Adolescents with hypertrofic cardiomyopathy, arithmogenic cardiomyopathy, familial cardiomyopathy, associated with sudden cardiac death (SCD), in presence of at least one factor of SCD. At younger ages — benefits and risks are assessed because of technical difficulties of the surgery.

• In case of congenital heart disease and LV disfunction.

• Non-compact myocardium and moderately decreased LVEF.

• Patients with tachycardia and Left Ventricular Assist Device.

4. Catheter ablation:

• In case of tachycardia-induced cardiomyopathy, if medicamental treatment is ineffective (in adolescence is the second-choice therapy).

• Frequent ventricular extrasistoles, cardiomyopathies of unknown origin if medicamental treatment is ineffective.

5. Ventricular Assist Device:

• As a bridge to transplantation in children who permanently need inotropic agents, with evidence of early reversable disfunction of at least one system of organs other than the heart.

• In children who are not eligible for transplantation — as long-term maintenance therapy.

Heart transplantation. Indications:

– advanced HF NYHA (Ross) IV class (III stage);

– severe concomittant arrythmia and thromboembolism;

– lack of effect from correct and long-term adequate drug therapy for HF;

– unfavourable prognosis for the next year of life.

In developed countries of Europe and the USA more than 500 heart transplantations are performed per year in patients under 17 years of age, of which about one fifth are performed in children under the age of one year. Survival rate in the first year after transplantation is 90 %. Five-year survival rate — 75 %.

CHAPTER 15
RHEUMATIC DISEASES

The **rheumatic diseases (collagen vascular** or **connective tissue diseases)** of childhood are characterized by autoimmunity and inflammation, which may be localized or generalized. The classic rheumatic diseases of children include juvenile idiopathic arthritis (JIA), formerly called *juvenile rheumatoid arthritis*, systemic lupus erythematosus (SLE), and juvenile dermatomyositis (JDM).

Vasculitis is a component of many rheumatic diseases. **Musculoskeletal pain syndromes** are a set of overlapping conditions characterized by poorly localized pain involving the extremities. Scleroderma, Behçet syndrome, and Sjögren syndrome are rare in childhood.

The differential diagnosis of rheumatological disorders typically includes infections, postinfectious processes, and malignancies.

History. The history can identify symptoms that reflect the source of the inflammation, including whether it is localized or systemic. Symptoms of systemic inflammation tend to be nonspecific. **Fever**, caused by cytokine release, can take many patterns. A hectic fever, without periodicity or pattern, is commonly foundin vasculitides such as Kawasaki disease but also occurs in children with underlying infection. Certain illnesses, such as systemic JIA, produce a patterned fever with regular temperature spikes once or twice a day. Other rheumatic illnesses cause low-grade fevers. Charting the child's fever pattern, particularly in the absence of antipyretics, is useful. **Rashes** occur in many forms, from evanescent to fixed and scarring. Other systemic symptoms (malaise, anorexia, weight loss, and fatigue) can vary from mild to debilitating.

Symptoms of localized inflammation vary depending on the involved site.

Arthritis, or inflammation of the synovium **(synovitis)**, leads to joint pain, swelling, and impaired ability to use the affected joint. Morning stiffness or gelling is commonly described. The child may be slow to arise in the morning or after long periods of inactivity and may have a limp. Children may refrain from usual activities and athletics. **Enthesitis** is inflammation at the insertion of a ligament to a bone. **Serositis**, inflammation of serosal lining such as pleuritis, pericarditis, or peritonitis, gives rise to chest pain, shortness of breath, or abdominal pain. **Myositis**, inflammation of the muscle, may lead to symptoms of muscle pain, weakness, or difficulty performing tasks of daily living. **Vasculitis**, inflammation of the blood vessels, leads to nonspecific symptoms of rash (petechiae, purpura) and edema when small vessels deep in the papillary dermis are involved; involvement of medium-sized vessels results in a circumscribed tender nodule.

Physical examination. A thorough history and physical examination is frequently sufficient to narrow the differential diagnosis and elicit the diagnosis.

• The child's overall appearance, evidence of growth failure, or failure to thrive may point to a significant underlying inflammatory disorder.

• The head and neck examination may show evidence of mucosal ulceration, seen in diseases such as SLE. The eye examination may show pupillary

irregularity and synechiae from uveitis or the nonpurulent conjunctivitis of Kawasaki disease. Diffuse lymphadenopathy may be found and is nonspecific.

• The respiratory and cardiac examinations may show pericardial or pleural friction rubs, indicating serositis.

• Splenomegaly or hepatomegaly raises suspicion of activation of the reticuloendothelial system that occurs in systemic JIA or SLE.

• The joint examination is crucial for the diagnosis of arthritis and may identify evidence of inflammation, such as joint swelling, effusion, tenderness, anderythema from increased blood flow. Joint contractures may be seen if the process is chronic. The joint lining, or synovium, may be thickened from chronic inflammation. Activation of epiphyseal growth plates in an area of arthritis can lead to localized bony proliferation and limb length discrepancies. Conversely, inflammation at sites of immature growth centers may lead to maldevelopment of bones, such as the carpals or tarsals, resulting in crowding, or the temporomandibular joints, resulting in micrognathia.

• A rash or evidence of underlying skin disorders, such as skin thickening from scleroderma or sclerodactyly, may be noted. Chronic Raynaud phenomenon may result in nail fold capillary changes, ulceration, or digital tuft wasting.

Common manifestations. The rheumatic diseases encompass a heterogeneous group of diseases with a shared underlying pathogenesis: disordered functioning of the immune system leading to inflammation directed against native proteins, with secondary increases in numbers of activated lymphocytes, inflammatory cytokines, and circulating antibodies. This antibody production can be nonspecific, or it can be targeted against specific native proteins, leading to subsequent disease manifestations. Although immune system hyperactivity may be self-limited, the hallmark of most rheumatic diseases of childhood is chronicity, or the perpetuation of the inflammatory process, which can lead to long-term disability.

Manifestations of Autoantibodies production:

– coombs-positive hemolytic anemia;

– immune neutropenia;

– immune thrombocytopenia;

– thrombosis (anticardiolipin, antiphospholipid, lupus anticoagulant);

– immune lymphopenia;

– antimitochondrial (primary biliary cirrhosis, SLE);

– antimicrosomal (chronic active hepatitis, SLE);

– antithyroid (thyroiditis, SLE);

– ANCA-cytoplasmic (granulomatosis with polyangiitis); ANCA-perinuclear (microscopic polyangiitis or other vasculitides); Anti-CCP (rheumatoid positive JIA).

Antinuclear antibodies to specific nuclear antigens and associated manifestations: Single-stranded DNA (nonspecific, indicates inflammation); Double-stranded DNA (SLE, renal disease); DNA-histone (drug-induced SLE); Sm (Smith) (SLE, renal, CNS); RNP (ribonucleoprotein) (SLE, Sjögren syndrome, scleroderma, polymyositis, MCTD); Ro (Robert: SSA) (SLE, neonatal lupus-

congenital heart block, Sjögren syndrome); La (Lane: SSB) (SLE, neonatal lupus [congenital heart block], Sjögren syndrome); Jo-1 (polymyositis, dermatomyositis); Scl-70 (systemic sclerosis); Centromere (CREST; limited scleroderma); PM-Scl (scleroderma, UCTD).

Initial diagnostic evaluation. Although rheumatic diseases sometimes present with nonspecific symptoms, especially early in the course, over time a characteristic set of symptoms and physical findings can be elicited. In conjunction with carefully chosen confirmatory laboratory tests, an appropriate differential diagnosis is made, and eventually the correct diagnosis and treatment plan is developed. Most rheumatological diagnoses are established by clinical findings and fulfillment of classification criteria. Laboratory testing should be judicious and based on a differential diagnosis rather than random screening in search of a diagnosis. Laboratory tests confirm clinical diagnoses rather than develop them.

Laboratory testing. Evidence of an underlying systemic inflammation may be indicated by elevated acute phase reactants, especially the ESR, but also the white blood cell count, platelet count, and C-reactive protein. The CBC may demonstrate a normochromic, normocytic anemia of chronic disease. These laboratory findings are nonspecific for any particular rheumatological diagnosis. Certain laboratory tests may help confirm a diagnosis, such as autoantibody production in SLE or muscle enzyme elevation in JDM, or identify increased risk for complications, such as uveitis in a patient with JIA with a positive antinuclear antibody.

Diagnostic imaging. Radiological studies should focus on areas of concern identified by history or physical examination. Radiography of joints in patients with arthritis on examination may be beneficial, but radiographic abnormalities may lag far behind the clinical examination. Tests with greater sensitivity, such as magnetic resonance imaging (MRI), may be useful when trying to differentiate between synovitis and traumatic soft tissue injury. MRI may also be useful to identify evidence of CNS involvement with SLE or evidence of myositis with JDM.

Juvenile Idiopathic Arthritis (JIA):

• *Acute febrile form* — episodic, evanescent pink macular rash, arthritis, hepatosplenomegaly, elevated white blood cell count (WBC), polyserositis.

• *Polyarticular form* — chronic pain and swelling of many joints, symmetrical distribution, low-grade fever, fatigue, rheumatoid nodules anemia, occasional iridocyclitis.

• *Pauciarticular form* — asymmetric chronic arthritis of a few joints, few systemic symptoms, painless synovitis, iridocyclitis in 30 % of patients.

• Rheumatoid factor positive in 15 % of patients, usually older children with polyarticular disease.

• Antinuclear antibody (ANA) often positive in pauciarticular disease with iridocyclitis.

• Joint fluid with normal glucose and 5000–60 000 neutrophils/μL.

Differential Diagnosis: traumatic joint injury; reactive arthritides; Henoch–Schönlein purpura, reactive arthritis, toxic synovitis of the hip, viral-associated

synovitis, rheumatic fever; acute joint infections; collagen-vascular disease — SLE, dermatomyositis. neoplastic disease — leukemia, lymphoma, neuroblastoma, bone and joint tumors.

Treatment:

– restore function and maintain joint mobility with physical therapy;

– NSAIDs;

– may use methotrexate, leflunomide, etanercept, infliximab in patients unresponsive to NSAIDs;

– iridocyclitis must be treated to prevent blindness. Local corticosteroid drops or ointment may be used. Unresponsive inflammation treated with methotrexate;

– in selected patients, use local corticosteroid in affected joints, synovectomy, joint replacement.

Iridocyclitis may develop insidiously in pauciarticular disease. Activity of eye disease does not correlate with arthritis. Routine ophthalmologic screening by slit lamp every 3 months is recommended.

Spondyloarthropathy: lower extremity arthritis, sacroiliitis, and low back pain; affects males over 10 years; inflammation of tendinous insertions characteristic; HLA-B27 positive in 80 % of patients, elevated ESR and CRP; episodic symptoms; acute uveitis may occur but not chronic iridocyclitis.

Differential diagnosis: other collagen-vascular disorders — JRA, SLE, dermatomyositis; in boys, ulcerative colitis may be associated with HLA-B27 positive ankylosing spondylitis; traumatic or overuse injury; acute infection or postinfectious arthropathy; leukemia, lymphoma, bone, or joint tumor; spine or disc disease.

Treatment: indomethacin and naproxen are more effective than salicylates; refractory cases may respond to methotrexate, etanercept, or infliximab; local corticosteroid injections contraindicated in Achilles tendonitis.

Pure spondyloarthropathy in childhood (in contrast to adults with the disorder) rarely progresses to joint destruction or ankylosis.

Enteropathic arthritis:

• Reactive arthritis usually of lower extremities several weeks after gastrointestinal infection with *Salmonella, Shigella, Yersinia* and *Campylobacter.*

• HLA-B27 individuals at greatest risk.

• May be associated with active inflammatory bowel disease (Crohn disease, ulcerative colitis, collagenous colitis) and celiac disease.

• Intestinal bypass surgery and intestinal bacterial overgrowth are risk factors.

• Other inflammatory symptoms — uveitis, stomatitis, hepatitis, erythema nodosum (Crohn disease), pyoderma gangrenosa (ulcerative colitis), urethritis.

Differential diagnosis: Behçet disease; Gonococcus and other bacterial joint infections; Lyme disease; JRA; Sarcoid.

Treatment: sulfasalazine and/or corticosteroids in patients with inflammatory bowel disease controls both GI disease and arthritis; gluten-free diet for patients with celiac disease; NSAIDs helpful in postinfection arthritis; Infliximab, methotrexate have been used; bacterial or parasitic pathogens in the stool should be treated.

Intestinal parasitic infestations also cause enteropathic arthritis. Check stools for Strongyloides stercoralis, Taenia saginata, Giardia lamblia, Ascaris lumbricoides, *and* Cryptosporidium *species when no obvious source is present.*

Pyogenic arthritis:

• Arises from adjacent osteomyelitis in infants (*S. aureus*).

• In older children arises during systemic infections with organisms having a predilection for joints (*S. aureus*, *Streptococcus* species, *Neisseria gonorrhea*, *Kingella kingae*, tuberculosis, *Salmonella* species).

• Risk increased in immunodeficiency, IV drug use, and sickle cell disease.

• Symptoms — fever, malaise, emesis, restricted movement.

• Joint aspiration for drainage and culture is key to diagnosis and therapy.

• Joint fluid WBC > 100,000/μL, ESR > 50.

• Joint X-rays are insensitive. WBC or gallium scan localizes infection.

Differential diagnosis: fever of unknown origin; noninfectious arthritis — inflammatory bowel disease, rheumatoid arthritis, Reiter syndrome, Lyme disease, rheumatic fever, systemic lupus, leukemia, drug reactions, autoimmune hepatitis; hemarthrosis with bleeding disorders.

Treatment: antibiotic therapy depends on culture and sensitivity testing of joint fluid; drainage of joint often needed for irrigation and debridement, especially the hip; tuberculous arthritis is usually spinal and requires drainage, immobilization, and sometimes casting for spine stabilization.

Infants are at higher risk of having multiple joint involvement with pyogenic arthritis than older children.

Systemic lupus erythematosus:

• Soluble immune complexes deposited in tissues attract lymphocytes and neutrophils. Complement fixation then produces inflammation in multiple systems — joints, serous linings, skin, kidneys, central nervous system, heart, lungs, liver.

• Fatigue, weight loss, fever, amenorrhea, joint pains, malar "butterfly" rash. Hypertension, encephalitis, renal disease, carditis also occur.

• ANA always positive in active, untreated disease. Leucopenia, anemia, thrombocytopenia, elevated ESR, elevated γ-globulin, Ag-AB complexes found in most cases.

• SLE is most common in girls 9–15 years.

• Early diagnosis, diagnosis of milder cases, more aggressive therapy has increased survival to 90 % at 5 years.

Differential diagnosis: rheumatic fever; rheumatoid arthritis; viral infections; collagen-vascular diseases and mixed connective tissue disease.

Treatment:

• Corticosteroids reduce morbidity and mortality from renal, cardiac, and CNS disease.

• Dermatitis, arthritis, and fatigue may respond to hydroxychloroquine.

• Pleuritic pain or arthritis treated with NSAIDs.

• Resistant cases may require azathioprine, cyclophosphamide, mycophenolate mofetil.

• Anticogulants may be required in patients with anticardiolopin or lupus anticoagulant antibodies to prevent or treat thrombotic events.

• Side effects of all therapies may be severe.

Elevated titers of anti-DNA antibody and depressed serum C3 accurately reflect activity of disease, especially renal, CNS, and skin disease.

Dermatomyositis:

• Vasculitis of small arteries and veins leads to intimal proliferation and thrombus formation in skin, muscle, kidney, retina, and GI tract with postinflammatory calcinosis.

• Pelvic and shoulder girdle weakness predominates. Dysphagia and dysphonia also occur due to esophageal and laryngeal motor weakness.

• 50 % have muscular pain.

• Purplish (heliotrope) rash on upper eyelids and extensor surfaces of knuckles, elbows, and knees progresses to scaling, atrophy, and calcinosis.

• Muscle enzyme levels elevated. ANA often positive. Electromyogram (EMG) shows myopathic change. Muscle biopsy indicated if characteristic skin rash is absent.

• Anti-Jo-1 antibodies associated with interstitial lung disease. Anti Mi-2 antibodies specific for dermatomyositis but present in only 25 % of cases.

Differential diagnosis: postviral myopathy; endocrine myopathies (Addison disease, hyperthyroid); other dermatologic conditions share some features — lichen planus, olymorphous light eruptions, seborrhea, SLE, psoriasis, contact and atopic dermatitis, drug eruption; other connective tissue disease and autoimmune diseases with myopathic component; muscular dystrophy, myasthenia gravis, mitochondrial myopathy, glycogen storage disease V and VII; rhabdomyolysis.

Treatment:

• Childhood dermatomyositis usually responds to corticosteroids.

• Methotrexate, IV immune globulin, cyclosporine in refractory cases.

• Physical therapy critical to prevent and treat muscle contractures.

• Nutritional supplementation with calories and protein may be helpful in maintaining quality of life.

• Calcium channel blockers of unproven efficacy in preventing calcinosis.

In adults, there is a sixfold increase in malignancy associated with dermatomyositis, mainly ovarian, gastric, and lymphoma. This is not the case in affected children.

Scleroderma:

• Localized disease (linear scleroderma and morphea) most common in childhood. Progressive systemic sclerosis rare.

• *Linear scleroderma* — streaks of indurated skin on extremities with slow progression to subcutaneous atrophy and joint contractures.

• *Morphea* — patchy induration and depigmentation.

• *Systemic sclerosis* — patients may have Raynaud phenomenon, fatigue, joint pain, contractures, dysphagia, abdominal pain, diarrhea, pulmonary fibrosis, hypertension, cardiac and renal failure.

• ANA usually positive. Anticollagen antibodies I–V usually negative. Skin biopsy sometimes needed to confirm diagnosis.

Differential diagnosis: other skin disorders (vitiligo, acrocyanosis, atopic dermatitis, pityriasis); dermatomyositis and other connective tissue disorders; Graft-versus-host disease; amyloidosis.

Treatment:

• Physical therapy to retain motor function and prevent contracture.

• Methotrexate and vitamin D analogues may limit extension of skin lesions especially in linear form.

• Systemic corticosteroids of questionable value in progressive systemic sclerosis. Penicillamine helpful in some cases.

• Specific therapy for hypertension. Calcium channel blockers for Raynaud phenomenon. Acid suppression for gastroesophageal reflux disease.

• Avoid skin trauma and sun exposure, protect extremities from cold, no smoking, avoid vasoconstrictors (pseudoephedrine), and avoid harsh skin cleansers and lotions.

A recent study found that 25 % of children with localized scleroderma had some extracutaneous symptoms including joint contractures (47 %), seizures and other neurologic symptoms (17 %), vascular insufficiency (9.3 %), and eye disease, especially uveitis (8.3 %).

Henoch–Schönlein purpura (IgA-associated vasculitis).

Etiology. Henoch-Schönlein purpura (HSP) is a vasculitis of unknown etiology characterized by inflammation of small blood vessels with leukocytic infiltration of tissue, hemorrhage, and ischemia. The immune complexes associated with HSP are predominantly composed of IgA, suggesting a hypersensitivity process.

Epidemiology. HSP is the most common systemic vasculitis of childhood and cause of *nonthrombocytopenic* purpura, with an incidence of 13 per 100,000 children. It occurs primarily in children 3–15 years of age, although it has been described inadults. HSP is slightly more common in boys than girls and occurs more frequently in the winter than in the summer months.

Clinical manifestations. HSP is characterized by rash, arthritis, and less frequently gastrointestinal or renal vasculitis. The hallmark of HSP is ***palpable purpura***, caused by small vessel inflammation in the skin, leading to extravasation of blood into the surrounding tissues, frequently with IgA deposition. The rash is classically found in dependent areas: below the waist, on the buttocks, and lower extremities. The rash can begin as small macules or urticarial lesions but rapidly progresses to purpura with areas of ecchymosis. The rash also can be accompanied by edema, particularly of the calves and dorsum of the feet, scalp, and scrotum or labia. HSP occasionally is associated with encephalopathy, pancreatitis, and orchitis.

Arthritis occurs in 80 % of patients with HSP and is most common in the lower extremities, particularly the ankles and knees. The arthritis is acute and very painful, with refusal to bear weight. Joint swelling can be confused with peripheral edema seen with the rash of HSP.

Gastrointestinal involvement occurs in about one half of affected children and most typically presents as mild to moderate crampy abdominal pain, thought to be due to small vessel involvement of the GI tract leading to ischemia. Less commonly, significant abdominal distention, bloody diarrhea, intussusception, or abdominal perforation occurs and requires emergent intervention. GI tract is typically seen during the acute phase of the illness, it may precede the onset of rash.

One third of children with HSP develop ***renal involvement***, which can be acute or chronic. Although renal involvement is mild in most cases, acute glomerulonephritis manifested by hematuria, hypertension, or acute renal failure can occur. Most cases of glomerulonephritis occur within the first few months of presentation, but rarely patients develop late renal disease, which ultimately can lead to chronic renal disease, including renal failure.

Laboratory and imaging studies. ESR, C-reactive protein, and WBC count are elevated in patients with HSP. The platelet count is the most important test, because HSP is characterized by nonthrombocytopenic purpura with a normal, or even high, platelet count, differentiating HSP from other causes of purpura that are associated with thrombocytopenia such as autoimmune thrombocytopenia, SLE, or leukemia. A urinalysis screens for evidence of hematuria. A serum blood urea nitrogen and creatinine should be obtained to evaluate renal function. Testing the stool for blood may identify evidence of gut ischemia. Any question of gut perforation requires radiological investigation.

Differential diagnosis. The diagnosis of HSP is based on the presence of two of four criteria: skin, joints, GI tract involvement, kidneys), which provides 87.1 % sensitivity and 87.7 % specificity for the disease. The differential diagnosis includes other systemic vasculitides and diseases associated with thrombocytopenic purpura, such as idiopathic thrombocytopenic purpura and leukemia.

Criteria definition:

– palpable purpura, raised, palpable hemorrhagic skin lesions in the absence of thrombocytopenia;

– bowel angina or Diffuse abdominal pain or the diagnosis of bowel ischemia;

– diagnostic biopsy: histological changes showing granulocytes in the walls of arterioles or venules; IgA deposits in vessel wall;

– pediatric age: less than 20 yr at onset of symptoms.

The diagnosis of Henoch–Schönlein purpura is based on the presence of 2 of four criteria.

Classification of systemic vasculitis. Antineutrofil cytoplasmic AB-associated vasculitis:

– granulomatosis with polyangiitis (GPA) (formerly known as Wegener granulomatosis);

– polyarteritis nodosa;

– eosinophilic granulomatosis with polyangiitis (formerly known as Churg–Strauss syndrome);

– microscopic polyangiitis (MPA).

Hypersensitivity syndromes:

– Henoch–Schönlein purpura;

– serum sickness (e.g., drug-related);

– vasculitis associated with infections.

Connective tissue disorders:

– systemic lupus erythematosus;

– dermatomyositis;

– juvenile idiopathic arthritis.

Giant cell arteritis:

– temporal arteritis;

– Takayasu arteritis.

Others: Behçet syndrome; Kawasaki disease; hypocomplementemic urticarial vasculitis.

Treatment. Therapy for HSP is supportive. A short-term course of NSAIDs can be administered for the acute arthritis. Systemic corticosteroids usually are reserved for children with GI and provide significant relief of abdominal pain. A typical dosing regimen is prednisone, 1 mg/kg/day for 1–2 weeks, followed by a taper schedule. Recurrence of abdominal pain as corticosteroids are weaned may necessitate a longer course of treatment. Acute nephritis typically is treated with corticosteroids but may require more aggressive immunosuppressive therapy (after kidney biopsy).

Complications. Most cases of HSP are monophasic, lasting 3–4 weeks and resolving completely. The rash can wax and wane, however, for 1 year after the initial episode of HSP. Parents should be warned regarding possible recurrences. The arthritis of HSP does not leave any permanent joint damage; it does not typically recur. Gastrointestinal involvement can lead to temporary abnormal peristalsis that poses a risk of intussusception, which may be followed by complete obstruction or infarction with bowel perforation. Any child with a recent history of HSP who presents with acute abdominal pain, obstipation, or diarrhea should be evaluated for intussusception. Renal involvement rarely may lead to renal failure.

Prognosis. The prognosis of HSP is favorable. Most children have complete resolution of the illness without any significant sequelae. HSP patients with renal disease (elevated blood urea nitrogen, persistent high-grade proteinuria) are at highest risk for long-term complications such as hypertension or renal insufficiency, particularly if the initial course was marked by significant nephritis. There is a long-term risk of progression to end-stage renal disease in less than 1 % of children with HSP. The rare patients who develop end-stage renal disease may require renal transplantation. HSP may recur in the transplanted kidney.

CHAPTER 16
KIDNEY DISEASES

16.1. INFECTION OF THE URINARY SYSTEM

Definition. *Infection of the urinary system (IUS)* — a non-specific inflammation in the urinary system without a clear indication of the level of damage (urinary tract, bladder, kidney parenchyma)

Urinary tract infection (UTI) is an inflammatory process in the urinary tract (in the pelvis, ureter, bladder, urethra) without lesions of the renal parenchyma.

Pyelonephritis — when UTI involved the kidney (renal parenchyma). Pyelonephritis is associated with fever and systemic involvement.

Cystitis is an inflammatory process in the urinary bladder, usually fever is absent or low grade.

Up to 50 % of children with a UTI have a structural abnormality of their urinary tract. UTI is important because if the upper tracts are affected it may damage the growing kidney by forming a scar, predisposing to hypertension and, if bilateral chronic renal failure.

Frequency and structure. 3 % of girls and 1 % of boys have a symptomatic UTI before the age of 11 years, and 50 % of them have a recurrence within a year. In the structure of the IUS pyelonephritis is approximately 60–65 %. The ratio of girls : boys — 8–9 : 1.

Factors contributing to the development of IUS in children. *Factors associated with macroorganism:*

1. Anatomical abnormalities of the urinary system and disturbance of the normal passage of urine.
2. Female gender. Inflammation of the external genitalia.
3. Immaturity of the immune defense, reducing antimicrobial immunity (neutrophil phagocytic activity, the level of secretory IgA, T-lymphocytes).
4. Factors leading to tubulointerstitial changes (crystals in the urine — oxalates, phosphates etc.).
5. Intestinal infections and disbiosis, constipation.

Factors associated with microorganism:

1. High “colonization” of potential uropathogenic microorganism (invasins, adhesins).
2. Resistance to antibacterial medications.
3. Products endotoxins.
4. Impedines (factors of persistence).
5. Metabolic features, L-shaped forms.
6. Atypical flora.

Etiology of UTI. Gram-negative family of Enterobacteriaceae: E. coli, Klebsiella, Proteus, Pseudomonas. The most common cause of acute pyelonephritis is E. coli — 90 %, which has a large set of pathogenicity factors.

Pyelonephritis. Pyelonephritis (PN) — microbial-inflammatory kidney disease (two or one kidney) with preferential localization of pathological process in the tubulointerstitial tissue and pyelo-caliceal lesions.

Classification of PN. PN is classified as primary or secondary, acute or chronic.

Primary pyelonephritis — when using modern methods of examination fails to identify the causes of distinct contributing fixing microorganisms in the tubulointerstitial tissue.

Secondary pyelonephritis — microbial-inflammatory process formed on the background of the anomalies or malformations of the urinary system — CAKUT (congenital abnormalities of the urinary tract) — vesico-urethral reflux (VUR), obstructive uropathy, megaureter, posterior urethral valves etc. Up to 50 % of children with UTI have a structural abnormality of their urinary tract — CAKUT.

UTI is important because — if the upper tracts are affected, it may damage the growing kidney by forming scars, predisposing to arterial hypertension, if bilateral — to chronic kidney disease (CRD).

Acute PN is classified according periods: 1) active manifestations; 2) regression of symptoms; 3) complete clinical and laboratory remission.

Chronic PN: the gold standard investigation for the detection of renal cortical scarring is static renal scintigraphy with DMSA. Periods: 1) relapse; 2) partial clinical and laboratory remission; 3) complete clinical and laboratory remission.

Assessment of renal function: 1) normal; 2) impaired of the partial kidney function; 3) CKD.

Pathogenesis. Upward path (80 %) of urinary tract infection and/or renal parenchyma-pyelonephritis is typical. Fixation and colonization of uropathogens with damage of the tubules and interstitial kidney tissue, clinical and laboratory features of pyelonephritis. Under the influence of appropriate treatment sanitation tissue from microorganisms occurs, restoration of function of the tubules and recovery. The formation conditions (from the microorganism and/or bacterial uropathogens) for persistent infection and chronic microbial-inflammatory processes possible.

Clinical features of UTI. Presentation of UTI varies with age:

In the newborn — symptoms are non-specific and include fever, poor feeding, vomiting and jaundice, septicemia may develop rapidly.

The classical symptoms of dysuria, frequency and loin pain become more common with increasing age.

Dysuria without a fever is often due to vulvitis in girls or balanitis in uncircumcised boys rather than a UTI.

Clinical features:

1. ***Intoxication syndrome.*** The temperature rises to febrile digits, paleness, weakness, drowsiness, fatigue, lack of appetite. In infants — refusal of feeding, fever, vomiting, diarrhea — a mask of intestinal infection or acute respiratory tract infection.

2. ***Pain or abdominal syndrome.*** In infants — the equivalent of pain could be cry, refusal of feeding, anxiety. In infants and preschool children, the pain is localized around the umbilical area due to irradiation in the solar plexus. In schoolchildren and adolescents pain is marked in the lumbar region.

3. ***Urinary syndrome*** — cloudy urine, proteinuria up 0.1 to 1–1.5 g/l, bacterial leucocyturia, decline in the relative density of urine, bacteriuria, casts.

4. ***Dysuria syndrome*** — rapid frequent (pollakiuria), painful (strangury) micturition, incontinence indicate the presence of lower urinary tract infections and urinogenic path of infections. Voiding of micturition in pyelonephritis is due to involvement in the pathological process of the bladder.

How to diagnose UTI:

1. ***CBC*** — leukocytosis with neutrophil shifts, increased ESR, could be anemia.

2. ***Urinalysis*** — leukocyturia, proteinuria, epithelium, casts.

3. ***Biochemical analysis of blood*** (urea, creatinine, electrolytes, increased CRP).

4. ***Urine culture flora*** and sensitivity/resistance to antibiotics (E. coli more than 10^5).

5. Biochemistry of urine: 24 hours urinary protein excretion, salts.

6. Immune system investigation.

Additional methods — investigation on chlamydia, mycoplasma (PCR), fungi, Mycobacterium tuberculosis (urine culture, methods of rapid diagnosis) when prolonged course of UTI and there is no effect on the "traditional" therapy, or positive family history.

Additional methods also include:

1. *Ultrasound:* helps to reveal structural renal disease, renal agenesis, vesico-urethral reflux (VUR), cysts etc (Fig. 16.1).

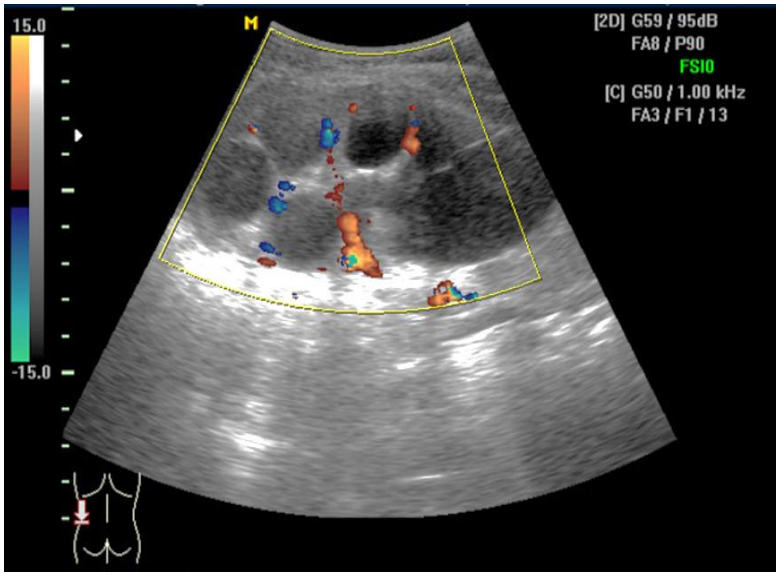


Fig. 16.1. Hydronephrotic transformation of the left kidney. Severe dilatation of pelvis and calyces. Doppler: reduced renal blood flow

2. *Micturition urography.* Voiding (Micturition) cystourethrography (MCUG) — assessment of anatomic and functional state of the bladder, urethra, reveals reflux (reverse flow urine during micturition).

Gold standard for diagnostic of vesico-urethral reflux. VUR divided into primary (developmental anomaly of the vesico-urethral junction) or secondary (associated with bladder pathology) (Fig. 16.2–16.5). Indications for MCUG — when hydronephrosis is bilateral, present in a solitary kidney or associated with ureteric dilatation. There are 5 grades of VUR (Fig. 16.2). Different types of VUR are shown on the Fig. 16.3–16.5.

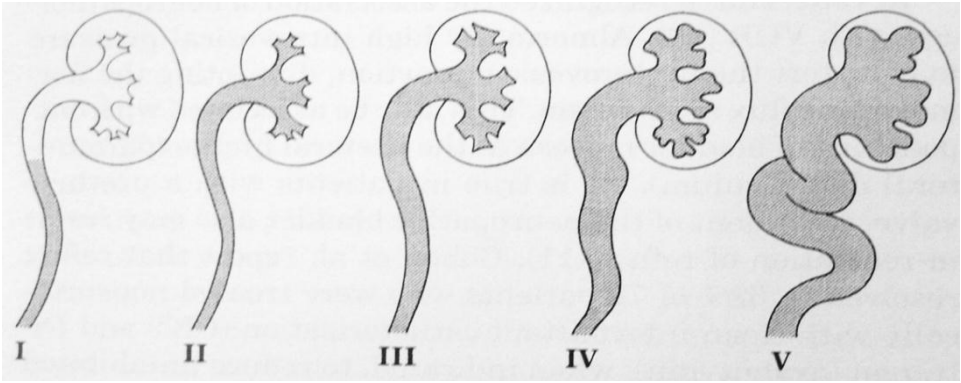


Fig. 16.2. Five grades of vesico-urethral reflux

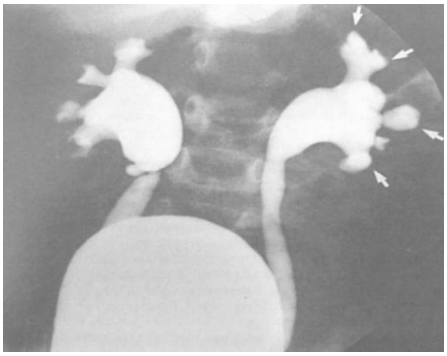


Fig. 16.3. Bilateral vesico-urethral reflux, stage V. Bilateral severe dilatation of pelvis, calyces, ureters

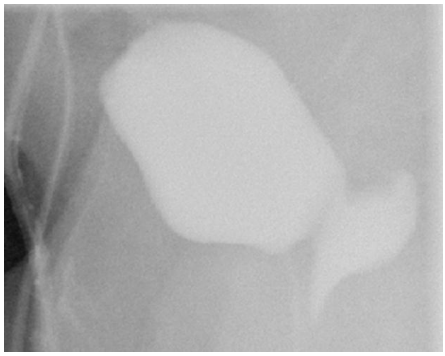


Fig. 16.4. Micturition with reflux in the vagina

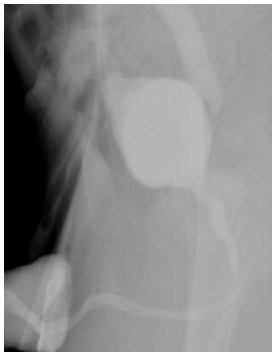


Fig. 16.5. Micturition with reflux in the foreskin

3. *Intravenous (IV) or Excretory urography reveals.* Anatomical features of the structure of the kidneys, their status, mobility, shape, size, structure and condition of the renal pelvis system, ureters, and bladder.

Indications for IV urography:

– suspicion of malformation of the urinary tract (Fig. 16.6, 16.7);
– obstructive uropathy, identified by ultrasound and radionuclide study;
– renal colic;
– recurrent abdominal pain of unknown etiology;
– voiding dysfunction.

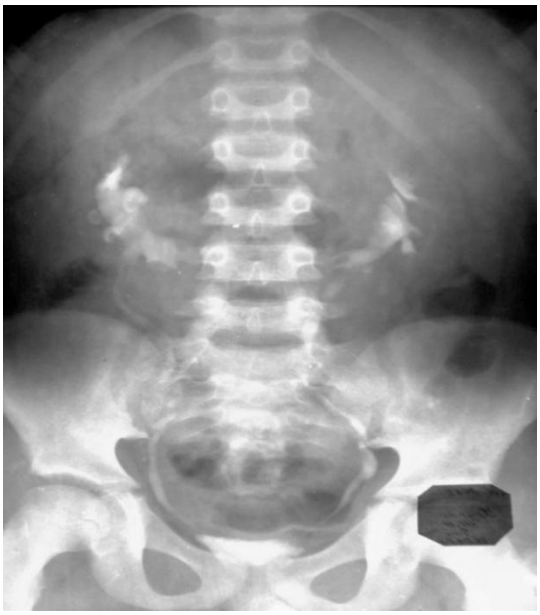


Fig. 16.6. Shoes-shoe kidney revealed by IV urography

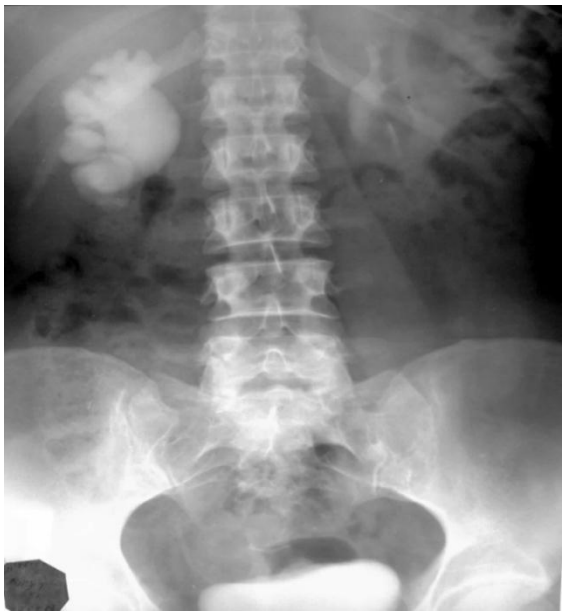


Fig. 16.7. Hydronephrotic transformation of the right kidney revealed by IV urography

Contraindications to the IV Urography:

– inflammatory diseases of the kidney in acute phase;

– high level of creatinine and urea in the blood;

– low urinary relative density;

– allergic reaction to the X-ray solution.

4. ***Renal scintigraphy. Indications for static kidney scan Ts99/DMSA:***

– anomalies relationship, hypoplastic kidney, polycystic disease, destructive lesion of the parenchyma, volume formation;

– detection of renal scarring tissue — the "gold standard" for the diagnostics of chronic pyelonephritis.

DMSA is taken up though not excreted by (predominately proximal) renal tubular cells (Fig. 16.8). The image produced is that of functioning renal cortical mass and technique is the gold standard investigation for the detection of renal cortical scarring (Fig. 16.8, 16.9). May also be helpful in identifying ectopic kidneys are confirming non-function. Information is also generated about differential renal function (the relative contribution of each kidney to total renal function).

Many children diagnosed with renal scarring may in fact have congenitally dysplastic kidneys.

Dynamic renography (the DTPA or MAG3 scan) is used to detect the presence and site of urinary tract obstruction. Isotope is injected with furosemide.

5. ***Cystoscopy.***

6. ***Computer scanning.***

7. ***Magnetic resonance imaging.***

8. Urologist/gynecologist — for diagnosis of penis (foreskin) or vulvitis (vaginitis) external genital infection.

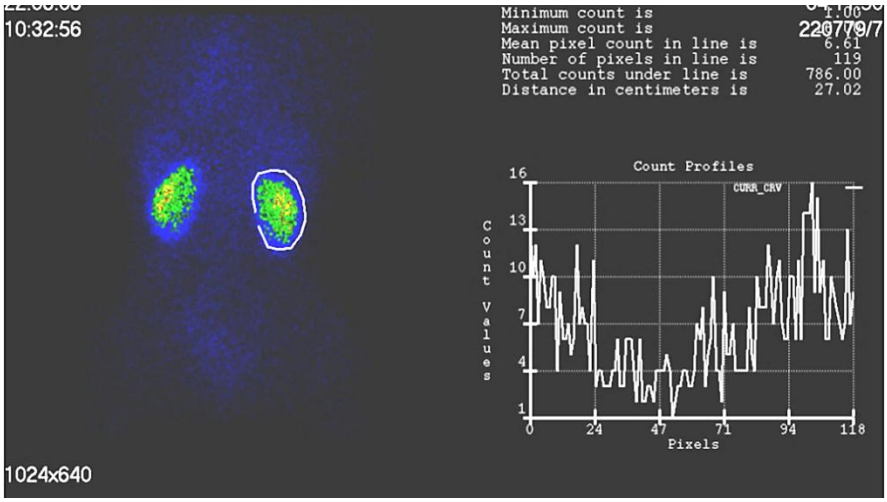


Fig. 16.8. Normal uptake of Ts 99

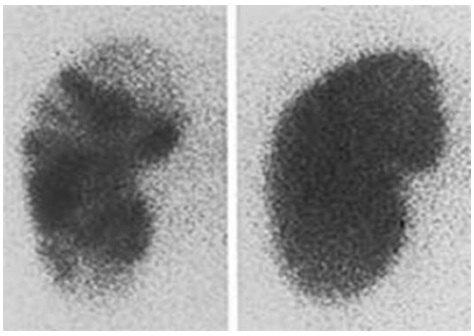


Fig. 16.9. Renal scars of the left kidney revealed by scan

Criteria for diagnosis of PN:

1. Systemic symptoms of intoxication.
2. Inflammatory reaction of blood: leukocytosis, neutrofilic shift, increased ESR, CRP.
3. Proteinuria up to 1 g/l in combination with leukocyturia and bacteriuria.
4. Reduction of tubular functions.
5. Changes of pyelo-caliceal system with ultrasound and X-ray examinations.

CRP is usually used as a diagnostic marker — more than 20 units are typical for pyelonephritis.

Cystitis. ***Cystitis*** — inflammation of the mucous of the bladder, accompanied by a violation of its functions.

Classification:

1. On etiology: infectious, radioactive, medications, postoperative.
2. According to the cystoscopy changes: diffuse, focal.
3. Acute, chronic (cystoscopy).

Clinical symptoms: frequent, painful micturition, painful palpation of the bladder, no signs of intoxication.

Urinary syndrome: white blood cells, desquamated epithelium; bacteria.

Laboratory data: neutrophils in the urine; increased number of squamous cells; terminal hematuria; proteinuria small, less than 0.1 g/l).

Therapy of UTI:

1. Regime (bed in acute PN, frequent emptying of the bladder, personal hygiene).
2. Diet (lacto-vegetarian).
3. High amount of liquids.
4. Infusion therapy if indicated (0.9 % sodium chloride, 5 % glucose).
5. Etiologic treatment (antibiotics).
6. Herbal medicine.
7. Physiotherapy.
8. Prophylaxis treatment if indicated.

Etiologic treatment: antibacterial medications, there are 3 groups of choice:

1. Protected penicillin (PP) or
2. Cephalosporin II or III generation or
3. Aminoglycosides.

Among ***Protected Penicillin's***:

1) amoxicillin + clavulanic acid (Augmentin, amoksiklav, flemoklav) — dosage 20–40 mg/kg/day;
2) ampicillin + sulbactam;
3) piperacillin + tazobactam (tazocin);
4) ticarcillin + clavulanic acid (Timentin).

Cephalosporin's generations II or III are highly active against E. coli.

Generation IV (Ceftaredim and cefepime) is advisable to appoint during a severe course of pyelonephritis and confirmed etiological role of Pseudomonas aeruginosa.

Prescription of the 1st generation of cephalosporin is impractical because they have insufficient activity against gram-negative flora.

The presence of oral and parenteral forms of the antibiotics can be used for one group of sequential therapy (start intravenous or intramuscular for 3–5–7 days and continue orally for the total duration of 10–14 days).

Aminoglycosides — Netilmicin (netromycin); Amikacin is the drug of choice in the treatment of PN in children caused by K. pneumoniae, Pseudomonas aer., Enterobacter spp.

Prescription in acute exacerbation of chronic PN Nitrofurans, Nitroxoline, Biseptolum, Nalidixic acid is impractical due to the fact that these drugs do not provide sanitation contribute to the renal parenchyma and chronic process.

Fluoroquinolones (ciprofloxacin, ofloxacin, etc.) in children is generally not used (before age 17–18 y.o.) (because of severe side effects on cartilages in experiment on young animals). An exception for fluoroquinolones is severe course of the disease with the release of uropathogens multiresistant to other antibiotics.

Cystitis or pyelonephritis with not severe course — use oral forms. In moderate and severe forms — sequential therapy — parenteral administration of AB drug (IV or Intra / muscular) for 5–7 days followed by oral administration of the same AB in the next 7–10 days, for example: Augmentin IV → Augmentin

orally; cefuroxime IV → cefuroxime (Zinnat) orally; cefamandole IV → oral cefaclor; ceftriaxone IV → ceftibuten (cedeks) orally.

The duration of AB therapy for treatment of pyelonephritis is 10–14 days, for cystitis — 5–7 days.

Medications for treatment of cystitis:

1. Augmentin (amoxicillin + clavulanic acide) in tabs or suspension — 20–40 mg/kg/day.
2. Nitrofurantoin in capsules 0.025 g and 0.05 g — 5–7 mg/kg/day.
3. Nalidixic acide in tabs 0.25 g and 0.5 g — 30–60 mg/kg/day.
4. Co-trimoxazole in tabs 0.12 g or 0.48 g, in suspension 240 mg/5 ml — dosage 6 mg/kg/day of trimethoprim.
5. Monural (fosfomycin trometamol). Powder 3 grams, children 1–2 gr. 1 time/day.

Indications and duration for prophylaxis therapy are presented in the Table 16.1.

Table 16.1

Prophylaxis (anti-recurrent) therapy: indications and duration

Indications	Duration
Children under 2 years after acute PN	During 2 months before micturition cystography
Obstructive uropathy	Long-time, before surgical correction
Vesico-urethral reflux	The duration of prophylaxis is long-term preservation of reflux
Relapsing UTI (3 or more relapses within a 1 year)	6 months – 1 year

Medications for prophylaxis (anti-recurrent) therapy. Use uroseptic medications in sub inhibitors doses (20 % of the therapeutic dose) overnight (Table 16.2).

Table 16.2

Medication	Dosage
Nitrofurantoin	1–2 mg/kg/1 time overnight
Co-trimoxazole	1–-2 mg/kg of trimethoprim 1 time overnight
Nalidixic acide	5–10 mg/kg/1 time overnight
Nitroxoline	3–5 mg/kg/1 time overnight

Additional therapy: correction of intestinal microflora (normal daily stool), vitamins A, E, C); phytotherapy; physiotherapy during the period of clinical and laboratory remission.

16.2. GLOMERULAR DISEASES (GLOMERULOPATHIES)

Definition. Glomerulopathies form the heterogeneous group of kidney diseases with initial glomerular lesion. The secondary involvement of other components of renal tissue (tubules, vessels or interstitium) may be observed later on. There is a huge variety of causes, pathogenetic patterns, clinical presentations

and morphological features, as well as course (natural history) and outcome in the group of glomerulopathies.

Classification. All glomerulopathies are divided into:

– ***primary or idiopathic*** — glomerular lesion occurs primarily in absence of any systemic condition, which may cause kidney disease;

– ***secondary*** — glomerular lesion is a result of systemic illness (more often systemic disease of connective tissue, for example systemic lupus erythematosus, systemic vasculitis, etc.).

According to the disease course glomerulopathy can be:

– ***acute*** (e.g. endocapillary glomerulonephritis (GN));

– ***chronic*** (e.g. membranoproliferative GN, IgA nephropathy, focal segmental glomerulosclerosis, etc.);

– ***rapidly progressive*** (extracapillary GN).

There are clinical classifications of glomerulopathies, which are based on clinical presentation and course of the disease, and morphological one, which is considered to be a "gold standard", predominantly in case of chronic illness. However, not always morphological diagnostics is needed (especially in case of acute illness or hormone sensitive nephrotic syndrome). That is why both classifications, based on clinical manifestations and morphological diagnosis, remain of importance in clinical practice.

Often there isn't strong correlation between the clinical pattern and morphological changes found on kidney biopsy. However, ***some clinical patterns may be designated***:

1. Nephritic syndrome, which is the most characteristic for acute poststreptococcal or post infectious (endocapillary) GN.

2. Nephrotic syndrome, which in young children is predominantly due to minimal changes disease.

3. Rapidly progressive GN, with nephrotic syndrome with hematuria and/or hypertension at presentation is characteristic for crescentic (extracapillary) GN.

4. Recurrent macroscopic hematuria (with or without proteinuria), which is often a sign of Berge's nephropathy.

According to the type of initial glomerular lesion glomerulopathies can be (Fig. 16.10).

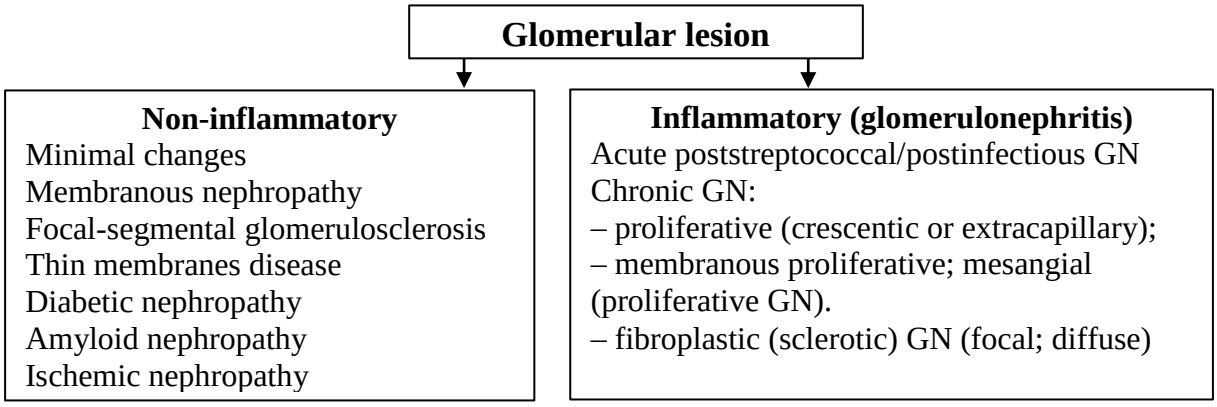


Fig. 16.10. Types of glomerular lesions

Non-inflammatory glomerulopathies are characterized by parenchymatous dystrophy or/and changes of glomerular basement membrane (GBM), disorganization or sclerosis of mesangial matrix. No or minimal signs of proliferation or glomerular infiltration can be observed. These are caused by, in majority of cases, non immune-mediated damage, for example, amyloid deposition.

In case of immune injury (in minimal changes nephrotic syndrome), the attack is targeted at visceral epithelial cells, which are called podocytes, and the type of lesion is called podocytopathy.

In inflammatory glomerulopathies (true glomerulonephritis) immune attack is targeted at endothelial cells, mesangium, epi-, peri- and intramembranous structures. Classical signs of inflammation are observed: infiltration, proliferation, exudation, alteration and function impairment. Immune mediated injury involves immunoglobulin's deposition and inflammatory cells migration from blood flow in glomerulus, these both may be resulting in direct damage to glomerular cells and in inflammatory response of residential glomerular cells, mesangial proliferation and hyperproduction of mesangial matrix, thickening of glomerular basement membrane, proliferation of parietal epithelial cells with crescents formation.

Analysis of clinical manifestations in conjunction with morphological glomerular and tubulointerstitial lesions gives the most informative data concerning likelihood of disease progression and response to treatment.

For proper treatment and illness progression monitoring, morphological verification (kidney biopsy) should be considered.

Acute glomerulonephritis. Acute post-streptococcal or post-infectious GN (APGN) is an acute immune kidney inflammation with predominant glomerular lesion. Exudation and endocapillary proliferation are observed in glomerulus on kidney biopsy. Up to 0.1–0.2 % of all kidney diseases in children. Children of age 5–12 are mostly affected, males : females ratio 2 : 1.

Etiology:

– throat (tonsillitis, scarlet fever) or skin (impetigo, streptodermia) infections, caused by streptococci ("nephritogenous", β-hemolytic, group A, types 1, 2, 4, 12, 49, 55 et al.);

– other infections: viral (flu et al.), tuberculosis, salmonella typhy infection etc.;

– vaccination (more often revaccinations).

In Belarus seasonality is observed — occurrence rises in February–March and October–November.

Predisposing factors: familial history; familial sensibility to streptococci; chronic infections, hypovitaminosis; cold weather.

Pathogenesis. APGN is a typical immune complex (IC) disease:

– Streptococcal toxins and enzymes (streptolysine, hyaluronidase, streptokinase et al.) initiate specific antibodies (AB) production, followed by circulating immune complexes formation;

– circulating immune complexes are deposited in glomeruli capillary walls, causing the pro-infectious factors production by glomerular cells;

– endocapillary proliferation — immune cells, including neutrophils, concentrate in glomerulus, predominantly endocapillary. Blood flow in affected capillary loops slows, permeability of glomerular basement membrane increases for erythrocytes and protein;

– antigenic mimicry between streptococcal and glomerular antigens (AG) is of particular importance in the pathogenesis of APGN.

Pathology. Kidneys look enlarged, with capsule easy to take off. Subcapsular hematomas' may be observed. Exudation and cells proliferation in glomeruli on light microscopy showed on Fig. 16.11 (hematoxylin-eosin stain) and Fig. 16.12 (silver stain).

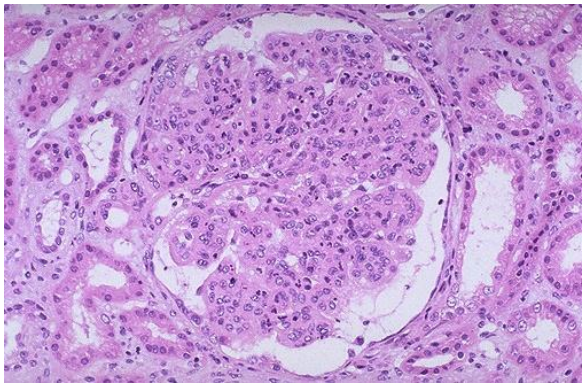


Fig. 16.11. Exudation and intracapillary proliferation in APGN. Numerous neutrophils can be seen in glomerulus (arrows). H&E stain, ×400

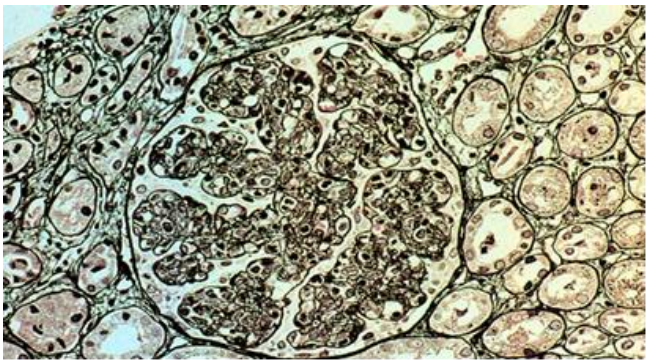


Fig. 16.12. Exudation and intracapillary proliferation in APGN, silver stain ×400

On electron microscopy, immunofluorescence or immunohistochemistry IgG or IgM deposits, C3 complement deposits are revealed (Fig. 16.13).

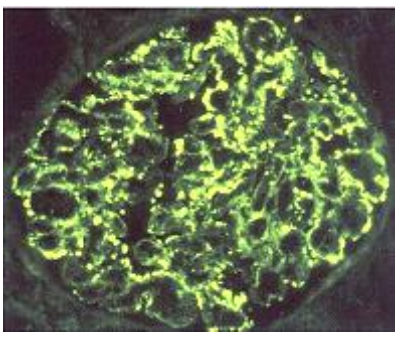


Fig. 16.13. Positivity for IgG on immunofluorescence

Duration of the changes in case of acute nephritis is up to 6 months.

Clinical presentation. Nephritic syndrome is most common. Less frequently nephrotic syndrome, nephrotic syndrome with hematuria and hypertension or asymptomatic changes in urinalyses (hematuria, proteinuria) may be observed. Natural history includes streptococcal infection 1–3 weeks prior to the disease onset. Child feels bad, becomes sleepy, complains of nausea, headaches, lack of appetite. Febrile or subfebrile fever may be observed. Sometimes complaints of stomachache or lower back pain can be present. Patient looks pale, puffy eyes (swollen eyelids), edema or pastosity of face and lower limbs can be found on clinical examination. Arterial hypertension, tachy- or bradycardia are present in majority of cases.

Patient develops **acute nephritic syndrome**, which includes:

– moderate proteinuria (1–2 g/l);

– hematuria: macrohematuria (when urine changes its color and becomes brown, reddish, coca-cola or beer like) or microhematuria (when urine discoloration is absent);

– urinary casts (hyaline, granular);

– decreased diuresis;

– arterial hypertension;

– edema.

Laboratory findings:

• Blood tests: anemia, leukocytosis, neutrophilic shift, eosinophils. Erythrocyte sedimentation rate (ESR) is increased.

• Mild decrease in serum albumin, mild increase in α2 и γ-globulins.

• High ASLO blood test in case of poststreptococcal GN.

• Decreased C3 component of complement.

In typical cases kidney biopsy is not necessary.

Morphological examination should be considered if:

– progressive course with high proteinuria, hematuria, increscent azotemia (urea, creatinine) and oliguria is observed (differential diagnosis with crescentic GN);

– systemic disease is suspected (lupus erythematosus, hemorrhagic vasculitis);

– C3-hypocomplementemia persists over 2–3 months;

– lack of effect of prior treatment;

– disease progression; persistent hypertension, lack of response to hypotensive treatment.

Treatment. General principles include bed regimen, diet and symptomatic therapy. Medications are prescribed according to severity and manifestation of disease, and its cause.

Patients should stay in bed while edematous. Children are gradually allowed to leave bed when feeling better and after arterial hypertension is being controlled. Diet should be low in salt and spices, low-caffeine. Fluid is given according to previous-day diuresis. Extrarenal fluid losses should be considered. Upon

normalization of blood pressure and resolving of edema salt intake can gradually be increased starting at 1 g/day. Protein intake should be lowered until normalization of blood creatinine and urea levels, as well as glomerular filtration rate is achieved.

Pharmacotherapy:

1. Antibiotics are used in case of streptococcal infection. Aminopenicillines, cephalosporins of 1st generation are generally used. Macrolides can be chosen in case of allergy to beta-lactam antibiotics.

2. Symptomatic treatment (Table 16.3):

– hypotensive (calcium-channel blockers, β-blockers);

– diuretics;

– in case of signs of hypercoagulation — anti-platelets (dipyridamole, pentoxiphylline).

Table 16.3

Pharmacotherapy of APGN

Groups	Drug	Dosage
Calcium-channel blockers	Amlodipine	0.06–0.2 mg/kg/day
	Nifedipine	0.25–0.5 mg/kg/day
β-blockers	Metoprolole	1–2 mg/kg/day
Diuretics	Furosemide	1–2 mg/kg qd or bid
Anti-platelets	Dipyridamole	5–7 mg/kg/day

Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers are used with caution because of risk of hyperkalemia (high potassium blood level).

Prognosis for survival and recovery of kidney function is favorable.

Rapidly progressive GN. Rapidly progressive GN (RPGN, crescentic GN, extracapillary proliferative GN) is a type of nephritic syndrome, which is accompanied by glomeruli crescent formation seen on a kidney biopsy (in over than 50 % of affected glomeruli) and characterized clinically by a rapid loss of renal function (decrease of glomerular filtration rate (GFR) of at least 50 % over a short period). This form of GN is relatively rear, especially in children. It is also called fulminant GN due to highly aggressive course comparing to APGN and rapid progression of renal function deterioration.

Several groups of RPGN are described according to pathogenesis:

– anti-GBM antibody disease (Goodpasture's syndrome, if lung and kidney involvement are present; anti-GBM disease if only kidneys are involved);

– immune complex disease (lupus nephritis, post infectious, systemic vasculitis, lupus et al.);

– pauci immune disease (Granulomatosis with polyangiitis (Wegener's granulomatosis), microscopic polyangiitis (MPA), renal-limited necrotizing crescentic glomerulonephritis (NCGN), Churg-Strauss syndrome). This group is characterized by absence of glomerular immune deposits on immunofluorescence. The vast majority of patients have circulating antineutrophil cytoplasmic antibodies (ANCAs).

Pathology. Crescents in over 50 % of glomeruli are seen on kidney biopsy (Fig. 16.14, 16.15).

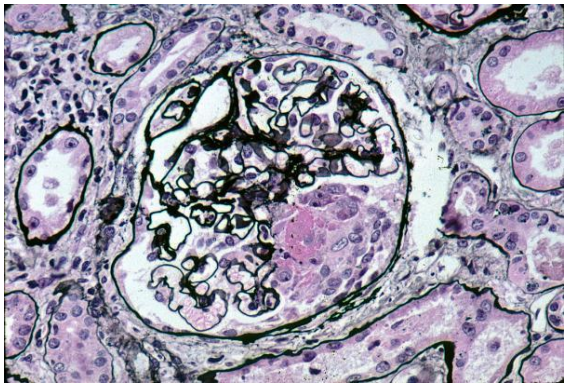


Fig. 16.14. Cellular crescent. H&E stain, ×400

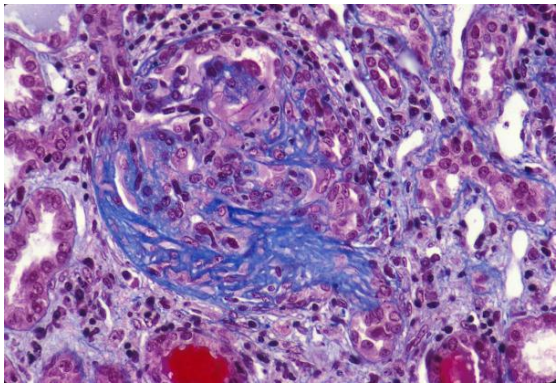


Fig. 16.15. Fibrous crescent. H&E stain, ×400

Presentation depends on type of RPGN, usually includes nephritic syndrome, or nephrotic syndrome with hematuria and hypertension. Patients are usually in severe condition. Symptoms include:

– severe paleness, severe arterial hypertension, edema, oliguria;

– proteinuria, macrohematuria, urine casts (hyaline, granular), hypostenuria;

– anemia;

– low serum protein;

– rapid decrease of GFR (more than 50 % over few days or weeks), accompanied by increase in serum creatinine and urea levels.

Diagnosis is made by results of morphological examination of kidney biopsy specimen, where over 50 % of glomeruli are found to be present with crescents.

Treatment: aggressive immunosuppressive treatment is prescribed as soon as possible upon diagnosis is made.

Pulse-therapy: methylprednisolone (30 mg/kg/day, max single dose 1000 mg) or cyclophosphamide (single dose of 500–750 mg/m^2) — 3 to 5 pulses synchronized with *plasmapheresis* (1 day — methylprednisolone "pulse", followed by plasmapheresis on the next day to remove pro inflammatory immune mediators, cytokines, antibodies).

Maintenance therapy includes *immunosuppressive therapy orally* (steroid 2 mg/kg/day + cytostatic agent) combined with anticoagulation therapy (heparin, low-molecular weight heparin, aspirin) and anti-platelets (dipyridamole, pentoxiphylline).

In most severe cases dialysis is needed (hemodialysis, hemodiafiltration et al.).

Prognosis is poor for renal survival.

Chronic GN. Chronic GN — heterogeneous group of chronic glomerulopathies, with predominant immune complex mechanism of glomerular lesion, different clinical and morphological presentation, course and outcome.

Etiology: rarely develops as evolution of APGN. More common is a primary chronic course, i.e. without acute attack.

Four main groups of etiological factors are described:

– infections (bacterial, viral);

– mechanic and physical factors (traumas, cold weather, sun exposure);

– allergic toxins (food, chemical substances, drug abuse, medicines);

– vaccines.

Morphological classification.

Not proliferative (non inflammatory):

– minimal changes nephropathy;

– membranous nephropathy;

– focal-segmental glomerulosclerosis.

Proliferative (inflammatory):

– mesangial proliferative GN;

– mesangiocapillary GN;

– fibroplastic GN.

Minimal changes nephropathy (lipoid nephrosis, small foot processes of podocytes disease, idiopathic nephrotic syndrome, minimal changes nephrotic syndrome) — the leading cause of nephrotic syndrome in childhood.

Boys to girls ratio is 2 : 1.

Onset after upper respiratory tract infection, allergic reaction is common. Atopy can be predisposing factor. Nephrotic syndrome is usually steroid sensitive, arterial hypertension and hematuria are not characteristic for this condition. Although there can be relapses of nephrotic syndrome, kidney function however remains normal for a long time. In general, prognosis is favorable.

Morphology. *Light microscopy:* glomeruli appear normal (Fig. 16.16).

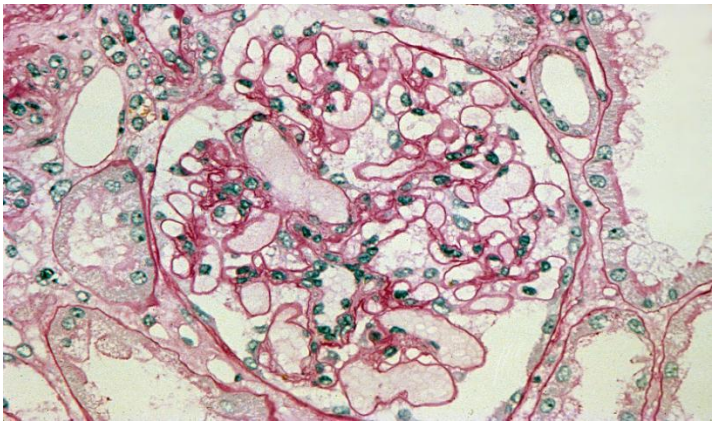


Fig. 16.16. Light microscopy — normal glomerulus. H&E stain, ×400

Immunofluorescence: absence of immune deposits.

Electron microscopy: normal podocytes (Fig. 16.17, *a*) and diffuse effacement of podocytes foot processes (Fig. 16.17, *b*).

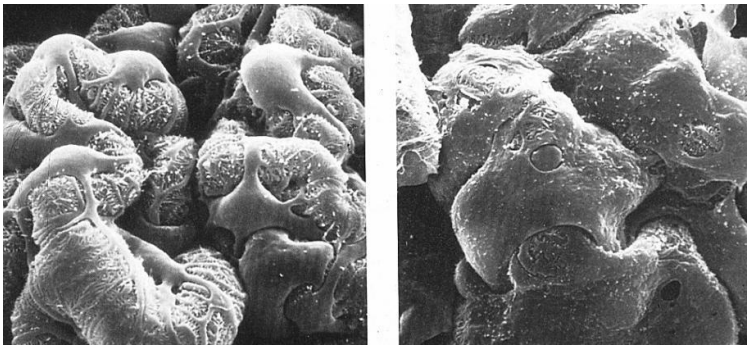
Nephrotic syndrome — includes 4 main criteria:

– massive proteinuria, mainly albuminuria (over 50 mg/kg/day);

– low serum protein level (low albumin, increased α2- and decreased γ-globulins);

– high blood cholesterol level (> 5.2 mmol/l);

– severe edema (the consequence of reduced oncotic pressure due to low serum protein).



a ***b***

Fig. 16.17. Electron microscopy:
a — normal podocytes foot processes; *b* — diffuse effacement of podocytes foot processes

Pathology:

– minimal changes nephrotic syndrome;

– focal-segmental glomerulosclerosis;

– membranous GN;

– mesangiocapillary GN.

Treatment:

1. *Standard protocol* — oral prednisolone 60 mg/m^2/24 h (2 mg/kg, max 80 mg per day), for 4 weeks (up to 6 weeks), then switch to alternate-day administration:

60 mg/m^2/48 h — 8 weeks;
45 mg/m^2/48 h —2 weeks;
30 mg/m^2/48 h — 2 weeks;
15 mg/m^2/48 h — 2 weeks.

Treatment duration from 4 to 5 months.

2. Proton pump inhibitors — omeprazole 1 mg/kg/day for children older than 5 years, almagel, gefal — for younger children.

3. Calcium, vit. D (osteoporosis prophylaxis).

4. Albumin i.v. (if serum albumin level is lower 20 g/l and or ascites is present).

5. Heparin 100–200 IU/kg, aspirin for hypercoagulation correction.

6. Immunoglobulin i.v. in case of intercurrent infection.

Nephrotic syndrome can be divided into groups according to response to steroids:

1. *Steroid sensitive* — complete remission on standard regimen of prednisolone during 4 to 8 weeks.

Steroid dependent — relapse of nephrotic syndrome occurred at the time of steroid treatment (usually with low dose of prednisolone) or within 2 weeks of steroids have been stopped.

Frequently relapsing — 2 and more relapses within 6 months or 3 and more relapses within one year.

2. *Steroid resistant* — failure to achieve full clinical and laboratory remission when treated with prednisolone in standard regimen for 4 to 8 weeks (kidney biopsy should be considered), or after pulse-therapy with methylprednisolone (single dose 20–30 mg/kg) for 3 consecutive days.

Frequently relapsing nephrotic syndrome:

– chlorambucil (leukeran) — 0.2 mg/kg 8 to 12 weeks — almost is not using any longer;

– cyclophosphamide — 2 mg/kg/24 h for 8 weeks;

– cyclosporine A — 4–6 mg/kg/24 h (under serum level control — target value 80–150 ng/ml) combined with alternate-day administration of oral prednisolone 1 mg/kg/48 h.

Steroid dependent nephrotic syndrome:

– cyclosporine A — 4–6 mg/kg/24 h (under serum level control — target value 80–150 ng/ml) combined with alternate-day administration of oral prednisolone 1 mg/kg/48 h, followed by mono therapy by cyclosporine up to 18–24 months;

– mycophenolate mofetil (MMP);

– tacrolimus;

– alkylating agents (chlorambucil, cyclophosphamide);

– MENDOZA protocol (Table 16.4) is not used nowadays;

– ACE inhibitors (enalapril 0.05–0.5 mg/kg) or ACE receptors blockers (losartan 25–100 mg/day, irbersartan 75–150 mg/day).

Table 16.4

MENDOZA protocol

Duration, weeks	**Metilprednisolone i.v.**	**Oral prednisolone**
1–2	30 mg/kg/48 h	–
3–10	30 mg/kg once a week	2 mg/kg/48 h
11–18	30 mg/kg twice per month	2 mg/kg/48 h
19–52	30 mg/kg once a month	2 mg/kg/48 h
53–78	30 mg/kg once per two months	2 mg/kg/48 h

Kidney biopsy should be considered in case of:

– steroid resistant nephrotic syndrome;

– steroid dependent and frequently relapsing nephrotic syndrome (3rd relapse);

– nephrotic syndrome with hematuria and hypertension;

– nephrotic syndrome in babies younger than 1 year (hereditary forms of nephrotic syndrome should be suspected — genetic testing) and in children older than 12 years old (renal disease secondary to systemic conditions, such as collagenoses or vasculitis, et al should be considered);

– treatment with cyclosporine A over 6 months — if serum creatinine level is increased, and urine gravity is decreased = cyclosporine nephrotoxicity should be considered).

Nephrotic syndrome with hematuria and/or hypertension. Clinical manifestations are similar to ones in nephrotic syndrome, but edema is less severe, but more persistent; high blood pressure; hematuria; anemia; increased serum γ-globulins. Treatment includes steroids and cytotoxic agents.

Focal-segmental glomerulosclerosis frequently (in over 80 % of patients) manifests as steroid resistant nephrotic syndrome. In less than one third of patients' clinical symptoms include microhematuria and arterial hypertension.

Light microscopy: focal (in some of glomeruli) and segmental (in some of glomerular capillary loops) glomerulosclerosis and/or hyalinosis (Fig. 16.18).

Electron microscopy: collapsed capillary loops in sclerosed segments, effacement of podocytes small foots in the rest of glomeruli.

Immunofluorescence: IgM, C3 deposits in sclerosed segments; negative in glomeruli, which appear normal on light microscopy (Fig. 16.19).

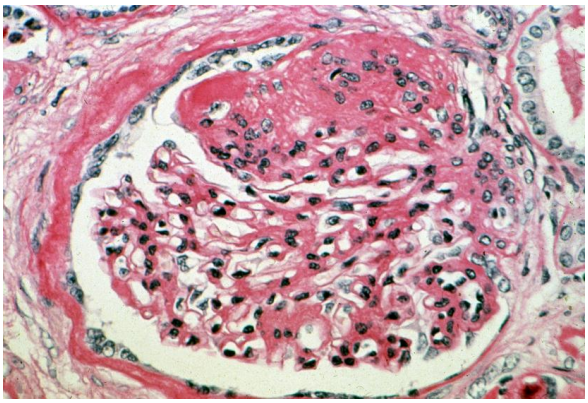


Fig. 16.18. Focal and segmental glomerulosclerosis. H&E stain, ×400

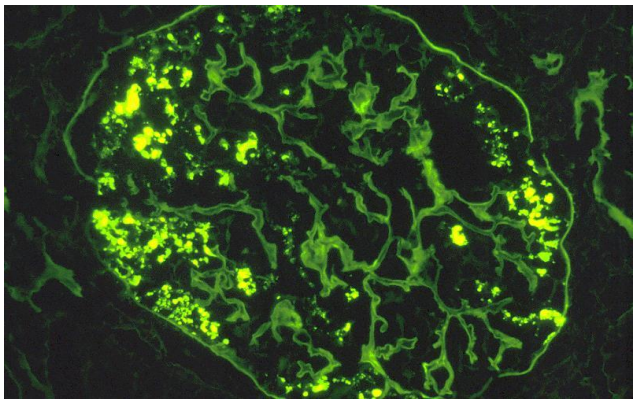


Fig. 16.19. IgM deposits in scleroses segments

Treatment:

1) cyclosporine A — 4–6 mg/kg/24 h (under serum level control — target value 80–150 ng/ml) combined with alternate-day prescribtion of oral prednisolone 1 mg/kg/48 h, treatment duration should not be less than 18 months (remission is achieved in 25–40 % of patients, however soon after the end of the treatment relapse often occurs);

2) cyclophosphamide;

3) tacrolimus;

4) mofetil mycophenolate.

Membranous nephropathy manifests as nephrotic syndrome, or (less frequently) presents with persistent proteinuria, microhematuria and hypertension.

Light microscopy: diffuse thickening of glomerular basement membrane. Glomerular basement membrane has a lot of spikes on John's stain of kidney biopsy specimen-diagnostic feature (Fig. 16.20).

Electron microscopy: subepithelial deposits, which are surrounded by electron-densitive substance, produced by podocytes — "membranous transformation" (Fig. 16.21).

Immunofluorescence: granular IgG, C3 deposits, less frequently IgM or IgA (Fig. 16.22).

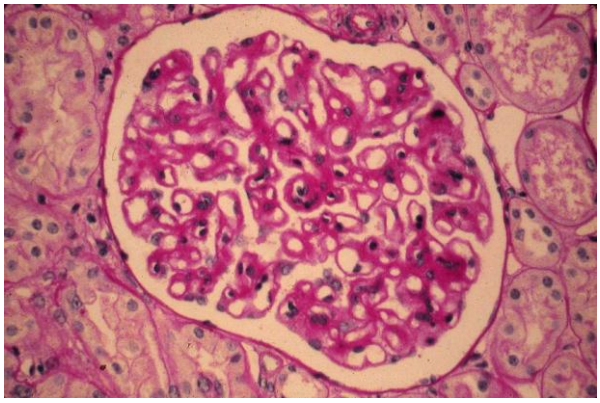


Fig. 16.20. Diffuse thickening of glomerular basement membrane. H&E stain, ×400

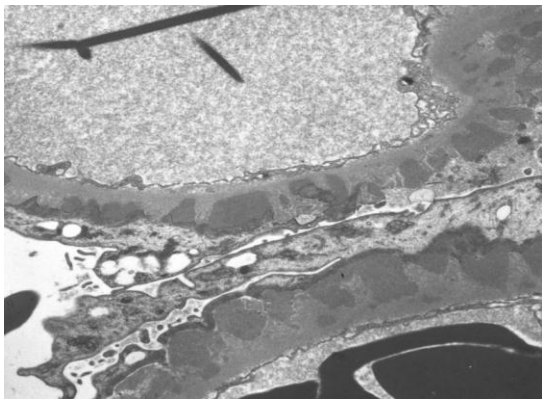


Fig. 16.21. Subepithelial deposits on electron microscopy

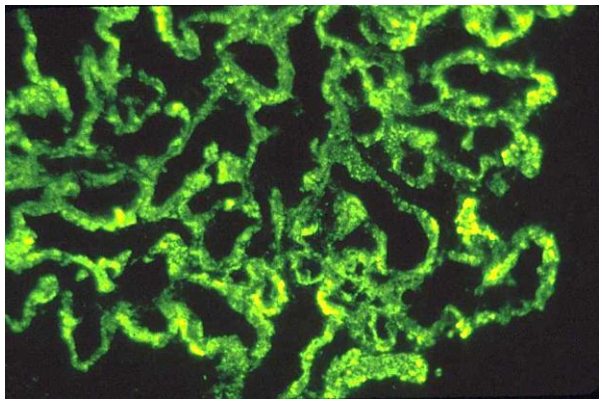


Fig. 16.22. Granular IgG deposits on immunofluorescence

There are no controlled studies on treatment of membranous nephropathy in children. According to symptoms can be used:

– ACE inhibitors in proteinuric patients;

– steroids for years long in nephrotic patients: oral prednisolone 2 mg/kg, max 60 mg per day for 4 to 8 week, after switch to alternate-day administration 2 mg/kg/48 h with gradual reduce to 10–30 mg/48 h for at least 6 months, up to 5 years;

– cyclophosphamide, cyclosporine A, monoclonal antibodies (rituximab);

– treatment of underlying condition (hepatitis B et al.).

Mesangial proliferative GN in children often appears to be primary. It can present as nephritic syndrome at onset with consequent development of nephrotic syndrome with hematuria and arterial hypertension. Low serum levels of C3 and C4 complement can be persistent.

Light microscopy: diffuse mesangial expansion due to mesangial proliferation and mesangial matrix overproduction (Fig. 16.23).

Electron microscopy: mesangial matrix enlargement, mesangial deposits.

Immunofluorescence: granular diffuse mesangial IgG, IgM, IgA, C3 complement deposits (Fig. 16.24).

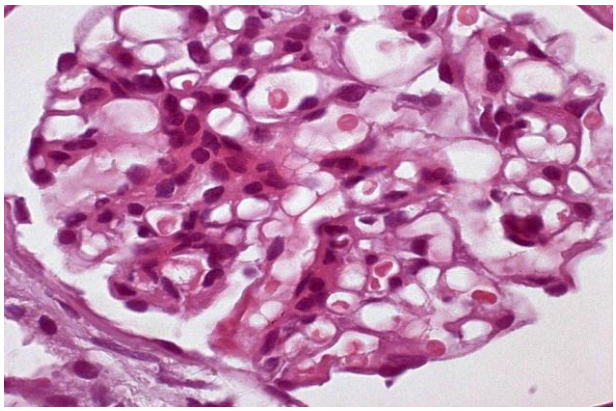


Fig. 16.23. Diffuse mesangial expansion due to mesangial proliferation and mesangial matrix overproduction. H&E stain, ×400

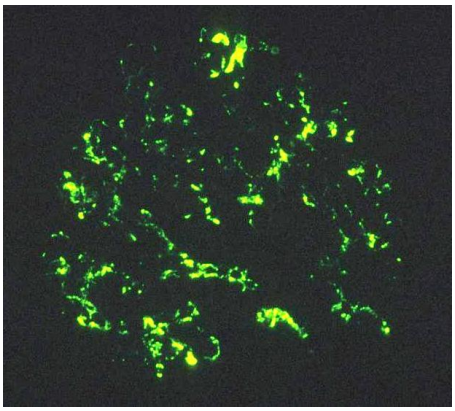


Fig. 16.24. Granular diffuse mesangial IgA deposits

Berger's nephropathy is a mesangial proliferative GN with predominant IgA deposition in mesangium (IgA nephropathy) (Fig. 16.25). In children an idiopathic IgA nephropathy is more common, secondary disease is less frequent (hemorrhagic vasculitis, SLE, intestinal diseases etc.).

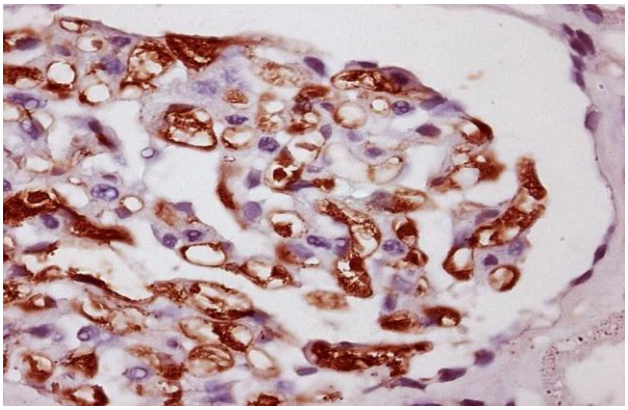


Fig. 16.25. Brown colored mesangial IgA deposits

Berger disease is highly variable, both clinically and pathologically. Clinical features range from asymptomatic hematuria to RPGN. Recurrent macrohematuria is considered to be most characteristic for IgA nephropathy. These episodes are often associated with upper respiratory tract infections (mainly tonsillitis or pharyngitis), and develop simultaneously or within a couple of days after the infection begins. Gross hematuria persists several days and can be accompanied by loin pain in a third to half of patients. Urine becomes brown or coca-cola like, sometimes fever and dysuria can be present.

Treatment:

– no special treatment is necessary in hematuric patients without or accompanied with mild proteinuria;

– in nephrotic patients steroids (60–30–15 mg/m^2 for 3 to 5 years);

– in proteinic patients omega-3 fatty acids (fish oil 4 g daily for 2 years), ACE inhibitors for a long time.

Prognosis: IgA nephropathy used to be considered a disease with favorable prognosis. However recent data from adult nephrologists show that 30–35 % of patients develop end stage renal disease by third or fourth decade of life.

Mesangial capillary GN can be variable in clinical manifestations and pathological changes.

Light microscopy: diffuse thickening and splitting of glomerular basement membrane (tram tracking), severe mesangial proliferation (Fig. 16.26).

Electron microscopy: splitting of glomerular basement membrane, mesangial expansion and hypercellularity.

Immunofluorescence: periferal, large deposits of C3 complement, rarely deposits of IgG, IgA, C4, fibrin (Fig. 16.27).

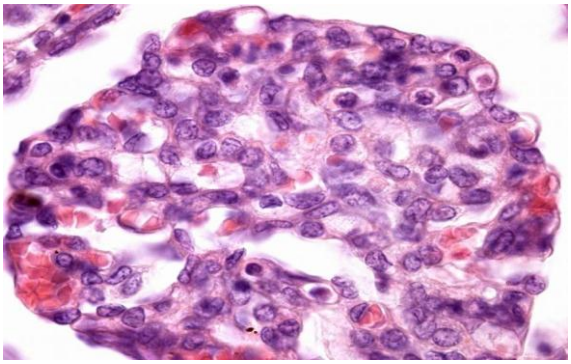


Fig. 16.26. Diffuse thickening and splitting of glomerular basement membrane, severe mesangial proliferation. H&E stain, ×400

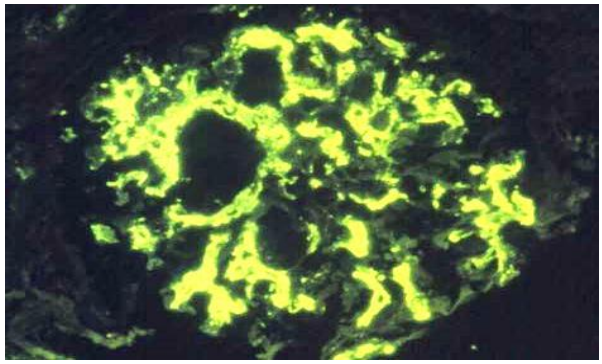


Fig. 16.27. Peripheral, large deposits of C3 complement

Pathology. 3 types are described: I type — with subendothelial deposits; II type — dense deposits disease (this type is considered to be a distinct disease); III type — transmembrane deposits.

There are no clinical differences between these types: different clinical manifestations such as proteinuria (from mild to nephrotic range), edema, nephrotic syndrome with hematuria and/or hypertension, asymptomatic changes in urinalyses (hematuria, proteinuria) can be seen in all types.

Etiology: the disease is idiopathic in majority of cases.

Children 7–10 years of age and older are mostly affected.

Males : females ratio 1 : 1.

There are different approaches to treatment of mesangial capillary GN.

– no special treatment is necessary in hematuric patients without or accompanied with mild proteinuria;

– in nephrotic patients steroidsfor1 to 5 years, sometimes after pulse-therapy with steroids;

– cyclosporine A;

– ACE inhibitors for a long time.

Prognosis: the disease has a progressive course with loss of renal function and progression to end-stage renal disease (10 year survival is 32 %).

16.3. Acute Kidney Injury (Acute Renal Failure). Chronic Kidney Disease (Chronic Renal Failure)

Acute renal failure (ARF) is a sudden or rapidly progressing, potentially reversible clinical-laboratory syndrome, related to the acute loss of kidney function. Usually, but not always, ARF is accompanied by oliguria.

Oliguria is diagnosed, when diuresis is less than 0.5 ml/kg per hour (in infants under 1 year of age less than 1 ml/kg per hour). Anuria is the diuresis less than 0.3 ml/kg per hour (in infants under 1 year of age less than 0.5 ml/kg per hour).

Oliguria is not equivalent to ARF, because ARF is addressed to the impared ability of kidneys to maintain homeostasis, whereas oliguria is the reduced urine output. Polyuria is the diuresis over than 2.5 ml/kg per hour.

There are two criteria needed to be present to diagnose ARF:

– presence of oliguria/anuria;

– more than 50 % of creatinine level rise from baseline or, in case the baseline is not known, from recommended upper limit for age.

The term ARF has been replaced by the term acute kidney injury (AKI). This is argumented by several reasons, first of which was the necessity to unify the criteria of the acute kidney injury/disfunction severity determination and stratification. As the time passed the new data has become available, which stated that even mild reversible increase in creatinine serum level is associated with significant rise of mortality. The diagnosis AKI is not included in International Disease Classification X (IDC-X), it is however recommended to specify it in casts just after the term ARF. The term AKI enables to more efficiently cover patients at risk kidney injury, in particular in case of 25 % from baseline estimated glomerular filtration rate (eGFR) deterioration and diuresis less than 0.5 ml/kg per hour during 8 hours and longer.

On an average ARF is varied from 3 to 8 cases per 1 million children aged 0–18 years, among them one third of cases is diagnosed in infants under 3 years old.

Causes of ARF. ***There are 3 groups of ARF causes:*** prerenal, renal, postrenal.

Prerenal causes are of the greatest significance in childhood, being observed in 80 % of all neonatal and early childhood cases of ARF.

Early stages of prerenal ARF are characterized by GFR deterioration without pathomorphological features of glomerular lesion and tubular function preserved.

Prerenal causes of ARF include:

1. Systemic hemodynamics impairment: hypovolemia (hemorrhage, severe burns, diarrhea and vomiting); decreased effective circulating volume (circulatory failure).

2. Renal ischemia: intrarenal blood redistribution (arterio-venouse intrarenal fistula); decreased renal blood flow (renal artery or vein thrombosis).

3. Decreased cardiac output without (heart failure, cardiac tamponade).

4. Combination of any above.

Renal causes include:

1. Ischemia caused by renal injury (prolonged renal ischemia).

2. Renal parenchymal disease:

– immune glomerulopathies: acute poststreptococcal glomerulonephritis, rapidly progressive glomerulonephritis, secondary glomerulopathies, ie systemic vasculitis (lupus nephritis, IgA glomerulonephritis in Schonlein-Henoch purpura, periarteriitis nodosa);

– tubulointerstitial lesions (tubulointerstitial nephritis, acute pyelonephritis).

3. Toxic tubular lesions:

a) endogenouse, caused by: myoglobin (rhabdomyolis, severe trauma, crush-syndrome); hemoglobin (severe hemolyse, hemolytic-uremic syndrome (HUS), snake vapor, hemolytic transfusion reaction); uric acid (tumor-lysis syndrome);

b) exogenous, caused by: antibiotics; anaesthetics; heavy metals (lead, mercury); ethylene glycol, contrast media, alcohol surrogate.

4. Combined: Reie syndrome.

Postrenal causes of ARF are*:*

1. Urethral (valves, stricturae);

2. Bladder trauma, neoplasm;

3. Ureteral — stenosis, obstruction (by blood clot, stone): internal, external.

In children postrenal causes constitute nearly 10 % of all ARF cases, with congenital abnormalities of urethra and ureter being the prevalent among them.

Hemolytic uremic syndrome. HUS is one of the major causes of ARF in infants, associated with HUS mortality rate varies from 5 % to 15 %, in the Republic of Belarus ≈ 2–2.5 %.

HUS is characterized by acute renal failure, microangiopathic hemolytic anemia and thrombocytopenia. Typical HUS accounts for a majority of cases (60–80 %), develops secondary to gastrointestinal infection caused by verotoxin-producing strains of E. coli 0157:H7, Shigella dysenteriae, Salmonella typhi, Yersinia enterocolitica, Campilobacter jejuni et al. In typical HUS clinical manifestations develop following a prodrome of bloody diarrhea, it therefore is referred to as D+ HUS or STEC-HUS. Usually it has a good prognosis.

Atypical HUS (aHUS) develops without preceding diarrhea. It can be sporadic (postinfectiuos — neuraminidase producing bacteria: Str. pneumoniae, Aeromonas hydrophila, Clostridium; Coxsackievirus, Influenza type A2, ECHO, adenoviruses; medicines (estrogen containing oral contraceptives, cyclosporin A); or vaccination associated (DTP, MMR, polio) and familial. Mutations in complement proteins are found in about half of patients with aHUS. These mutations lead to over activation of complement and cause complement-mediated thrombotic microangiopathy (TMA). aHUS is a chronic disease with recurrent course and high risk of multiple organs damage (permanent kidney damage, stroke, heart attack).

Thrombotic thrombocytopenic purpura (TTP, Moskowitz disease) shares many clinical signs with aHUS and formerly was considered to be a variant of aHUS. Today it is found to be a separate disease due to evidence of different pathogenetic mechanisms involved. TTP is found to be a clotting disorder,

associated with lack of protease that is responsible for breakdown of von Willebrand factor (VWF) multimers (this protease is designated as ADAMTS13 — A Disintegrinlike And Metalloprotease with ThromboSpondin type 1 motif 13). Low activity of ADAMTS13 is found to be caused by inhibiting autoantibodies in sporadic cases or mutations.

ARF: Classification.

According to the cause: 1) prerenal; 2) renal; 3) postrenal.

According to the urine output: 1) without oliguria (non-oliguric ARF); 2) with oliguria/anuria (oliguric/anuric ARF).

There are 4 stages in ARF course: 1) initial; 2) oligoanuric; 3) diuresis restoration and polyuria; 4) outcome.

AKI classification is presented in the Table 16.5.

Table 16.5

RIFLE AKI classification in children
(A. Akcan-Arikan, M. Zappitelli, L. Loftis et al., 2007)

Class	GFR	Diuresis
Risk	eGFR decrease by 25 %	< 0.5 ml/kg/hour 8 hours and longer
Injury	eGFR decrease by 50 %	< 0.5 ml/kg/hour 16 hours and longer
Failure	eGFR decrease by 75 % or eGFR < 35 ml/min/1,73 m^2	< 0.3 ml/kg/hour 24 hours and longer or anuria > 12 hours
Loss	ARF persisting more than 4 weeks	
End Stage Renal Disease	ARF persisting more than 3 months	

AKI staging (KDIGO, 2012)

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline OR ≥ 26.5 μmol/l increase	< 0.5 ml/kg/h for 6–12 hours
2	2.0–2.9 times baseline	< 0.5 ml/kg/h for Ss 12 hours
3	3.0 times baseline	< 0.3 ml/kg/h for > 24 hours
	OR Increase in serum creatinine to ≥ 4.0 mg/dl (≥ 353.6 μmol/l)	OR Anuria for > 12 hours
	OR Initiation of renal replacement therapy OR decrease in eGFR to < 35 ml/min per 1.73 m^2	

Estimated GFR (eGFR) is the GFR that is estimated using Schwartz equation:

$$\text{eGFR (ml/min/1.73 m}^2\text{)} = \frac{40 \times \text{Height (sm)}}{\text{Serum creatinine (mcmol/l)}}$$

Pathogenesis of ARF is uniform in all causes and includes following: renal vasoconstriction, which causes tissue ischaemia; decrease in glomerular capillaries permeability, which causes GFR reduction; tubular obstruction by desquamated epithelium; transepithelial filtrate backflow into peritubular space.

One of the most important points in AKI pathogenesis is given to hemodynamic factors, mediated by *tubuloglomerular feedback mechanism*. Under physiological conditions this mechanism functions to decrease blood flow and GFR in order to prevent tubular damage in case of their excessive volume overload. In AKI damage to proximal epithelium causes decrease in sodium and water reabsorption in proximal tubules. Juxtaglomerular apparatus reacts on increased sodium and water amount in distal tubules (which under normal conditions would mean water overload) and secrets vasoactive peptides, first of all renin, into blood flow. Activation of renin-angiotensin-aldosterone system causes and maintains the afferent arteriole constriction and therefore redistribution of renal blood flow, which consequently causes arteriole blood flow limitation and GFR decrease. These changes normally result in sodium and water excretion. But in case of AKI activation of *tubuloglomerular feedback mechanism* decreases renal blood flow and therefore exacerbates tubular ischaemic damage.

When oligoanuria develops, hemodynamic factor stops playing a key role, because tubular damage has already happened. At this stage attempts to enhance renal blood flow fail to result in GFR increase.

As a consequence of impaired tubular reabsorption water excretion increases. This is why after restoration of glomerular filtration polyuria develops.

At the outcome stage renal hemodynamics is considered to play the major role. Increase in renal blood flow consequently causes GFR increase and leads to higher diuresis.

Pathogenesis of ARF according to the cause (prerenal, renal and postrenal) is schematically shown at the Fig. 16.28–16.30.

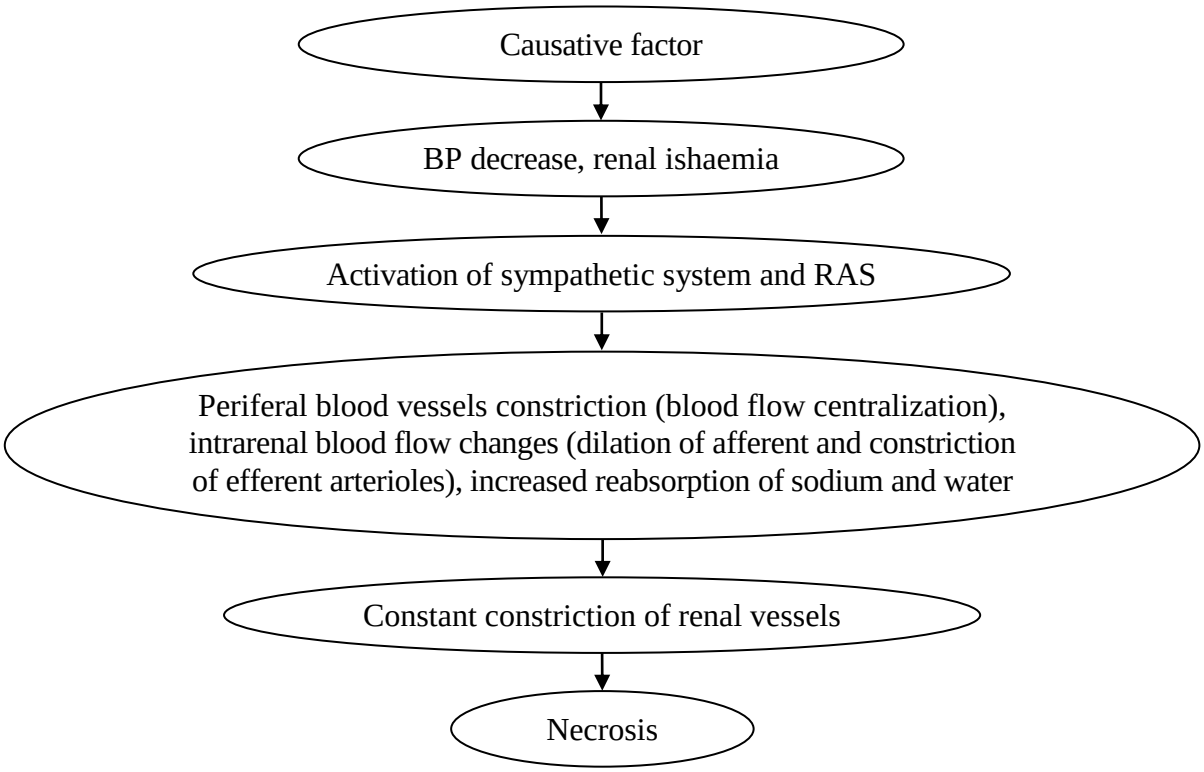


Fig. 16.28. Pathogenesis of prerenal ARF

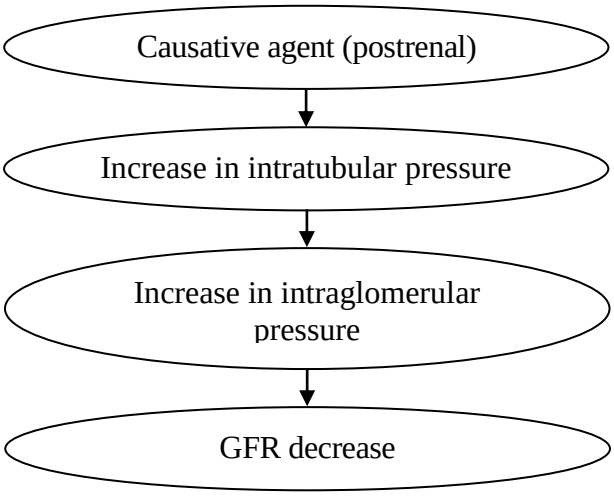


Fig. 16.29. Pathogenesis of renal ARF

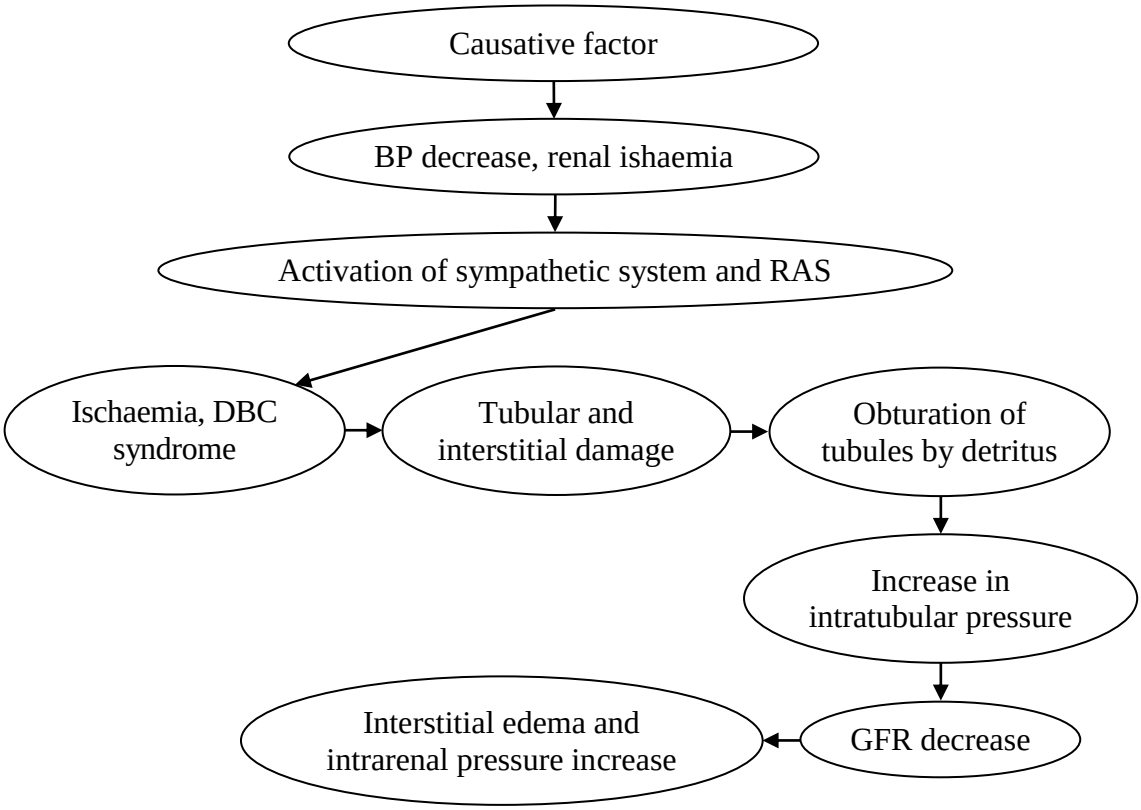


Fig. 16.30. Pathogenesis of postrenal ARF

Pathology. Tubules and interstitium are mostly affected. Glomeruli are intact or minimally affected (except ARF developed in patients with glomerulonephrites). Tubular damage is characterized by: tubular necrosis (necrosis of tubular epithelium with undamaged tubular basement membrane), i.e. toxic nephropathies (Fig. 16.31); tubulorrhexis (destuction of tubular basement membrane in addition to necrosis of tubular epithelium), ie “schok kidney” (Fig. 16.32).

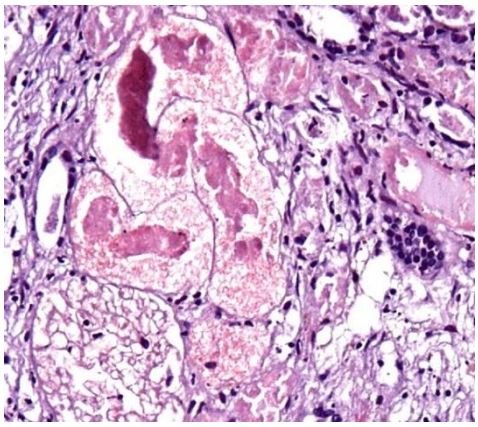


Fig. 16.31. Necrosis of tubular epithelium with undamaged tubular basement membrane (HE, ×40)

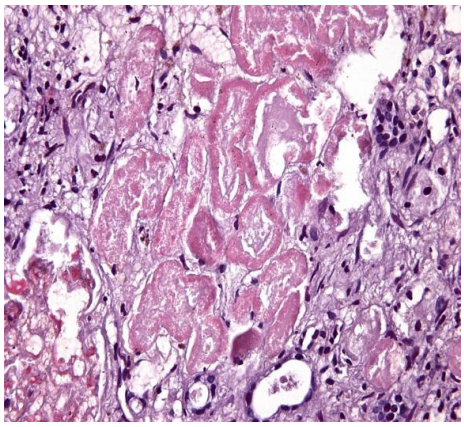


Fig. 16.32. Tubulorrhexis (HE, ×40)

Tubular epithelium distrophy and dilation of tubules are caused by reduction in water reabsorption, increase in intratubular pressure and therefore disruption or disfunction of tubules. Tubulonecrosis (necrosis of tubules) develops within first 48 hours of causative agent action. Epithelial cells of proximal tubules are most sensitive to ischaemia.

Cortical necrosis is the most severe and often irreversible condition, because necrosis is seen also in glomeruli (glomerular capillaries and mesangium) and Bowmen capsule.

Clinical presentation. ARF is the cyclic condition, which classically undergoes 4 consequent stages:

– initial (manifestation);

– oligoanuric;

– diuresis restoration and polyuria;

– outcome.

Symptoms of ARF include:

1) absolutely or relatively decreased diuresis, less often — polyuria (typical symptom of the stage III);

2) decreased specific gravity of the urine;

3) various changes in urinalyses, which depend on the cause of the ARF (proteinuria, hematuria, hemoglobinuria, leucocyturia, cylindruria);

4) changes of blood biochemical tests:

– rise in serum creatinine level (which happens more rapidly than rise in urea level) (N up to 88 mcmol/l);

– elevated blood urea level (N up to 8.35 mmol/l);

– increased level of blood potassium (N 3.7–5.2 mmol/l), which is observed in 60 % of patients (note, that acidosis enhances hyperkalemia and alkalosis reduces it);

– increased concentration of Mg (N 0.78–0.99 mmol/l) and P (N 0.65–1.62 mmol/l);

– decrease in blood concentration of Ca (N 2.0–2.8 mmol/l), Cl (N 96–107 mmol/l), Na (N 135–145 mmol/l);

5) acid-base balance changes: metabolic acidosis and respiratory alkalosis;

6) CBC: changes depend on underlying cause and may include anemia, trombocytopenia, low hematocrit, high neutrophils with left shift, low lymphocytes, low monocytes and eosinophils;

7) coagulation changes: hypercoagulation; increased fibrinogen level; rise in fibrinogen-degradation products (FDP test); diminished fibrinolysis.

There are such novel markers used to diagnose early stages of ARF available as:

– increased level of Cystatin C can be observed as early as 6–8 hours upon initiation of ARF. Rise in blood concentration of Cystatin C is the marker of glomerular injury, and rise in urine concentration of Cystatin C is the marker of tubular injury. Cystatin C is the marker of functional, not the structural lesion;

– NGAL ("renal troponin" or lipocalin-2) level rises in 2 hours after initiation of ARF and is considered to be the biomarker of structural damage. Increased concentrations of NGAL are observed in blood and urine as well;

– NAG (N-acetyl-β-D-glucosaminidase) is the brush border enzyme of proximal tubules epithelial cells, which is also very early marker of ARF.

Both NGAL and NAG appear to be the most sensitive markers of AKI.

At *the initial stage* of ARF clinical presentation include first of all symptoms of the underlying disease. The initial stage duration may vary from hours to days, which depends on the etiology and manifests with reduced (or sometimes increased) diuresis and general symptoms. Vomiting, abdominal pain, stupor, progressive decrease of diuresis and decline of specific gravity of the urine are commonly seen at the initial stage of ARF. This stage is potentially reversible after restoration of renal blood flow and resolution of interstitial edema. That is why early diagnosis and intervention are of great importance in managing patients with ARF.

At t*he oligoanuric stage* all the typical symptoms of ARF are seen. Duration of this stage may vary from days to weeks depending on cause and adequacy of treatment performed, especially at the initial stage. As the disease progresses typical uremic symptoms are observed: nausea, vomiting and diarrhea; neuromuscular irritability and spasms, convulsions, drowsiness, stupor or coma; arterial hypertension, muffled heart sounds, systolic murmur; peripheral or generalized edema.

Major laboratory changes at the oligoanuric stage include elevation of blood urea nitrogen (BUN) and serum creatinine levels, hyperkalemia and metabolic acidosis. At this stage following complications may be observed: cardiac arrest caused by hyperkalemia; severe volume overload and pulmonary/cerebral edema; uremic encephalopathy, which can progress to coma.

Recovery (polyuric) stage is characterized in, that glomerular filtration gradually restores with consequent rise in urine production, while tubular reabsorption remains impaired. Patient's condition remains severe, muscle hypotonia, weakness are often seen. This stage can also be divided in two periods: early (rise in diuresis, but elevation of BUN and serum creatinine is still observed) and late (normalization of nitrogen homeostasis occurs). Low specific

gravity of urine is characteristic of the polyuric stage, also proteinuria, leucocyturia, hematuria (according to the cause of ARF) may be seen. BUN and serum creatinine levels remain elevated, later start to gradually decrease. Dehydration and hypokalemia due to high tubular losses of electrolytes and water are common at the polyuric stage.

Duration of the polyuric stage varies between 1 to 3 months. Most common complications: dehydration; loss of electrolytes; infections. Lethal outcome at this stage can be caused by severe disturbances of water-electrolytes homeostasis and infections.

The outcome stage is diagnosed upon normalization of BUN and serum creatinine levels. At this stage gradual restoration of kidney functions happens, which can take up to 3 years. At the same time chronic renal disease can gradually develop.

Diagnostics. ARF work up should include:

• Careful patients medical history (look for diarrhea, vomiting, hypoxia, medicines, possible toxins exposure).

• Physical examination (drowsiness, fever, skin discoloration, rash, arterial hypertension/hypotension, fluid balance — dehydration or volume overload, urine output estimated hourly).

• Laboratory tests:

– CBC and erythrocyte sedimentation rate (ESR);

– urinalysis;

– blood chemistry tests (total protein, urea, creatinine, electrolytes, bilirubin, transaminases, lactate dehydrogenase, amylase, lipase, C- reactive protein (CRP);

– coagulation tests;

– acid-base balance;

– eGFR;

– NGAL, NAG, Cystatine C;

– blood culture;

Imaging. Urinary tract ultrasound (in majority of cases of ARF kidneys appear to be enlarged and echo bright) to exclude obstruction, look for signs of CRF — small or cystic kidneys. In majority of cases of ARF kidneys are enlarged and echo bright. Doppler ultrasound — to assess if there any abnormality of renal blood flow present.

Approach considerations. In case of HUS following tests should additionally be administered: Stool culture; Verotoxin producing E. coli detection tests (O157:H7); Haptoglobin test; Complement test (if atypical HUS is considered).

If acute nephritis is considered, additionally should be investigated: Strep test; Throat (or wound) swab culture and sensitivity; Antistreptolysin O test; Complement C3 and C4, IgA, IgM, IgG; ANA.

If etiology remains unclear kidney biopsy should be considered.

Treatment. General guidlines:

1) treat the cause;

2) proper diet according to usage und the type of the renal replacement therapy (RRT);

3) restore effective circulating volume and effective renal blood flow;

4) manage anemia, electrolyte disturbances, acidosis, uremia;

5) stimulation of diuresis (with caution);

6) prophylaxis and treatment of infectious complications (consider dose adjustment of antimicrobials and antifungals based on guidelines according to the eGFR and use of the RRT);

7) control BP (hypotensive therapy);

8) symptomatic treatment: antipyretics if febrile; anticonvulsants; digestive enzymes supplementation if needed;

9) physical therapy and rehabilitation.

At the oligoanuric stage management of ARF should ultimately be started with accurate assessment of patients' fluid volume status. Treatment should be intended to keep a patient in a euvolemic status (Table 16.6).

Table 16.6

Fluid volume status assessment and correction

Volume status	Clinical signs	Management
Dehydration	Tachycardia, cold limbs, central-peripheral temperature gradient above 2 °C, capillary refill time (CRT) > 3 seconds, low BP, dry skin and mucous membranes, sunken eyes, altered skin turgor	Replace fluid: i/v infusion of 10–20 ml/kg of isotonic solution within 30 minutes, than assess diuresis and repeat infusion if needed
Euvolemia	–	I/v infusion of 10–20 ml/kg of isotonic solution within an hour, than i/v furosemide 2–4 mg/kg
Volume overload	Tachycardia, gallop rhythm of the heart, high BP and central venous pressure, hepatomegaly	I/v furosemide 2–4 mg/kg, RRT if no effect observed

Restoration of the effective circulating volume is the main goal of conservative treatment at early stages of ARF:

1) blood products transfusion to treat hemorrhage;

2) 20 % albumin for nephrotic syndrome;

3) hypertonic sodium chloride if the salt-wasting condition is observed;

4) any crystalloid solution can be used (normal saline, dextrose, Ringer's lactate).

Patient's weight should be measured twice daily and urine output should be controlled hourly. Volume correction depends on fluid volume status of a patient and urine output:

Fluid volume = insensible losses 400 ml/m^2/24 hours (or 30 ml/kg/24 hours) + + 100 % urine replacement (if euvolemic) or restrict to 50–75 % (if overloaded) + + current losses replacement (hemorrhage, diarrhea, vomiting, tachypnoe).

Diuretics are administered if no intravascular fluid volume deficit is observed. Furosemide and mannitol are most often used. Furosemide is administered i/v in

a single dose 2–4 mg/kg 3 to 6 times per 24 hour or i/v infusion 5–10 mg/kg within 30–60 minutes. Following after administration of furosemide rise in urine production doesn't mean restoration of kidney function or predict better outcome, but is still very important to manage fluid overload and hyperkalemia.

If no effect is observed upon administration of 10 mg/kg following use of furosemide is contraindicated. Initiation of RRT should thus be considered.

Mannitol can be only administered in presence of diuresis in patient. Infusion of 20 % solution is administered as a single dose 0.2–0.5 g/kg within 30–60 minutes. In case the positive effect is seen (rise of urine output) mannitol can be administered at a dose 0.5–1.0 g/kg per 24 hours as continuous 24 hours infusion. Efficacy is best observed when administered before or at the time of initiation of renal ischaemia.

Management algorithm in case ARF is suspected:

1) urine output per hour should be accurately monitored;
2) fluid administration as a 10–20 ml/kg infusion of isotonic solution within 2 hours according to the fluid volume status of a patient;
3) furosemide at a single dose 2–4 mg/kg i/v;
4) then:

a) if diuresis reaches 1 ml/kg/hour, prerenal ARF is most likely:

– no response;

– continue rehydration therapy 5–15 ml/kg/hour with accurate monitoring of urine output per hour and volume status of a patient;

– if oliguria is still present repeat furosemide at the same single dose twice — in 2 and 4 hours after the first injection;

b) if peripheral edema or central venous pressure above 8 cm H_2O are observed infusion should be terminated;

c) if restoration of diuresis is not observed upon 6 hours of rehydration therapy and three injections of furosemide, renal ARF is most likely and the patient should be transferred to the center, providing RRT.

Euphyllinum administration at a dose 0.4–0.8 mg/kg/hour or 10–20 mg/kg/ 24 hours can also be beneficial due to improvement of renal peripheral blood flow.

Hyperkalemia correction is necessary when serum level of potassium is above 5.5 mmol/l. Low potassium diet is prescribed (foods that are high in potassium include most fresh fruits and vegetables, such as bananas, oranges and orange juice, spinach and greens (collard, kale), potatoes). Potassium-containing solutions and medicines should be avoided. Table 16.7 illustrates an emergency management of hyperkalemia.

Moderate decrease of blood *sodium* level in patients with oliguria or anuria usually appears to be secondary to administration of hypotonic solutions. If the level of Na is lower than 118 mmol/l *hyponatremia* becomes symptomatic. Clinical presentations include vomiting, seizures and encephalopathy and are caused by cerebral edema and hemorrhages. Management of hyponatremia requires water restriction and RRT. In polyuric patients hyponatremia may be

caused by excessive urinary loss of electrolytes, which can be assessed by electrolytes measurement in urine. In this case correction with glucose solutions and 3 % sodium chloride solution is performed:

$$Na\ (mmol) = (125 - Na_{patient}) \times weight\ (kg) \times 0.6$$

Table 16.7

Emergency treatment of hyperkalemia

Medicine	Dosage
Salbutamol (aerosolum 0.1 mg per single dose)	every 20 minutes within an hour
Calcium gluconate (10 % solution)	0.5–1 ml/kg i/v slowly within 10 minutes t.i.d. or q.i.d.
Sodium hydrocarbonate (8.4 % solution (1 ml contains 1 mmol $NaHCO_3$))	single dose 2–3 mmol/kg (dilute in 10 % dextrose) iv within 10–30 minutes
Glucose (10 % solution) with insulin	Glucose 0.5–1 g/kg/hour + insulin 1 IU per 4 g of pure glucose
Cation exchange resin	0.5–2 g/kg/day orally or rectally (with 30–50 ml 10 % glucose solution)
Lactulose	Age adjusted dose

RRT should be started if patient has a serum sodium level is higher than 160 mmol/l or lower than 125 mmol/l.

Correction of *metabolic acidosis* should be performed gradually if the bicarbonate level is lower than 18 mmol/l because of significant risk of adverse effects (acid pH of cerebrospinal fluid when treated rapidly with sodium bicarbonate infusions; faster rate of tissue lactate production). 8.4 % solution of sodium hydrocarbonate is prescribed orally or intravenously. The dose depends on the level of HCO_3 and is defined using following formulation:

$$NaHCO_3\ (mmol) = (18 - HCO_{3\ patient}) \times weight\ (kg) \times 0.5$$

If using IV infusion the defined amount of the 8.4 % sodium hydrocarbonate solution is diluted in 0.9 % solution of sodium chloride or 5 % glucose and is infused slowly (over a period not less than 1 hour). Correction (especially if performed rapidly) of acidosis may be accompanied by decrease in Ca^{2+} concentration, thus its level should be closely monitored.

Severe metabolic acidosis with the level of HCO_3 lower than 10 mmol/l is considered to be an indication for RRT because of the risk of complications if large amounts of sodium hydrocarbonate are required.

Hypertension in ARF is usually a consequence of increased amount of extracellular volume. Treatment is started with limiting liquids and sodium intake. Diuretics and hypotensive drugs are concomitantly used: furosemide is administered intravenously 1–5 mg/kg per day; sodium nitroprusside is administered as slow intravenous infusion at a low initial rate 0.3–0.5 mcg/kg/min with upward titration up to 8 mcg/kg/min until the desired effect is achieved. Single dose of sublingual nifedipine (0.05–0.5 mg/kg) can also be used.

As normal food intake is usually limited in patients with ARF, enteral (tube feeding) or parenteral nutrition should be prescribed to prevent undernutrition. In a majority of cases hypertonic glucose solutions (10 % to 20 %) with insulin are administered intravenously at an initial rate 0.2–0.25 g/kg/hour. Amino acids are also used (0.15 g/kg/hour). If administering amino acids supplementation, sufficient calories intake should be maintained (to utilize 1 g of nitrogen 200–300 kcal are required).

RRT is used to correct electrolyte disturbances, fluid overload, acid-base balance disturbances, to lower urea and creatinine concentrations. There are two modalities available to provide acute dialysis — peritoneal dialysis and hemodialysis. The choice is made according to age of the patient, complications observed, hemodynamics stability and condition of the patient.

To initiate acute hemodialysis, the central venous catheter is placed and heparinization is needed, which can produce adverse effects in case hypocoagulation is observed. Peritoneal dialysis doesn't cause serious changes of hemodynamics, thus enabling its use in infants and hemodynamically unstable patients. Indications for emergent dialysis in ARF are shown in Table 16.8.

Table 16.8

Indications for emergent dialysis in ARF

Clinical signs of uremia	Value
Anuria	> 24 hours
Oliguria	> 36–48 hours
Serum level of urea	> 30 mmol/l
Serum level of creatinine	> 350 mcmol/l
Hypercatabolic ARF with increase of urea level	> 10 mmol/l per 24 hours
Following conditions in case of ineffectiveness of conservative interventions	
Severe fluid overload (pulmonary/cerebral edema, hypertension, pericarditis), neurological manifestations of uremia or electrolyte disturbances	–
Hyperkalemia	> 6 mmol/l
Hyponatremia	< 125 mmol/l
Hypernatremia	> 160 mmol/l
Metabolic acidosis with pH	< 7.2
Metabolic acidosis with HCO_3 level	< 10 mmol/l
Hypocalcemia with seizures and high serum level of phosphates	–

At the polyuric stage free access to water and salt is prescribed to prevent dehydration and excessive loss of electrolytes. Additional potassium supplementation is administered. Body weight, daily fluid intake and diuresis, serum level and urinary excretion of electrolytes should be monitored to provide proper correction. Diet slowly returns to normal, calories intake rises. Protein intake can be slowly increased to the level 1.5–2 g/kg within several weeks, under the close control of serum urea level.

Prognosis. Renal survival prognosis depends on the cause of ARF and the age of a patient. Complete recovery of renal functions can be observed, if prerenal

ARF was diagnosed and treated properly. Among causes of renal ARF most favorable prognosis is considered in tubulointerstitial nephritis and ischemia caused renal damage. Postrenal ARF may have favorable course if the cause is treated timely (urological intervention).

Chronic renal failure develops in 10 to 20 % of patients within 3 to 5 years after renal ARF. Regular follow-ups with accessing of kidney function (laboratory tests and instrumental investigations) are therefore required.

Chronic renal failure and chronic kidney disease. Chronic renal failure is defined as a permanent and irreversible reduction of glomerular filtration rate below the normal range (90–120 ml/min/1.73 m^2).

The term chronic kidney disease (CKD), being referred to a more wide range of conditions, replaces the formerly used term chronic kidney failure. Whatever the underlying etiology, once the loss of nephrons and reduction of functional renal mass reaches a certain point, the remaining nephrons begin a process of irreversible sclerosis that leads to a progressive decline in the GFR.

In the early stages, there may be few signs or symptoms and CKD may not be apparent. When CKD reaches an advanced stage, which means that significant percentage of nephrons is lost, dangerous levels of fluid, electrolytes and wastes can build up in a body. Adverse outcomes of chronic kidney disease can often be prevented or delayed through early detection with routine laboratory measurements. and treatment. Early stages of chronic kidney disease can be detected through routine laboratory measurements.

The guidelines define CKD as either kidney damage or a decreased eGFR as per Schwartz equation of less than 60 mL/min/1.73 m^2 for at least 3 months, irrespective of the underlying etiology (diagnosis).

Individuals are classified as having CKD if one of the following criteria is present for at least 3 months: any pathologic abnormalities or markers of kidney damage in blood or urine tests, irrespective of the level of eGFR; any markers of kidney damage, proven by imaging studies or biopsy; decreased eGFR of less than 60 mL/min/1.73 m^2, with or without other signs of kidney damage. eGFR is the main criteria to grade CKD. Grading of CKD according to eGFR level is shown in Table 16.9.

Table 16.9

Grading of CRF

Grade	GFR (ml/min/1.73 $m^{2)}$	Features
1	> 90 — kidney damage with normal or increased GFR	renal parenchymal disease present
2	90–60 — kidney damage with mild decrease of GFR	usually no symptoms but blood biochemistry abnormalities
3	60–30 — moderate decrease of GFR	biochemistry abnormalities, poor growth, appetite
4	30–15 — severe decrease of GFR	more severe symptoms
5	< 15 — kidney failure	requires RRT

As shown in the Table 16.9, any chronic disease with renal parenchymal lesion and preserved or slightly reduced eGFR can be referred to as CKD grade 1 or 2 (chronic glomerulonephritis, obstructive uropathy, early asymptomatic stages of diabetic nephropathy). The rationale for including individuals with eGFR ≥ 60 mL/min/1.73 m^2 is that eGFR may be normal or even increased (due to hyperfiltration in preserved glomeruli) despite substantial kidney damage and that patients with kidney damage are at increased risk of the two major outcomes of CKD: loss of kidney function and development of cardiovascular disease. At these stages specific treatment of the underlying cause can prevent or slow down further loss of nephrons and progression to CRF (which is referred to Grades 3–4 of CKD). Once CKD progresses to Grades 3–4, further progression to end-stage renal disease (ESRD) is considered to be unavoidable. At these stages treatment is prescribed to manage complications of CRF — anemia, osteodystrophy et al.

Etiology. Distribution of kidney diseases leading to ESRD in children:

– 40 % — CAKUT — congenital anomalies of kidneys and urinary tract, structural malformations;

– 25 % — glomerulonephritis;

– 20 % — hereditary GP;

– 10 % — systemic diseases;

– 5 % — miscellaneous / unknown.

The definitive diagnosis of the underlying cause requires biopsy or imaging studies, which can be associated with risk of complications. Therefore, these procedures are often avoided in patients with grades 3 or higher of CKD unless a definitive diagnosis would change either the treatment or prognosis.

Guidelines recommend to assess and manage *risk factors* of progression of CKD. Some of them can be modified (obesity, hypertension, proteinuria), others can not (genetic predisposition, race, age, gender).

Obesity is often associated with hypertension, albuminuria and dyslipidemia. Any of these factors can potentially influence on the progression of CKD. Obesity leads to glomerular hyperperfusion and hyperfiltration, hypertension enhances hyperperfusion and hyperfiltration in unaffected nephrons. Proteinuria leads to direct injury to podocytes and tubular epithelial cells.

Low birth weight or prematurity are associated with congenital reduction in nephron number and predisposition to arterial hypertension and CKD in future.

Puberty is a critical period for individuals with CKD. Rapid decrease of kidney function is often observed in adolescents with CKD (activity of sex hormones, disbalance between number of functioning nephrons and rapidly increased height and body weight during growth spurt).

Individuals that have factors of risk and progression of CKD and GFR over 90 ml/min/m^2 without markers of kidney damage are classified by guidelines as an additional group — “at increased risk” of CKD. Such actions as screening and CKD risk reduction are recommended. Factors of initiation and progression of CKD are shown in the Table 16.10.

Table 16.10

Factors of initiation and progression of CKD

Factors, that can initiate CKD	Factors, that lead to progression of CKD
Persisting activity of underlying cause (autoimmune diseases, diabetes, urinary tract infection, obstructive uropathy etc.)	Proteinuria (microalbuminuria)
	Hyperglycemia
	Arterial hypertension
	Dyslipoproteinemia
Arterial hypertension	Hyperhomocysteinemia
Drugs toxicity	Anemia
	Acidosis
Obesity	Abnormalities of calcium and phosphorus homeostasis
	Smoking

Patophysiology. With the progression of CKD complications of reduced kidney function develop. In the course of CKD following common complications develop: anemia; hyperparathyroidism and bone disease; acidosis; AH; growth retardation and puberty delay.

Anemia. Anemia results from the loss of erythropoietin synthesis in the kidneys, functional or absolute iron deficiency, blood loss (either occult or overt), the presence of uremic inhibitors (eg, parathyroid hormone (PTH), spermine, etc), reduced half life of circulating blood cells, deficiencies of folate or Vitamin B_{12} etc. Anemia causes anorexia, weakness, and cardiovascular disease and therefore worsens prognosis in individuals with CKD.

CKD — mineral and bone disorder (CKD-MBD). Bone disease is the common complication of CKD, results from disorders of calcium-phosphorus metabolism and secondary hyperparathyroidism with high bone turnover or osteomalacia and dynamic bone disease (with normal or low PTH level). During the progression of CKD kidneys lose their ability to excrete phosphorus, which leads to elevation of the serum level of phosphorus. Thus production of active metabolite of vitamin D (calcitriol) results from either reduced kidney mass or direct suppression by elevated serum phosphorus. Lower than normal levels of calcitriol lead to reduced absorption of calcium in GI tract and hypocalcemia. Hypocalcemia, reduced calcitriol synthesis, and elevated serum phosphorus levels stimulate the production of PTH, stimulation of osteoblasts and result in high bone turnover with decreased cortical bone and increased risk of fracture.

Acidosis. Metabolic acidosis develops with decrease of kidney mass usually in individuals with eGFR less than 30–40 ml/min/1.73 m^2. It results from inability of kidneys to excrete acids that are produced through ammoniagenesis. If tubular lesion is severe, there can also be loss of bicarbonates in urine observed. Patients with tubular-interstitial disease as underlying cause of CKD usually have more severe acidosis, which can be observed even if eGFR is over 30 ml/min/1.73 m^2. Acidosis is associated with numerous sequelae — mineral bone disease, altered protein metabolism, skeletal muscle protein breakdown and decreased synthesis of albumin, nutritional problems resulting from nausea and loss of appetite,

chronic inflammation, impaired cardiac function and may contribute to progressive decline of eGFR.

Arterial hypertension. AH can be both a cause and a complication of CKD. Major factors that cause AH in CKD are salt and water retention due to impaired ability to excrete sodium and increased vascular resistance due to activation of the renin-angiotensin system (RAS) (resulting from scars formation or compression of vessels by cysts), activation of sympathetic nervous system, imbalance of vasoactive substances (vasoconstrictor and vasodilator prostaglandins, reduced synthesis of nitric oxide, increased endothelin production). If not controlled AH is a factor for CKD progression and cardiovascular disease. On its turn, CKD is an independent risk factor for cardiovascular morbidity and mortality. Increased intraglomerular pressure causes glomerular hyperfiltration and contributes to proteinuria and further damage to nephron and therefore to progressive decline in renal function.

Growth retardation. Malnutrition and growth retardation can both result from and lead to other consequences of CKD, such as metabolic acidosis, anemia and osteodystrophy. Wasting and stunting are associated with greater risk of morbidity and mortality.

Children with CKD are at significant risk of protein-energy malnutrition. Nutrition is a major factor driving growth in infants, whereas growth and sex hormones in addition to nutrition influence the growth in childhood and adolescence. Spontaneous calorie, water and electrolytes intake is often inadequate in children with CKD, especially in infants, which has a great impact on their growth and development. The earlier the age at which kidney failure occurs, the more likely growth will be affected. Growth and developmental deficits that arise from infancy not always can be fully corrected in future.

Clinical presentation. Signs and symptoms of CKD develop over time if kidney damage progresses slowly. They may include:

– nausea, vomiting;
– loss of appetite;
– fatigue and weakness, sleep problems;
– changes in diuresis (oliguria/anuria or polyuria);
– arterial hypertension;
– cognitive impairment;
– muscle twitches and cramps;
– swelling of feet and ankles;
– persistent itching;
– chest pain, shortness of breath, if fluid builds up in the lungs.

Signs and symptoms of kidney disease are often nonspecific, meaning they can also be caused by other illnesses. Kidneys are highly adaptable and able to compensate for lost function, signs and symptoms may not appear until irreversible damage has occurred. For example, patients often don’t complain of headaches even if severe hypertension is present.

The major goal of **treatment of CKD** — patients should look, feel and behave like their healthy peers. Conservative treatment is to delay progression of CKD and to postpone RRT as long as possible. When managing this group of patients the main principle "do not harm" should be applied: spare the vascular bed; avoid (nephro)toxic drugs; surgery can wait; improve growth before RRT; dialysis can wait.

For every individual with CKD an individual plan of care should be provided by multidisciplinary team based on the CKD grade, course and complications, nutritional status and growth, comorbidities and previous treatment. This plan should include measures to identify progression of CKD and complications, general lifestyle recommendations, nutrition and medical therapy.

Lifestyle modification. Management of pediatric CKD patients aims for them to live a life as normal as possible. Children with CKD usually have reduced physical activity and social functioning compared with peers. These may lead to obesity, depression and poor quality of life, and is associated with higher risk of cardiovascular morbidity and mortality.

CKD individuals are to be incouraged to undertake physical activity (according to their health and tolerance), optimally for at least 30 minutes 5 times per week, preferably leisure sports, no competitions are allowed. Education is an important part of the childrens' development. Pediatric CKD patients should receive all necessary classes. Education should be adapted to be well tolerated and children to feel as involved in social and school life and communication with peers as possible.

Nutrition. Guidlines recommend to monitor closely patients growth and development, frequently reevaluate and modificate the nutrition plan of care for chidren with CKD stages 2 to 5. Alterations to fluid or dietary intake of protein, carbohydrate and/or fat, phosphorus, sodium, potassium, or calcium may be required. Vitamin, mineral, or trace element supplements also may be needed.

Energy intake should be 100–120 % of RDA for chronological age, with the following adjustment according to response (ie, weght gain or loss). If no response — early intervention with supplemental nutritional support (preferably oral intake of energy-dense diet and commercial supplements) should be initiated. When energy requirements cannot be met with oral supplementation, tube feeding should be considered.

No limitation of protein is required in individuals with eGFR higher than 25 ml/min/m^2. Children with CKD do not significantly benefit from low-protein diet. Moreover, such diet can produce negative effect on the growth rate of the patient. With the progression of CKD and decrease of GFR lower than 25 ml/min/m^2 protein restriction is needed, because it reduces metabolic acidosis due to reduction in daily acid load, reduces hyperparathyroidism due to lowering of phosphorus intake, counteracts polyuria because of the reduction in osmotic load.

Diet should be balanced and contain healthy fat and carbohydrates.

Sodium intake restriction is recommended for children with CKD, especially those who have hypertension. Sodium intake should not exceed the age based RDI.

Restriction of potassium, phosphorus or water intake is recommended based on complications observed (for patients who have CKD-MBD, hyperkalemia or oliguria and volume overload, accordingly). If water restriction is needed, energy-dense diet is prescribed to provide sufficient calorie intake. Conversely patients with polyuria are at risk of dehydration and electrolyte disturbances. When managing this group of patients, free water access and salt supplementation (NaCl 1–3 mmol/kg per day) under close control of blood chemistry may be needed.

Medical treatment. When prescribing any medicine, a physician should take into account GFR of the patient. Potentially kidney toxic drugs should be avoided.

Patients with CKD G1–G2 may benefit from specific treatment of the causative disease. Additionally, assessment and diminishment of risk factors are performed to postpone the progression of the disease. Early detection and management of comorbidities is also important.

Management of patients with CKD G3–G5 is based on monitoring of CKD progression and its complications. Early and correct treatment of the complications and comorbidities plays the pivotal role in the care of the CKD patients.

Hypertension. BP-lowering agents are recommended in children with CKD and blood pressure (BP) consistently above 90th percentile for age, height and sex. Treatment regimens are to be tailored taking into consideration daily rhythms of BP (as per ambulatory blood pressure monitoring (ABPM)). Target BP is BP consistently lower than 50th percentile for age, height and sex. Five main classes of hypotensive agents are used:

– angiotensin-converting enzyme inhibitors (ACE inhibitors);
– angiotensin II receptor blockers (ARB);
– calcium channel blockers;
– beta-blockers;
– diuretics.

Interruption of the RAAS is one of the major goals when treating hypertension, therefore ACE inhibitors and ARB are considered to be the first-line hypotensive agents irrespective of the level of proteinuria. When considering administration of ACE inhibitors eGFR should be taken into account. In patients with eGFR lower than 25 ml/min/m^2 their use is contraindicated.

It is preferred that hypotensive agents (if BP not properly controlled) to be titrated upward up to maximal daily dose according to BP. Only after that an additional drug should be prescribed. Drugs that can be administered as a single daily dose should be preferred.

Table 16.11 shows the most commonly used antihypertensive drugs.

Anemia. Iron replacement therapy should be started as initial treatment of anemia in CKD patients. If no effect is seen, treatment with erythropoietin is initiated 50–150 Units/kg IV/SC 3 times weekly initially. If the patient is on dialysis, IV route is preferred (at the end of dialysis session). If the level of hemoglobin approaches or exceeds 110 g/l, the dose should be reduced or treatment interrupted.

Table 16.11

Medical treatment of hypertension

Group	Drug	Dosage
ACE inhibitors	Enalapril	Initial 0.08 mg/kg/day PO or divided q12hr; may be increased q2 weeks according to BP; not to exceed 0.58 mg/kg/day or 40 mg/day
	Captoprile	Infants: initial 0.15–0.3 mg/kg/dose q6–24hr Children: initial 0.3–0.5 mg/kg/dose; q6–12hr Titrate upward to maximum 6 mg/kg/day
ARB	Losartan	Children ≥ 6 years Initial 0.7 mg/kg/day (not to exceed 50 mg/day), increase according to BP up to 1.4 mg/kg/day (or 100 mg/day)
CCB	Amlodipine	0.06–0.2 mg/kg/day
	Nifedipine	0.25–0.5 mg/kg/day
β-blockers	Metoprolole	1–2 mg/kg/day
	Atenolole	1 mg/kg/day
Diuretics	Furosemide	1–2 mg/kg qd or bid
	Hydrochlorthiazide	< 6 months: 1–3 mg/kg/day PO q12hr (max 37.5 mg/day) 6–24 months: 1–2 mg/kg/day PO or divided q12hr (max 37.5 mg/day) ≥ 2 years: 1–3 mg/kg/day (max 100 mg/day)
	Spironolactone	1–3.3 mg/kg/day PO or divided q12hr; not to exceed 100 mg/day

CKD-MBD. Treatment of CKD-MBD is targeted at lowering of serum phosphorus if high and maintaining the level of calcium. Dietary phosphate restriction is required in hyperphosphatemia (plant-based phosphate is absorbed less than animal-based, avoid processed foods to avoid phosphorus-containing additives). It is suggested that dietary phosphorus intake be reduced to 80 % of the AI or RDA.

Phosphate-lowering therapy with phosphate binders (calcium-free or calcium-containing) should be prescribed if persistent and progressive hyperphosphatemia is observed despite dietary phosphorus restriction. Aluminium-containing phosphate binders can only be recommended as the single course with duration up to one month.

Maintaining the target level of calcium in serum requires individualized approach, because of the adverse effects of both hypocalcemia and hypercalcemia. However adequate calcium intake is necessary for the development and growth during childhood. Recommended daily allowances (RDA) and age-specific ranges of blood level of calcium and phosphorus are shown in Table 16.12. As for calcium, intake up to 200 % of RDA is considered to be relatively safe in children older than 1 year of life.

Vitamin D. If vitamin D deficiency (according to serum level of 25(OH)D) is observed, supplementation with vitamin D2 or D3 is required. If secondary hyperparathyroidism is found to be severe and progressive, substitution with active metabolites of vitamin D is prescribed:

– dihydrotachysterol (AT10) 15–45 μg/kg per day;

– alphacalcidol (One alpha Leo) 40–100 ng/kg;

– calcitriol (Rocaltrol) 20–60 ng/kg.

Treatment with vitamin D analogues should be started with low doses irrespective of the initial level of PTH. Then the dose is titrated upward gradually according to the response of PTH to avoid hypercalciuria.

Table 16.12

Age-specific normal ranges of blood levels and RDA of Calcium and Phosphorus

Age	Calcium		Phosphorus	
	Normal serum range, iCa, mmol/L	RDA, mg	Normal serum range, mmol/L	RDA, mg
0–6 months	1.22–1.4	210	1.68–2.71	100
7–12 months	1.20–1.4	270	1.62–2.52	275
1–3 years	1.22–1.32	500	1.45–2.10	460
4–5 years		800		500
6–8 years	1.15–1.32		1.16–1.87	
9–12 years		1300		1250
>12 years	1.12–1.3		0.74–1.45	

Poor growth. Management of growth failure includes first of all adequate nutrition and correction of metabolic disturbances. However, if growth retardation is observed, despite the optimal nutritive support and good control of metabolic parameters, and the patients' height is found to be less than 2 standard deviation (SD) for age below the mean for the age and gender administration of recombinant human growth hormone in dosage 0.05 mg/kg/day or 30 IU/m^2/week is needed. Patients' height should be followed, treatment is considered to be ineffective and should be stopped if the growth rate increases for less than 2 cm per year compared to the previous year.

Metabolic acidosis. Oral bicarbonate supplementation is needed in CKD pediatric patients with serum bicarbonate concentrations < 22 mmol/l. The initial dose of sodium bicarbonate is 1–3 mmol/kg/day PO divided q4–6hr. 1 g of baking soda contains 12 mmol of bicarbonate, 1 tsp — 44 mmol.

Other conditions. Additional treatment may be needed if other conditions and complications of CKD develop. These may include: treatment of neurological complications; correction of hyperuricemia; statins in case of hypercholesterolemia; fish oil or non-saturated fatty acids to correct hypertriglyceridemia; correction of mild hyperkalemia with cation exchange resin 0.5–2 g/kg/day PO or PR (administered with 30–50 ml 10 % glucose solution) or lactulose in age-adjusted dose.

Vaccination. Pediatric CKD patients are to be provided with all recommended childhood vaccines with respect to their immune status (live viral vaccines are avoided in patients receiving immunosuppressive therapy). The *influenza* vaccine should be given to all children with CKD annually. *Pneumococcal* vaccination is particularly important in children with nephrotic syndrome and those with CKD. Booster doses should be given every 5 years after

initial dose. All patients who are likely to require dialysis and before transplantation must be assessed for the level of Hepatitis B antibodies and if necessary given the *Hepatitis B* vaccination. Booster doses may be required, as the decline of antibodies titers may be observed in patients receiving RRT.

RRT. RRT is discussed and planned in all patients with progressive CKD and CKD less than 15 ml/min/m^2. Appropriate education and counseling about different RRT modalities, transplant options, vascular access surgery are extremely important to improve patients' compliance and psychosocial development.

Three types of RRT are used: hemodialysis, peritoneal dialysis and transplantation, which can be from living donor or cadaver. The exact method is chosen according to the age, individual risks and health of the patient, ie causative disease, complications and comorbidities.

The absolute indications for initiation of RRT are: uremia associated neurologic consequences; hypertension that fails to respond to antihypertensive therapy; pulmonary edema unresponsive to diuretics; pericarditis; bleeding tendency; refractory nausea or vomiting.

Relative indications to initiate dialysis include less severe uremic symptoms, hyperkalemia, hyperphosphatemia, malnutrition, progressive severe CKD-MBD and growth failure.

Timing of living donor transplant. Transplantation is the major method of treatment of pediatric patients with CKD. Transplantation from a living donor can be performed pre-emptively (when a patient doesn't receive dialysis) or on dialysis. However, there is no strict guideline available that provides indications for the timing of transplantation. Likelihood of improvement of patients' symptoms should be assessed and balanced with risks of transplant surgery and prolonged immunosuppression, required after transplantation.

CHAPTER 17
DISEASES OF THE BLOOD SYSTEM IN CHILDREN

17.1. ANEMIA

Anemia is a syndrome defined as a reduction of the hemoglobin (Hb) concentration below the range of values in healthy, often with a simultaneous decrease in the number of red blood cells (RBC), which leads to hypoxia.

Normal Hb level (g/l) in children: for 1–3 days of age — 180 g/l; for 4–14 days — 160 g/l; for 2–4 weeks — 120 g/l; for 1–6 months — 115 g/l; for 6 months – 6 years — 110 g/l; for older than 6 years — 120 g/l.

Classification. There is no single international classification of anemia. All anemias could be classified according to the severity and pathogenesis.

According to the severity: 1 — mild (Hb level less than normal till 90 g/l); 2 — moderate (Hb 90–70 g/l); 3 — severe (Hb < 70 g/l).

According to the pathogenesis:

I. ***Acute blood loss.***

II. ***Inadequate production of red blood cells.***

1. *Iron deficiency anemia* (the most common cause of anemia globally).

2. *Anemia of kidney disease* results from erythropoietin (EPO) deficiency. The synthesis of EPO is regulated by the oxygen tension in the periglomerular kidneys cells. Hypoxia drives the synthesis of EPO and its release into the bloodstream, which stimulates the maturation and development of erythrocyte precursors in the bone marrow result in an increase in RBC mass, bringing additional oxygen to the kidney, and completing the feedback loop by downregulating production of EPO. Decline in kidney function is accompanied by a reduction of EPO production.

3. *Endocrine anemias* result from deficiencies or excess of hormones that contribute to blood cell development. Hypothyroidism may be associated with anemia and macrocytosis, adrenal cortical insufficiency with normocytic anemia. Decreased levels of serum testosterone may lead to a mild anemia in males.

4. *Pure red cell aplasia* in children may be the result of hereditary disorders, such as congenital hypoplastic anemia (Diamond–Blackfan anemia), or infection (e.g., viral, Parvovirus B19) or an immunologic phenomenon (systemic lupus erythematosus). In contrast to aplastic anemia, in which two or more cell lineages are affected, pure red cell aplasia is characterized by preservation of the white blood cells and platelets count.

5. *Bone marrow replacement* is also known by the term myelophthisis. The blood forming bone marrow space is taken over by cells or material that should not be there. Causes include hematologic malignancies such as leukemia or lymphoma, metastatic cancer, infection with fungi or other microorganisms, and fibrosis (in conjunction with primary myelofibrosis).

6. *Sideroblastic anemias* represent an uncommon group of hereditary and acquired disorders in which iron is not effectively used in Hb synthesis leading to

iron accumulation in the mitochondria of red blood cell precursors. The deposition of iron leads to the morphologic entity of ringed sideroblasts in the bone marrow when it is stained for iron. Exactly as the name implies, ringed sideroblasts are cells in which ironladen mitochondria encircle at least one-third of the circumference of the erythroblast nucleus. At least five iron-laden mitochondria need to be seen encircling the nucleus to make diagnostic criteria. Hereditary forms are rare and may be X-linked, autosomal dominant, or recessive. Acquired forms may occur after exposure to drugs (cyclosporine, vincristine) or toxins (ethanol).

7. *Anemia of inflammation* (also known as the anemia of chronic disease) is commonly encountered in association with infections, rheumatologic diseases, diabetes mellitus, and malignancy. Cytokines lead to an increase in hepcidin levels, which reduces iron absorption in the GI tract and increase iron retention in the reticuloendothelial system (RES). In addition, cytokines reduce the production of EPO and response to it, proliferation of erythron and RBC half-life.

8. *Folate and vitamin B12 deficiency* are two types of megaloblastic anemia that lead to maturation abnormalities in all three cell lineages. These disorders share the pathophysiology of impaired synthesis of DNA. Folate deficiency is related to inadequate dietary intake or to increased requirements due to RBC hemolysis. Vit B12 is released from food in the acidic environment of the stomach and binds to the intrinsic factor that is secreted by the parietal cells in the stomach. This complex then travels to the terminal ileum where it is absorbed. Vit B12 deficiency may result from different causes including inadequate stomach acidity, pernicious anemia (autoimmune phenomena destroying the parietal cells), structural lesions due to Crown's disease, surgical resection of portions of the GI tract. Inadequate dietary intake is observed in vegans.

III. *Destruction of red blood cells (hemolytic anemia).*

Normally RBC circulate for about 100 to 120 days before they are cleared by the RES. Premature RBC destruction may result from intrinsic defects such as abnormal Hb molecules, cytoskeletal proteins, enzymes, or extrinsic defects of RBC (mechanical forces and antibody or complement-mediated RBC breakdown).

1. *Intrinsic defects:*

• *Hemoglobinopathies* include structural mutations (sickle cell anemia) or defects in the synthesis of the globin chain (alpha- and beta-thalassemia).

Hemoglobin consists of two pairs of globin chains; abnormalities in these proteins are named hemoglobinopathies. From 9 wk of fetal life, the major Hb is HbF ($\alpha 2\gamma 2$). HbA ($\alpha 2\beta 2$) appears at 1 mo. of fetal life, but does not become the dominant Hb until birth, when HbF starts to decline. HbA2 ($\alpha 2\delta 2$) is a minor Hb that appears shortly before birth and remains at a low level after birth. The final Hb distribution pattern that occurs in childhood is not achieved until at least 6 mo. of age or later. The normal Hb pattern is $\geq$ 95 % HbA, $\leq$ 3.5 % HbA2 and < 2.5 % HbF. Among the most common structural mutations is a glutamine to valine substitution at position 6 of the β-globin gene results in the production of HbS, which tends to polymerize in its deoxygenated state. Heterozygotes with one

copy of HbS (sickle cell trait) are relatively protected against malaria infection. This structural mutation thus provides a survival advantage, and selective pressure leads to persistence of the mutation. Homozygotes with two copies of HbS have sickle cell anemia.

The thalassemia syndromes are a heterogeneous group of inherited anemias characterized by defects in the synthesis of one or more globin chain subunits of Hb. Clinical manifestations are diverse, from asymptomatic hypochromia and microcytosis to profound anemia, which can be fatal in utero or in early childhood if untreated. Thalassemia trait is common in individuals from Africa, Asia, and the Mediterranean Basin.

• *Red blood cell membrane defects* result from a variety of defects affecting the RBC cytoskeleton or the membrane itself. Defects lead to changes that reduce the resiliency of RBC as they pass through the narrow passageways in the spleen. Spherocytes are formed resulting in hemolysis. Hereditary spherocytosis is most common in Northern European. Liver disease is very common cause of an acquired RBC membrane defect. Abnormalities in the lipid composition of the RBC membrane result in cells that are abnormally stiff and unable to rebound from deformities that arising from transit of the circulation. Paroxysmal nocturnal hemoglobinuria represents a rare type of acquired membrane defect that is derived from a stem cell defect leading to the reduction or absence of phosphatidylinositol glycan-linked membrane proteins and is associated with the hemolysis of RBC through the unopposed constitutive activation of complement cascade.

• *Red blood cell enzyme* defects are the most common RBC abnormalities. Glucose-6-phosphate dehydrogenase (G-6-PD) is required for function of the hexose monophosphate shunt in the RBC. This provides the RBC with reduction capacity against oxidant stress. Mutations in G-6-PD are very common and have been preserved in populations because of their relative protection against infection with the malaria parasite, like sickle cell anemia. Mutations carries (especially males, because it's X-linked) have RBC that are susceptible to hemolysis under conditions of oxidant stress (antimalarials, nitrofurans and sulfonamides drugs).

2. *Extrinsic to the erythrocyte defects:*

• *Mechanical causes of hemolysis.* Microangiopathic hemolytic anemias include disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, and HUS. Abnormalities in the microvasculature result in shearing of the RBC and the formation of RBC fragments called schistocytes. Infections (malaria, clostridia) can lead to mechanical disruption of the RBC membrane. Malignant hypertension and vasculitis are additional etiologies producing mechanical destruction of RBC. Malfunctioning mechanical valves, as well as long-distance running can also result in the mechanical destruction of RBC.

• *Autoimmune hemolytic anemia* results from antibodies formation that binds RBC and complement resulting in destruction in the circulation (intravascular hemolysis) or in clearance in RES (extravascular hemolysis). Warm and cold

autoantibodies are often idiopathic but may be associated with hematologic malignancies such as chronic lymphoid leukemia or rheumatologic disorders.

• *Alloimmune hemolytic anemia* results from exposure of an individual to foreign RBC. In children this most commonly results from blood transfusion in which there are mismatched minor antigens.

Classification of anemia according to the type of erythropoiesis: normoblastic (IDA, acute blood loss) or megaloblastic (folate and Vit B12 deficiency).

Classification of anemia according to the volume of RBC (MCV): microcytic (iron deficiency (IDA), thalassemia), normocytic (acute blood loss, anemia of renal disease), or macrocytic (folate and Vit B12 deficiency, aplastic anemia, myelodysplasia, chronic liver disease).

Classification of anemia according to the amount of HB in RBC (color index, MCH, MCHC): hypochromic (IDA, sideroblastic, thalassemia), normochromic (acute blood loss, sickle cell anemia) or hyperchromic (folate and Vit B12 deficiency).

Classification of anemia according to the ability of the erythroid bone marrow to regenerate. The reticulocyte count measures the production and release of newly formed RBC. In anemia the absolute reticulocyte count should be at least 100,000/μL. It corresponds to a reticulocyte index of at least 2 % and represents an appropriate response to blood loss or to hemolysis (regenerative). If index is more than 5 % anemia is hyperregenerative. Normal (0.2–2 % — hyporegenerative) or decreased (< 0.2 % — aregenerative) reticulocytes indicate the presence of a RBC maturation abnormality (sideroblastic anemia, folate and Vit B12 deficiency) or a hypoproliferative process (IDA without treatment, anemia of renal disease, endocrine anemias, pure red cell aplasia, bone marrow replacement, inflammation).

Iron metabolism. Iron is essential for cellular function, and iron-containing compounds are found in all cells. Most of the body's iron is contained within the heme moiety of Hb, with smaller amounts in myoglobin and other heme proteins and cellular enzymes. Storage iron is sequestered in a nontoxic form in ferritin and hemosiderin within the RES and liver. A small amount of iron circulates in plasma bound to transferrin. Iron-containing compartments: *Hb iron* (≈ 65 %); *tissue iron* (myoglobin and other heme proteins and cellular enzymes, such as cytochromes, catalase and peroxidase (≈ 10 %)); *storage iron* (ferritin and hemosiderin (≈ 25 %)); *transport iron* (a small amount of iron circulates in plasma bound to transferrin (< 1 %)).

Most body iron is taken up by RBC precursors in the bone marrow and incorporated into Hb. Hemoglobin iron is removed from senescent RBC taken up at the end of their lifespan by macrophages. The iron is removed from the heme ring and recycled to the bone marrow for Hb production. Iron is continuously recycled between RES and bone marrow, and this system supplies most of the iron needed for RBC production. The majority of circulating iron derives from destruction of 20 mL of RBC daily in RES, which liberates about 20 mg of iron.

Iron from senescent RBC is transported from RES via plasma, bound to transferrin. Release of iron from macrophages is mediated by ferroportin (cellular iron exporter). The abundance of ferroportin on the macrophage membrane is regulated by hepcidin, a liver-derived hormone that binds ferroportin, leading to its degradation. Hepcidin level is reduced in iron deficiency and increased in iron overload and inflammation. A further 1–2 mg of iron/day is derived from dietary iron absorption and is also transported via plasma. The iron taken up from dietary sources replaces small amounts of iron lost daily from the body, mainly by exfoliation of epithelial cells. Circulating iron is rapidly removed from the plasma, primarily by nascent RBC precursors in the bone marrow, with smaller portions going to other cells and to iron stores.

The average iron content of the Western diet is 10–20 mg/day, of which only 10 % is absorbed. Heme iron is absorbed more efficiently than nonheme and is the best source of dietary iron. Heme is absorbed intact in the duodenum, and the iron is removed from the heme ring within the enterocytes and enters the same pool as nonheme iron. Ferric (Fe^{3+}) iron in food must be reduced to ferrous (Fe^{2+}) before absorption. The low stomach pH solubilizes iron and helps maintain it in the ferrous state during transport to the proximal duodenum. Nonheme iron absorption is enhanced by formation of complexes with peptides from meat. Vit C enhances absorption of nonheme iron by chelating ferrous iron at acid pH in the stomach and maintaining its solubility in alkaline pH of duodenum, where iron absorption takes place. Nonheme iron can be bound to food phytates in vegetable fiber and polyphenols in tea, which impair absorption.

Iron absorption is influenced by iron stores, and absorption is enhanced in patients with iron deficiency. It's mediated by hepcidin, the central regulator of iron metabolism. Hepcidin binds to ferroportin of duodenal enterocytes, causing it to be degraded. Ferroportin is more abundant when hepcidin levels are lower, leading to increased transfer of iron to the systemic circulation. Hepcidin production is increased in the presence of excess iron stores or inflammation and decreased in iron deficiency or hypoxia. Increased erythropoietic activity, as occurs in hemolytic conditions, increases iron absorption especially when accompanied by increased ineffective erythropoiesis. Transferrin-bound iron is delivered primarily to red cell precursors in the bone marrow via binding of transferrin to specific transferrin receptors on the outer cell membrane. Smaller amounts are delivered to other cells throughout the body. The Tf-TfR complex is internalized, after which the iron is released into the cytosol, and apo-Tf is recycled intact to the plasma.

Iron utilization and storage. Most iron is incorporated into Hb, myoglobin, cytochromes, and a small amount into nonheme enzymes. The remaining iron is stored as ferritin and hemosiderin, mainly in macrophages and hepatocytes. Ferritin is the major form of storage iron, which can be mobilized for increased demands. Hemosiderin is composed of aggregates of ferritin molecules that have partially lost their protein shells. It is a more stable and less soluble form of

storage iron. However, all the iron stored in both ferritin and hemosiderin can be mobilized if needed to replace losses. Iron normally is removed from the body only when cells are lost, especially epithelial cells of the GI tract, skin and renal tubules, and decidua from menstrual cycles. In some pathology, e.g., GI blood loss or hemoglobinuria, iron is lost from the body in the form of heme. There is no physiologic mechanism for regulating iron excretion. Therefore, body iron balance is maintained by control of intestinal iron absorption.

Stages of iron depletion:

1. *Pre-latent iron deficiency.* Initially, when iron stores become depleted, sufficient iron is still available for RBC production, and Hb levels remain normal. Tissue iron levels also remain normal, although the serum ferritin begins to fall. Diagnostic criteria: ↓ SF, no clinical manifestations.

2. *Latent iron deficiency.* As iron levels continue to decrease, tissue iron may start to become depleted. Serum ferritin and iron are low; serum Tf is increased, and the percent of saturation of the transferrin with iron is decreased. Hb and MCV remain normal, but there may be a few hypochromic red cells on peripheral smear; RDW may become elevated, as the first sign of developing iron deficiency anemia. Diagnostic criteria: ↓SF, ↓SI, ↑Tf, clinically manifested by iron deficiency.

3. *IDA.* Once iron stores have been fully depleted, there is no longer sufficient iron to maintain RBC production and, as losses continue, anemia results. RBCs become progressively hypochromic and microcytic. Diagnostic criteria: ↓Hb, normal or ↓RBC, ↓MCV, ↓MCH, ↑RDW, RI < 2 %, ↓SF, ↓SI, ↑Tf, clinically manifested by anemic syndrome and amplification of iron deficiency.

Causes of iron deficiency:

1. *Deficient intake.* Iron stores can be inadequate at birth as a result of maternal deficiency or prematurity, as half of the infant's stores accumulate in the last month of fetal life. Cow's milk and breast milk are equally poor in iron, but breast-fed infants absorb about 50 % of the iron, versus 10 % from cow's. The bioavailability of iron in breast milk is much greater than in cow's. The amount of iron in the newborn is about 75 mg/kg. If low iron is present in the diet, the iron stores present at birth will be depleted by 1–2 months in a premature and by 4 months in a full-term infant. So even breast-fed infants are at high risk for ID and should take iron supplements from 1–2 months in premature and from 4 months in full-term infants.

2. *Increased demand:* growth (low birth weight, prematurity, multiple births, adolescence), cyanotic congenital heart disease. The most common cause of IDA is inadequate intake during the rapidly growing years of infancy and puberty.

3. *Blood loss:* perinatal (transplacental bleeding, fetofetal bleeding, ruptured umbilical cord); postnatal (chronic gastritis, erosions and ulcers of GI tract, parasites, recurrent epistaxis, menstrual loss, hematuria, bleeding disorders).

4. *Impaired absorption:* malabsorption, celiac disease, inflammatory bowel disease.

Clinical symptoms:

1. *Pica* — obsessive consumption of substances with no nutritional value such as ice, sand, starch and dirt, clay, paper.

2. *Changes in the skin and its appendages* due to the fact that epithelial tissues have high iron requirements because of rapid growth and turnover, characterized by a decrease in the elasticity and dryness of the skin, lichenification on the extensor surfaces of large joints; dryness, brittleness and increased hair loss, striation and deformation of nails — spooning of the nails, in which the nails are concave instead of convex (koilonychias).

3. *Atrophic changes in the mucosal epithelium*: atrophic gingivitis, stomatitis, glossitis, angular cheilitis (ulcerations or fissures at the corners of the mouth), esophagitis (dysphagia, characterized by difficulty swallowing dry food).

4. *Muscle weakness* is manifested by a decrease in muscle strength.

5. *Immune system:* increased risk of infection.

6. *Central nervous system:* irritability, decreased attentiveness, reduced cognitive performance, impaired psychomotor and mental development.

Diagnostics:

1. Hb is decreased, RBC is normal or decreased.

2. Hypochromic microcytic RBC, indices MCV, MCH, MCHC less than normal for age.

3. RDW greater than 14.5 %, RI less than 2 %.

4. Serum ferritin is decreased.

5. Therapeutic responses to oral iron: reticulocytosis with peak on 5–10 days after starting of therapy; following Hb level rises on average by 2.5–4.0 g/L/day.

The most reliable criterion of iron-deficiency anemia is the Hb response to an adequate therapeutic trial of oral iron. A reticulocytosis followed by a significant rise in Hb level occurs. The absence of these changes implies that iron deficiency is not the cause of anemia or treatment recommendations are violated. Iron therapy should then be discontinued and further diagnostic studies implemented.

Treatment of IDA:

1. Diet balanced in iron, proteins, rich in vitamins and microelements. Maintain breast-feeding for at least 6 months, if possible or use an iron-fortified infant formula until 1 year.

2. Optimal age-appropriate day regimen.

3. Identification and elimination the cause of IDA.

4. Iron therapy. Anemia should not be treated with iron unless a diagnosis of iron deficiency has been confirmed.

Principles of iron therapy:

1. It is impossible to treat ID only by a diet, since iron absorption from food is strictly limited, we need to use iron therapy.

2. The minimum duration of iron therapy is 12 weeks and consists of 2 steps:

– full therapeutic dose for 4–10 weeks (until Hb and the RBC indices becomes normal);

– replenishment of storage iron, carried out at half the daily dose, for at least 8–16 weeks (normal serum ferritin concentration).

3. Oral iron replacement is usually the treatment of choice. Parenteral iron drugs are used only in malabsorption or poor compliance.

4. The daily dose of oral iron is calculated on the content of elemental iron in the drug, depending on the severity of the anemia and child's body weight: mild to moderate anemia recommended dose is 5–7 mg/kg (in children 0–3 yrs max 8–10 mg/kg), in children ≥ 50 kg 2–4 mg/kg/day, and after prophylactic dose — at half the daily dose.

5. Drug of choice is Iron (III)-hydroxide polymaltose complex. It has similar efficacy, good tolerability and rarely side effects than drugs containing iron salts.

6. Iron salts such as ferrous sulfate are associated with a high incidence of GI side effects: nausea, vomiting, constipation, diarrhea, and permanent staining of tooth enamel.

7. Iron therapy is contraindicated in case of an active infectious process.

Prophylaxis of iron deficiency:

• Iron looses of 500–700 mg are typical with pregnancy: 250 mg transferred to the fetus and the remainder lost with the placenta and via hemorrhage. Pregnant women thus need additional iron supplementation 20–30 mg/day orally. Further iron is required to replace losses during lactation (50 mg/day orally). Adequate prevention of ID during pregnancy and lactation is the key to creating adequate iron stores in the newborn and maintaining them in the 1st year of life.

• Infants at high risk for ID should take iron supplements at a daily dose of 2 mg/kg (from 1–2 months of age in premature and from 4 months in full-term) until they receive iron-rich food.

• All full-term infants without risk factors who are breastfed or mixed fed should take iron supplements 1 mg/kg/day from 4 months until they receive iron-rich food.

• Children over one year of age with ID risk factors (low-iron formula, low meat intake, low socioeconomic status) should take iron supplements at a daily dose of 1 mg/kg in courses of 6–8 weeks.

• When a child reaches a body weight of 50 kg, the max daily prophylactic dose of the iron is 50 mg.

• Seven-day courses of iron therapy are indicated for girls with severe or prolonged menstruation at a daily dose of 50 mg/day after each cycle.

Infants at high risk for iron deficiency:

1. Increased iron needs: low birth weight, prematurity, multiple gestation, high growth and weight rate, chronic hypoxia (cyanotic heart disease, low Hb at birth).

2. Blood loss: perinatal bleeding.

3. Diet: early cow's milk intake, early solid food intake, low iron formula, frequent tea intake (inhibits iron absorption), low Vit C intake (reduces iron absorption), low meat intake, breast-feeding > 6 months without iron supplements, frequent infections, low socioeconomic status.

17.2. HEMATOLOGICAL MALIGNANCY

Leukemia is the neoplastic proliferation of hematopoietic cells, the most common childhood malignancy (≈ 41 % of all malignancies in children less than 15 years old), uncontrolled proliferation of immature and abnormal white blood cell precursors of varying hematopoietic lineage and aberrant differentiation. Usually originates in the bone marrow, where normal blood cells are replaced by leukemic cells. Morphological, immunological, cytogenetic, biochemical, and molecular genetic factors characterize different subtypes which display various.

The following types of leukemia are distinguished:

1) acute lymphoblastic leukemia (ALL) (more than 25 % blast) — for 80 % of childhood leukemia;

2) acute myeloid leukemia (AML) (more than 20 % blast) ≈ 11 %;

3) chronic myeloid leukemia (CML) ≈ 2–3 %;

4) AUL: acute undifferentiated and acute mixed lineage leukemia (AMLL).

Scheme of normal hematopoiesis is shown in the Fig. 17.1.

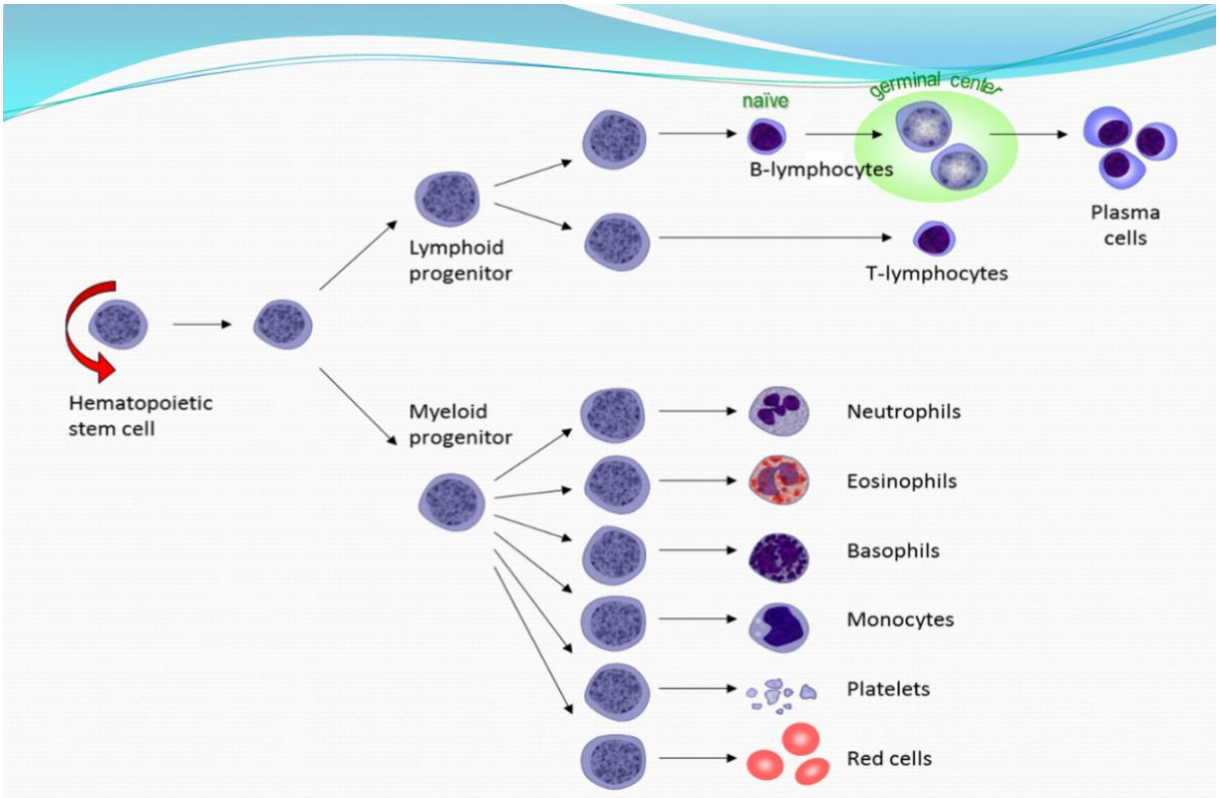


Fig. 17.1. Normal hematopoiesis

The etiology of leukemia is unknown. Chromosomal aberrations, several genetic and environmental factors are associated with childhood leukemia.

Predisposing factors.

***Genetics*.** In monocytic twins, there is a 20 % or greater increased risk of leukemia within months after the co-twin develops leukemia. High risk in: Trisomy 21 (14 times higher), Monosomy 7, Neurofibromatosis type 1, Fanconi anemia (high fragility of chromosomes), Bloom syndrome, Kostmann syndrome,

Poland syndrome (absence of pectoralis major muscle and variable ipsilateral upper extremity defects), agammaglobulinemia, ataxia-telangiectasia (high fragility of chromosomes), other bone marrow failure syndromes along with inherited translocation syndromes and inherited mutations.

Ionizing radiation. Atomic bomb survivors (from Hiroshima and Nagasaki) developed leukemia with an incidence of 1 : 60, within a radius of 1.000 m of the epicenter, occurring after 1–2 years (peak incidence after 4–8 years). There was predominance of ALL in children and AML in adults, which may reflect the different pathogenesis in various age groups.

Chemicals and drugs: Benzene (related to AML), Chloramphenicol (related to ALL), Chemical warfare agent, i.e., nitrogen mustard (AML), Cytotoxic agents, e.g., correlation between alkylating agents and Hodgkin disease and other malignancies. There is a higher incidence of leukemia (usually AML), ovarian carcinoma, and other solid tumors after exposure to ionizing radiation.

Infections. Human T-cell leukemia virus (HTLV) has been demonstrated in adults to be linked to T-cell lymphoma, association between Epstein–Barr virus and occurrence of Burkitt lymphoma. HIV infection and/or immunodeficiency are associated with a higher incidence of malignancy and, particularly, non-Hodgkin Lymphoma. In humans, vertical or horizontal transmission of leukemia has not been demonstrated except in rare cases of a mother with leukemia to her newborn or in identical twins with prenatal leukemia. There is an association between immunodeficiency and development of lymphomas and lymphoid leukemias (i.e., congenital hypogammaglobulinemia, Wiskott–Aldrich syndrome, HIV infection).

Pathogenesis. The etiology and/or predisposition indicate a correlation between leukaemogenesis and different risk factors: chromosome instability/fragility, immunodeficiency, environmental exposures (ionizing radiation, chemicals, and viruses).

Cytogenetic alterations of genes that encode key regulatory and signal transduction pathways. Chromosomal deletions, mutations, or chemical alterations (i.e., methylation) of DNA may lead to inactivation of the tumor suppressor gene or activation of proto-oncogenes. Molecular changes, such as those involving the Bcl-2 or p53 pathways, may disturb normal apoptosis. Various methodologies (polymerase chain reaction, PCR; fluorescence-activated cell sorting, FACS) can detect leukemic cells with chromosomal alterations, clonal antigen receptors, or immunoglobulin rearrangements with high sensitivity and specificity.

Acute lymphoblastic leukemia. ALL is the most common malignancy in childhood. About 85 % of cases of ALL are derived from progenitors of B cells, about 15 % from T cells, and 1 % from B cells. The typical age of manifestation is 2–10 years, with the peak incidence between 2–5 years; more frequently in boys. Predisposing factors: hereditary and acquired (ionizing radiations, therapeutic radiations, nuclear fallout, diagnostic X-rays, chemical agents, viruses).

Predisposing genetic conditions: Down syndrome, Fanconi syndrome, Bloom syndrome, Diamond–Blackfan anemia, Schwachman syndrome,

Klinefelter syndrome, Turner syndrome, neurofibromatosis, ataxia-telangiectasia, severe combined immune deficiency, paroxysmal nocturnal hemoglobinuria etc.; environmental factors — ionizing radiation, drugs, alkylating agents, nitrosourea, benzene exposure, advanced maternal age. Mechanism of leukaemogenesis: activation of a proto-oncogene to an oncogene when it is translocated to a transcriptionally active site, formation of a chimeric transcription factor, formation of a fusion protein with enhanced tyrosine kinase activity, activation of FTL3 receptor, inactivation of tumor suppressor gene pathway. Scheme of hematopoiesis is shown in the Fig. 17.2.

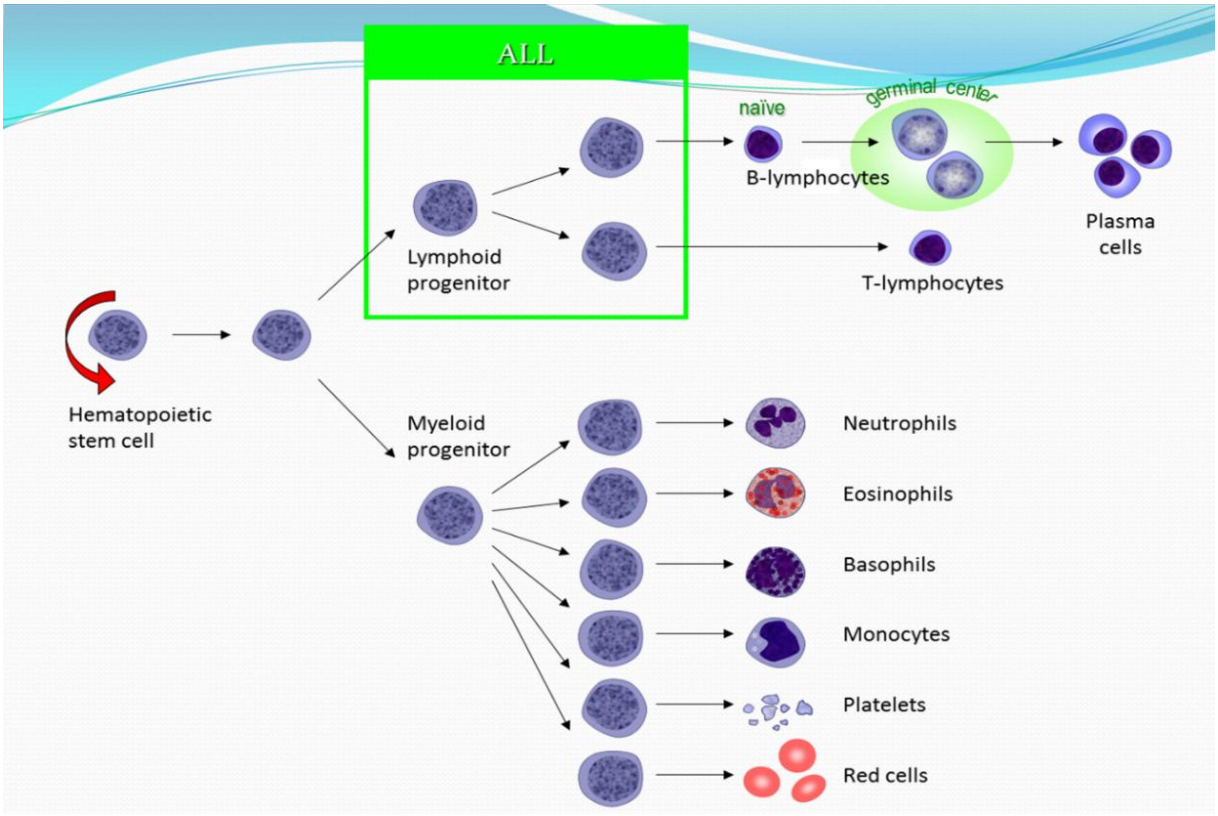


Fig. 17.2. Hematopoiesis in ALL

Symptoms: fever, fatigue, bone/joints pain, weight loss, purpura and bleeding, lymphadenopathy, sternal tenderness, mediastinal mass.

The history and symptoms reflect the degree of bone marrow infiltration by leukemic cells and the extra medullary involvement of the disease. The duration of symptoms may be days to several weeks or months. Sometimes diagnosis in an asymptomatic child results from an incidental finding in a CBC. Often low-grade fever, signs of infection, fatigue, bleeding (i.e., epistaxis, petechiae), and pallor may present. The symptoms depend on the degree of cytopenia: *anemia* (pallor, fatigue, tachycardia, dyspnea etc); *leukopenia* (fewer, infections etc); *thrombocytopenia* (petechiae, mucosal bleeding, epistaxis, and prolonged menstrual bleeding).

Skin. Besides signs of bleeding, in neonatal leukemia, maculopapular skin infiltration, often a purplish color (leukemia cutis), can be observed; it is more common in acute monocytic subtype of AML.

Eye. Bleeding due to high white blood cell count and/or thrombocytopenia. Retina: infiltration of local vessels and bleeding.

Ear, nose, and throat. Lymph node infiltration, isolated or multiple. Mikulicz syndrome: infiltration of salivary glands and/or lacrimal glands.

Central nervous system. About 5 % of patients have CNS leukemia with meningeal signs and symptoms: morning headache, vomiting, papilledema, or focal neurological signs such as cranial nerve palsies, hemiparesis, and seizures. Diagnosis by analysis of cerebrospinal fluid: CNS I (no lymphoblasts); CNS II (less than 5 cells/cm^3, but with leukemic blasts on centrifugation); CNS III (at least 5 cells/cm^3, with leukemic blasts or cranial nerve palsy); a traumatic lumbar puncture also appears to result in higher risk of CNS relapse and requires intensified intrathecal therapy.

Cardiac involvement. Leukemic infiltration or hemorrhage; cardiomegaly, cardiac tamponade due to pericardial infiltration; tachycardia, low blood pressure, heart failure.

Mediastinum. Enlargement due to leukemic infiltration by lymph nodes and/or thymus. Life-threatening superior vena cava syndrome (especially T-cell ALL).

Pleura and/or pericardium. Pleural and/or pericardial effusion.

Gastrointestinal involvement. Hepatomegaly and/or splenomegaly. Gastrointestinal leukemic infiltration is frequent, but mostly asymptomatic, rarely manifested as typhlitis. Perirectal infection with ulceration, pain, and fewer.

Renal involvement. Renal enlargement, common in precursor B-/B-cell or T-cell. Possible hematuria, hypertension.

Bone and joint involvement. Bone pain initially present in 25 % of patients. Bone or joint pain, sometimes with swelling and tenderness due to leukemic infiltration of the periosteum. Radiological changes: diffuse demineralization, osteolysis, transverse metaphyseal lucency, increased subperiosteal markings, hemorrhage, or new bone formation.

Classification. The classification of ALL depends on characterizing the malignant cells — according to the determination of the morphology, phenotypic characteristics as measured by cell membrane markers, and cytogenetic and molecular genetic features.

The French-American-British (FAB) classification based on morphology and cytochemistry was in use for many years and is now substituted by the WHO classification. FAB classification: ALL L1, ALL L2, ALL L3. In childhood L1 is the most common type, in adults is L2. Morphology include: size of blast, cytoplasm, N/C Ratio, cytoplasmic vacuoles, nuclear membrane, nucleoli characteristics. FAB does not include immunophenotyping, cytogenetics, molecular characteristics, immunological subtype of ALL, biphenotypic leukemia, has limited relevance to therapeutic or prognostic implications.

WHO classification of ALL (2008):

1. B-lymphoblastic leukemia/lymphoma, NOS.

2. B-lymphoblastic leukemia/lymphoma with recurrent abnormalities: t (9; 22), BCR ABL1; t (v; 11q23) MLL rearrangement; t (12; 21) ETV6-RUNX1, with hypodiploidy, with hyperdiploidy, t (5; 14) il3-igh, t (1; 19) E2A-PBX1 (tcf3-pbx1).

3. T-lymphoblastic leukemia/lymphoma.

Immunological classification:

1. B ALL (pro B ALL, common B ALL, pre B ALL, mature B ALL).
2. T ALL.
3. Mixed lineage acute leukemia.
4. Undifferentiated acute leukemia.

Uncommon variants of ALL: small cell variant (blast cells are small and may be mistaken for lymphocytes); hand mirror variants (a subtype with cytoplasmic protrusion); ALL with eosinophilia; granular cell ALL (cells are large and demonstrate azurophilic granulaes).

Diagnostics:

1. *CBC:* anemia, thrombocytopenia, leukocytes could be normal, low or high.
2. *Biochemistry:* increased level of alkaline phosphatase, lactate dehydrogenase, uric acid; a decreased level of alanine aminotransferase, aspartate aminotransferase, urea, and creatinine.
3. *Coagulogram*: low levels of prothrombin, fibrinogen, factors V, IX, X.
4. *Chest X-Ray*.
5. *Ultrasonography*: cor, abdomen, pelvis, testis.
6. *CT, MRI*.
7. Blood *culture* and bacteria carrying tests (skin, mucous, urine).
8. *Urine analysis*.
9. *Lumbar puncture.*
10. *Virology* (hepatitis, herpes, cytomegalovirus).
11. *Bone marrow:* morphology, immunophenotype, and cytogenetics: leukemic cells are not often observed in the peripheral blood in routine laboratory tests (leukemic blasts may not be seen in the peripheral blood smear). Leukemia is diagnosed by the examination of the bone marrow, more often it is aspirated from the posterior iliac crest. A normal marrow contains less than 5 % blasts.

ALL demonstrates more than 30 % of the bone marrow cells as a homogeneous population of lymphoblasts. Bone marrow smear hyper- or normocellular; normal hematopoietic elements diminished; blasts > 30 % (ALL) and > 20 % (AML).

ALL L1: small size of blasts; cytoplasm scanty basophilic; N/C Ratio high; nuclear membrane regular; nucleoli — invisible or indistinct.

ALL L2: large heterogenous blasts; cytoplasm moderate; N/C Ratio lower; cytoplasmic vacuoles variable; nuclear membrane irregular with clefting; nucleoli prominent, 1–2.

ALL L3 (Burkitt leukemia): large homogenous blasts; cytoplasm — moderate intensely basophilic; N/C Ratio lower; cytoplasmic vacuoles prominent; nuclear membrane — regular; nucleoli — prominent, 1–2.

12. *Cytochemistry:* determination of a leukemia type. Peroxidase positive results in myeloblasts with cytoplasmic granules. Esterase (α-naphthyl acetate esterase) used in identification of mono- or histiocytic elements. Leukocyte alkaline phosphatase: low or no activity in granulocytes of CML. Periodic acid-Schiff (PAS): most circulating leukocytes are PAS positive. PAS is strongly positive in lymphoblasts, especially in T-cell lymphoblasts. Sudan black is usually positive in myeloid cells/especially immature cells.

13. *Immunophenotyping:* used for diagnosis, classification, prognosis, monitoring of minimal residual disease.

Immunological characterization. Monoclonal antibodies to leukemia-associated antigens differentiate between types of leukemic cells. Subtypes of leukemic populations based on immunophenotyping in different maturational stages can be identified by Fluorescence-Activated Cell Sorting (FACS) analysis:

• Precursor B cells mainly positive for CD19, CD22, and sometimes CD24 and CD10.

• Precursor T and mature T cells mainly positive for CD3, CD7, CD5 and CD2.

Clinical importance of immunophenotyping:

• 85 % of children with common ALL (usually precursor B-cell ALL) are HLA-DR- and CD10-positive, which indicates a good prognosis.

• Children with T-cell ALL are characterized by older age (peak at 8 years of age), with a ratio of male to female of 4 : 1; high initial leukocyte count; mediastinal enlargement; high proliferation rate; or frequent extra medullary manifestation (initially and at relapse).

• Early precursor T-cell ALL (ETP-ALL) represents a high-risk subtype and usually expresses stem cells and myeloid markers (e.g., CD34, CD117); it is negative for CD1a and CD8 and weakly expresses CD5.

• In ALL relapse, the immunological phenotype is usually the same as at initial diagnosis.

Biochemical characterization. Some cellular enzymes provide further diagnostic differentiation between ALL and AML: Terminal Deoxynucleotidyl Transferase (is absent in normal lymphocytes); Deoxyribonuclease (DNase); Activity in all circulating ALL cells, with the exception of mature B-cell ALL; 5-Nucleotidase (decreased level of 5-nucleotidase in T lymphoblasts).

14. *Cytogenetic examination.* In 85 % of children with leukemia, an abnormal karyotype in the malignant clone is detectable. The analysis combines chromosome banding with fluorescence in situ hybridization (FISH) with spectral karyotyping (SKY) and with comparative genomic hybridization (CGH). The cytogenetic abnormalities reflect the number of chromosomes (ploidy) and the structure of chromosomes (rearrangements). The DNA index defines the cellular DNA content, determined by flow cytometry.

Molecular genetics: establishment of lineage-DNA analysis; identification of translocation; detection of relapse; detection of minimum residual disease (FISH, PCR).

Treatment. Treatment of ALL is subdivided into ***remission induction, consolidation with CNS prophylaxis, and maintenance phase***. During the maintenance phase, delayed intensification phase, interim maintenance phase, etc., in the treatment are used sometimes. In parallel to remission treatment, decrease in hemoglobin, white blood cells is seen as a side effect. Parents and patients should have a clear understanding of each stage of therapy and the associated side effects.

1. *Induction of remission:*

• Elimination of leukemic cells by a combination of vincristine, prednisone, or dexamethasone and additional cytotoxic agents such as daunorubicin, doxorubicin, and L-asparaginase.

• L-asparaginase or polyethyleneglycol (PEG)-conjugated L-asparaginase with a longer half-life and less frequent dosing has been recognized as a key drug during induction and consolidation treatment of ALL.

• Duration of induction treatment: 4–5 weeks.

• Regression of organ enlargement can be observed within the first 2 weeks.

• Rate of first remission in ALL: 90–95 %. For prophylaxis of CNS leukemic disease, intrathecal chemotherapy, usually methotrexate, and/or cytosine arabinoside, is often given on first treatment before, during, and after remission has been achieved. The addition of preventive cranial irradiation is now only applied to children with initially slow responding T-cell ALL.

• Remission means disappearance of all signs of leukemia on clinical examination and peripheral blood analysis, bone marrow analysis with less than 5 % leukemic cells morphologically, and normal hematopoiesis established. Much more sensitive methods of detecting persistent leukemic cells or MRD are increasingly being used to define remission status.

• Stratification according to MRD status: in low-risk ALL being MRD-negative at the end of induction, reduced treatment can be used; intermediate-risk — by significant MRD detection at the end of induction is often treated with intensified consolidation; and high-risk ALL is treated with re-intensified treatment blocks.

2. *Consolidation treatment:*

• Without continuation of treatment beyond remission, leukemia will reappear within weeks or months.

• When remission with normal hematopoiesis is achieved, further intensive chemotherapy is necessary to reach a complete eradication of leukemic cells.

• Combinations of different cytotoxic drugs reduce the number of remaining leukemic cells and the development of resistance against chemotherapies.

• High-dose intravenous methotrexate of different dosing schedules and infusion durations appears to benefit all risk groups.

3. *Maintenance treatment:*

• Risk-adapted maintenance treatment of different duration prevents recurrence of ALL.

• Duration of treatment is 1.5–2.5 years with daily 6-mercaptopurine and once weekly methotrexate. Different maintenance schedules and chemotherapy combinations are being tested in cooperative group trials.

• The dosage of cytotoxic agents must continuously be adapted to the child's condition and blood cell counts at weekly to biweekly intervals.

• A lifestyle as normal as possible like before the diagnosis should be encouraged during maintenance treatment.

Prognostic factors:

– age (less than 2 years or more than 10 years old), male gender;
– initial WBC count (more than 50,000/μl);
– cytogenetics;
– immunologic subtype;
– response to initial therapy;
– MRD.

ALL in infants. Initially high WBC, massive organ enlargement, severe thrombocytopenia, high rate of CNS involvement, poor response to treatment, and high rate of relapse in comparison with childhood ALL, particularly extra medullary relapse. Leukemic cells in infants mainly display a more primitive phenotype (often HLA-DR-positive, CD19+, CD10-negative, Ig or T-cell receptor genes in germline configuration). There is involvement of chromosome 11 [11q23, MLL/AF4ALL — 1 gene rearrangement, t (4; 11)] and simultaneous occurrence of lymphoid and myeloid markers; Ig genes are often in germline configurations.

Patients with particularly poor prognostic features (with the t (9; 22) translocation known as the Philadelphia chromosome) may undergo bone marrow transplantation during the first remission. In ALL, this chromosome is similar but not identical to the Philadelphia chromosome of chronic myelogenous leukemia.

Complications:

1. Specific: side effects of cytostatic therapy.
2. Tumor lysis syndrome.
3. Non-specific: infectious and non-infectious.

Accompanying therapy is always used for preventing complications.

Prognosis. Overall survival is approximately 80 % with modern treatment. The disease is fatal without effective therapy.

Acute myeloid leukemia (AML). AML results from abnormal, malignant proliferation in the myeloid cells precursors, accounts for about 5 % of the cases of childhood malignancies and less than 20 % of all acute leukemia's. The frequency of AML remains stable throughout childhood, with increases under the age of two yrs and during adolescence; the incidence increases dramatically after 55 years old. There are no gender differences and a slightly higher incidence in Caucasian children. Scheme of hematopoiesis in AML is shown in the Fig. 17.3.

Etiology. Several chromosomal abnormalities associated with AML have been known, but no predisposing genetic or environmental factors can be

identified in most patients. Risk factors: ionizing radiation; chemotherapeutic agents (e.g., alkylating agents, epipodophyllotoxin), organic solvents; paroxysmal nocturnal hemoglobinuria; Down syndrome, Fanconi anemia, Bloom syndrome, Kostmann syndrome, Shwachman–Diamond syndrome, Diamond–Blackfan syndrome, Li–Fraumeni syndrome, neurofibromatosis type 1.

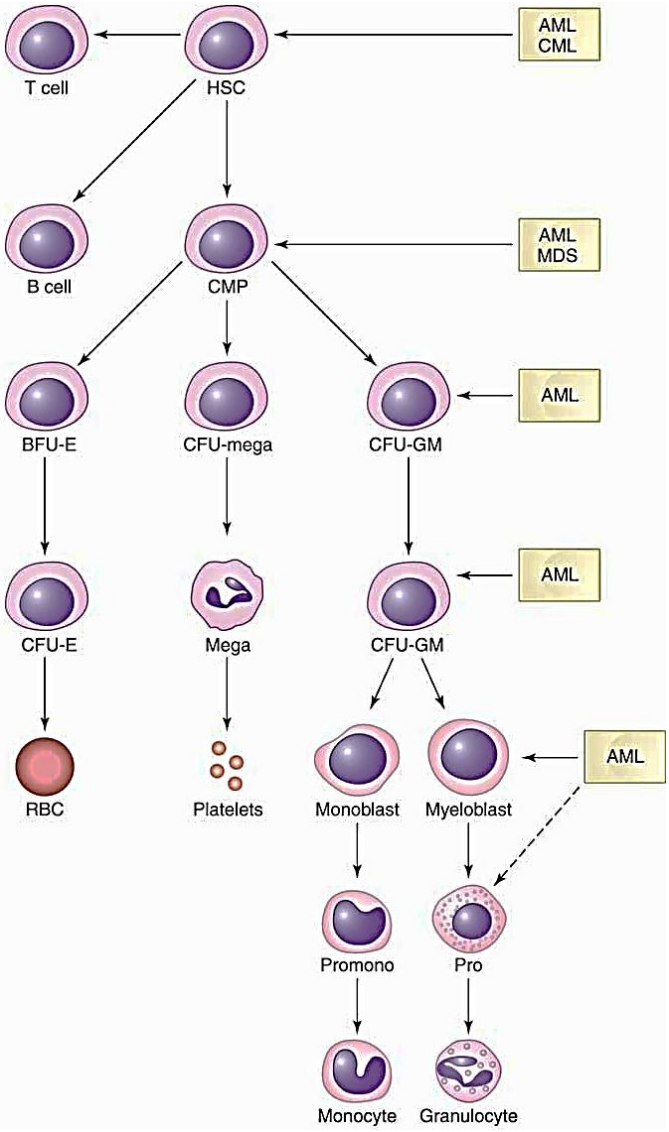


Fig. 17.3. Hematopoiesis in AML

Classification. The most common classification of the subtypes of AML is the ***FAB system***. This system is based on morphologic criteria alone, but current practice also requires the use of flow cytometry for identification of cell surface antigens and of chromosomal and molecular genetic techniques for additional diagnostic precision, and also to aid the choice of therapy:

– Ml — AML without the signs of maturation;
– M2 — AML with the signs of maturation;
– M3 — acute promyelocyte leukemia (PML);
– M4 — acute myelomonocytic leukemia;
– M5 — acute monocytic leukemia;

– M6 — erythroleukemia;
– M7 — acute megakaryocyte leukemia.

WHO classification is shown on the Table 17.1.

Table 17.1

WHO classification of AML

Group	Subgroups
AML with recurrent genetic abnormalities	AML with t(8; 21)(q22; q22), *AML1(CBFα)/ETO* Acute promyelocytic leukemia, AML with t(15; 17)(q22; q12), (*PML/RARα*), and variants (FAB M3) AML with abnormal bone marrow eosinophils: inv(16)(p13q22) or t(16; 16)(p13; q22), (*CBFβ/MYH11*) AML with 11q23(*MLL*) abnormalities
AML with multilineage dysplasia	Following myelodysplastic syndrome or myelodysplastic syndrome/ myeloproliferative disorder Without prior myelodysplastic syndrome
AML and MDS — therapy-related	Alkylating agent related Topoisomerase tyre II inhibitor-related (some can be lymphoid) Other types
AML not otherwise categorized	AML minimslly differentiated (FAB M0) AML without maturation (FAB M1) AML with maturation (FAB M2) Acute myelomonocytic leukemia (FAB M4) Acute monoblastic and monocytic leukemia (FAB M5) Acute erythroid leukemia (FAB M6) Acute megakaryoblastic leukemia (FAB M7) Acute basophilic leukemia Acute panmyelosis with myelofibrosis Myeloid sarcoma

Bone marrow examination performed for differential diagnoses from blood assessment or for protocol requirements.

Enumeration of blasts/blast equivalents by morphology and differential cell count: previously > 30 % blasts on BM aspirate (per FAB criteria); as per recent WHO criteria, AML is defined by greater than 20 % blasts on BM aspirate.

Patients with certain cytogenetic abnormalities are considered to have AML regardless of blast percentage: t(8; 21) (q22; q22), inversion (16)(p13q22); t(16; 16) (p13; q22), and t(15; 17) (q22; q12).

Unique situations compromising blast count: fibrosis and/or necrosis; predominance ($\geq$ 50 %) of erythroid lineage; marked hypocellularity; technically poor specimen.

Periodic Acid Schiff (PAS) stain reacts primarily with glycogen, generating a fuchsian coloured precipitate. Cytochemical staining for myeloperoxidase is important in establishing the lineage of myeloblasts.

Immunophenotyping:

– AML with minimally differentiated — immunological markers CD13, CD34, HLA-DR, CD33, CD117, CD2, CD7, TdT;

– AML without maturation — CD13, CD14, CD33, CD34;

– AML with maturation and with t (8; 21) — CD34, CD56;

– acute promyelocytic leukemia — CD13, CD33, HLA-DR absent, CD34 negative;

– acute myelomonocytic leukemia with abnormal eosinophils and inversion 16 — CD13, CD34, CD11b, CD11c, CD14, CD33;

– acute monocytic leukemia and 11q23 abnormalties — CD14, CD4, CD36, CD64;

– erythroleukemia — Glycophorin 7, Transferrin receptor CD71;

– acute Megakaryocytic leukemia — cCD41, cCD42b, cCD61.

Patients with AML often present with the following symptoms: bleeding, leukostasis, tumor lysis syndrome, and infections. Other general signs and symptoms of leukemia can also occur.

Besides thrombocytopenic bleeding, there is often coagulopathy, with mucosal (epistaxis, oral bleeding), gastrointestinal, or CNS bleeding. Coagulopathy results in disseminated intravascular coagulation (DIC), which occurs in parallel with infection and/or release of proteins with anticoagulant activities from the leukemia cells (e.g., thromboplastin). DIC is most frequently observed in acute promyelocytic leukemia. Therapies include platelet transfusion when platelet count is less than 20×10^9/l depending on the condition of the patient. Substitution of coagulation factors is controversial. In severe anemia, packed red blood cell transfusions are necessary.

If WBC is higher than 200×10^9/l, leukemic blasts may clump intravascularly. Small vessels may be blocked, resulting in hypoxia, infarction, and hemorrhage; this occurs mostly in the lungs and CNS. Because of the large size of AML blasts compared to lymphoblasts, leukostasis may occur with a WBC higher than 100×10^9/l; this is especially true in monocytic and myelomonocytic subtypes of AML. Therapies include rapid cytoreduction if WBC is more than $100–200 \times 10^9$/l by leukapheresis or exchange transfusion to be considered. Hydroxyurea for prevention of rebound phenomena after leukapheresis. Prevention of tumor lysis syndrome.

Table 17.2

ALL versus AML

Sighs	ALL	AML
Age	Mainly children	Mainly adults
Lymphadenopathy	Usually present	Usually absent
Gum hypertrophy	negative	positive in M4/M5
Skin infiltration	negative	positive in M4/M5
Granulocytic sarcoma	negative	Positive in few cases
Mediastinal mass	positive in T-ALL	negative
Associated DIC	negative	Positive in M3

Treatment. ***Induction therapy:***

• Cytarabine (e.g., ara-C) and anthracyclines (e.g., daunorubicin or liposomal daunorubicin L-DNR (reduction of cardio-toxicity)), nucleoside inhibitors, and

target monoclonal antibody-toxin fusions (e.g., anti-CD33-calicheamicin, gemtuzumab, ozogamicin, or Mylotarg) leaving to approximately 85 % remission (less than 5 % blasts in bone marrow) within 8 weeks of starting treatment.

• Other combinations, such as 6-thioguanine or etoposide in combination with daunorubicin or other anthracyclines, such as idarubicin or mitoxantrone or fludarabine, cytarabine, and idarubicin, result in similar remission rates of about 85 %. The overall survival, however, is not superior because of higher toxicity-related morbidity.

• While anti-CD33 MAB (gemtuzumab, ozogamicin) showed no significant differences to classical induction treatment in terms of remission rates, subgroup analyses have indicated improvement in event-free and overall survival in some subtypes of AML.

• Tyrosine kinase inhibitors or proteasome-directed drugs are in clinical evaluation.

• CNS prophylaxis includes either intrathecal cytarabine (ara-C) or cytarabine in combination with methotrexate and prednisone. Of note, intrathecal ara-C should not be given concurrently with high-dose, systemic ara-C as the combination can result in severe transverse myelitis and paralysis. There are no definitive data that cranial radiation provides better outcomes than intrathecal CNS leukemia prophylaxis. The incidence of CNS relapse is decreased to less than 5 % in patients treated with intrathecal and systemic chemotherapy that includes high-dose ara-C.

• Supportive therapy and prophylaxis (antibacterial, antiviral, antifungal) and use of hematopoietic growth factors reduce morbidity and mortality. Granulocyte colonystimulating factor (G-CSF) or granulocytemacrophage CSF (GM-CSF) shortens the periods of neutropenia and diminishes the frequency of infections and days of hospitalization, but do not influence on the rate of remission or outcome.

• MRD detection at the end of induction or in the post remission setting is associated with a poor prognosis.

Remission and postremission therapy. Consolidation and intensification therapy over the course of approximately 6–12 months result in an overall survival between 50 and 60 %. Some treatment programs use maintenance therapy, although this approach has not proven to be of benefit in multiple other studies when intensive chemotherapy is used.

17.3. HEMORRHAGIC DIATHESIS

Hemorrhagic diathesis is characterized by the tendency to bleeding and repeated hemorrhages occurred spontaneously or caused by injuries. Injury can be quite insignificant, which would never provoke bleeding in a healthy individual.

Etiology and pathogenesis are quite varied. Some types are hereditary but many can be caused by external factors. Avitaminosis (deficiency of vitamins C and P), some infections (long-standing sepsis, louse born typhus, virus hemorrhagic fevers, and icterohemorrhagic leptospirosis), allergy, liver, kidneys, and blood system diseases can provoke the onset of hemorrhagic diathesis.

Classification. Hemorrhagic diathesis can be classified by the pathogenesis into two major groups:

1) due to disordered capillary permeability (hemorrhagic vasculitis, vitamin C deficiency, some infectious diseases, trophic disorders, etc.);

2) due to disorders in the blood coagulation and anticoagulation system. This group is subdivided into the following:

A. Caused by disordered blood coagulation system:

1) 1rst phase: congenital deficit of plasma components of thrombo-platelet formation (factors VIII, IX, XI), haemophilias A, B, C, etc.; deficit of thrombocyte components (thrombocytopathy, e.g. thrombocytopenic purpura);

2) 2nd phase: deficit of plasma component of thrombin formation — factors II, V, X, the presence of antagonists to them and of their inhibitors;

3) 3rd phase: deficit of plasma components of fibrin formation-factors I (fibrinogen) and XII.

B. Caused by accelerated fibrinolysis (due to increased synthesis of plasmin and insufficient synthesis of antiplasmin).

C. Caused by disseminated intravascular coagulation (thrombohaemorrhagic syndrome or coagulopathy of consumption) in which all procoagulants are utilized during DIC and the fibrinolysis system is activated.

This concise classification is only conventional because several pathogenic factors are often involved. It covers a large group of diseases, both hereditary and acquired, and also secondary syndromes arising against the background of the main disease (metastasizing malignant tumor, burns, etc.).

Hemostasis. Primary haemostasis is initiated when platelets adhere, using a specific platelet collagen receptor glycoprotein Ia/IIa, to collagen fibers in the vascular endothelium. This adhesion is mediated by von Willebrand factor (vWF), which forms links between the platelet glycoprotein Ib/IX/V and collagen fibrils. The platelets are then activated and release the contents of their granules into the plasma, in turn activating other platelets and white blood cells. Platelets undergo a change in their shape which exposes a phospholipid surface for coagulation factors that require it. Fibrinogen links adjacent platelets by forming links via the glycoprotein IIb/IIIa. In addition, thrombin activates platelets.

The coagulation cascade of secondary hemostasis has two pathways, the Contact Activation pathway (formerly known as the Intrinsic Pathway) and the Tissue Factor pathway (formerly known as the Extrinsic pathway) that lead to fibrin formation. It was previously thought that the coagulation cascade consisted of two pathways of equal importance joined to a common pathway. It is now known that the primary pathway for the initiation of blood coagulation is the Tissue Factorpathway.

Tests for function of the coagulation system:

– common: aPTT, INR (PT), TCT, bleeding time, Ddimer;

– other: mixing test (whether an abnormality corrects if the patient’s plasma is mixed with normal plasma), antiphosholipid antibodies, coagulation factor

assays, genetic tests (eg. factor V Leiden, prothrombin mutation G20210A), dilute Russell viper venom test (dRVVT), platelet function tests, thromboelastography (TEG) or thromboelastometry (ROTEG).

Bleeding time: time interval between the skin puncture and spontaneous, unassisted stoppage of bleeding. Methods — "Duke's method", "ivy" bleeding time, normal bleeding time — 1–5 min.

Clotting time: time interval between entry of blood into glass capillary tube, or a syringe, and formation of fibrin threads. Method: "Wright's capillary glass tube", "Duke's drop", "Lee and white test-tube". Normal clotting time — 3–6 min.

Prothrombin time: normal P.T. — 15–20 sec. Clinical significance: bleeding tendency occurs below 20 % (Normal plasma prothrombin = 30–40 mg/dl). Low prothrombin suggests Vit. K def. or liver and biliary diseases. Prolonged suggests deficiency of factor II, V, VII, and X.

The contact factor pathway is initiated by activation of the "contact factors" of plasma, and can be measured by the activated partial thromboplastin time (aPTT) test.

The quantatative and qualitative screening of fibrinogen is measured by the thrombin time (TCT). Measurement of the exact amount of fibrinogen present in the blood is generally done using the Clauss method for fibrinogen testing. Many analysers are capable of measuring a "derived fibrinogen" level from the graph of the Prothrombin time clot.

If a coagulation factor is part of the contact or tissue factor pathway, a deficiency of that factor will affect only one of the tests: thus hemophilia A, a deficiency of factor VIII, which is part of the contact factor pathway, results in an abnormally prolonged aPTT test but a normal PT test. The exceptions are prothrombin, fibrinogen and some variants of FX which can only be detected by either aPTT or PT.

Clinical signs of secondary hemostasis violation. Deep hemorrhages (hemorrhages in the joints, muscles, interfascial spaces); towering ecchymosis; delayed post-traumatic and postoperative hemorrhages and hemorrhages.

Disorders of hemostasis:

1. Disorders of the platelet and vessel wall: immune thrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura (TTP), hemolytic-uremic syndrome (HUS), Glanzmann's thrombasthenia, Bernard–Soulier syndrome (abnormal glycoprotein Ib-IX-V complex), storage pool disorders, paroxysmal nocturnal hemoglobinuria, gray platelet syndrome: deficient alpha granules; delta storage pool deficiency: deficient dense granules.

2. Disorders of coagulation and thrombosis:

– disseminated intravascular coagulation;

– factor deficiencies: hemophilia A (factor VIII deficiency), hemophilia B (factor IX deficiency, "Christmas disease"), hemophilia C (factor XI deficiency, mild bleeding tendency), Von Willebrand disease (the most common bleeding disorder);

– factor inhibitors.

3. Disorders predisposing to thrombosis: heparin-induced thrombocytopenia and thrombosis ("white clot syndrome"); antiphospholipid syndrome (lupus anticoagulant, anticardiolipin antibody), factor V Leiden and activated protein C resistence; prothrombin mutation; protein C deficiency; protein S deficiency; antithrombin deficiency; abnormally raised levels of factor VIII and factor XI.

Vasculopathies and vasculitis. Develops due to the primary lesion of the vascular wall with possible secondary development of coagulation and platelet abnormalities. Includes hereditary hemorrhagic telangiectasia, Ehlers–Danlo syndrome, Marfan syndrome, giant hemangiomas in the hemangioma with thrombocytopenia, IgA vasculitis Henoch–Schönlein, hemorrhagic fevers, hypovitaminosis C and B, etc.

Trombocytopenies and trombocytopathies. Develops due to the primary lesion of the megakaryocytic-platelet sprout.

Thrombocytopenia: redistribution of thrombocytes and their deposition in the spleen; increased destruction (SLE, ITP); increased platelet consumption and thrombus formation (TTP); use of certain drugs.

Thrombocytopathy: characterized by abnormal platelets and/or violation of their functions (Glązmann's thrombastenias and von Willebrand's disease).

Hereditary coagulopathies: haemophilia A, hemophilia B, von Willebrand's disease, deficiency of clotting factors.

Acquired coagulopathies: vitamin K-dependent coagulopathies (arise when liver function is deficient, vitamin K absorption is abnormal, vitamin K deficiency is deficient, drugs such as coumarin are administered), ICE, liver pathology (leads to deficiency of many coagulation factors), pathological inhibitors of coagulation ("lupus" anticoagulant, specific inhibitors of coagulation — AT, specific to individual coagulation proteins).

Disturbances of stabilization of fibrin, increased fibrinolysis, including in the treatment of direct and indirect anticoagulants, fibrinolytics (streptokinase, urokinase, alteplase, etc.).

Other acquired coagulation disorders: a deficiency of clotting factors may occur in somatic diseases (eg, in amyloidosis, factor X deficiency).

Purpura — coloured petechial hemorrhages and bruises in the skin characterized by spontaneous hemorrhages beneath the skin, mucous membrane and internal organ.

Types of capillary abnormality: primary (congenital or hereditary), seen in children; secondary (symptomatic); allergies, infections, drugs, cancer.

Platelet disoders:

1. *Thrombocytopenic purpura (Werlhof's disease)* — is a hemorrhagic diathesis due to the deficit of blood platelets, was first described by P. Werlhof in 1735. TTP occurs mostly in young females. The etiology and pathogenesis are unknown. Immune-allergic mechanism is involved in 50 % of cases: anti-thrombocytic antibodies are produced and fixed on the surface of thrombocytes to damage them and to prevent their normal separation from megakaryocytes.

Triggers may be infection, toxicosis, individual hypersensitivity to certain foods and medicines. In some cases, is caused by hereditary insufficiency of certain enzyme thrombocyte systems which is activated by some additional factors.

Pathological anatomy. Multiple hemorrhages in the skin and the internal organs are characteristic. The spleen may be considerably enlarged. Separation of thrombocytes from megakaryocytes in the bone marrow is disordered (according to histological findings).

Clinical signs. Multiple hemorrhages on the skin and mucosa: small dots (petechiae) or large spots (ecchymosis). Hemorrhage may be spontaneous and due to insignificant injuries, mild contusion, pressure on the skin, etc. Hemorrhagic lesions are first purple, then darken to cherry-red and brown, lighten to yellow and disappear in several days. But new lesions develop to succeed the disappearing ones. Bleeding from the nose, GI tract, kidneys or uterus are not infrequent; hemorrhages into the internal organs (brain, fundus oculi, myocardium, etc.) are also possible. Grave and prolonged bleedings arise in extraction of teeth or in other minor operations. The tourniquet test (especially the pinch test) is positive. Spleen and the lymph nodes are usually not enlarged; tapping on the bones is painless.

Labs. Thrombocyte counts are usually less than 50×10^9/l; in some cases only single blood platelets can be found. The degree of bleeding can be assessed by the degree of thrombocytopenia. Hypochromic anemia can develop after profuse bleeding. The clotting time is normal in most cases, but it can be slightly longer (due to the deficit of thromboplastic factor III of blood platelets). The bleeding time increases to 15–20 min and more; clot retraction is disordered. Throm-boelastography reveals greatly increased reaction and clotting time.

2. von Willebrand disease — is the most common inherited bleeding disorder. Autosomal dominant, prevalence 1 case per 1000. The hallmark of the disease is defective platelet adhesion to subendothelial components caused by a deficiency of the plasma protein vWf. This factor is a large, multimeric protein synthesized, processed, and stored in the Weibel–Palade bodies of the endothelial cells, and it is secreted constitutively following stimulation. vWf has a major role in primary hemostasis as mediator of the initial shear-stress-induced interaction of the platelet to the subendothelium via the glycoprotein Ib complex. In addition, von Willebrand protein acts as a carrier and stabilizer of factor VIII by forming a complex in the circulation. In the absence of vWf, the factor VIII level is low. In classic hemophilia A, the factor VIII level is low because of a deficiency of factor VIII itself, whereas in von Willebrand disease, the factor VIII level is low because of a deficiency in its carrier protein.

Von Willebrand disease is a relatively mild bleeding disorder, except for homozygous who has severe bleeding often indistinguishable from classic hemophilia. The bleeding manifestations are predominantly skin related and mucocutaneous (i.e., easy bruising, epistaxis, GI hemorrhage). Most episodes occur following trauma or surgery. Menorrhagia is common, often exacerbated by

the concurrent administration of cyclooxygenase inhibitors. Pregnant patients with this disease usually do not have problems.

Labs. Bleeding time is prolonged because von Willebrand protein is phase-reactant (i.e., increased synthesis in the presence of inflammation, infection, tissue injury, and pregnancy), a mild prolonged bleeding time may be normalized, resulting in difficulty in diagnosis. In addition to the prolonged bleeding time, characteristic abnormalities in platelet aggregation tests occur. Platelets aggregate normally to all agonists except ristocetin. The antibiotic ristocetin induces binding of the von Willebrand protein to platelets, similar to what happens with platelets following vessel wall injury in vivo. Ristocetin-induced platelet aggregation correlates with the platelet-aggregating activity of the von Willebrand protein. Levels of coagulation factor VIII are also low, resulting from a decrease in vWf.

Immune thrombocytopenic purpura (ITP) is one of the most common autoimmune disorders. It occurs in 2 distinct clinical types, an acute self-limiting form observed almost exclusively in children (5 cases per 100,000 persons), and a chronic form, observed mostly in adults (3–5 cases per 100,000) and rarely in children. ITP is caused by autoantibodies to platelets. The antigenic target in most patients appears to be the platelet glycoprotein IIb/IIIa complex. Platelets with antibodies on their surface are trapped in the spleen, where they are efficiently removed by splenic macrophages. The mechanism of origin of these antibodies is not known. Antibodies may be directed towards the viral antigens and then cross-react with platelet antigens. They persist because of the failure of immune surveillance mechanisms to repress it. These antibodies can also react with the developing megakaryocytes in bone marrow, leading to decreased protection of platelets (ineffective thrombopoiesis).

ITP occurs commonly in otherwise healthy individuals and only rarely as the initial manifestation of lupus and other autoimmune disorders. HIV infection is often associated with immune thrombocytopenia in both adults and children.

Acute ITP affects both genders equally and has a peak incidence in children aged 3–5 years. Most patients have a history of antecedent acute viral syndrome. Onset is sudden, with symptoms and signs depending on the platelet count. Bleeding is usually mild unless the platelet count drops below 20,000/l. With platelets 20,000–50,000/l, petechiae and ecchymosis are observed following mild trauma. With platelets below 10,000/l, generalized petechiae, ecchymosis, and mucosal bleeding occur. With platelets below 2000/l, widespread ecchymosis, hemorrhagic bullae, and retinal hemorrhage occur.

Physical examination reveals only petechiae and ecchymosis. Lymphadenopathy or splenomegaly suggests other secondary causes of thrombocytopenia rather than ITP. The peripheral smear shows a decreased number of platelets. Often, the smear shows giant platelets, which is a reflection of increased thrombopoietin-induced stimulation of the bone marrow. At times, the smear may show eosinophilia and lymphocytosis, possibly reflecting hypersensitivity to the inciting viral antigens. The bone marrow shows an increase

in the number of megakaryocytes and signs of thrombopoietin-induced megakaryocyte stimulation (increase in number and ploidy, decrease in cytoplasm) resulting in large platelets in the periphery.

Thrombocytopenia in an otherwise healthy child with normal white and red blood cell counts almost always results from ITP. Findings from a careful history and physical examination help exclude other causes of thrombocytopenia, such as lupus and HIV infection. Acute leukemia is unlikely to manifest as an isolated thrombocytopenia without any abnormalities in the smear. Bone marrow examination is necessary only if atypical features (other abnormalities in the smear, sternal tenderness, lymphadenopathy, splenomegaly) or an unusual clinical course is evident. This is typically observed in adults aged 20–0 years. It has an insidious onset, and a history of an antecedent infection need not be present.

Chronic ITP is more common in females than in males. As in childhood ITP, the bleeding manifestations depend on the platelet count.

The diagnosis of ITP is established by the exclusion of other causes of thrombocytopenia. CBC should be examined to rule out thrombotic thrombocytopenic purpura (TTP) (fragments) or spurious thrombocytopenia resulting from clumping. Often, the smear shows giant platelets, which is a reflection of the increased thrombopoietin-induced stimulation of bone marrow. Bone marrow examination, which is not always necessary, shows increased megakaryocytes.

Posttransfusion purpura typically occurs 10 days following a transfusion and can be induced by a small amount of platelets contaminating a RBC transfusion or fresh frozen plasma transfusion. The thrombocytopenia responds to intravenous immunoglobulin (IVIG). Other platelet alloantigens are occasionally implicated in posttransfusion purpura.

The prevalence of ***neonatal alloimmune thrombocytopenia*** is 1 case in 200 term pregnancies; for clinically apparent disease, the prevalence is 1 case in 1500 term pregnancies. It is the most common cause of severe neonatal thrombocytopenia. Maternal antibodies against the fetal platelet antigens inherited from the father but absent in the mother, cross the placenta and induce severe thrombocytopenia. Typically, the diagnosis is considered when bleeding or severe thrombocytopenia occurs in a baby after an otherwise uncomplicated pregnancy. The affected infant may have intracranial hemorrhage, and the disorder is associated with a relatively high mortality rate. The platelet count should be checked immediately after delivery and 24 hours later as it continues to fall.

Hemophilia A (factor VIII deficiency) and hemophilia B (factor IX deficiency) — rare bleeding disorders due to inherited deficiencies of coagulation factors.

Haemophilia A (Classic) Factor VIII deficiency, Haemophilia B (Christmas Disease) Factor IX deficiency clinically similar: occur in approximately 1 in 5,000 male births, up to 90 % of congenital bleeding disorders; hemophilia A is approximately 5 times more common than B.

Inherited as a sex linked recessive trait with bleeding manifestations only in males, genes which control factor VIII and IX production are located on the X chromosome; female carriers transmit the abnormal gene.

Pathophysiology. Factors VIII and IX participate in a complex required for the activation of factor X. After injury, the initial hemostatic event is formation of the platelet plug, together with the generation of the fibrin clot that prevents further hemorrhage. In hemophilia A or B, clot formation is delayed and is not robust. Severity is dependent on blood levels of functioning factor VIII or IX, varies markedly between families but is relatively constant among family members in successive generations, remains relatively unchanged throughout life.

Classification. According to % of normal factor level:

– severe < 1 %, bleeding after trivial injury or spontaneous;

– moderate 1–5 %, bleeding after minor injury; occasional spontaneous bleeds;

– mild 6–30 %, bleeding following major trauma, surgical or dental procedures.

Clinical signs. *Joints (hemarthrosis):* knees, ankles and elbows most common sites begin as the child begins to crawl and walk. Many bleeds occur between the ages of 6 and 15 years. Single joint bleed: stiffness, swelling, pain, loose pack position.

Subacute hemarthrosis develops after repeated bleeds into the joint. Synovium becomes inflamed, hypertrophy, hyperplasia and increased vascularity of synovial membrane. Hemosiderosis: hemoglobin of intra articular blood is degraded and iron deposited into the joint space.

Chronic arthropathy: progressive destruction of a joint. Pannus (inflammed synovium), enzymes begin to destroy articular cartilage. Microfracture and cyst formation in subchondral bone. End stage: firbrous joint contracture, and disorganization of articular surfaces.

Muscle bleeds: beeding into muscle or soft tissue. Less tendency to recurrent bleeds. Sites: iliopsoas, calf, upper arm and forearm, thigh, shoulder area, buttock. Symptoms: pain, swelling, muscle spasm. Complications: nerve compression, contracture.

Other sites of bleeding: abdomen, GI tract, intracranial bleeds, around vital structures in the neck.

Laboratory data. Factor VIII or factor IX deficiency leads to prolongation of APTT. In severe hemophilia, APTT is usually 2–3 times the upper norm. All other screening tests normal. The specific assay for factors VIII and IX will confirm the diagnosis of hemophilia.

Management. Replacement of missing clotting factor: plasma products, cryoprecipitate, concentrates of factor VIII factor IX.

Early, appropriate therapy is the hallmark of excellent hemophilia care. Mild to moderate bleeding, levels of factor VIII or factor IX must be raised to hemostatic levels in the 35–50 % range. For life-threatening or major hemorrhages, the dose should aim to achieve levels of 100 % activity.

Adoption of prophylaxis as a gold standard of hemophilia management has been supported by the results of numerous trials. Recent observations suggest

protective effect of early start of prophylaxis on inhibitor development. The feasibility of indefinite extension of prophylaxis in adulthood has been intensively discussed. Substantial progress has been achieved also in the treatment of hemophilia with inhibitors, including the availability of effective bypassing agents and the adoption of immune tolerance induction as a first choice therapy for newly developed inhibitors. Despite promised reports on prophylaxis with bypassing agents, the routine use of this treatment in inhibitor patient has still major limitations.

Complications. One of the most troublesome complications of factor replacement in hemophilia is the development of inhibitory antibodies to factor VIII or factor IX in a subset of the hemophilia population (20–30 %, and 3–5 %, respectively). It is still not possible to predict with certainty the patients who will develop inhibitors. Risk factors that have been explored include the nature of the underlying mutation, with those leading to substantial loss of coding information representing greater risk; high intensity product exposure; CNS bleeding; and African-American race.

Current methods for eradicating inhibitors rely on regimens termed immune tolerance induction (ITI), which require daily infusion of high doses of clotting factor concentrates, for periods ranging up to 18 months. This successfully abolishes inhibitors in ~ 60–80 % of cases of haemophilia A, with a much lower success rate, on the order of 15 %, for haemophilia B.

With mild factor VIII hemophilia, the patient's endogenously produced factor VIII can be released by the administration of desmopressin acetate.

Other treatment: analgesics (no aspirin), good dental care, education — lifelong management, psychological counseling.

Acute and long term management of musculoskeletal problems.

Acute bleeds: immediate replacement factor; immobilize joint; No weight bearing; immediate medical attention if complications arise.

After 24 hours: continue minimal or no weight bearing for lower extremity bleed; active range of motion; gentle stretching; corrective positioning (splinting ??); isometric strengthening; progress to isotonic.

Long term: repeated musculoskeletal examination (annual or biannual); measurement of leg length, girth, ROM, strength, gait, function; physiotherapy treatment: based on assessment findings; prophylactic factor replacement; usually provided every 2–3 days to maintain a measurable plasma level of clotting factor (1–2 %) when assayed just before the next infusion (trough level).

Education: importance of early factor replacement; use of helmet when riding tricycle/bicycle; sports: contact sports discouraged for severe hemophiliacs; swimming, cross country skiing, tennis, golf, baseball, bicycling — generally considered safe; footwear.

Long-term complications of hemophilia A and B include: chronic arthropathy; development of an inhibitor to either factor VIII or factor IX; risk of transfusion-transmitted infectious diseases.

CHAPTER 18
EMERGENCY

18.1. COMA

Coma is a state of complete loss of consciousness with a lack of reaction to any stimuli (including painful ones) and dysfunctions of all analyzers, impaired blood circulation, respiration, and metabolic processes. In coma there is a disturbance of the fuctioning of the cerebral hemisheres ad/or the reticular activating system of the brainstem. The level of awareness may range from excessive drowsiness to unconsciousness and assesed by Glasgow Coma Scale (Table 18.1). Coma is a life-threatening condition, the outcome is largely determined by the timeliness of the assessment of the situation and the adequacy of the urgent medical measures taken.

Table 18.1

Glasgow Coma Scale

Opening arbitrarily to the addressed speech to pain stimulus absent	**Glasgow Coma Scale (4–15 years)**	**Children's Come Scale (les 4 years)**	**Score**
Eyes	Open spontaneously	Open spontaneously	4
	Verbal command	React to speech	3
	Pain	React to pain	2
	No response	No response	1
Best motor response			
Verbal command	Obeys	Spontaneous or obeys verbal command	6
Painful stimulus	Localizes pain	Localizes pain	5
	Withdraws	Withdraws	4
	Abnormal flexion	Abnormal flexion (decorticate posture)	3
	Extension	Abnormal Extension (decerebrate posture)	2
	No response	No response	1
Best verbal response	Oriented and converses	Smiles, orientated to sounds, follows objects, interacts	5
	Disoriented and converses	Fewer than usual words, spontaneous irritable cry	4
	Inappropriate words	Cries only to pain	3
	Incomprihesible sounds	Moans to pain	2
	No response	No response	1

Symptoms: inability to voluntarily open the eyes; a non-existent sleep-wake cycle; lack of response to physical (painful) or verbal stimuli; depressed brainstem reflexes, such as pupils not responding to light; abnormal, difficulty, or irregular breathing or no breathing at all when coma was caused by cardiac arrest; scores between 3 and 8 in Glasgow scale.

Causes:

– infection (meningitis or meningoencephalitis);

– methabolic (diabetes mellitus, inborn errors of methabolism, hepatic failure, AKI, hypoglycemia);

– poisoning;

– status epilepticus;

– traumatic brain injury;

– intracranial tumor or haemorrage / infarct / abscess;

– hypertension.

In contrast to adults most children have a diffuse methabolic insult rather than a structural lesion.

Diagnosis. Although diagnosis of coma is simple, investigating the underlying cause of onset can be rather challenging. As such, after gaining stabilization of the patient's airways, breathing and circulation (the basic ABCs) various diagnostic tests, such as physical examinations and imaging tools (CT scan, MRI, etc.).

Primary assessment and resuscitation:

– *airway* — is it secure?

– *breathing* — is respiratory effort sufficient?

– *circulation* — treat shock

– *disability* — check blood glucose

– *exposure* — e.g. look for meningococcal purpuric rash.

Secondary assessment and emergency treatment. Examination:

– Is there raised intracranial pressure — abnormal breathing, posture, pupils, fundi (papilloedema or retinal haeorrhages)?

– Bradycardia and hypertension suggest impeding brain stem.

Treatment. Treat the treatable:

– hypoglycemia;

– poisoning;

– diabetes mellitus;

– septicemia / meningitis;

– herpes simplex encephalitis

18.2. ADRENAL INSUFFICIENCY

Primary adrenal insufficiency. Primary adrenal insufficiency (PAI) is defined by the inability of the adrenal cortex to produce sufficient amounts of glucocorticoids and/or mineralocorticoids. First described by T. Addison and is commonly termed Addison's disease. Prevalence is 93–140 per 1 000 000. Most common cause in children is Congenital Adrenal hyperplasia.

Causes of PAI. Congenital:

1. Congenital adrenal hyperplasia. Affected gene CYP21, HSD3B2, CYP11B2, StA R, POR), clinical phenotype: salt wasting, ambiguous genitalia, virilization.

2. Congenital adrenal hypoplasia. Affected gene DAX1: hypogonadotropic hypogonadism; SF1: XY sex reversal, polysplenia/asplenia; CDKN1C: IMAGe

syndrome (IUGR, adrenal hypoplasia, metaphyseal dysplasia, genitourinary abnormality), Pllister Hall syndrome, Meckel syndrome, Pena Shokeir syndrome.

3. ACTH insensitivity syndrome: familial glucocorticoid deficiency type 1 and 2, DNA repair defect.

4. Metabolic diseases: adrenoleukodystrophy, peroxisomal disorder, cholesterol disorder, mitochondrial disorder.

Acquired:

1. Autoimmune adrenalitis (Addison disease): isolated autoimmune adrenalitis; autoimmune polyendocrinopathy type 1 — AIRE gene mutation (hypoparathyroidism, chronic mucocutaeneous candidiasis); autoimmune polyendocrinopathy type 2 — CTLA-4 gene mutation (autoimmune thyroiditis, type 1 DM, vitiligo).

2. Bilateral haemorrhage/infarction, trauma; Waterhouse–Friderichsen syndrome; anticoagulation, APLA.

3. Infection. Viral: HIV, CMV. Fungal: coccidioidomycosis, histoplasmosis, blastomycosis, cryptococcosis. Mycobacterial: tuberculosis.

4. Infiltrative. Hemochromatosis, histiocytosis, sarcoidosis, amyloidosis, neoplasm.

5. Drugs: mifepristone, aminoglutethimide, mitotane, ketoconazole, etomidate, metyrapone, tyrosine kinase inhibitors (e.g., sunitinib).

Clinical features. ***Adrenal insufficiency:***

– fatigue;

– weight loss;

– postural dizziness;

– anorexia, abdominal discomfort;

– hyperpigmentation (skin creases, buccal mucosa, areola, scars, knuckles, elbow);

– low BP with increased postural drop;

– failure to thrive;

– seizure secondary to hypoglycemia.

Adrenal crisis: severe weakness; syncope; abdominal pain; nausea, vomiting; confusion; hypotension; abdominal guarding; reduced consciousness, delirium.

Most symptoms are nonspecific and present chronically, often leading to delayed diagnosis: prolonged cholestatic jaundice, failure to gain weight and hypoglycemia in neonates and infants; salt craving in minerelocorticoid deficiency; virilization in congenital AH. No hyperpigmentation in Secondary AI.

Diagnosis:

– 8:00 AM serum cortisol level ≤ 3 mcg/dL — highly suggestive of the diagnosis;

– ACTH level two fold greater than the upper limit of the normal range along with a 8 AM cortisol < 5 mcg/dL is consistent with PAI;

– ACTH low in secondary AI;

– serum cortisol < 10 ug/dl at the time of hypoglycemia (critical sample) suggest the diagnosis of AI;

– during acute illness cortisol < 18 mcg/dL can be indicative of AI;

– 17-OH progesterone;

– low serum aldosterone with elevated plasma renin activity is the hallmark of mineralocorticoid deficiency;

– hyponatremia;

– hyperkalemia;

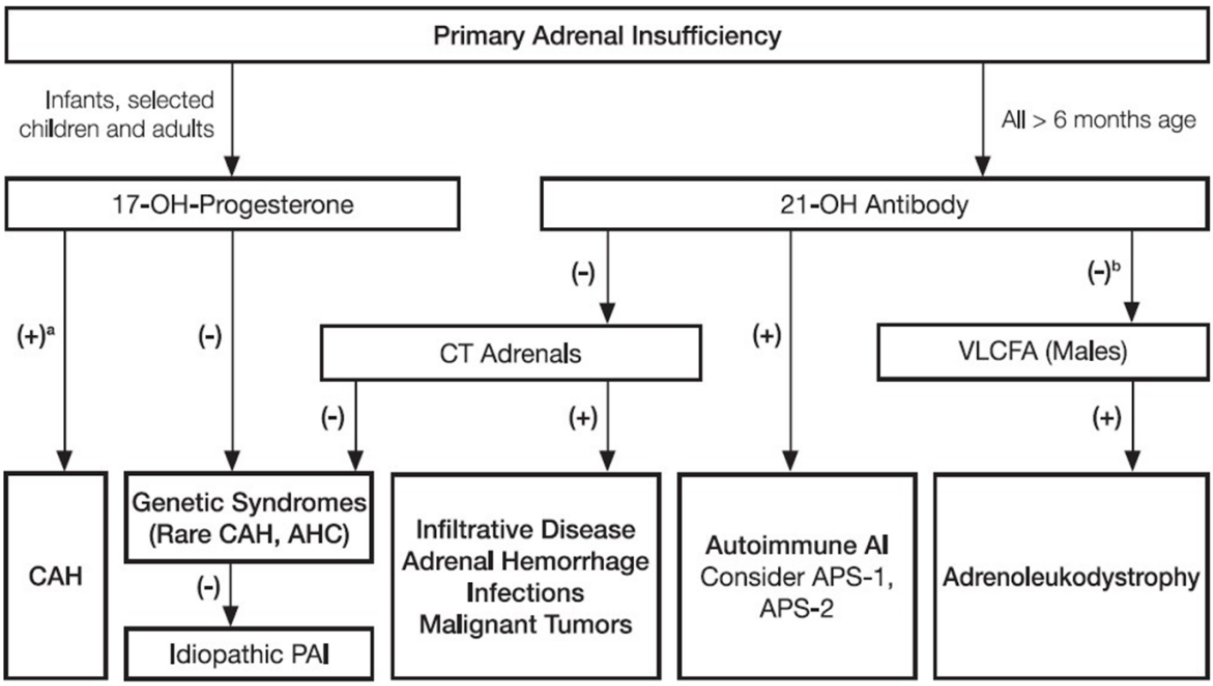
– hypoglycemia;

– metabolic acidosis;

– normocytic anemia, lymphocytosis, eosinophilia.

Dynamic testing of adrenal function. Cosyntropin (synacthen) DOSE (im/iv): infants — 15 ug/kg; < 2 yrs — 125 ug; > 2 yr — 250 ug. Serum cortisol after 30 minute: normal > 16 ug/dl. Acton Prolongatum: 60 iu/ml, available as 5 ml vial. Dose: 25 IU im; serum cortisol after 60 minute: normal > 18 ug/dl.

Etiological evaluation: antibodies against 21-htdroxylase or 17 hydroxylase; plasma VLCFA level; USG, CT adrenal; genetic study.



Adrenal crisis. Signs and symptoms:

– neonate with atypical genitalia;

– knows patient of AI;

– patient on chronic corticosteroid treatment;

– patient with other autoimmune deficiency;

– hyperpigmentation or vitiligo;

– critically ill patient with shock not responding to fluids and ionotropes.

Management. Don't delay in treatment. Baseline sample for electrolytes, glucose, cortisol, ACTH, PRA, 17OH P.

Stress glucocorticoid: Inj Hydrocortisone iv 50–100 mg/m^2 bolus followed by hydrocortisone 50–100 mg/m^2/d divided q 6 h; If BSA not available: 0–3 years — 25 mg, 3–12 years — 50 mg, > 12 years — 100 mg iv.

Shock: NS bolus 20 ml/kg over, up to total 60 ml/kg within 1 hour.

Hypoglycemia: 0.5–1 gm/kg of dextrose iv 2–3 ml/min (D10W 5–10 ml/kg or D25W 2–4 ml/kg.

Glucocorticoid replacement:

• Cortisol secretory rate in children 6–8 mg/m^2/day.

• The recommended replacement glucocorticoid in children is Hydrocortisone: Primary AI other than CAH — 8–12 mg/m^2/d, CAH — 10–15 mg/m^2/d.

• In three divided doses — highest dose in the morning, last dose 4–5 hours before bed time.

• Minerelocorticoid replacement.

• Fludrocortisone 0.1 mg daily.

• Newborn with CAH may require higher dose up to 0.4 mg.

• Infants, especially below 6 months require NaCl supplementation of 1 to 2 g/d (17 to 34 mmol/d), divided in several feedings.

Stress dose. What is considered as stress: fever > 38.0 °C; trauma; vomiting, diarrhea; critical illness; anaesthesia; surgery.

Sick day management:

• Hydrocortisone replacement doses doubled (38 °C) or tripled (39 °C) until recovery (usually 2 to 3 d).

• Increased consumption of electrolyte containing fluids as tolerated. Gastroenteritis/vomiting/unable to tolerate orally.

• IV hydrocortisone 50 mg/m^2 or estimate; infants, 25 mg; school-age children, 50 mg; adolescents, 100 mg.

Monitoring of treatment: every 3–6 months; glucocorticoid:

– biochemical monitoring with cortisol has no value;

– clinical assessment, including growth velocity, body weight, blood pressure, general wellbeing and energy levels.

Minerelocorticoid: serum electrolytes, blood pressure.

Newer therapies:

– continuous subcutaneous hydrocort infusion pump;

– dual release hydrocortisone (Plenandren);

– delayed and sustained multiparticulate hydrocortisone (Chronocort);

– hydrocortisone liquid formulation;

– hydrocortisone mini pill (< 5 mg tablets/granules);

– gene therapy with lentivirus for ALD.

18.3. Fever in Children

The core temperature of the body refers to the temperature of the deep tissues of the body, and in normal circumstances it is very tightly regulated. When a person is too hot, the amount of blood flowing through the skin by opening up

the tiny capillary blood vessels increases. This radiates away the excess of heat and sweating can further enhance this. When a person is too cold, skin blood vessels shut down and conserve heat within the internal organs. If necessary, the body can generate more heat by shivering.

In children the part of the human brain that controls the body temperature is not fully developed, and the body temperature in infants and children is less constant than that in adults. Childs temperature may rise and fall very quickly, and children are more sensitive to the temperature of his or her surroundings.

In children the body temperature may be measured using any of an electronic or a chemical dot thermometer, or infrared tympanic thermometer.

The normal temperature in the child's mouth or inside ears is 36 to 36.8 °C. The rectal temperature gives the most accurate reading of the body temperature, (the closest to "core" temperature). It is slightly higher (about 0.5 °C) than the readings taken from the mouth or ear. The average normal rectal temperature is 37.2–37.8 °C. The temperature readings from the armpit are not reliable and are about 0.5 °C lower than the mouth temperature.

Fever is an important part of the body's mechanisms of defence against viruses and bacteria. Fever requiring further tests is defined as:

– more than 38 °C in a baby yonger than 3 months;

– more than 39 °C in a baby older than 3 months.

During early childhood extremely high temperature is 39.5–40.5 °C.

One of the major goals of the evolution of a sick child is to identify the seriously ill child who requires specific therapeutic intervention. The causes of a serious illness in the acutely febrile child vary depending on the age. The infant in the first 3 month of life is more susceptible to sepsis and meningitis.

The acutely ill child with a serious illness is identified by:

– observation — for specific evidence of a serious illness, normal visual behavior is an important indicator of well-being;

– a thorough history taking, including the check for ill contacts, immunization history, parents' concerns and perception of a fever in their child;

– physical examination: a general level of interaction, skin color, hydration, an assessment of fontanel tension (it can be determined if the fontanelle is depressed, flat, or bulging). During the oropharyngeal examination (it is important to document the presence of enanthemas caused by Coxsackie virus, inflammation or exudates on the tonsils, which may be viral or bacterial);

– measurements (temperature — the degree of fever, the heart rate, the presence of tachycardia out of proportion to the fever; respiratory rate — the presence of tachypnea, cutaneous perfusion should be assessed by the warmth and capillary refill time, BP — hypotension), presence or absence of symptoms and signs indicating a serious illness;

– risk factors evaluation;

– use of screening laboratory tests.

Features indicating a low risk of a serious illness:

– activity: normal behavior: a child responds normally, is content and smiles, strong normal cry, stays awake or awakens quickly if roused;

– color: a normal color of the skin, lips and tongue;

– normal RR, normal HR;

– normal hydration;

– generally normal when there is no fever at time of the examination.

A child may be managed at home but parents have to seek medical advice if the child:

– stops drinking;

– has a dry mouth, no tears, and sunken fontanelle;

– has a non-blanching rash: take a glass tumbler and press it firmly against any rash. If the spots can be seen through the glass and do not fade;

– has a convulsion;

– gets worse;

– if the fever is present for no less than 5 days.

Features indicating an intermediate risk of a serious illness (children need admission):

– activity — abnormal behavior: not responding normally and decreased activity, prolonged stimulation required to awake a child;

– color — pallor;

– breathing: nasal flaring, tachypnea (RR > 50 breaths/min in 6–12 months of age and more than 40 breaths/min in more than 12 months of age), desaturation in the air (< 95 % in the air), chest crackles;

– hydration: capillary refill time more than 3 sec., dry mucous membranes, poor feeding, reduced urine output;

– fever no less than 5 days;

– swelling of the limb or the joint.

Features indicating a high risk of a serious illness:

– activity: child is unresponsive, appears ill and decreased activity, weak high-pitched or continuous cry;

– color: pale, mottled, blue;

– breathing: grunting, severe distress;

– hydration: reduced skin turgor;

– non-blanching rash;

– bulging fontanelle;

– neck stiffness;

– seizures or focal neurology;

– bile-stained vomiting.

Patients with these features have a life-threatening illness and need urgent treatment.

Differential diagnosis:

1. Meningococcal disease (an ill-looking child, non-blanching rash, purpuric lesions more than 2 mm, capillary refill time no less than 3 s, neck stiffness).

2. Meningitis (bulging fontanelle, neck stiffness (a child with menin-gitis will hold the neck stiffly and will often cry when any attempt is made to flex the neck), the Kernig and Brudzinski signs may be sought at this time, a depressed level of consciousness, seizures).

3. Herpes simplex encephalitis (a depressed level of consciousness, focal seizures, focal neurology).

4. Pneumonia (grunting, tachypnea, chest recession, nasal flaring).

5. Urinary tract infection (lethargy or irritability, vomiting, poor feeding, abdominal pain or tenderness, urinary frequency or dysuria, more than 5 white blood cells/high-power field on a spun urine specimen or hematuria).

6. Other: viral infection, bacterial gastroenteritis, bacteremia, the respiratory tract infection, osteomyelitis, endocarditis, rheumatic fever, post-vaccination fever, malaria, tuberculosis.

If there is no apparent source of infection despite fever, then the investigation should include the following:

1) blood (culture, full blood count, C-reactive protein (CRP), electrolytes);

2) urine: tests for UTI;

3) lumbar puncture: consider if the clinical assessment dictates;

4) chest X-ray: consider in case of white blood cell count.

Signal points of severe disease. The febrile infant in the first 3 months of life has yet to achieve immunologic maturity and, therefore, is at a greater, risk for serious bacterial infection than the child beyond 3 months of age. In all febrile children, the higher the fever is; the greater the risk of serious illness (bacteremia). An elevated C-reactive protein value may also distinguish bacterial from viral infection.

Treatment. The fever of variable degrees accompanies the most acute infections. If the febrile child has features indicating a low risk of a serious illness and is older than 3 months and feels well, the child may be followed expectantly. However, high temperature increases restlessness, accentuates insensible fluid loss from the skin and the lungs — because of the tendency to dehydration, caused by fever, maintenance of fluid intake is important.

In most cases the intake of small sips of fluids at frequent intervals is preferable, rather than large amounts are less frequently. Parents should encourage their child to drink an adequate amount of fluids.

Control of fever is advisable. Although opinions differ, measures are usually taken to reduce the temperature when it exceeds 38.5 °C.

Actions to reduce a fever may help make the child feel more com-fortable.

The simplest and the most effective way to help a child with a fever is to take off some of the child's clothes, so heat can escape from their body more easily.

But, if a child has goose bumps or starts to shiver, the environment is too cold and they will not lose heat. Do not put the child in the cold at this time because their skin will get cold while their inside temperature will go up.

Medications (antipyretics). This is the most effective way to treat a fever.

Acetaminophen (brand names: Tylenol, Paracetamol, Panadol) reduces the fever by direct acting on a hypothalamic heat-regulating center, increasing dissipation of the body heat via vasodilatation and sweating.

The dose of acetaminophen should be calculated based upon the childs weight, but not age. The dose is 10–15 mg/kg per dose orally.

When the child is vomiting, acetaminofen may be given rectally in the form of suppositories. Acetaminophen may be given every 4 to 6 hours as needed but should not be given more than 6 times per day (60 mg/kg/day). Acetaminophen should not be used in children younger than 3 months of age.

Ibuprofen (brand names: Motrin, Advil, Nuprin, Medipren) inhibits prostaglandin formation. The dose is 5–10 mg/kg per dose orally every 6–8 hours. Ibuprofen should not be used in children younger than 6 months. May be given in capsules (200 mg), caplet (100, 200 mg), oral drops (40 mg/ml), susp. (100 mg/ 5 ml), tabs (200, 400, 600, 800 mg), chewable tabs (50, 100 mg). Don't exceed the dose of 30 mg/kg/day.

These treatments can reduce the child's discomfort and lower the child's temperature by 1 to 1.5 °C.

Giving the combinations of acetaminophen and ibuprofen increases the chance of giving the wrong dose of one or the other of the medications.

Aspirin is contraindicated for treatment of fewer for children under the age of 18 years. It can cause a rare but serious illness known as Reye syndrome.

A child with a fever may not feel hungry, and it is not necessary to force them to eat. Fluids such as milk (cows or breast), formula, and water should be offered frequently. If the child is unwilling or unable to drink fluids, the parent should consult the child's health care provider.

Rest. Having a fever causes most children to feel tired and achy. During this time, the parents should encourage their child to rest as much as the child wants. It is not necessary to force the children to sleep or rest if they begin feel better.

The limit of physiologic thermoregulation is 41.1 °C and fevers in this range indicate bacteremia, but CNS infection is possible, as well as pneumonia, or pathologic hyperthermia.

Hyperthermic syndrome in children, causes of hyperthermia.

1. Sudden exo- and endotoxin release during the treatment of infection.

2. External heating — if a child is left in a closed automobile (the temperature raises very quickly).

3. Malignant hyperthermia during anesthesia (with halothane and succinylcholine derivatives in genetically sensitive persons).

4. Drug-induced (ecstasy, methamphetamine).

5. Neuroleptic malignant syndrome.

The diagnosis can be made in children with a high fever and pallor, thirst, nausea, sweating prominent, weakness, headache, disorientation, muscle cramps on exertion, salt and water depletion.

Pulse (tachycardia) + breathing (tachypnea) + limbs (cool and mottled) = shock!

Heart stroke — life-threatening failure of thermoregulation, rectal tempereture is more than 40 °C. Patient is incoherent, combative, shivering, vomiting, comatose; may have seizures, nuchal rigidity, decerebrate posturing and multiple organ system failure.

Treatment:

1. Cool the patient with cool ice, and fans.
2. Position (in shock — elevate the legs to improve venous return).
3. Intravenous fluids — perfusion needs to be restored with crystalloid infusion of I.V. bolus of normal saline 10 ml/kg, can be given over 30 min and repeated if necessary. If more than 20 ml/kg is required, consider endotracheal intubation and ventilatory support.
4. The water and electrolyte deficit needs to be replaced. Calculating fluid requirements:

• 24-hour fluid requirements: 100 ml/kg — for the first 10 kg of bodies weight; + 50 ml/kg — for the second 10 kg of weight; + 20 ml/kg — for the remaining weight above 20 kg;

• 24-hour electrolyte requirements: sodium — 2–4 mmol/kg; potassium — 1–2 mmol/kg.

5. If a patient is fasting, the type of fluid given should contain dextrose (usually 10 %), sodium chloride, and added potassium chloride.
6. Admit to intensive care for monitoring.
7. Administer 100 % oxygen.

Febrile seizures. Occur in 2–3 % of children between 3 months and 5 years. More than 90 % of are generalized, lasting less 5 minutes and occurring early in an infectious illness causing fever. Acute viral respiratory infection is the most common associated illness. Other infections associated with febrile seizure — gastroenteritis (Shigella, Campylobacter), urinary tract infection, roseola infantum.

Only 1–2.4 % of children with a febrile seizure have subsequent epilepsy. Risk factors for later epilepsy: fever < 38.8 °C, seizure lasting > 15 minutes, > 1 seizure in the same day, focal seizure, abnormal baseline neurologic status, age < 1 year, family history of epilepsy.

Management:

– check serum glucose, electrolytes, calcium;

– investigate nontypical seizure with immediate spinal tap and brain imaging and EEG at least 1 week after seizure.

Differential diagnosis:

– electrolyte (especially sodium and calcium) and blood glucose abnormalities;

– seizures associated with breath-holding spells or syncope;

– head trauma;
– central nervous system infection;
– new-onset epilepsy.

Treatment:

– control fever — acetaminophen or ibuprofen;
– stop ongoing seizure. Drugs rarely needed as seizures are usually brief;
– diagnostic evaluation for unusual seizures or risk factors;
– educate parents about future fever control;
– anticonvulsant prophylaxis can reduce recurrent febrile seizures and may be appropriate after the second febrile seizure;
– use diazepam at onset and for duration of febrile illness;
– use a regular bedtime dose phenobarbital;
– phenytoin and carbamazepines are ineffective.

Pearl: *Simple febrile seizures do not have any long-term adverse consequences. Minor EEG abnormalities seen in ~ 20 % of children after a febrile seizure have little value in predicting risk of recurrence or long-term prognosis.*

18.4. SEIZURES IN CHILDREN

Convulsive syndrome (seizures). Seizures or convulsions are a paroxysmal, time-limited change in motor activity and/or behavior of the child that results from abnormal electrical activity in the brain. Seizures are common in the pediatric age group (occur in about 5–10 % of children).

Etiology:

1. Most seizures in children are provoked by somatic diseases originating outside the brain, such as a high fever.
2. Infection, systemic sepsis.
3. Syncope.
4. Unintentional and intentional head trauma.
5. Hypoxia.
6. Ingestion of drugs and other toxins.
7. Cardiac arrhythmias.
8. Metabolic abnormalities.
9. CNS infections such as meningitis.

Epilepsy (less than one third of seizures in children, a condition in which seizures are triggered recurrently from within the brain). Epilepsy is considered to be present when two or more unprovoked seizures occur at an interval greater than 24 hours apart.

For acute evaluation of the first seizure, the physician should search for potentially life-threatening causes of seizures.

Initial evaluation of an infant or child during or after a seizure should include an assessment of the adequacy of the airway, ventilation, and cardiac function, as well as measurement of temperature, blood pressure, and glucose.

After emergency life-supporting therapies, useful diagnostic tests include:

– blood: glucose, calcium, magnesium, electrolytes and creatinine levels;

– WBC differential;

– lumbar puncture;

– brain imaging: CT, MRT;

– arterial blood gas;

– the eye grounds should be examined for the presence of papilledema;

– toxicological analyses of blood and urine.

Febrile convulsions. Febrile convulsions are the most common seizure disorder in childhood, generally have a favourable prognosis but may also signify a serious underlying acute infectious disease such as sepsis or bacterial meningitis. A febrile convulsion is usually associated with a core temperature that increases rapidly to more than 39 °C. It is initially generalized and tonic-clonic in nature. It lasts for a few seconds and rarely up to 15 min, it is followed by a brief postictal period of drowsiness, and occurs only once in 24 hours.

Convulsive status epilepticus (one seizure lasting 30 min or multiple seizures during 30 min without regaining consciousness) is often due to central nervous system infection (viral or bacterial meningitis).

Approximately 30–50 % of children have recurrent seizures with later episodes of fever, and a small minority has numerous recurrent febrile seizures.

Factors associated with increased recurrence risk of seizures include:

– age less than 12 months;

– lower temperature before the seizure onset;

– a positive family history of febrile seizures;

– complex features.

Febrile seizures are not associated with reduction in later intellectual performance, and most children with febrile seizures have only a slightly greater risk of later epilepsy than the general population.

Factors associated with a substantially greater risk of later epilepsy include:

– presence of complex features during the seizure or postictal period;

– positive family history of epilepsy;

– initial febrile seizure before 12 months of age;

– delayed developmental milestones, or a pre-existing neurologic disorder.

The risk of epilepsy is much higher than in the general population in children with one or more complex febrile seizures, especially if the seizures are focal in children with an underlying neurologic disorder. The incidence of epilepsy is more than 9 % when several risk factors are present, compared with an incidence of 1 % in children who have febrile convulsions and no risk factors.

During the evaluation, a physician’s most important responsibility is to determine the cause of the fever and to rule out meningitis or encephalitis. If any doubt exists about the possibility of meningitis, a lumbar puncture with examination of the cerebrospinal fluid is indicated.

A lumbar puncture should be strongly considered in children less than 12 months of age as well as in those of 12–18 months of age, especially if seizures are complex or sensorium remains clouded after a short postictal period.

Seizure-induced CSF abnormalities are rare in children, and all patients with abnormal CSF after a seizure should be thoroughly evaluated for causes other than seizure. The possibility of viral meningoencephalitis should also be kept in mind, especially the one caused by herpes simplex. Viral infections of the upper respiratory tract, roseola (and non-roseola human herpes virus 6 and 7 infections), and acute otitis media are most frequently the causes of febrile convulsions.

Aside from glucose determination, laboratory testing such as serum electrolytes and toxicology screening should be ordered based on indi-vidual clinical circumstances such as evidence of dehydration.

An EEG is not warranted after a simple febrile seizure but may be useful for evaluating patients with complex or atypical features or with other risk factors for later epilepsy.

Similarly, neuroimaging is not useful for children with simple febrile convulsions, but may be considered for children with atypical features, including focal neurologic signs or pre-existing neurologic deficits.

Treatment:

1. At any stage, if there is respiratory depression, intubate the trachea and support breathing.

2. Routine management of a normal infant with simple brief febrile convulsions includes a careful search for the cause of the fever.

3. Antipyretics have not been shown to prevent seizure recurrences; they may reduce discomfort and are reassuring.

4. In a setting where support for ventilation can be provided, consideration should be given to treating seizures lasting more than 5 min with a benzodiazepine as a first-line therapy.

5. Prolonged anticonvulsant prophylaxis for preventing recurrent febrile convulsions is controversial and no longer recommended for most children.

6. Antiepileptics such as phenytoin and carbamazepine do not prevent febrile seizures.

7. Phenobarbital prevents recurrent febrile seizures but may also decrease a cognitive function in the treated children compared with the untreated children.

8. Sodium valproate is also effective for the prevention of febrile seizures, but the potential risks of the drug do not justify its use in a disorder with an excellent prognosis regardless of the treatment. The incidence of fatal valproate-induced hepatotoxicity is the highest in children less than 2 years old.

9. If parental anxiety is very high, oral diazepam may be used as an effective and safe method of reducing the risk of recurrence of febrile seizures. At the onset of each febrile illness, oral diazepam, 0.3 mg/kg every 8 hours (1 mg/kg per 24 hours), is administered for the duration of the illness (usually 2–3 days).

The side effects are usually minor, but the symptoms of lethargy, irritability, and ataxia may be reduced by adjusting the dose.

Another approach for selected patients with recurrent complex febrile seizures is to prescribe diazepam in the form of a gel that can be given rectally at the time of a seizure in a dose of approximately 0.5 mg/kg for children aged 2–5 years. This will usually terminate the seizure and prevent recurrence over 12 hours. Preventive anticonvulsant treatment or treatment after the seizure have not been shown to reduce the risk of later epilepsy in higher risk patients.

The drugs diazepam and lorazepam I.V. are used for initial management. Rectal diazepam (gel) is an effective and safe treatment to abort episodes of acute repetitive seizures in children and is available as Diastat gel in 2.5, 5, and 10 mg doses for children.

Anticonvulsants in status epilepticus:

1) 0–5 min: airway, breathing, circulation resuscitation (ABC):

– establish I.V. access;

– monitor vital signs especially pulse oximetry saturation;

– give 100 % oxygen via mask;

2) 5–15 min: start anticonvulsants:

– use I.V. Lorazepam (50–100 mg/kg, up to 4 mg) or

– rectal diazepam (0.5 mg/kg, up to 10 mg);

– if there is no response, repeat the dose after 5–10 min;

3) 15–35 min: if seizure persists:

– load with I.V. phenytoin (15–20 mg/kg, at rate less than 1 mg/kg per minute) or

– I.V. phenobarbital (15–20 mg/kg, at rate less than 1 mg/kg per minute);

4) 45 min: refractory seizure:

– load with I.V. phenytoin or phenobarbital (whichever was not given above);

– additional phenobarbital (5 mg/kg per dose, every 30 min to maximum of 30 mg/kg can be used).

Refractory seizure: intensive care:

– if seizures persist, intensive care should be initiated;

– intubate the trachea and support breathing;

– intensive care medications include midazolam and thiopentone;

– EEG monitoring.

CHAPTER 19
SCHEME OF PEDIATRIC HISTORY

1. The passport

Name

Surname of the child

Age Date of birth

Address (residence)

Date of hospitalization

Discharging date (Do not mention if the patient is still in hospital, date of history taking)

Treatment period (Do not mention if the patient is still in hospital, last date of history taking)

2. Complaints of the patient (parents or relatives) at the moment of hospitalization and examination by the student

3. Anamnesis of the disease (specifying each symptom or complaint)

Onset — when did the symptom start?

Acute or gradual — did it come on suddenly or has it got worse gradually?

Duration — minutes / hours / days / weeks / months / years?

Progression — has it got worse/better or stayed same over the stated time frame?

Intermittent or continuous — is the symptom always there or does it come and go?

Have you tried any medications & did the organism respond? — e.g. fever & paracetamol

Aggravating or relieving factors? — e.g. vomiting triggered by feeding

Any contact with similar illness in others/siblings, or infectious outbreaks?

Does anyone in the family have any similar symptoms?

At the end after collecting the concerned complaints and anamnesis come to know about the affected systems and organs. Sometimes it also helps relative diagnosis of the suspected disease.

4. Anamnesis of life

Hereditary and family anamnesis (age of members of the family and their diseases). Draw a family tree.

Pregnancy and Birth History (children under 3 years):

• From which pregnancy and birth.

• Toxemia during the 1st and 2nd period of present pregnancy (nausea, vomiting, hypertension, nephropathy, eclampsia).

• Diseases during the present pregnancy, and the treatment.

• Mother's nutrition. Professional hazards.

• Problems with previous pregnancy and birth (if any).

• Birth: period, preterm or post-term birth.

Neonatal period:

• Weight, length of the body.

• 1st cry (immediately/cyanosed/apneic).

• Jaundice (parameters of bilirubin, medical assistance, etc.).

• Possible gynecological trauma.

• Time of placement of infant to mother's breast.

• Child's weight on the discharge from the maternity center.

• Day of the detachment of the umbilical cord and healing of the umbilical wound.

• Possible diseases during this period.

Physical and neuro-psychological development (NPD) of the child: smiling, ability to hold the head, sit, crawl, stand, walk, talk — compared with normal for this age (children under 1 year):

• Dynamics of weight and length on the first year and in the next years.

Feeding history (significant in child < 2 years, anemic or malnourished):

• Type of feeding: breast-feeding (duration), formula-feeding (at what age, composition of formula, amount, frequency), weaning (when, what, amount, frequency).

• Current diet/change in diet during the illness.

Behavior of the child at school and relationship with other children.

Significant illnesses in the past: when and which, duration and complications.

Immunization (check vaccination card): types of vaccinations given, age at which started, doses and adverse effects.

5. Allergic anamnesis

Allergic diseases among relatives; reactions to medicines, food, plants, clothes, household items**,** domestic animals etc.

6. Social-economic conditions (satisfactory or unsatisfactory)

7. Status praesens objectivus (the data of objective signs)

General appearance of the patient. General condition of the child (satisfactory, moderate, severe, very severe). How the patient feels, reaction to other people. Position in the bed (active, passive, compelled). Consciousness (clear, sopor, absent). Mood (quiet, depressed, excited). Sleep. Temperature.

Anthropometrical parameters: weight and length (height) of the body, circumference of the head and chest, characteristics according to percentile tables (the conclusion about physical development).

Skin: color and its disorders (pallor, icterus, hyperemia, cyanosis), elasticity, moisture (moist, dry), rash (localization and character: color, lesion type, size, shape, painful, itchy etc.), hemorrhages, scars, peeling. Skin temperature (cold, hot). Skin appendages (hair, nails).

Mucous membranes: color, moisture, hemorrhages, erosion, enanthema, aphtae, ulcers and other pathological changes.

Subcutaneous layer: uniformity of distribution, thickness, condensation, edema (their localization and distribution); degree of hypotrophy, obesity; tissue turgor.

Muscular system: General development of muscles: underdeveloped, satisfactory (according to the age), muscle tone, palpatory tenderness, pain on moving, developmental anomalies of muscles (atrophy, hypertrophy, hypotonic, hypertension, paralysis and paresis).

Bone system: size and form of the head, their deformities (frontal, occipital, parietal tubercle, craniotabes etc.), sizes of the frontal fontanel, the bones density.

Form of the thorax, rachitic "rosary", Harrison fissure, "rickety thickening of wrists and ankles", "the strings-of-pearls", curvatures of the backbone and extremities, platypodia. Form, size, quantity, consistency, mobility, tenderness, edema and hyperemia of joints. Number of teeth: primary, permanent teeth.

Attention! While composing this particular section of the case history it is necessary to mention the specific symptoms according to the age of the child. For example: such symptoms of rickets as rachitic "rosary", "strings-of-pearls" and other are seen only in 1–2 years of life as rickets is diagnosed only at this age. Such symptoms are not to be specified in grown up individuals.

***Lymphatic system*:** if lymph nodes are palpated, then it is necessary to specify the place of their localization, number, size, shape, consistency, tenderness, fusion with surrounding tissues.

Pulmonary system. *Dyspnea*, its severity and characteristics. *Cough:* moment of the onset and characteristics (dry cough (non-productive), productive cough, barking cough), frequency (persistent or paroxysmal cough), severity and duration of paroxysm, its painfulness (painful, painless), presence of reprises. *Sputum:* mucous, purulent, mucopurulent, with blood. *Chest pain:* localization and character of pain (acute, dull pain). Is the pain associated with the intensity of movements, physical exercises, breathing depth or cough? *Nose:* free or disturbed nasal breathing. Nasal discharge: amount of discharge, its characteristics (mucous, purulent, bloody). *Voice:* loud, clear, husky, quiet, hoarseness, aphonic, snuffling. *Chest:* normal, emphysematous, rickets chest deformation, "pigeon", funnel-shaped, etc. Rachitic rosary (large beads under the skin of the rib cage). Symmetry of chest expansion during breathing. Intercostal spaces (protrude, drowned, not changed).

Comparative percussion of the lungs (sound on percussion — normal, dull, local deafness, tympanus (high) or low sound over the infiltrated tissue).

Topographic percussion of the lungs. Lungs border when percussing on mid-clavicular, mid-axillar and scapular lines on both sides

Auscultation. Breathing patterns: puerile, vesicular, rough, weakened, extended exhalation, amphoric, absence of respiratory murmurs. *Râles:* dry (whistling, buzzing), moist (large, medium, small bubbling), crepitation. Presence of pleural friction rub. Respiratory rate per minute.

Cardiovascular system. *Apical thrust* of the heart (diffuse or not), is determined visually or by palpation (in which intercostal space).

Percussion: borders of the heart (right, left in the 5th or 4th intercostal space, in the 3rd intercostal space and vascular fascicle).

Auscultation: heart sounds (clear, dull, flapping), tones splitting. Accents, gallop rhythm (atrial, ventricular). Heart murmurs and their relation to the phases of cardiac function (systolic and diastolic).

Assessment of vessels: arteries inspection, the degree of arteries and jugular veins pulsation.

Pulse: rate per minute, the degree of tension (weak, satisfactory), rhythm (regular, arrhythmic). Respiratory arrhythmia and other kinds of arrhythmias. The value of the arterial and venous blood pressure (systolic and diastolic).

Digestive system. *Oral cavity:* color of the mucosa, presence of thrush, redness, rashes, spots, ulcers. Number of teeth, caries. *Tongue:* dry, moist, coated, its color, "raspberry", "geography", presence of teeth marks.

Throat: hyperemia (diffuse or limited), tonsils (normal or hypertrophy) and the degree of their enlargement, presence of fur (friability, fibrin, necrotizing etc.), fur color (white, yellow, grayish-white, gray, dirty), presence of purulent follicles, abscesses, ulcers. The posterior wall of the pharynx: hyperemia, cyanotic, coated.

Uvula: hyperemic, edematous, the uvula and soft palate mobility, the enlargement of follicles on the back of the throat.

Halitosis: fetid, sweetish, putrid, acetone and so on.

Presence of regurgitation, nausea, vomiting (single, repeated).

Abdomen: configuration, presence of flatulence, abdominal retraction, participation in the act of breathing, visible peristalsis and antiperistalsis, presence of venous network, divergence of the abdominal muscles, presence of hernias (inguinal, umbilical, femoral, linea alba), infiltration, invagination, pain, symptoms of the peritoneum irritation: Chauffer pain area, Desjardins, Mayo–Robson, Shchetkin–Blumberg's, Voskresensky's signs and others. Tension of the abdominal muscles on palpation: general or localized.

Liver: pain in the right upper quadrant (constant, paroxysmal), their power, irradiation. Borders of the liver (upper, lower), the size of the liver by Kurlov. Palpation of the liver: the edge (sharp, curved), consistency (elastic, dense, solid), surface (smooth, nodular), tenderness and its localization. Palpation of the gallbladder. Cystic symptoms (Murphy's, Kehr's, Mussy's, Orthner's signs and other).

Spleen: presence of pain in the left upper quadrant (dull, sharp). Palpation: sensitivity, density, roughness. Percussion: determination of the size.

Stool: (solid, liquid, semi-liquid, bulky, watery, scant), color, odor, presence of pathological impurities.

Genitourinary system. Pain in the lumbar region and its characteristics. Swelling in the kidneys area. Palpation of the kidneys and their displaceability. Pasternatsky's symptom. Bladder (palpation, percussion). Pain on micturition. Urine volume, color, frequency of micturition and discharge from the urethra

(pus, blood). The condition of the scrotum and testicles. Development of sexual organs in girls. Biological maturity (sexual formula: Ma, Ax, P, Me).

Thyroid gland. Size, consistency, Von Graefe's sign, Mobius sign.

Vision. Nystagmus, strabismus (heterotropia), ptosis, anisocoria, visual acuity, blurred vision, "flies before eyes", diplopia, keratitis, conjunctivitis, exophthalmus, palpebral fissures, finger tremor/jerks.

Hearing. Acuity (normal, decreased). Ear discharge, tenderness on palpation of tragus or mastoid process.

Nervous system. Consciousness (clear, confusion, stupor, sopor, unconsciousness, coma), delirium, hallucinations. Correspondence of age and psychological development. *Behavior*: active, passive, anxious. *Headaches*: periodic, permanent, their localization, presence of nausea, vomiting. Dizziness. Tinnitus, noise in ears, head, fainting, readiness for convulsions, convulsions.

Gait: normal, lurch, ataxia, paralytic walking. Romberg test. Presence of eyelids tremor when the eyes are closed.

Pupils: size, symmetry of papillary response to light (papillary light reflex).

Reflexes: tendinous, abdominal, conjunctival, pharyngeal. Presence of pathological reflexes. Dermographism.

Skin sensitivity: decreased, increased (tactile, pain, thermal). Meningeal signs (rigidity of neck and back muscles, Kernig's sign, Brudzinski's signs: upper, middle, lower). Infants: bulging fontanels, pulsating fontanels, Lessage's symptom.

8. Preliminary clinical diagnosis

Based on the results of assessment (complaints, anamnesis morbi, epidemiological anamnesis, findings of objective clinical assessment).

Concomitant diagnoses.

9. Plan of the patient examination and treatment

A. Primary and additional diagnostic methods.

B. 1) Regimen; 2) diet; 3) medical treatment:

Etiologic treatment;

Pathogenetic treatment;

Symptomatic treatment.

Signature.

10. Laboratory findings and results of additional clinical assessment by specialists (including interpretation of analyses)

All the laboratory findings, instrumental investigations, X-Ray, as well as results of additional clinical assessment by specialists should be listed and interpreted in terms of dynamic changes.

11. Substantiation of the diagnosis (main)

Should be carried out according to specific patient's data using the anamnestic, clinical and laboratory findings.

12. Differential diagnosis

Specify the relevant syndrome or symptom on which the differential diagnosis of similar infectious and non-infectious diseases is carried out.

Describe common symptoms of the diseases to differentiate and analyze their distinct features.

13. Diary

Every day fill in the description of patient's clinical state during the supervision period. Specify if the improvement occurs, or no changes or progression of the disease is observed.

Date	Detailed description of patient's clinical state at the date of evaluation	Recommendations (at the date of evaluation)

Body temperature: morning–evening

Signature_____

14. Prognosis

Favorable, unfavorable. Potential residual effects of the infectious disease survived.

15. Epicrisis report

Name, surname

Age

Admitted to the hospital date,

at the _____day of the disease

Diagnosis on admission to the hospital _____

Clinical diagnosis (main)

Complications

Concomitant diagnosis

Nosocomial infection (date)

Treatment (list all the medicines, specify day and course doses for antibiotics)

Effect of the treatment

Outcome

Discharged from the hospital for out-patient follow-up by pediatrician or other medical specialist (specify) _____ date, or continues the treatment at the hospital at the end of the supervision by the student

Detailed recommendations, including regimen, diet, etc.

Recommendations if the treatment course should be continued at home

Duration of hospital treatment _____ days

16. Follow up

What specialist should perform the follow-up in case of the given infectious disease? What should be included in the follow-up assessment and how long should it last? What are the criteria of the admission to the school or kindergarten after the infectious disease?

Signature_____

LITERATURE

1. *Avery's* diseases of the newborn. Neonatal Guidelines 2022–2024. 11th ed. 2024.

2. *2021* ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure / T. McDonagh [et al.] // European Heart Journal. 2021. P. 1–128.

3. *Pediatric* heart failure: a practical guide to diagnosis and management / D. Masarone [et al.] // Pediatrics and neonatology. 2017. Vol. 58. P. 303–312.

4. Toronto resident's handbook of neonatology / K. A. Boone [et al.]. 2022.

5. *Lisauer, T.* Illustrated textbook of paediatrics / T. Lissauer, G. Clayden. 4th ed. Elsevier, 2012.

6. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012: clinical practice guideline for the evaluation and management of chronic kidney disease // Kidney inter. Suppl. 2013. 3. P. 1–150.

7. KDOQI. KDOQI Clinical Practice Guideline for Nutrition in Children with CKD: 2008 update. Executive summary // Am. J. Kidney Dis. 2009. N 53 (3 Suppl 2). S11–104.

8. Kidney disease: improving global outcomes (KDIGO) CKD-MBD. Update Work Group. KDIGO 2017. Clinical practice guidelines update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease — mineral and bone disorder (CKD–MBD) // Kidney International Suppl. 2017. N 7. P. 1–59.

9. *Foxall, F.* Cardiac Arrhythmia Recognition : an easy learning guide / F. Foxall 2010. P. 1–152.

10. *Bayes de Luna, A.* Clinical arrhythmology / A. Bayes de Luna ; with the collaboration of D. Goldwasser [et al.]. 2011. P. 95–290.

11. *Pediatrics* : textbook for students / N. S. Paramonova [et al.]. Minsk : Novoie znanie, 2021. 597 p.

Additional

1. *Paramonova, N. S.* Introduction to pediatrics : the manual / N. S. Paramonova. Grodno : GSMU, 2015. 360 p.

2. *Nelson* textbook of pediatrics. In 2 vol. Vol. 1 / R. M. Kliegman [et al.] ; emer. ed. R. E. Behrman. 20th ed. Philadelphia : Elsevier, 2016.

3. *Nelson* textbook of pediatrics. In 2 vol. Vol. 2 / R. M. Kliegman [et al.] ; emer. ed. R. E. Behrman. Philadelphia : Elsevier, 2016.

4. *Nelson* textbook of pediatrics: 2 volume set / ed. by R. M. Kliegman, J. St. Geme. 21th ed. USA, 2020. P. 9865–1094.

5. *Pediatrics* : guidance aid / ed. O. Tiazhka. Kyiv : AUS Medicine Publishing House, 2015. 240 p.

6. *Pediatrics* : textbook / ed. by O. Tiazhka. 2nd ed., reprint. Vinnytsia : Nova Knyha, 2016. 544 p.

7. *Pediatrics* : textbook / T. O. Kryuchko [et al.] ; eds. T. O. Kryuchko, O. Y. Abaturov. Kyiv : AUS Medicine Publishing, 2017. 208 p.

8. *Rovbut, T. I.* Pediatrics: the manual for the students of the faculty of international students / T. I. Rovbut. Grodno : GSMU, 2020. 204 p.

9. *Bezler, J. A.* Pneumonia in children : the manual / J. A. Bezler. Minsk : BSMU, 2016. 27 p.

10. *Kazyra, I. A.* Cardiac arrhythmias in children : the manual / I. A. Kazyra. Minsk : BSMU, 2017. 32 p.

11. *Glomerulonephritis* in children : the manual / I. A. Kazyra [et al.]. Minsk : BSMU, 2017. 20 p.

12. *Козыро, И. А.* Инфекция мочевой системы у детей = Urinary tract infection in children : учеб-метод. пособие / И. А. Козыро, Ж. А. Безлер. Минск : БГМУ, 2016. 14 с.

13. *Козыро, И. А.* Врожденные пороки сердца у детей = Congenital heart diseases in children : учеб-метод. пособие / И. А. Козыро, Ж. А. Безлер. Минск : БГМУ, 2015. 24 с.

14. *Kazyra, I. A.* Acute and chronic renal failure (acute kidney injury and chronic kidney disease) in children / I. A. Kazyra. Minsk : BSMU, 2020. 30 p.

15. *Kozarezov, S. N.* Anemia in children : the manual / S. N. Kozarezov. Minsk : BSMU, 2021. 20 p.

Appendix

Physical development (centiles)

Centilies weight/ length	Centiles (bodies length)				
	3–10	**10–25**	**25–75**	**75–90**	**90–97**
97–90	Low, sharply disharmonious (body mass excess of 2nd degree)	Lower than medium, sharply disharmonious (body mass excess of 2nd degree)	Average, sharply disharmonious (body mass excess of 2nd degree)	Higher than average, sharply disharmonious (body mass excess of 2nd degree)	High, sharply disharmonious (body mass excess of 2nd degree)
90–75	Low, disharmonious (body mass excess of 1st degree)	Lower than average, disharmonious (body mass excess of 1st degree)	Average, disharmonious (body mass excess of 1st degree)	Higher than average, disharmonious (body mass excess of 1st degree)	High, disharmonious (body mass excess of 1st degree)
75–25	Low, harmonious	Lower than average, harmonious	Average, harmonious	Higher than average, harmonious	High, harmonious
25–10	Low, disharmonious (body mass deficiency of 1st degree)	Lower than average, disharmonious (body mass deficiency of 1st degree)	Average, disharmonious (body mass deficiency of 1st degree)	Higher than average, disharmonious (body mass deficiency of 1st degree)	High, disharmonious (body mass deficiency of 1st degree)
10–3	Low, sharply disharmonious (body mass deficiency of 2nd degree)	Lower than average, sharply disharmonious (body mass deficiency of 2nd degree)	Average, sharply disharmonious (body mass deficiency of 2nd degree)	Higher than average, sharply disharmonious (body mass deficiency of 2nd degree)	High, sharply disharmonious (body mass deficiency of 2nd degree)

Normal respiratory rate in children (breaths/minute)

Age	Respiratory rate (breaths/minute)
Under 3 months	40–45
4–6 mo.	35–40
7–12 mo.	30–35
2–3 years	25–30
5–6 years	Approx. 25
10–12 years	20–22
14–15 years	18–20

Normal resting pulse rate in children (beats/minute)

Age	Heart rate (beats/minute)
< 3 months	120–170
4–6 months	100–150
7–12 months	80–120
1–3 years	70–110
3–6 years	65–110
6–12 years	60–95
12 years and older	60–85

Heart rate (centiles)

Age	Centiles			
	10	25	75	90
Newborn	110	120	130	140
1	100	110	120	130
2	80	95	110	120
3–4	80	90	105	120
5–7	75	82	100	110
8–10	72	80	95	108
11–13	70	80	95	108
14–15	70	80	95	108
16–17	65	80	95	110

Diuresis (ml/kg/hour)

Age	Diuresis (ml/kg/hour)	Density
10 day	2.5	1.002–1.004
2 month	3.5	1.002–1.006
1 year	2	1.006–1.010
2–7 years	1.7	1.010–1.020
11–14 years	1.4	1.008–1.022
Adults	0.8	1.011–1.025

Differentiation of Pleural Fluid

	Transudate	Exudate	Complicated empyema
Appearance	Clear	Cloudy	Purulent
Cell count	< 1000	> 1000	> 5000
Cell type	Lymphocytes, monocytes	PMNs	PMNs
LDH	< 200 U/L	> 200 U/L	> 1000 U/L
Pleural/serum LDH ratio	< 0.6	> 0.6	> 0.6
Protein > 3 g	Unusual	Common	Common
Pleural/serum protein ratio	< 0.5	> 0.5	> 0.5
Glucose[*]	Normal	Low	Very low[*] (< 40 mg/dL)
pH[*]	Normal (7.40–7.60)	7.20–7.40	< 7.20, chest tube placement required
Gram stain	Negative	Usually positive	> 85 % positive unless patient received prior antibiotics

* Low glucose or pH may be seen in malignant effusion, tuberculosis, esophageal rupture, pancreatitis (positive pleural amylase), and rheumatologic diseases (e.g., systemic lupus erythematosus).

CONTENT

Учебное издание

Козыро Инна Александровна

ДЕТСКИЕ БОЛЕЗНИ

PEDIATRIC DISEASES

Учебное пособие

Ответственная за выпуск Е. К. Филипович
Компьютерная вёрстка Н. М. Федорцовой

Подписано в печать 05.12.24. Формат 60×84/16. Бумага писчая «Снегурочка».
Ризография. Гарнитура «Times».
Усл. печ. л. 20,23. Уч.-изд. л. 22,2. Тираж 99 экз. Заказ 678.

Издатель и полиграфическое исполнение: учреждение образования
«Белорусский государственный медицинский университет».
Свидетельство о государственной регистрации издателя, изготовителя,
распространителя печатных изданий № 1/187 от 24.11.2023.
Ул. Ленинградская, 6, 220006, Минск.

ISBN 978-985-21-1697-8