„VICTOR BABEŞ" UNIVERSITY
OF MEDICINE AND PHARMACY
FROM TIMIŞOARA

NEONATOLOGY

basic concepts

Coord.:
Professor Mărioara Boia PhD.

Authors:
Daniela Iacob
Aniko Maria Manea
Ileana Enătescu
Mirabela Dima
Manuela-Marina Pantea-Talpai
Daniela-Eugenia Popescu

MANUALE

„Victor Babeş" Publishing House
Timişoara, 2026

Editura „Victor Babeş”

Piața Eftimie Murgu nr. 2, cam. 316, 300041 Timișoara

Tel./Fax 0256 495 210

e-mail: evb@umft.ro

https://www.umft.ro/ro/organizare-evb/

Director: Prof. univ. dr. Sorin Ursoniu

Colecția: MANUALE

Coordonatori colecție: Prof. univ. dr. Codruţa Şoica

Prof. univ. dr. Daniel Lighezan

Referent științific: Prof. univ. dr. Nicolae Balica

Traducător: Manuela-Marina Pantea-Talpai

Indicativ CNCSIS: 324

ISBN 978-606-786-601-8

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LIST OF ABBREVIATIONS

1,25(OH)2D	– 1,25-dihydroxyvitamin D
17-OH-progesterone	– 17-hydroxyprogesterone
25(OH)D	– 25-hydroxyvitamin D
AAP	– American Academy of Pediatrics
ACEI	– angiotensin-converting enzyme inhibitors
ACTH	– adrenocorticotropic hormone
acyl-CoA	– acyl coenzyme A
ADH	– antidiuretic hormone
AI	– adrenal insufficiency
AKI	– acute kidney injury
ALP	– alkaline phosphatase
AMH	– Anti-Müllerian hormone
ANF	– atrial natriuretic factor
APTT	– activated partial thromboplastin time
ARF	– acute renal failure
ASD	– atrial septal defect
ATP	– adenosine triphosphate
AV	– atrioventricular
AVSD	– atrioventricular septal defect
BCG	– tuberculosis vaccine (Bacillus Calmette-Guérin)
bFGF	– basic fibroblast growth factor
BM	– breast milk
BP	– blood pressure
BPD	– bronchopulmonary dysplasia
Ca2+	– calcium
CAH	– congenital adrenal hyperplasia
CFT	– capillary refill time
CH	– congenital hypothyroidism
CHD	– congenital heart defect
CHF	– congestive heart failure
Cl-	– chloride
CMV	– cytomegalovirus
CNS	– central nervous system
CPAP	– continuous positive airway pressure
CRF	– chronic renal failure
CRH	– corticotropin-releasing hormone
CRP	– C-reactive protein
CSF	– cerebrospinal fluid
CT	– computed tomography
CXR	– chest X-ray
DHT	– dihydrotestosterone
DI	– diabetes insipidus
DIC	– disseminated intravascular coagulation
DM	– diabetes mellitus
DSD	– disorders of sex development
ECG	– electrocardiogram
ECMO	– extracorporeal membrane oxygenation
EEG	– electroencephalogram
ELBW	– extremely low birth weight
EOM	– early-onset meningitis

EOS – early-onset sepsis
FFP – fresh frozen plasma
FiO_2 – inspired oxygen fraction
FSH – follicle-stimulating hormone
FT3 – free triiodothyronine
FT4 – free thyroxine
FTA-ABS – specific treponemal test
G6PD – glucose-6-phosphate dehydrogenase
GBS – Group B Streptococcus
GIR – glucose infusion rate
GLUT-1 – Glucose Transporter 1 – immunohistochemical marker specific to infantile hemangiomas
Hb – hemoglobin
HCG – human chorionic gonadotropin
HDN – hemolytic disease of the newborn
HFOV – high-frequency oscillatory ventilation
HIE – hypoxic-ischemic encephalopathy
HIV – human immunodeficiency virus
HLHS – hypoplastic left heart syndrome
HMF – human milk fortifier
HPA – hypothalamic-pituitary-adrenal axis
HR – heart rate
IEM – inborn errors of metabolism
INR – International Normalized Ratio
IPF – interstitial pulmonary fibrosis
IUGR – Intrauterine Growth Restriction
IVC – inferior vena cava
IVH – intraventricular hemorrhage
IVIG – intravenous immunoglobulin
K+ – potassium
KHE – Kaposi's hemangioendothelioma
LGA – large for gestational age
LH – luteinizing hormone
LISA/MIST – minimally invasive techniques for surfactant administration
LMWH – low molecular weight heparin
LOM – late-onset meningitis
LOS – late-onset sepsis
LP – powdered milk
L-T4 – levothyroxine
LVH – left ventricular hypertrophy
MAS – meconium aspiration syndrome
MRI – magnetic resonance imaging
Na+ – sodium
NEC – necrotizing enterocolitis
NHD – neonatal hemorrhagic disease
NICU – neonatal intensive care unit
NO – inhaled nitric oxide
NPO – nil per os/oral fasting
NSAIDs – nonsteroidal anti-inflammatory drugs
OP – osteopenia of prematurity
P – phosphorus
PaO_2 / $PaCO_2$ – arterial partial pressures of oxygen and carbon dioxide

PCC – prothrombin complex concentrate
PCR – polymerase chain reaction
PCT – procalcitonin
PDA – patent ductus arteriosus
PEEP – positive end-expiratory pressure
PGE – prostaglandin
PHACE – acronym for Posterior fossa, Hemangioma, Arterial, Cardiac, Eye
PIP – peak inspiratory pressure
PN – parenteral nutrition
PPD – tuberculin skin test
PPHN – persistent pulmonary hypertension
PROM – premature rupture of membranes
PT – prothrombin time
PTH – parathyroid hormone
PVH – periventricular hemorrhage
PVL – periventricular leukomalacia
RBC – red blood cell count
RDS – respiratory distress syndrome
RICH / NICH – types of congenital hemangiomas with rapid / absent regression
RPR – rapid nontreponemal test
RR – respiratory rate
RSV – respiratory syncytial virus
RVH – right ventricular hypertrophy
RVOTO – right ventricular outflow tract obstruction
SGA – small for gestational age
SIADH – syndrome of inappropriate antidiuretic hormone secretion
SIMV – Synchronized Intermittent Mandatory Ventilation
SpO_2 – peripheral oxygen saturation
STH – somatotropin
SVC – superior vena cava
SVT – supraventricular tachycardia
T3 – triiodothyronine
T4 – thyroxine
TAPVR – abnormal total pulmonary venous return
$tcPCO_2$ – transcutaneous partial pressure of carbon dioxide
$tcPO_2$ – transcutaneous partial pressure of oxygen
TGA – transposition of the great arteries
TOF – Tetralogy of Fallot
TPHA – treponemal test
TPN – total parenteral nutrition
TRH – thyrotropin-releasing hormone
TSH – thyroid-stimulating hormone
TTN – transient neonatal tachypnea
VDRL – nontreponemal serological test
VEGF – vascular endothelial growth factor
VG – guaranteed volume
VSD – ventricular septal defect
WMI – white matter injury

I. RESPIRATORY SYSTEM DISEASES

I.1. EMBRYOLOGICAL DEVELOPMENT. CHARACTERISTICS

The respiratory system comprises all structures involved in gas exchange between the body and the external environment. In the newborn, it is one of the most fragile and immature systems, and its immediate adaptation to extrauterine life is a critical stage. The embryological development of the lung is a complex process that takes place between the 4th and 38th weeks of gestation, with well-defined stages, each corresponding to progressive structural and functional maturation.

A. Stages of Embryonic Lung Development

- **Embryonic period (weeks 4–7)**

Lung formation begins in the 4th week of intrauterine life, when a respiratory diverticulum (pulmonary bud) appears from the ventral wall of the foregut. This bud divides into two symmetrical evaginations—the future pulmonary lobes. At this stage, the trachea, main bronchi, and primary segmentation of the bronchial tree form. Separation defects during this period lead to malformations such as tracheoesophageal fistula.

- **Pseudoglandular period (weeks 7–17)**

The lung takes on a glandular appearance, consisting of terminal bronchioles but without alveoli. This is a period of intense proliferation, but the lung is immature in terms of gas exchange. Interruption of development at this stage is incompatible with extrauterine life.

- **Canalicular period (weeks 17–26)**

Respiratory bronchioles differentiate, and the first alveolar ducts appear. The epithelium thins, and the capillary network begins to approach the alveolar lumen. Type II pneumocytes, responsible for the secretion of pulmonary surfactant—a substance essential for alveolar stability—begin to appear. From weeks 24–26, the lung becomes potentially viable with appropriate ventilatory support.

- **Saccular period (weeks 26–36)**

Primary alveolar sacs form, and the connection between the alveolar epithelium and capillaries is established. The amount of surfactant increases significantly, reducing alveolar surface tension. Newborns born after 32 weeks can breathe spontaneously, albeit with difficulty.

- **Alveolar period (from 36 weeks – up to 2–3 years postnatal)**

After birth, the alveoli multiply rapidly—from approximately 20 million at birth to over 250 million by age 2. The process of alveolarization and lung maturation continues into early childhood.

B. Pulmonary surfactant

Surfactant is a complex of phospholipids (primarily dipalmitoyl-phosphatidylcholine) and specific proteins (SP-A, SP-B, SP-C, SP-D) secreted by type II pneumocytes. Its primary function is to reduce alveolar surface tension, preventing the collapse of the alveoli during exhalation. Surfactant deficiency, characteristic of preterm infants, causes respiratory distress syndrome (RDS). Secretion begins around week 24, but reaches functional levels only after 34 weeks of gestation. Its synthesis is stimulated by cortisol, thyroxine, and catecholamines—which is why prenatal administration of corticosteroids accelerates lung maturation.

C. Fetal Circulation and Adaptation to Extrauterine Life

In utero, the lungs are collapsed and do not participate in oxygenation. Fetal circulation is directed through physiological shunts:

- the ductus venosus (shunt between the umbilical vein and the inferior vena cava);
- foramen ovale (right-to-left interatrial communication);
- the ductus arteriosus (connects the pulmonary artery to the aorta).

After birth, pulmonary expansion and increased oxygen pressure cause rapid pulmonary vasodilation and the closure of these shunts. This transition must occur smoothly; any disturbance (asphyxia, hypoxia, infection) can lead to persistent pulmonary hypertension.

D. Neonatal Respiratory Characteristics

A newborn's breathing differs profoundly from that of an adult, both structurally and functionally:

- The airways are narrow, with increased resistance;
- The chest is compliant, and the respiratory muscles are underdeveloped;
- The number of alveoli is reduced, and the alveolar walls are thick;
- Breathing is predominantly diaphragmatic and unstable;
- Oxygen reserves are low, which explains the vulnerability to hypoxia;
- Neurological control of breathing is immature, favoring apnea of prematurity.

At birth, the first breaths require high pressures (≈40–60 cmH_2O) to open the collapsed alveoli and clear fetal lung fluid. Subsequently, the fluid is actively reabsorbed through sodium channels in the alveolar epithelium.

E. Factors influencing the respiratory transition

The transition from intrauterine to extrauterine breathing is influenced by:

- gestational age (lung maturity);
- type of delivery (cesarean vs. vaginal);
- the fetus's metabolic and acid-base status;
- the presence of maternal or fetal infections;
- exposure to antenatal corticosteroids;
- perinatal treatments (oxygen, ventilation, surfactant).

Preterm newborns, those born via cesarean section without labor, or those from complicated pregnancies (diabetes, asphyxia) are predisposed to respiratory difficulties.

F. Prognosis and the importance of lung maturity

Lung maturity is the primary determinant of neonatal respiratory prognosis. Preterm infants born before 28 weeks have an increased risk of respiratory distress syndrome, bronchopulmonary dysplasia, and apnea. Preventive interventions (antenatal corticosteroids, tocolysis, specialized perinatal management) have significantly reduced neonatal respiratory mortality in recent decades.

G. Key Points

- Lung development proceeds through five stages, from the respiratory bud to the mature alveolus.
- Surfactant is essential for alveolar stability; its deficiency causes RDS.
- The postnatal respiratory transition depends on alveolar expansion and pulmonary vasodilation.
- Prematurity remains the primary risk factor for neonatal respiratory failure.
- An understanding of pulmonary embryology is the foundation for diagnosing all neonatal respiratory disorders.

I.2. RESPIRATORY DISTRESS SYNDROME

I.2.1. DEFINITION

Respiratory distress syndrome (RDS) is an acute condition in the newborn caused by a deficiency of pulmonary surfactant and alveolar-capillary immaturity, leading to alveolar collapse, hypoxemia, and respiratory failure. It is the most common cause of respiratory distress in preterm infants, but it can also occur in term newborns with disorders of surfactant synthesis or inactivation.

I.2.2. EPIDEMIOLOGY. INCIDENCE

The incidence of RDS is inversely proportional to gestational age. Approximately:

- 60–80% of newborns under 28 weeks develop RDS;
- 30–40% between 28–32 weeks;
- <5% at over 37 weeks.

The condition is more common in boys, in preterm infants from twin pregnancies, and in newborns born to diabetic mothers. Mortality has decreased dramatically in recent decades due to antenatal administration of corticosteroids, the use of exogenous surfactant, and modern ventilation.

I.2.3. PATHOPHYSIOLOGY

RDS is a direct consequence of surfactant deficiency. Surfactant, produced by type II pneumocytes, reduces alveolar surface tension, allowing for uniform alveolar expansion during inspiration and preventing their collapse during expiration.
In its absence:

- The alveoli collapse (diffuse atelectasis);
- Lung compliance decreases (the lung becomes stiff);
- Respiratory effort and oxygen consumption increase;
- Hypoventilation, hypoxemia, and acidosis occur;
- Pulmonary vasoconstriction is triggered, maintaining fetal shunts (foramen ovale, ductus arteriosus).

This creates a vicious cycle of hypoxia and acidosis, which exacerbates pulmonary immaturity. In severe cases, hyaline lesions develop—deposits of fibrin and cellular debris that cover the alveoli, giving the histological appearance of "hyaline membrane disease."

I.2.4. RISK FACTORS

- Prematurity—the primary determinant;
- Male sex;
- Maternal diabetes (delays surfactant synthesis);
- Cesarean delivery without labor (absence of fetal catecholamine release);
- Perinatal asphyxia;
- Pulmonary hemorrhage or hypothermia;
- Genetic predisposition (SP-B, ABCA3 mutations) – rare, severe forms.

I.2.5. CLINICAL DIAGNOSIS

Symptoms usually appear immediately or within the first 6 hours of life:

- Tachypnea (>60 breaths/min);
- Expiratory grunting;
- Intercostal and subcostal retractions;
- Cyanosis and signs of hypoxia;
- Use of accessory muscles.

The Silverman–Anderson score is used to quantify the severity of distress (0–10 points), based on retractions, chest movement, nostril flaring, and grunting.

I.2.6. LABORATORY AND IMAGING STUDIES

- **Chest X-ray**

It is the key element in the diagnosis. Typical appearance:

- Diffuse, granular opacity ("ground-glass");
- Visible bronchiolar air lines ("air bronchogram");
- Reduced lung volume (elevated diaphragms).
- **Arterial blood gas analysis**
    - Hypoxemia (PaO_2 < 50 mmHg);
    - Hypercapnia ($PaCO_2$ > 60 mmHg);
    - Mixed acidosis (metabolic and respiratory).
- **Pulmonary ultrasound**

A modern, noninvasive method: identifies the "compact lung" pattern, the absence of A-lines, and the presence of diffuse B-lines—typical of RDS.

- **Exclusion of other causes**

It is important to differentiate from:

- Transient tachypnea of the newborn (TTN);
- Congenital pneumonia;
- Meconium aspiration syndrome;
- Persistent pulmonary hypertension.

I.2.7. DIFFERENTIAL DIAGNOSIS

The differential diagnosis of respiratory distress syndrome must be made with other common causes of neonatal respiratory failure:

- Transient tachypnea of the newborn (TTN) – usually occurs in term newborns, especially after cesarean delivery without labor. Onset occurs within the first two hours of life. Chest X-ray shows pulmonary hyperinflation and interlobar fluid lines. The course is rapidly favorable, with symptoms resolving within 48–72 hours.
- Congenital pneumonia – may present similarly to RDS, but onset is often later, and involvement is uneven. Chest X-ray shows irregular opacities, sometimes lobar. Laboratory tests reveal leukocytosis, elevated C-reactive protein (CRP), and positive blood cultures.
- Meconium aspiration syndrome – characteristic of post-term newborns born via aspiration of meconium-stained amniotic fluid. Chest X-ray reveals dense, nodular alveolar infiltrates with hyperinflation and flattening of the diaphragms. It may be associated with persistent pulmonary hypertension.
- Persistent pulmonary hypertension of the newborn (PPHN) – causes severe hypoxemia, refractory to oxygen therapy. The diagnosis is confirmed by echocardiography, showing a persistent right-to-left shunt through the ductus arteriosus or patent foramen ovale.
- Cardiogenic pulmonary edema – may occur in newborns with congenital heart defects. Chest X-ray shows cardiomegaly and pulmonary congestion.
- Congenital pulmonary malformations—cysts, pulmonary sequestration, or diaphragmatic hernia—can mimic RDS but have distinct imaging features

I.2.8. MANAGEMENT

A. Prevention

- Antenatal administration of corticosteroids (betamethasone or dexamethasone) to women at risk of preterm birth, between 24–34 weeks;
- Avoidance of elective preterm births;
- Management of maternal diabetes;
- Ensuring delivery at a facility with neonatal care.

B. Postnatal management

1. Initial stabilization

- Warming and prevention of hypothermia;
- Maintaining a neutral head position;
- Humidified oxygen, titrated to saturation (90–95%);
- Correction of acidosis and blood glucose levels;
- Adequate circulatory support.

2. Noninvasive ventilation

For mild–moderate cases:

- CPAP
    - initial pressure 5–6 cmH□O, with adjusted FiO□;
    - Goal: to keep the alveoli open and reduce respiratory effort.

3. Administration of exogenous surfactant

Treatment of choice for the underlying cause. Indications:

- Newborns <32 weeks with clinical and radiological signs of RDS;
- Oxygen requirements >30–40% under CPAP.

Intratracheal administration (bolus or minimally invasive technique – LISA/MIST).
Types: natural (from bovine/porcine lungs) or synthetic.
The dose may be repeated every 6–12 hours if necessary.

4. Mechanical ventilation

Indicated in severe cases or CPAP failure.
Objective: adequate oxygenation with minimal pressures (protective strategy).
Modern modes: SIMV, VG, HFOV.

5. Supportive therapy

- Fluids with caution (risk of pulmonary edema);
- Total parenteral nutrition initially, followed by gradual enteral feeding;
- Empirical antibiotic therapy until infection is ruled out;
- Correction of anemia and electrolyte imbalances.

I.2.9. PROGNOSIS

The prognosis depends on gestational age, birth weight, and the timing of treatment initiation. With modern management, survival rates for preterm infants born before 32 weeks exceed 90%. However, 20–30% of severe cases may develop bronchopulmonary dysplasia. Complete recovery is the norm in children with mild disease and early treatment.
Complications:

- Bronchopulmonary dysplasia (a consequence of prolonged ventilation);
- Pulmonary hemorrhage;
- Persistent pulmonary hypertension;
- Ventilator-associated sepsis;
- Retinopathy of prematurity (due to excessive oxygen therapy).

I.2.10. CONCLUSIONS. KEY POINTS

Key points

- RDS is caused by surfactant deficiency and pulmonary immaturity.
- The diagnosis is clinical and radiological.
- Antenatal corticosteroids and exogenous surfactant have revolutionized the prognosis.
- CPAP is the first-line therapy; mechanical ventilation is reserved for severe cases.
- Prevention remains the most effective strategy through antenatal lung maturation.

Self-assessment questions

- What is the role of pulmonary surfactant in the physiology of neonatal respiration?
- What are the main clinical and radiological manifestations of RDS?
- What criteria indicate the need for exogenous surfactant administration?
- How is RDS prevented in preterm infants?
- What are the main complications and preventive measures in neonatal mechanical ventilation?

I.3. APNEA

I.3.1. DEFINITION

Neonatal apnea is defined as a respiratory pause of at least 20 seconds, or a shorter pause associated with bradycardia (<100 bpm), cyanosis, or a drop in oxygen saturation. It is common in preterm infants, resulting from the immaturity of the respiratory centers, but it can also occur in term newborns in the context of severe illnesses (sepsis, hypoglycemia, metabolic disorders, seizures, etc.).

I.3.2. EPIDEMIOLOGY. INCIDENCE

Apnea occurs in:

- over 80% of newborns under 28 weeks;
- 50% between 30–32 weeks;
- rarely in term infants (<5%).

Episodes of apnea are more frequent in the first days of life and decrease as the central nervous system matures, usually disappearing before 36–37 weeks postconception.

Types of apnea:

- Central apnea – complete absence of respiratory effort due to immaturity of the bulbar centers that control breathing;
- Obstructive apnea – respiratory effort is present, but with obstruction of the upper airways (hypotonia, excessive head flexion, reflux);
- Mixed apnea – a combination of the two, the most common form (≈50–60% of cases).

I.3.3. PATHOPHYSIOLOGY

The breathing of the preterm newborn is unstable, dependent on chemical (CO□, O□) and thermal stimuli. The immaturity of the respiratory centers in the brainstem causes the response to hypoxia or hypercapnia to be ineffective. Repeated episodes lead to hypoxemia, bradycardia, and brain damage if they persist.

I.3.4. RISK FACTORS

- Prematurity (the most important);
- Systemic infections (sepsis, meningitis);
- Hypothermia;
- Hypoglycemia or hypocalcemia;
- Gastroesophageal reflux;
- Severe anemia;
- Metabolic disorders (acidosis, hyponatremia);
- Exposure to medications (narcotics, magnesium, benzodiazepines).

I.3.5. CLINICAL DIAGNOSIS

Apnea manifests as:

- obvious respiratory pause;
- cyanosis, bradycardia, or pallor;
- decreased oxygen saturation (SpO□ <85%);
- sometimes paradoxical chest movements or respiratory efforts without airflow (obstructive apnea).

Episodes may occur spontaneously or during sleep, feeding, handling, or even during nasal suctioning.

Diagnosis is clinical and based on monitoring:

- **Direct observation**

The duration of the pause, the presence of respiratory effort, bradycardia, and cyanosis are recorded.

- **Cardiorespiratory monitoring**

This is standard in neonatal intensive care units:

- it measures heart rate, O□ saturation, and chest movements;
- it allows differentiation between central and obstructive apnea.

I.3.6. LABORATORY AND IMAGING STUDIES

Performed to rule out other causes:

- Complete blood count, CRP, blood cultures – sepsis;

- Blood glucose, calcium, electrolytes – metabolic disorders;
- Arterial blood gas analysis – acidosis, hypoxia;
- ECG – bradyarrhythmias;
- Brain ultrasound – intraventricular hemorrhage;
- Respiratory polygraphy – for recurrent or severe cases.

I.3.7. DIFFERENTIAL DIAGNOSIS

Apnea must be differentiated from:

- Reflex syncope episodes (due to aspiration or reflux);
- Seizures;
- Episodes of transient desaturation without respiratory pause;
- Respiratory arrests secondary to severe hypoxia, asphyxia, or CNS malformations.

I.3.8. MANAGEMENT

Treatment of apnea depends on its severity and underlying cause.

A. General measures

- Correct head positioning (neutral or slight extension);
- Optimal thermoregulation;
- Continuous cardiorespiratory monitoring;
- Gentle tactile stimulation during the episode (touching the soles of the feet or the back);
- Ensuring airway patency (gentle suction if necessary).

B. Specific treatment

- Apnea of prematurity
    - Methylxanthines (respiratory stimulants): Caffeine citrate – first-line treatment.
    - Loading dose: 20 mg/kg (IV or oral);
    - Maintenance dose: 5–10 mg/kg/day;
    - Alternatively: theophylline (rarely used today).

Caffeine increases the sensitivity of respiratory centers to CO□, improves diaphragmatic tone, and reduces episodes of apnea.

    - Nasal CPAP – to keep the airways open in obstructive or mixed apnea.

- Secondary apnea

Treatment targets the cause:

- Antibiotics in sepsis;
- Correction of hypoglycemia, hypocalcemia, acidosis;
- Treatment of gastroesophageal reflux if confirmed.

C. Mechanical ventilation

Indicated in cases of frequent or severe episodes refractory to pharmacological treatment. Goal: prevention of hypoxia and recurrent bradycardia.

I.3.9. PROGNOSIS

Apnea of prematurity is transient. It usually resolves by 36–37 weeks postconception. It does not leave neurological sequelae if properly managed. The prognosis is more guarded in apnea secondary to infections, cerebral hemorrhages, or CNS malformations.

Criteria for discontinuing monitoring and discharge:

- absence of apnea/bradycardia episodes for at least 5–7 days;
- complete respiratory stability without stimulants.

I.3.10. CONCLUSIONS. KEY POINTS

- Neonatal apnea = respiratory pause ≥20 sec or associated with bradycardia/cyanosis;
- Central apnea – without respiratory effort; obstructive apnea – with effort but no airflow;
- It is common in preterm infants due to the immaturity of the respiratory centers;

- Caffeine citrate is the treatment of choice;
- Most cases resolve spontaneously by 36–37 weeks postconception.

Self-assessment questions

- How is neonatal apnea defined, and what are its main forms?
- What is the pathophysiological mechanism of apnea of prematurity?
- What investigations are useful for ruling out secondary causes?
- What is the role of caffeine in the treatment of apnea?
- What are the criteria for discontinuing cardiorespiratory monitoring in preterm infants?

I.4. TRANSIENT NEONATAL TACHYPNEA

I.4.1. DEFINITION

Transient neonatal tachypnea (TTN) is an acute and benign respiratory disorder of the newborn, characterized by tachypnea (>60 breaths/minute) and mild signs of respiratory distress occurring immediately after birth or in the first hours of life, which resolve spontaneously within 24–72 hours. It results from delayed resorption of fetal lung fluid, leading to reduced lung compliance and transient hypoxia.

I.4.2. EPIDEMIOLOGY. INCIDENCE

TTN occurs in approximately 1–2% of term newborns and in 5–10% of near-term newborns (34–37 weeks). The incidence is significantly higher in infants born via cesarean section without labor, in infants of diabetic mothers, and in male newborns. The course is usually benign, without complications, but requires careful monitoring to rule out other, more serious causes of respiratory distress.

I.4.3. PATHOPHYSIOLOGY

During intrauterine life, the fetal lungs contain an isotonic fluid produced by the alveolar epithelium. During labor and immediately after birth, this fluid is actively reabsorbed through the sodium channels in the alveolar epithelium, a process stimulated by catecholamines released at birth and by increased oxygen pressure. In the case of TTN:

- The pulmonary fluid is not completely cleared;
- A film of fluid persists in the alveoli and interstitium;
- Pulmonary compliance decreases and mild hypoxia occurs;
- Compensatory tachypnea develops to maintain oxygenation.

The transient accumulation of alveolar fluid explains the self-limiting course—as the fluid is reabsorbed, breathing normalizes.

I.4.4. RISK FACTORS

The main predisposing factors for TTN are:

- Cesarean section without labor (absence of the physiological stress of childbirth);
- Male sex;
- Late preterm birth (34–37 weeks);
- Maternal diabetes;
- Macrosomia;
- Mild birth asphyxia;
- Polyhydramnios or placenta previa (rapid deliveries, persistent pulmonary fluid).

I.4.5. CLINICAL DIAGNOSIS

Symptoms usually appear within the first 1–2 hours of life:

- Tachypnea (60–120 breaths/min);
- Mild costal retractions;

- Flaring of the nostrils;
- Mild expiratory grunting;
- Mild cyanosis (improves with oxygen).

Unlike RDS, respiratory effort does not progressively worsen. The child is active, general tone is good, and pulmonary auscultation reveals preserved vesicular breath sounds, sometimes with fine rales.

I.4.6. LABORATORY AND IMAGING STUDIES

- Chest X-ray
  - Pulmonary hyperinflation (flattened hemidiaphragms);
  - Interlobar fluid lines (Kerley B lines);
  - Thickening of the pulmonary hilums;
  - Occasionally, fluid in the pleural spaces.
- Arterial blood gas analysis
  - May show moderate hypoxemia (PaO□ 50–70 mmHg) and mild hypercapnia;
  - pH usually remains normal or slightly decreased.

Other investigations

- Laboratory tests are normal; inflammatory markers (CRP, white blood cell count) are not elevated;
- Pulmonary ultrasound reveals moderate B-lines, with normal pleura and no consolidations—a finding specific to TTN.

I.4.7. DIFFERENTIAL DIAGNOSIS

Transient tachypnea must be differentiated from:

- Respiratory distress syndrome (RDS) – primarily affects preterm infants; chest X-ray showing a "ground-glass" appearance and reduced lung volume;
- Congenital pneumonia – irregular opacities, fever, elevated CRP;
- Meconium aspiration – alveolar infiltrates, hyperinflation;
- Persistent pulmonary hypertension (PPHN) – severe hypoxemia, refractory to oxygen;
- Structural abnormalities (diaphragmatic hernia, pulmonary cysts) – asymmetric findings, severe distress.

I.4.8. MANAGEMENT

Treatment of TTN is supportive and symptomatic, as the condition is self-limiting. The primary goal is to maintain oxygenation and prevent complications.

A. General measures

- Monitor vital signs and oxygen saturation (SpO□ 90–95%);
- Ensure thermoregulation;
- Positioning in the supine or slightly inclined position;
- Limiting unnecessary handling;
- Delayed enteral feeding or 10% glucose infusion until respiration stabilizes.

B. Respiratory support

- Humidified oxygen via nasal cannula or hood, at low concentrations (FiO□ 25–40%);
- In moderate cases: nasal CPAP (pressure 5–6 cmH□O) to keep the alveoli open and facilitate alveolar fluid resorption;
- Mechanical ventilation is rarely necessary, only if apnea or severe hypoxemia occurs.

C. Medical treatment

No specific treatment is required. Antibiotics are administered only if a congenital infection is suspected. Diuretics (e.g., furosemide) are not recommended, as they may worsen dehydration.

I.4.9. PROGNOSIS

TTN has an excellent prognosis. Symptoms improve progressively within 24–48 hours and resolve completely within a maximum of 72 hours. It leaves no pulmonary sequelae and is not associated with a risk of recurrence. The prognosis is very good if there are no other comorbidities (severe prematurity, congenital heart disease, etc.).

I.4.10. CONCLUSIONS. KEY POINTS

Key points

- TTN is caused by delayed reabsorption of fetal lung fluid;
- It occurs mainly in term newborns delivered by cesarean section without labor;
- It manifests as mild tachypnea and self-limiting respiratory distress;
- Diagnosis is clinical and radiological;
- Treatment is exclusively supportive, with mild oxygen therapy and monitoring.

Self-assessment questions:

- What is the main pathophysiological mechanism of transient tachypnea of the newborn?
- What factors predispose to the development of TTN?
- What are the main clinical and radiological differences between TTN and respiratory distress syndrome?
- What therapeutic measures are recommended for TTN?
- When is mechanical ventilation necessary in this condition?

I.5. CONGENITAL PNEUMONIA

I.5.1. DEFINITION

Congenital pneumonia is a pulmonary infection present at birth or manifesting within the first 48–72 hours of life, resulting from intrauterine or intrapartum transmission of pathogens. It is characterized by acute inflammation of the lung parenchyma, alveolar inflammatory infiltrate, and impaired respiratory function.

I.5.2. EPIDEMIOLOGY. INCIDENCE

The incidence ranges from 1 to 5 cases per 1,000 live births, being higher in preterm infants, newborns with premature rupture of membranes (PROM), and those born to mothers with perinatal infections. Congenital pneumonia accounts for up to 20% of causes of neonatal respiratory distress and is associated with increased mortality in preterm infants under 32 weeks.

Etiology:

- **Routes of transmission**
  - Transplacental (intrauterine) – via maternal hematogenous infection (e.g., Listeria, viruses, Treponema pallidum, CMV, Toxoplasma).
  - Ascending (intrapartum) – the most common; microorganisms from the maternal genital tract enter the amniotic fluid and are aspirated by the fetus.
  - Early postnatal – through contamination during resuscitation maneuvers, mechanical ventilation, or contact with medical personnel.
- **Germs involved**
  - Gram-negative bacteria: Escherichia coli, Klebsiella, Enterobacter, Pseudomonas;
  - Gram-positive bacteria: Group B Streptococcus (GBS), Staphylococcus aureus;
  - Anaerobes and mycoplasmas (rare);
  - In some cases: Listeria monocytogenes, Ureaplasma urealyticum, Chlamydia trachomatis.

I.5.3. PATHOPHYSIOLOGY

Aspiration of infected amniotic fluid leads to:

- alveolar and interstitial inflammation;
- purulent exudate and bronchiolar obstruction;
- impaired gas exchange;
- the development of hypoxemia, hypercapnia, and respiratory acidosis.

In severe cases, the inflammatory process can progress to pulmonary edema, atelectasis, and diffuse alveolar damage, resembling acute respiratory distress syndrome.

I.5.4. RISK FACTORS

- Premature and prolonged rupture of membranes (>18 hours);
- Maternal chorioamnionitis;
- Maternal colonization with Group B Streptococcus;
- Prematurity;
- Perinatal asphyxia;
- Early mechanical ventilation;
- Aspiration of meconium or infected fluid.

I.5.5. CLINICAL DIAGNOSIS

The clinical presentation is variable—ranging from mild forms with isolated tachypnea to severe respiratory failure.

Symptoms appear in the first hours or days of life:

- Tachypnea (>60/min);
- Costal and subcostal retractions;
- Expiratory grunting;
- Cyanosis;
- Lethargy, hypothermia, or fever;
- Feeding difficulties;
- In severe cases—apnea, septic shock, signs of multiple organ failure.

The course may be rapidly progressive, requiring urgent therapeutic intervention.

I.5.6. LABORATORY AND IMAGING STUDIES

1. Chest X-ray

Findings are nonspecific but suggestive:

- Irregular alveolar and interstitial infiltrates, often bilateral;
- Areas of lobar consolidation or atelectasis;
- Normal or increased lung volume;
- Occasional pleural effusions.

2. Laboratory tests

- Leukocytosis or leukopenia;
- Thrombocytopenia;
- Elevated CRP, positive procalcitonin;
- Positive blood cultures (in 30–50% of cases);
- Cultures from tracheal aspirate (for causative pathogens).

3. Arterial blood gas analysis

- Hypoxemia, hypercapnia, mixed acidosis.

4. Other investigations

- Pulmonary ultrasound: subpleural consolidations and air bronchogram;
- Viral tests or PCR for specific agents (CMV, Listeria, Chlamydia).

I.5.7. DIFFERENTIAL DIAGNOSIS

- Respiratory distress syndrome (RDS) – occurs in preterm infants, chest X-ray showing a uniform "ground-glass" appearance, without leukocytosis.
- Transient tachypnea – rapid onset, self-limiting course, chest X-ray showing hyperinflation.
- Meconium aspiration – coarse alveolar infiltrates, hyperinflation, post-term context.
- Pulmonary hemorrhage – dense opacities, acute course, blood in tracheal aspirate.

I.5.8. MANAGEMENT

Treatment is complex, requiring a multidisciplinary approach: respiratory support, antimicrobial therapy, and intensive care.

A. General measures

- Admission to a neonatal intensive care unit;
- Maintenance of normal body temperature;
- Humidified oxygen therapy;
- Continuous monitoring of SpO□, heart rate, and respiration;
- Moderate fluid restriction to prevent pulmonary edema.

B. Respiratory support

- Oxygen via nasal cannula or CPAP for moderate cases;
- Conventional or high-frequency mechanical ventilation (HFOV) for severe cases;
- In refractory cases – inhaled nitric oxide (NO) therapy or ECMO (extracorporeal membrane oxygenation).

C. Antimicrobial therapy

Initiated empirically, immediately after culture collection.

First-line regimen:

- Ampicillin + Gentamicin – covers GBS, Listeria, and Gram-negative bacteria.

Alternatives in severe or resistant cases:

- Cefotaxime + Amikacin;
- Vancomycin if Staphylococcus aureus is suspected;
- Adjust therapy based on antibiotic susceptibility testing.

Duration of treatment:

- 7–10 days in mild cases;
- 14–21 days in severe cases or cases with bacteremia.

D. Supportive therapy

- Initially parenteral nutrition, followed by gradual enteral feeding;
- Correction of metabolic imbalances (acidosis, hypoglycemia);
- Transfusions if severe anemia is present;
- Monitoring of renal and hepatic function.

I.5.9. PROGNOSIS

The prognosis depends on:

- gestational age;
- the severity of the infection;
- the causative agent;
- the timing of initiation of antibiotic therapy.

Mild cases have a favorable prognosis. Premature infants and those with systemic infections may require prolonged ventilation and are at increased risk of chronic pulmonary complications.

Complications:

- Acute respiratory failure;
- Sepsis;
- Pulmonary or pleural abscesses;

- Bronchopulmonary dysplasia;
- Post-hypoxic neurological sequelae;
- Increased mortality in preterm infants (<32 weeks).

I.5.10. CONCLUSIONS. KEY POINTS

Key points:

- Congenital pneumonia occurs within the first 72 hours of life, as a result of intrauterine or perinatal infection;
- Symptoms may mimic RDS but are associated with signs of systemic infection;
- Diagnosis is based on respiratory symptoms, chest X-ray, and inflammatory markers;
- Treatment consists of prompt empirical antibiotics and respiratory support;
- Prevention includes maternal screening for GBS and administration of intrapartum prophylaxis.

Self-assessment questions:

- What are the main routes of transmission for congenital pneumonia?
- Which pathogens are most commonly involved in the etiology of this disease?
- How is congenital pneumonia distinguished from respiratory distress syndrome?
- What are the principles of initial empirical therapy?
- What measures can prevent the onset of congenital pneumonia?

I.6. MECONIUM ASPIRATION SYNDROME

I.6.1. DEFINITION

Meconium aspiration syndrome (MAS) is an acute respiratory condition in the newborn, characterized by respiratory failure caused by the aspiration of amniotic fluid contaminated with meconium, before or during birth. Meconium, the first fetal stool, is a viscous, greenish-black substance composed of epithelial cells, mucus, and digestive enzymes; when aspirated into the airways, it causes mechanical obstruction, inflammation, and chemical alveolar damage.

I.6.2. EPIDEMIOLOGY. INCIDENCE

MAS occurs almost exclusively in term or post-term newborns.

- The incidence is 1–2% of all births, but up to 5–10% of newborns exposed to meconium-stained amniotic fluid.
- It is more common in fetuses experiencing intrauterine stress (hypoxia, acute fetal distress).
- Mortality has decreased significantly in recent decades due to improvements in neonatal resuscitation and modern treatments, but severe forms remain associated with persistent pulmonary hypertension and multi-organ dysfunction.

I.6.3. PATHOPHYSIOLOGY

Meconium aspiration may occur:

- in utero, during episodes of fetal hypoxia (which causes relaxation of the anal sphincter and fetal “gasping” breaths);
- intrapartum, at birth;
- immediately postnatally, at the first breath.

Once aspirated, meconium:

1. Mechanically obstructs the airways, causing alternating areas of atelectasis and hyperinflation (a “valve” effect);
2. Causes inflammation and pulmonary edema through a chemical irritant effect;
3. Inactivates surfactant and disrupts alveolar function;
4. Causes pulmonary vasoconstriction → persistent pulmonary hypertension (PPHN).

The end result is severe hypoxemia and mixed respiratory failure (obstructive + inflammatory).

I.6.4. RISK FACTORS

- Post-term pregnancy (>41 weeks);
- Acute fetal distress (bradycardia, decelerations on monitoring);
- Chronic intrauterine hypoxia (preeclampsia, maternal hypertension);
- Maternal-fetal infections (chorioamnionitis);
- Difficult or precipitous delivery;
- Low Apgar score at 1 and 5 minutes;
- Absence of labor (scheduled cesarean delivery without contractions – retained meconium).

I.6.5. CLINICAL DIAGNOSIS

Symptoms appear immediately after birth or within the first few hours of life. General signs:

- Severe respiratory distress (tachypnea, expiratory grunting, chest retractions);
- Cyanosis, persistent hypoxemia;
- Diminished vesicular breath sounds, moist rales, and prolonged expiration;
- Yellowish-green skin, umbilical cord, and nails stained with meconium;
- Low Apgar score (<7).

The course may be rapidly progressive, with increased oxygen requirements and ventilation difficulties.

I.6.6. LABORATORY DIAGNOSIS

1. **Chest X-ray**

- Pulmonary hyperinflation (flattened diaphragms);
- Irregular alveolar, perihilar, and basal infiltrates;
- Areas of atelectasis alternating with hyperlucency ("mosaic" effect);
- Occasionally pneumothorax or pneumomediastinum secondary to barotrauma.

2. **Blood gas analysis**

- Severe hypoxemia;
- Hypercapnia and respiratory acidosis;
- In severe cases – metabolic acidosis secondary to hypoperfusion.

3. **Laboratory tests**

- Leukocytosis or elevated CRP may be present (associated with bacterial infection);
- Blood cultures (to rule out congenital pneumonia).

4. **Echocardiography**

- Useful for identifying persistent pulmonary hypertension (right-to-left shunt via the ductus arteriosus or foramen ovale).

I.6.7. DIFFERENTIAL DIAGNOSIS

Transient tachypnea of the newborn (TTN) – benign course, uniform hyperinflation;

- Congenital pneumonia – more uniform infiltrates, fever, elevated CRP;
- Respiratory Distress Syndrome (RDS) – premature infants, stiff lungs, "ground-glass" appearance on chest X-ray;
- Primary persistent pulmonary hypertension (PPHN) – no infiltrates, but with refractory hypoxemia.

I.6.8. MANAGEMENT

The goals of treatment are:

1. Ensuring adequate oxygenation and ventilation;
2. Preventing barotrauma complications;
3. Treating pulmonary hypertension;
4. Preventing secondary infections.

A. General measures

- Newborns with meconium-stained amniotic fluid should be evaluated promptly at birth;
- Oropharyngeal suctioning prior to stimulation is no longer recommended by current AAP guidelines;
- Resuscitation is performed according to the standard protocol, with priority given to oxygenation;
- Avoid ventilation with excessive pressures.

B. Respiratory support

- Titrated oxygen therapy (SpO□ 90–95%);
- CPAP in moderate cases;
- Conventional mechanical ventilation in cases of severe respiratory acidosis;
- High-frequency ventilation (HFOV) – recommended for refractory hypoxemia;
- Inhaled nitric oxide (NO) – reduces pulmonary hypertension and improves oxygenation;
- In critical cases: ECMO (extracorporeal membrane oxygenation).

C. Pharmacological therapy

- Empirical antibiotics (ampicillin + gentamicin) – for the prevention of secondary infection;
- Exogenous surfactant – indicated in moderate–severe cases, as meconium inactivates endogenous surfactant;
- Sedatives and muscle relaxants – only during controlled ventilation, to reduce oxygen consumption.

D. Supportive measures

- Correction of acidosis and hypoglycemia;
- Maintenance of normal body temperature;
- Initially parenteral nutrition, then enteral after stabilization.

I.6.9. PROGNOSIS

Most cases have a favorable outcome with appropriate treatment. However, severe forms may require prolonged ventilation, and mortality ranges from 5–15% depending on severity and comorbidities. The long-term prognosis is good, with no respiratory sequelae if oxygenation was adequately maintained.

Complications:

- Persistent pulmonary hypertension (PPHN);
- Pneumothorax, pneumomediastinum;
- Secondary pulmonary infections;
- Chronic respiratory failure (bronchopulmonary dysplasia);
- Hypoxic brain damage.

I.6.10. CONCLUSIONS. KEY POINTS

Key points:

- MAS occurs at term or post-term due to meconium aspiration;
- It causes mechanical obstruction, inflammation, and inactivation of surfactant;
- Chest X-ray shows hyperinflation and irregular alveolar infiltrates;
- Treatment is supportive: careful ventilation, surfactant, NO, antibiotic therapy;
- Prevention depends on proper monitoring of high-risk pregnancies and adequate resuscitation at birth.

Self-assessment questions:

- What are the main pathophysiological mechanisms of MAS?
- What radiological features are characteristic of meconium aspiration syndrome?
- What is the role of exogenous surfactant in this condition?

- What measures should be taken during the resuscitation of a newborn with meconium-stained amniotic fluid?
- What pulmonary complications may arise in the course of MAS?

I.7. BRONCHOPULMONARY DYSPLASIA

I.7.1. DEFINITION

Bronchopulmonary dysplasia (BPD) is a chronic lung disease of the preterm infant, characterized by persistent oxygen dependence after 28 days of life and structural lung changes caused by prolonged mechanical ventilation, intensive oxygen therapy, and pulmonary inflammation. BPD is the primary respiratory complication in newborns with respiratory distress syndrome (RDS) treated with long-term ventilation and oxygen therapy.

I.7.2. EPIDEMIOLOGY. INCIDENCE

BPD affects 20–40% of preterm infants weighing <1000 g and with a gestational age <28 weeks. With increased survival of extremely preterm infants, the incidence has risen, although modern forms are milder. BPD is a major cause of long-term pulmonary morbidity and repeated hospitalizations in the first years of life.

I.7.3. PATHOPHYSIOLOGY

The pathophysiology of BPD is multifactorial and complex. The main mechanisms involved are:

1. Oxygen-induced lung injury (oxygen toxicity) – free radicals cause oxidative stress and destroy alveolar tissue.
2. Barotrauma and volutrauma – high-pressure mechanical ventilation damages the alveolar and capillary epithelium.
3. Chronic inflammation – caused by infections, aspiration, or systemic inflammation.
4. Alveolar growth deficit – premature infants who are ventilated early have immature lung development, with a reduced number of alveoli and capillaries.
5. Vascular maturation disorders – lead to secondary pulmonary hypertension.

Currently, two forms are described:

- "classic" BPD (described by Northway, 1967): fibrotic damage, fibrosis, epithelial metaplasia;
- "New" (modern) BPD: affects extremely preterm infants, with incomplete alveolar development and minimal inflammation, but with diffuse capillary involvement.

I.7.4. RISK FACTORS

- Severe prematurity (<28 weeks);
- Prolonged mechanical ventilation (>7 days);
- Exposure to high-concentration oxygen (FiO□ > 0.4);
- Respiratory or systemic infections;
- Patent ductus arteriosus (PDA);
- Vitamin A deficiency;
- Intrauterine growth restriction (IUGR);
- Prenatal inflammation (chorioamnionitis).

I.7.5. CLINICAL DIAGNOSIS

Newborns with BPD typically exhibit prolonged oxygen dependence and persistent signs of respiratory distress following initial treatment of RDS.

Clinical signs:

- Tachypnea and increased respiratory effort;
- Chest retractions, expiratory grunting;

- Cyanosis on oxygen withdrawal;
- Episodes of desaturation, bradycardia;
- Decreased muscle tone, difficulty feeding;
- Slow weight gain.

On auscultation: diminished vesicular breath sounds, fine crackles, sometimes wheezing.

I.7.6. LABORATORY AND IMAGING STUDIES

1. Chest X-ray

- Classic appearance: alternating hyperlucent and opaque areas ("mosaic pattern");
- Peribronchial thickening;
- In severe forms – "spongy lung" appearance, with atelectasis and hyperinflation.

2. Blood gas analysis

- Mild chronic hypoxemia;
- CO□ retention (hypercapnia);
- Progressive metabolic compensation (elevated HCO□⁻).

3. Other investigations

- Echocardiography – to detect pulmonary hypertension;
- Pulmonary function tests (if age permits);
- Inflammatory markers may be slightly elevated in active forms.

Diagnostic criteria (according to NIH, 2018)

The diagnosis of bronchopulmonary dysplasia is established in newborns with a gestational age of less than 32 weeks who require supplemental oxygen for at least 28 days after birth. Severity is assessed at 36 weeks postconception (or at discharge, if earlier) and classified into three grades:

- Mild form: no need for supplemental oxygen at 36 weeks post-conception;
- Moderate form: requires low-concentration oxygen, below 30% (FiO□ < 0.3), with or without noninvasive support (e.g., CPAP);
- Severe form: requires oxygen at a concentration ≥30% (FiO□ ≥ 0.3) and/or mechanical ventilation (including high-frequency ventilation).

This simplified classification allows for a direct correlation between the level of respiratory support and the degree of lung involvement. Additionally, it has prognostic value—mild forms resolve completely, while severe forms are frequently associated with pulmonary hypertension and long-term oxygen requirements.

I.7.7. MANAGEMENT

Treatment of BPD is supportive and preventive, aimed at reducing inflammation and pulmonary stress and promoting alveolar development.

A. Prevention

- Use of noninvasive ventilation (early CPAP);
- Administration of exogenous surfactant as needed;
- Avoidance of hyperoxia (target SpO□ 90–95%);
- Administration of antenatal corticosteroids to mothers at risk of preterm birth;
- Control of perinatal infections.

B. General measures

- Titrated oxygen therapy (SpO□ 90–95%);
- Moderate fluid restriction;
- High-calorie diet with increased protein intake;
- Vitamin A and antioxidant supplements (vitamin E).

C. Pharmacological treatment

- Diuretics (furosemide, thiazides) – to reduce pulmonary edema;
- Bronchodilators (β2-agonists) – for wheezing or bronchial obstruction;

- Systemic corticosteroids (dexamethasone, hydrocortisone) – in severe cases, to facilitate extubation;
- Inhaled corticosteroids – for maintenance, at low doses;
- Treatments for pulmonary hypertension – sildenafil, nitric oxide.

D. Ventilation

- Preferably noninvasive (CPAP, NIPPV);
- Mechanical ventilation with low pressures and moderate frequencies;
- In severe cases – high-frequency ventilation (HFOV).

E. Follow-up

- Monthly monitoring of blood gas levels and growth;
- Complete vaccination (including anti-RSV and influenza);
- Avoidance of exposure to cigarette smoke;
- Control of respiratory infections (prophylaxis with palivizumab during RSV season).

I.7.8. PROGNOSIS

The prognosis depends on the severity and gestational age. Most mild cases resolve completely by age 2. Moderate and severe cases may require home oxygen therapy and carry a risk of repeated hospitalizations. Mortality remains elevated in severe BPD associated with pulmonary hypertension. In the long term, episodes of wheezing, obstructive ventilatory disorders, and susceptibility to respiratory infections may persist.

Complications:

- Persistent pulmonary hypertension;
- Chronic respiratory failure;
- Recurrent respiratory infections;
- Growth retardation;
- Neuropsychological developmental disorders.

I.7.9. CONCLUSIONS. KEY POINTS

Key points

- BPD is the leading chronic lung disease in preterm infants;
- It results from the interaction of mechanical ventilation, oxygen therapy, and inflammation;
- Diagnosis is based on oxygen dependence for ≥28 days;
- Treatment is supportive: oxygen, nutrition, diuretics, vitamins, corticosteroids;
- Prevention through noninvasive ventilation and avoidance of hyperoxia is essential.

Self-assessment questions

- What are the main mechanisms involved in the development of BPD?
- What criteria defined bronchopulmonary dysplasia according to the NIH?
- What preventive measures can reduce the risk of BPD in preterm infants?
- What is the role of corticosteroids and vitamins in the management of BPD?
- What long-term complications can occur in a child with BPD?

I.8. PERSISTENT PULMONARY HYPERTENSION

I.8.1. DEFINITION

Persistent pulmonary hypertension of the newborn (PPHN) is a severe condition characterized by the persistence of elevated pulmonary pressure after birth, which causes a right-to-left shunt through the foramen ovale and/or ductus arteriosus and, consequently, refractory hypoxemia. Normally, after birth, pulmonary vascular pressure drops rapidly, facilitating oxygenation. In PPHN, this adaptive process is delayed or absent, leading to persistent fetal circulation.

I.8.2. EPIDEMIOLOGY. INCIDENCE

PPHN occurs in approximately 1–2 newborns per 1,000 live births. It is more common in term or post-term newborns, but it can also occur in preterm infants, especially in the context of meconium aspiration, congenital pneumonia, or perinatal asphyxia. Although the incidence is relatively low, PPHN accounts for 5–10% of neonatal deaths associated with severe respiratory failure.

I.8.3. PATHOPHYSIOLOGY

During intrauterine life, pulmonary circulation pressure is high, and only a small portion of blood reaches the lungs. After birth, pulmonary expansion and increased oxygen pressure cause vasodilation of the pulmonary arterioles, dramatically decreasing vascular resistance.
In PPHN, this process is disrupted. The main pathophysiological mechanisms are:

1. Persistent pulmonary vasoconstriction—caused by hypoxia, acidosis, or inflammation;
2. Vascular remodeling – thickening of the pulmonary arteriolar wall, reducing the lumen;
3. Vascular hyporeactivity to oxygen and endogenous NO;
4. Persistent shunts at the foramen ovale and ductus arteriosus, with blood shunting from right to left.

These changes lead to severe hypoxemia, refractory to conventional oxygen therapy.

I.8.4. RISK FACTORS

PPHN may be idiopathic or secondary to other conditions. The main causes include:

- Meconium aspiration;
- Congenital pneumonia or neonatal sepsis;
- Perinatal asphyxia;
- Hypothermia or metabolic acidosis;
- Hypoglycemia, hypocalcemia;
- Respiratory distress syndrome (RDS);
- Prenatal exposure to COX inhibitors (e.g., indomethacin);
- Pulmonary hypoplasia (e.g., in congenital diaphragmatic hernia).

I.8.5. CLINICAL DIAGNOSIS

The clinical picture is dominated by severe hypoxemia, disproportionate to the radiological findings. Symptoms appear in the first hours of life and may include:

- Intense, persistent cyanosis that does not resolve completely with oxygen;
- Tachypnea, expiratory grunting, and chest retractions;
- Low oxygen saturation (SpO□ < 85%) despite adequate ventilation;
- A difference >10% between preductal (right hand) and postductal (foot) oxygen saturation—a sign of a right-to-left shunt;
- In severe cases: lethargy, hypotension, metabolic acidosis, signs of shock.

I.8.6. LABORATORY DIAGNOSIS

1. **Arterial blood gas analysis**

- Severe hypoxemia (PaO□ < 50 mmHg), variable hypercapnia;
- Mixed acidosis (metabolic and respiratory).

2. **Echocardiography (gold standard)**

- Confirms right-to-left shunt;
- Demonstrates elevated pulmonary systolic pressure;
- Excludes structural congenital heart defects.

3. **Chest X-ray**

- Variable appearance: ranging from nearly normal lungs to infiltrates depending on the underlying cause (e.g., MAS, pneumonia).

4. Other investigations

- Tests for infection (blood culture, CRP);
- Serial blood gas monitoring;
- Lactate measurement (to assess tissue perfusion).

I.8.7. DIFFERENTIAL DIAGNOSIS

Cyanotic congenital heart defects (e.g., transposition of the great vessels);

- Severe meconium aspiration;
- Neonatal sepsis;
- Severe respiratory distress syndrome;
- Congenital pulmonary hypoplasia.

Echocardiography is essential for differential diagnosis.

I.8.8. MANAGEMENT

Treatment aims to:

1. Reduce pulmonary vascular resistance;
2. Improve oxygenation and tissue perfusion;
3. Correct precipitating causes (acidosis, hypothermia, hypoglycemia).

A. General measures

- Warming and maintaining normothermia;
- Controlled oxygen therapy, avoiding hyperoxia;
- Maintain pH between 7.35–7.45 (hypocapnia may exacerbate vasoconstriction);
- Correct metabolic acidosis;
- Hemodynamic stabilization with fluids and inotropes (dopamine, dobutamine).

B. Respiratory support

- Gentle mechanical ventilation with low pressures (to avoid barotrauma);
- High-frequency ventilation (HFOV) in refractory cases;
- Extracorporeal membrane oxygenation (ECMO) for uncontrollable critical cases.

C. Specific therapy

- Inhaled nitric oxide (NO)
    - The treatment of choice for PPHN;
    - Selective pulmonary vasodilator;
    - Administered at a concentration of 5–20 ppm;
    - The clinical response is observed as a rapid increase in SpO□ and PaO□.
- Sildenafil
    - Alternative or adjunctive therapy to NO;
    - Administered orally or intravenously;
    - Increases NO availability and reduces pulmonary pressure.
- Tolazoline (rarely used today)
    - Nonspecific vasodilator, with a risk of hypotension.
- Surfactant
    - In cases associated with respiratory distress or meconium aspiration.

D. Management of secondary causes

- Empirical antibiotics (ampicillin + gentamicin) until sepsis is ruled out;
- Specific treatment of MAS, pneumonia, or pulmonary hypoplasia, as indicated.

I.8.9. PROGNOSIS

The prognosis depends on the severity of hypoxemia and the underlying etiology. Most mild and moderate cases respond favorably to treatment with NO and careful ventilation. Secondary forms of MAS or asphyxia may progress more slowly, requiring prolonged respiratory support. Survival exceeds 85% in centers with access to intensive care and ECMO.

Complications

- Severe hypoxia and neurological damage;
- Right heart dysfunction;
- Severe metabolic acidosis;
- Renal failure secondary to hypoperfusion;
- Neonatal mortality (10–20% in severe cases).

In the long term, surviving children may experience recurrent episodes of wheezing and impaired pulmonary pressure regulation.

I.8.10. CONCLUSIONS. KEY POINTS

Key points

- PPHN is caused by the persistence of fetal pulmonary pressure after birth;
- It manifests as oxygen-refractory hypoxemia;
- The diagnosis is confirmed by echocardiography;
- The main treatment is inhaled nitric oxide, followed by sildenafil and ventilatory support;
- The prognosis is favorable with early treatment and multidisciplinary management.

Self-assessment questions

- What are the main pathophysiological mechanisms involved in PPHN?
- What distinguishes PPHN from cyanotic congenital heart diseases?
- What is the role of nitric oxide in the treatment of PPHN?
- How are forms refractory to standard treatment managed?
- What complications can occur in severe, untreated PPHN?

I.9. PULMONARY HEMORRHAGE

I.9.1. DEFINITION

Pulmonary hemorrhage (PH) is an acute, often dramatic complication characterized by blood extravasation into the lower airways and alveoli, leading to acute respiratory failure. It is one of the most serious neonatal emergencies, occurring more frequently in preterm infants and critically ill ventilated newborns.

I.9.2. EPIDEMIOLOGY. INCIDENCE

The incidence of pulmonary hemorrhage ranges from 1 to 12 cases per 1,000 live births, increasing significantly in preterm infants weighing <1,500 g. It usually occurs within the first 3 days of life and is associated with high mortality (30–50%), especially in infants with bronchopulmonary dysplasia, patent ductus arteriosus (PDA), or severe sepsis.

I.9.3. PATHOPHYSIOLOGY

The primary mechanism involves increased pulmonary capillary pressure associated with damage to the alveolar-capillary barrier, which allows blood to leak into the alveoli. There are multiple contributing factors:

- Increased pulmonary hydrostatic pressure, caused by left-to-right shunting through the patent ductus arteriosus;
- Hypoxia and acidosis, which impair endothelial permeability;
- High-pressure mechanical ventilation, which exacerbates blood extravasation;
- Coagulation disorders (DIC, thrombocytopenia, factor deficiencies);
- Capillary fragility in preterm infants;
- Systemic infections that induce diffuse inflammation.

The end result is alveolar flooding with blood, a reduction in the gas exchange surface area, and the onset of severe hypoxemia.

I.9.4. RISK FACTORS

- Severe prematurity (<32 weeks);
- High-pressure mechanical ventilation (PIP > 25 cmH□O);
- Patent ductus arteriosus (PDA);
- Respiratory distress syndrome treated with surfactant (redistribution of pulmonary blood flow may trigger hemorrhage);
- Perinatal asphyxia;
- Severe neonatal infections;
- Coagulation disorders (DIC, thrombocytopenia);
- Rapid volume transfusions.

I.9.5. CLINICAL DIAGNOSIS

Onset is sudden and dramatic, usually in a child who is already on ventilation or experiencing respiratory distress. Manifestations include:

- Acute respiratory deterioration: sudden drop in oxygen saturation, apnea, bradycardia;
- Foamy or bloody blood in tracheal secretions (sometimes via the mouth or nose);
- Hypotension, pallor, cyanosis;
- Acute anemia;
- A sudden decrease in oxygen requirements following surfactant treatment, followed by deterioration—an important sign of pulmonary hemorrhage;
- In mild cases, only mild hemoptysis and moderate hypoxia may be observed.

The diagnosis is primarily clinical and is based on the observation of blood in the airways, associated with sudden respiratory deterioration.

I.9.6. LABORATORY AND IMAGING STUDIES

- Chest X-ray: diffuse bilateral opacities, with an “alveolar flooding” appearance; sometimes gravitational (basal) distribution.
- Blood gas analysis: severe hypoxemia, hypercapnia, metabolic acidosis;
- Complete blood count: sudden drop in hemoglobin and hematocrit;
- Coagulogram: may show prolonged PT/aPTT, hypofibrinogenemia, thrombocytopenia.
- Echocardiography: useful for identifying a significant patent ductus arteriosus.

I.9.7. DIFFERENTIAL DIAGNOSIS

- Aspiration of maternal blood (from the upper airways—pharynx, stomach);
- Congenital pneumonia with hemoptysis;
- Severe respiratory distress syndrome (without visible blood in the airways);
- Pulmonary hemorrhage secondary to systemic coagulopathy (e.g., generalized DIC).

For confirmation, the Apt–Downey test may be performed (fetal hemoglobin differs from maternal hemoglobin).

I.9.8. MANAGEMENT

Treatment of pulmonary hemorrhage is a major emergency and requires simultaneous measures for resuscitation, hemorrhage control, and correction of predisposing factors.

A. Initial Stabilization

- Ensure airway patency;
- Carefully suction blood from the trachea;
- Administer 100% oxygen and initiate immediate assisted ventilation;
- Continuous monitoring of SpO□, heart rate, and blood pressure.

B. Respiratory support

- Mechanical ventilation with positive pressure (minimum effective PIP for adequate oxygen saturation);
- Increase positive end-expiratory pressure (PEEP) to 6–8 cmH□O to limit blood leakage;
- In severe cases, high-frequency ventilation (HFOV) for gas stabilization;
- Administration of exogenous surfactant after bleeding has stopped (restores alveolar function).

C. Replacement therapy and hemostasis

- Transfusions of whole blood or packed red blood cells (10–15 ml/kg);
- Correction of coagulation disorders with fresh frozen plasma and platelets;
- Administration of vitamin K (1 mg IV or IM);
- In refractory cases, recombinant activated factor VII may be used (off-label, in specialized centers).

D. Treatment of the underlying cause

- Ligation or pharmacological closure of the patent ductus arteriosus (indomethacin, ibuprofen, intravenous paracetamol);
- Infection control (empirical antibiotic therapy);
- Adjustment of ventilatory pressures.

I.9.9. PROGNOSIS

The prognosis is guarded in severe cases, especially in extremely preterm infants. The survival rate depends on:

- gestational age;
- the presence and control of the ductus arteriosus;
- the speed of therapeutic intervention.

In mild or moderate cases, pulmonary recovery is complete, with no sequelae. However, children who have had severe pulmonary hemorrhage may subsequently develop bronchopulmonary dysplasia or restrictive ventilatory disorders.

Complications:

- Severe acute respiratory failure;
- Acute anemia and hypovolemia;
- Cerebral hypoxia, intraventricular hemorrhage;
- Posthemorrhagic pulmonary fibrosis;
- Recurrence, especially in ventilated preterm infants with persistent PDA.

I.9.10. CONCLUSIONS. KEY POINTS

Key points

- Pulmonary hemorrhage is a major respiratory emergency in the newborn;
- It occurs frequently in ventilated preterm infants and those with patent ductus arteriosus;
- The diagnosis is clinical: blood in the airways + sudden deterioration;
- Treatment includes careful ventilation, transfusion, and correction of coagulopathy;
- The prognosis depends on the promptness of intervention and the severity of the underlying condition.

Self-assessment questions

- What are the pathophysiological mechanisms involved in neonatal pulmonary hemorrhage?
- What risk factors are associated with the development of neonatal pulmonary hemorrhage in preterm infants?
- What are the main emergency measures in the management of PH?
- How is PH distinguished from aspiration of maternal blood?
- What role do surfactant and PEEP play in stabilizing patients with PH?

I.10. AIR LOSS SYNDROMES

I.10.1. DEFINITION

Air leak syndromes represent a group of respiratory complications in which air escapes from the alveoli or small airways into extraluminal spaces, reaching the pleura, mediastinum, pericardium, subcutaneous tissue, or even the venous system.

The most common forms include:

- Pneumothorax – air in the pleural space;
- Pneumomediastinum – air in the mediastinum;
- Pneumopericardium – air in the pericardial sac;
- Pulmonary interstitial emphysema (PIE) – air in the pulmonary interstitium;
- Pneumoperitoneum – air in the abdominal cavity (rare, secondary to tension pneumothorax).

I.10.2. EPIDEMIOLOGY. INCIDENCE

Air leak syndromes occur in 1–2% of term newborns and up to 10–15% of mechanically ventilated preterm infants.

The risk is significantly increased in:

- newborns with respiratory distress syndrome;
- those ventilated at high pressures (PIP > 25 cmH□O);
- infants with bronchopulmonary dysplasia;
- meconium aspiration or congenital pneumonia.

I.10.3. PATHOPHYSIOLOGY

The common mechanism is alveolar rupture due to overdistension, increased pressure, or fragility of the lung parenchyma.

The extravasated air follows the path of least resistance and may accumulate:

- in the interstitium (interstitial emphysema);
- in the pleural space (pneumothorax);
- in the mediastinum or pericardium;
- in the subcutaneous tissues.

In severe cases, air leakage causes mechanical compression of the lungs and heart, leading to hypoxemia and circulatory collapse.

I.10.4. RISK FACTORS

- High-pressure mechanical ventilation;
- High-volume ventilation in preterm infants (barotrauma/volutrauma);
- Respiratory distress syndrome;
- Meconium aspiration;
- Resuscitation with excessive pressures at birth;
- Severe hypoxia;
- Bronchopulmonary dysplasia;
- Pulmonary infections.

I.10.5. CLINICAL DIAGNOSIS

Clinical signs depend on the location and volume of the extravasated air.

1. Pneumothorax

- Sudden onset with worsening respiratory distress;
- Cyanosis, bradycardia, decreased SpO□;
- Chest asymmetry, distended hemithorax;

- Increased distance between the hyperresonant percussion sound and decreased vesicular breath sounds on the affected side;
- In tension pneumothorax—mediastinal shift and circulatory collapse.

2. Pneumomediastinum

- Moderate respiratory distress;
- Fine crackles on palpation of the upper chest;
- Radiological sign of the "winged heart" (air around the thymus).

3. Pneumopericardium

- Extremely rare, but serious;
- Cardiac tamponade – tachycardia, hypotension, diminished heart sounds;
- Radiological confirmation: clear outline of the heart delineated by air.

4. Interstitial pulmonary emphysema

- Progressive onset, with hypoxemia and respiratory distress;
- Radiologically – irregular translucent lines, distributed in a "network" pattern within the lung parenchyma;
- Frequently bilateral.

I.10.6. LABORATORY AND IMAGING STUDIES

- **Chest X-ray**

This is the primary diagnostic method:

- Pneumothorax: free air between the lung and the chest wall, partial lung collapse;
- Pneumomediastinum: air in the pericardial space and beneath the sternum ("air around the thymus");
- Pneumopericardium: air around the heart, clear demarcation between the heart and the lungs;
- Interstitial emphysema: a fine network of translucent lines between the bronchi and blood vessels.

- **Chest transillumination**

Useful in the incubator—when shone on the chest, the light passes intensely through the air-filled area (rapid confirmation).

- **Pulmonary ultrasound**

Noninvasive method – the absence of "lung sliding" and the "lung point" sign confirm pneumothorax.

I.10.7. DIFFERENTIAL DIAGNOSIS

- Respiratory distress syndrome (without hypertransparency);
- Hemothorax (fluid-air level, not free air);
- Extensive pneumonia (infiltrative opacities);
- Lobar atelectasis (localized collapse without air leakage).

I.10.8. MANAGEMENT

Treatment depends on the severity and location of the air leak.

A. General measures

- Immediately stop excessive ventilation;
- Ensure oxygenation and circulatory stabilization;
- Monitor SpO□ and ventilatory pressures;
- Position the newborn on the affected side (promotes re-expansion of the contralateral lung).

B. Specific treatment

- Small, asymptomatic pneumothorax
    - Close observation and oxygen therapy (accelerated nitrogen resorption effect).
- Symptomatic pneumothorax

    - Emergency needle decompression (22G catheter in the second intercostal space, midclavicular line);
    - Followed by pleural drainage with a thin tube (10–12 Fr), connected to a water-filled system;
    - Ventilation adjustment (reduced pressures, low PEEP).
- Interstitial emphysema (IE)
    - Selective positioning (lateral decubitus on the affected side);
    - High-frequency ventilation (HFOV) to reduce alveolar microtrauma;
    - In severe unilateral cases – selective intubation of the contralateral bronchus.
- Pneumopericardium
    - Emergency pericardial puncture under ultrasound guidance;
    - Followed by continuous drainage until stabilization.
- Pneumomediastinum
    - Usually benign – resolves spontaneously within 24–72 hours with supportive care.

I.10.9. PROGNOSIS

Most mild cases (pneumomediastinum, small pneumothorax) resolve completely. Severe cases, associated with ARDS or prolonged ventilation, may require intensive care and carry a risk of death (10–20%). The prognosis depends on prompt recognition and control of ventilatory pressures.
Complications:

- Severe hypoxemia and acidosis;
- Additional barotrauma;
- Right heart failure (in tension pneumopericardium);
- Recurrence, especially in patients with BPD;
- Post-traumatic pulmonary fibrosis (rare).

I.10.10. CONCLUSIONS. KEY POINTS

Key points:

- Air leak syndromes are caused by alveolar rupture and air extravasation;
- The most common are pneumothorax and interstitial emphysema;
- Diagnosis is based on chest X-ray and lung ultrasound;
- Treatment ranges from observation to emergency pleural drainage;
- Prevention consists of careful ventilation and low pressures in preterm infants.

Self-assessment questions:

- What is the common mechanism underlying air leak syndromes?
- What distinguishes pneumothorax from pneumomediastinum clinically and radiologically?
- How is a tension pneumothorax treated in a newborn?
- What role does HFOV play in the management of interstitial emphysema?
- What measures can prevent air leaks in ventilated preterm infants?

I.11. MANAGEMENT OF RESPIRATORY DISORDERS

I.11.1. MONITORING RESPIRATORY FUNCTION

I.11.1.1. DEFINITION

Respiratory function monitoring refers to the set of clinical and paraclinical methods used to assess the efficiency of ventilation, oxygenation, and gas exchange in the newborn. The goal is the early detection of respiratory distress and the assessment of response to treatment.

I.11.1.2. CLINICAL IMPORTANCE

The newborn's breathing differs significantly from that of an adult:

- The chest wall is compliant, and the respiratory muscles are immature;
- There are fewer alveoli (only 20–30% of the final number);

- The oxygen reserve is low;
- Central control of respiration is unstable (predisposing to apnea).

Therefore, any pulmonary impairment (RDS, TTN, MAS, PPHN) can rapidly lead to hypoxemia and acidosis. Close monitoring is essential for adjusting treatment and preventing complications.

I.11.1.3. Clinical parameters assessed

Monitoring always begins with direct observation of the newborn:

- Respiratory rate (RR): normal 30–60/min; >60 = tachypnea, <30 = respiratory depression.
- Respiratory effort: observe costal retractions, expiratory grunting, and nasal flaring.
- Chest symmetry: uneven movements may indicate pneumothorax or atelectasis.
- Skin color: central cyanosis = severe hypoxemia; pallor = hypoperfusion.
- Capillary refill time: normal <3 seconds; prolonged = peripheral hypoperfusion.
- Peripheral oxygen saturation (SpO□): continuously monitored by pulse oximetry.

I.11.1.4. Methods for monitoring respiratory function

- **Continuous clinical observation**

The first and most important method. It includes assessment of chest movements, type of breathing (abdominal, paradoxical), and breath sounds.

- **Pulse oximetry**

Noninvasive monitoring of SpO□; placement of the sensor on the right hand (preductal) or on the foot (postductal). A difference >10% suggests a right-to-left shunt (PPHN).

- **Blood gas analysis**

Determines the actual levels of oxygen, carbon dioxide, and blood pH. It is the standard method for assessing ventilation and oxygenation.

- **Transcutaneous monitoring**

Sensors applied to the skin estimate PaO□ and PaCO□ in real time; useful in preterm infants or during prolonged ventilation.

- **Capnography**

Measures the end-tidal CO□ (EtCO□) concentration; used primarily in mechanical ventilation.

I.11.1.5. Modern complementary techniques

- Inductive respiratory plethysmography: simultaneously assesses chest and abdominal movements.
- Transthoracic electrical impedance: monitors lung volume and detects apnea.
- Pulmonary ultrasound: an emerging, noninvasive method capable of identifying atelectasis, effusions, and pneumothorax.

I.11.1.6. Alarm parameters

- SpO□ < 88% in term infants or <85% in preterm infants;
- Respiratory rate <30/min or >80/min;
- Persistent respiratory grunting;
- Central cyanosis;
- Pronounced chest retractions;
- Recoloration time >4 seconds.

These signs indicate the onset of severe respiratory distress and the need for intervention (oxygen therapy, CPAP, mechanical ventilation).

I.11.1.7. Common Interpretation Errors

- False-positive peripheral cyanosis in hypothermia;
- Pulse oximeter artifacts (movement, poor perfusion);
- Underestimation of hypercapnia—may be present even with normal SpO□;
- Lack of correlation between objective data and clinical assessment.

I.11.1.8. Conclusions. Key points

Key points:

- Respiratory monitoring should be initiated immediately after birth in all at-risk newborns;

- Clinical observation remains the most valuable method, supplemented by instrumental measurements;
- Pulse oximetry and blood gas analysis are indispensable in the assessment of respiratory failure;
- Subtle changes (respiratory rate, respiratory effort, SpO□) may precede acute deterioration;
- Interpretation must always be made within the clinical context.

Self-assessment questions

- What are the main clinical parameters of respiratory function in the newborn?
- What is the significance of the preductal–postductal SpO□ difference?
- What are the advantages and limitations of pulse oximetry?
- Which parameters indicate the onset of severe respiratory distress?
- Why is the correlation between objective monitoring and clinical observation important?

I.11.2. BLOOD GAS MONITORING

I.11.2.1. Definition

Blood gas monitoring (blood gas analysis) is the method used to assess acid-base balance and the efficiency of gas exchange (oxygenation and CO□ elimination) in the newborn's blood. It is the gold standard for assessing ventilation, oxygenation, and metabolic status, especially in patients with respiratory distress or on ventilator support.

I.11.2.2. Types of Samples

- Arterial blood: provides the most accurate information on oxygenation and ventilation; it is collected from the radial, ulnar, or tibial artery or via an umbilical arterial catheter.
- Capillary blood: useful for repeated monitoring; correlates well with PaCO□ and pH, but underestimates PaO□.
- Venous blood: not used for assessing oxygenation, but only for metabolic guidance (pH, lactate).

In newborns, the choice of sample type depends on hemodynamic stability and available vascular access.

I.11.2.3. Parameters Analyzed and Clinical Significance

1. **pH (7.35–7.45)**

- Reflects overall acid-base balance.
- Respiratory acidosis: elevated PaCO□ (>50 mmHg).
- Metabolic acidosis: Low HCO□⁻ (<18 mmol/L).
- Alkalosis: pH >7.45 – frequently secondary to hyperventilation.

2. **PaCO□ (35–45 mmHg)**

- Measures the efficiency of alveolar ventilation.
- Increase → hypoventilation, CO□ retention (e.g., RDS, apnea, respiratory depression).
- Decrease → hyperventilation, frequently iatrogenic in mechanical ventilation.

3. **PaO□ (60–80 mmHg in term infants; 50–70 mmHg in preterm infants)**

- Direct indicator of arterial oxygenation.
- Low values → hypoxemia; excessively high values (>100 mmHg) → risk of pulmonary toxicity and retinopathy of prematurity (ROP).

4. **HCO□⁻ (18–22 mmol/L) and base excess (–2 to +2 mmol/L)**

- Represents the metabolic component.
- Low HCO□⁻ and negative BE → metabolic acidosis (shock, tissue hypoxia).
- Elevated HCO□⁻ → compensatory metabolic alkalosis.

5. **SaO□ (% arterial saturation)**

- Determined directly by analyzer; correlates with SpO□ measured noninvasively by pulse oximeter.

6. **Plasma lactate**

- Early marker of tissue hypoperfusion and hypoxia; values >2 mmol/L suggest incipient shock.

I.11.2.4. Interpretation of Arterial Blood Gas Analysis

Interpretation must be done in a clinical context, analyzing step by step:

1. Check the pH (acidosis or alkalosis);
2. Assess PaCO□ – respiratory or metabolic cause;
3. Analyze HCO□⁻ and BE – metabolic compensation;
4. Evaluate PaO□ and SaO□ – degree of oxygenation;
5. Correlate with clinical signs (respiratory rate, SpO□, respiratory effort).

Clinical examples:

- Pure respiratory acidosis: pH ↓, $PaCO_2$ ↑, normal HCO_3^- → hypoventilation (RDS, apnea).
- Metabolic acidosis: pH ↓, HCO_3^- ↓, $PaCO_2$ normal → shock, hypoxia, NEC.
- Respiratory alkalosis: pH ↑, $PaCO_2$ ↓ → hyperventilation.
- Metabolic alkalosis: pH ↑, HCO_3^- ↑ → gastric losses, diuretic treatment.

I.11.2.5. Monitoring frequency

Depends on the severity of the case:

- In acute distress or mechanical ventilation: every 1–3 hours;
- During stabilization: 2–4 times/day;
- After changing ventilator settings: every 15–30 minutes;
- After initiation of surfactant or oxygen therapy: immediately and at 1-hour intervals.

I.11.2.6. Common errors and pitfalls

- Incorrect sampling (air bubbles → false hypoxemia);
- Delay in analysis → decrease in PaO_2 and increase in $PaCO_2$;
- Capillary sample taken during vasoconstriction → falsely altered values;
- Lack of correlation with clinical data and pulse oximetry.

I.11.2.7. Complications of arterial sampling

- Local hematoma;
- Distal ischemia (especially in the radial artery);
- Infection at the puncture site;
- Transient arterial spasm.

For prevention, the modified Allen test and alternating puncture sites are recommended.

I.11.2.8. The Role of Arterial Blood Gas Analysis in Respiratory Management

Blood gas analysis guides all major decisions:

- Adjustment of ventilator pressures (PIP, PEEP, FiO□);
- Determining the timing for surfactant administration;
- Early identification of hypercapnia or silent hypoxia;
- Assessment of the effectiveness of oxygen therapy and noninvasive ventilation.

I.11.2.9. Conclusions. Key points

Key points:

- Arterial blood gas analysis is the gold standard for evaluating neonatal respiratory failure;
- *pH, PaO□, and PaCO□* are the most important parameters;
- Interpretation must always be done in the clinical context;
- Extreme PaO□ values can be just as dangerous as hypoxemia;
- Proper collection and rapid analysis are essential for valid results.

Self-assessment questions:

- What is the difference between arterial, capillary, and venous samples in blood gas analysis?
- Which parameter most accurately reflects alveolar ventilation?
- How is respiratory acidosis distinguished from metabolic acidosis?
- What role does blood gas analysis play in adjusting mechanical ventilation?
- What are the main sources of error in interpreting blood gas results?

I.11.3. OXYGEN THERAPY

I.11.3.1. Definition

Oxygen therapy is the controlled administration of oxygen to maintain adequate tissue oxygenation and prevent hypoxia. In newborns, oxygen is considered a drug, requiring precise dosing and careful monitoring to avoid toxicity.

I.11.3.2. Physiological Purpose

- Ensuring an adequate supply of oxygen to the tissues;
- Reducing respiratory effort and hypoxia;
- Preventing metabolic acidosis secondary to hypoperfusion;
- Support in respiratory failure of various causes (RDS, TTN, PPHN, MAS).

I.11.3.3. Indications

Oxygen therapy is indicated in all situations resulting in documented arterial hypoxemia or clinical signs of hypoxia:

- SpO□ < 90% (in term infants) or < 88% (in preterm infants);
- PaO□ < 50 mmHg;
- Respiratory distress (grunting, chest retractions, tachypnea);
- Recurrent apnea;
- Congenital pneumonia;
- Meconium aspiration syndrome;
- Persistent pulmonary hypertension of the newborn (PPHN).

I.11.3.4. General principles of administration

1. Use the lowest effective concentration of oxygen (minimum FiO□ that maintains SpO□ at the desired target).
2. Continuous monitoring of SpO□ via pulse oximetry.
3. Gradual adjustment of FiO□ based on blood gas analysis and saturation.
4. Avoidance of hyperoxia—which is just as dangerous as hypoxia

I.11.3.5. Oxygenation Targets (according to AAP and European Guidelines, 2023)

Oxygenation targets in newborns vary depending on gestational age and underlying pathology.

- Preterm infants under 32 weeks should be maintained at a peripheral oxygen saturation (SpO□) between 90 and 94%, corresponding to an arterial oxygen pressure (PaO□) of approximately 50–70 mmHg.
- Lower values increase the risk of hypoxia and brain damage, while higher values promote retinopathy of prematurity (ROP).
- Term newborns require a slightly higher saturation, between 92 and 96%, which corresponds to a PaO□ between 60 and 80 mmHg.
- In this range, adequate tissue oxygenation is ensured without exposing the lungs to oxidative stress.
- In persistent pulmonary hypertension of the newborn (PPHN), a saturation of 94–98% is targeted to maintain a PaO□ of 70–90 mmHg, as oxygen also acts as a pulmonary vasodilator in this situation.
- 44Exceeding these values (PaO□ above 100 mmHg) indicates hyperoxia, a situation in which the fr44 e (FiO□) must be reduced. Values above 100 mmHg are potentially toxic and should be avoided.

I.11.3.6. Methods of oxygen administration

1. **Nasal cannula**

- Provides a low oxygen flow rate (0.5–2 L/min).
- Indicated for mild cases of respiratory distress.
- Advantages: well tolerated, allows for oral feeding.
- Limit: inability to precisely control FiO□.

2. **Oxygen hood**
- Creates an environment with a constant O□ concentration (30–60%).
- Indicated for newborns who require moderate supplemental oxygen but are breathing spontaneously.
- Oxygen must be humidified and warmed (34–36°C).
- Requires continuous measurement of FiO□ inside the hood.

3. **Nasal CPAP (Continuous Positive Airway Pressure)**
- Maintains constant positive pressure in the airways.
- Prevents alveolar collapse and increases oxygenation.
- Indicated for RDS, TTN, and apnea of prematurity.
- Requires careful monitoring of pressures (4–6 cmH□O) and SpO□.

4. **Mechanical ventilation**
- Used in severe respiratory failure, when simple oxygen therapy is ineffective.
- Allows for complete control of FiO□, PIP, PEEP, and tidal volume.
- Requires frequent blood gas analysis and continuous monitoring.

I.11.3.7. Prevention and control of hyperoxia

Hyperoxia causes oxidative damage through the formation of free radicals, which affect the lungs, retina, and central nervous system.

Major adverse effects include:
- Retinopathy of prematurity (ROP) – abnormal proliferation of retinal vessels;
- Chronic lung damage (bronchopulmonary dysplasia);
- Cerebral vasoconstriction and periventricular necrosis;
- Systemic oxidative stress.

Therefore:
- Do not administer uncontrolled oxygen;
- Adjust FiO□ gradually, based on SpO□ and PaO□;
- Discontinue oxygen as soon as saturation stabilizes.

I.11.3.8. Monitoring during oxygen therapy
- Continuous pulse oximetry (pre-ductal and post-ductal SpO□);
- Periodic arterial blood gas analysis (PaO□, PaCO□, pH);
- Observation for signs of respiratory distress;
- Assessment of the temperature and humidity of the administered gas;

I.11.3.9. Complications of oxygen therapy
- Hyperoxia and retinopathy of prematurity;
- Atelectasis due to nitrogen resorption;
- Oxidative lung injury;
- Systemic vasoconstriction and cerebral hypoperfusion;
- Suppression of the respiratory center in newborns with chronic hypercapnia.

I.11.4. MECHANICAL VENTILATION

I.11.4.1. Definition

Mechanical ventilation is a set of techniques by which the newborn's breathing is assisted or completely replaced by a ventilator, with the aim of maintaining oxygenation and CO□ elimination within physiological limits. It is used when spontaneous breathing is ineffective or the respiratory effort becomes dangerous for the infant.

I.11.4.2. Indications

Mechanical ventilation is initiated in the following situations:
- Acute respiratory failure with severe hypoxemia (PaO□ < 50 mmHg in 100% oxygen);
- Hypercapnia with respiratory acidosis (PaCO□ > 60 mmHg and pH < 7.25);
- Recurrent apnea or respiratory pauses >20 seconds;

- Excessive respiratory effort with muscle fatigue (profound chest retractions, moaning);
- Ineffective ventilation under CPAP (continuous positive airway pressure);
- Postoperative period following major thoracic or abdominal surgery;
- Severe pulmonary edema, meconium aspiration, or pulmonary hemorrhage.

I.11.4.3. Physiological goals

Mechanical ventilation aims to:

- maintain adequate arterial oxygenation (PaO□ 50–80 mmHg);
- to eliminate carbon dioxide (PaCO□ 35–55 mmHg);
- reducing respiratory effort and oxygen consumption;
- preventing alveolar collapse by maintaining positive end-expiratory pressure (PEEP).

I.11.4.4. General Principles of Operation

A neonatal ventilator delivers small volumes of air (2–6 mL/kg) at high respiratory rates (30–60/min).

Breathing is controlled by adjusting several essential parameters:

- PIP (Peak Inspiratory Pressure): the maximum pressure during inspiration, which determines the tidal volume.
- PEEP (Positive End-Expiratory Pressure): the pressure maintained at the end of exhalation, which prevents atelectasis.
- FiO□ (Fraction of Inspired Oxygen): the fraction of inspired oxygen, expressed as a percentage.
- Inspiratory time (Ti): the duration of the inspiratory phase, which influences oxygenation.
- Respiratory rate: the number of ventilatory cycles per minute.

I.11.4.5. Types of mechanical ventilation

1. Conventional ventilation (IPPV, SIMV)

This is the standard form of ventilation, in which each inspiration is controlled by the machine. SIMV synchronizes ventilatory cycles with the child's spontaneous breaths, reducing the risk of asynchrony. It is the method of choice in RDS and neonatal pneumonia.

2. Continuous positive airway pressure (CPAP)

It maintains a constant positive pressure in the airways, allowing for spontaneous breathing. It is preferred in moderate forms of respiratory failure and to avoid intubation.

3. High-frequency oscillatory ventilation (HFOV)

Delivers extremely small volumes but at very high frequencies (300–900 breaths/minute). Ensures effective ventilation at low pressures, reducing the risk of barotrauma. Indicated for severe RDS, interstitial emphysema, pneumothorax, or refractory PPHN.

I.11.4.6. Initiation of mechanical ventilation

Start with "safety" settings, then adjust progressively:

- Initial PIP: 16–20 cmH□O in term infants; 14–18 cmH□O in preterm infants;
- PEEP: 4–6 cmH□O;
- Respiratory rate: 30–50/min;
- FiO□: 0.4–0.6, adjusted according to SpO□;
- Inspiratory time: 0.35–0.45 seconds.

Arterial blood gas analysis is repeated 30–60 minutes after initiation for optimization.

I.11.4.7. Monitoring of the ventilated patient

Continuous monitoring is mandatory and includes:

- Heart rate and oxygen saturation (SpO□);
- Arterial blood gas analysis (pH, PaCO□, PaO□);
- Ventilator pressures and volumes displayed by the device;
- Clinical signs of respiratory effort, asynchrony, or excessive chest distension;
- Periodic chest X-ray to check lung expansion and the position of the endotracheal tube.

I.11.4.8. Weaning

Begin after blood gas levels have stabilized and oxygen requirements have decreased.

Main steps:

- Gradual reduction of PIP and ventilatory rate;
- Maintain PEEP at 4–5 cmH□O;
- Assess the ability to breathe spontaneously;
- Switching to pressure support ventilation (PSV) or CPAP;
- Extubation after 2–3 hours of stability with FiO□ < 0.3 and SpO□ > 90%.

I.11.4.9. Complications

Mechanical ventilation, although life-saving, carries significant risks:

- Barotrauma: alveolar injury due to excessive pressure;
- Volutrauma: alveolar distension due to high volumes;
- Atelectotrauma: repeated collapse of the alveoli;
- Nosocomial infections and ventilator-associated pneumonia;
- Bronchopulmonary dysplasia (BPD): a chronic lung disease of premature infants;
- Tracheal injuries due to prolonged intubation;
- Hemodynamic disturbances (decreased cardiac output due to increased intrathoracic pressure).

I.11.4.10. The role of the medical team

Neonatal mechanical ventilation requires the collaboration of a multidisciplinary team:

- neonatologist – determines the indication and parameters;
- intensive care nurse – continuously monitors vital signs and the ventilator;
- respiratory physical therapist – ensures postural drainage and bronchial hygiene;
- biomedical engineer – checks the functionality of the equipment.

I.11.4.11. Conclusions. Key points

Key points:

- Mechanical ventilation is initiated only when spontaneous breathing is ineffective;
- The primary goal is to maintain oxygenation and CO□ elimination at the lowest possible pressures;
- Close monitoring prevents barotrauma and complications;
- Weaning must be performed gradually and under continuous supervision;
- Training of the specialized medical team is crucial for the success of ventilation.

Self-assessment questions:

- What are the main indications for mechanical ventilation in newborns?
- Which ventilatory parameters must be continuously monitored?
- What distinguishes conventional ventilation from high-frequency ventilation?
- What are the main complications associated with prolonged ventilation?
- What criteria must be met for safe extubation?

I.11.5. EXTRACORPOREAL MEMBRANE OXYGENATION

I.11.5.1. Definition

Extracorporeal membrane oxygenation (ECMO) is an advanced life support technique in which the patient's blood is circulated extracorporeally through a semipermeable membrane that oxygenates the blood and removes carbon dioxide, temporarily replacing lung (and sometimes cardiac) function. ECMO is used when conventional and high-frequency ventilation (HFOV) can no longer maintain adequate oxygenation and ventilation.

I.11.5.2. Historical Context and Evolution

The first clinical uses of ECMO in newborns date back to the 1970s, with the development of cardiopulmonary bypass circuits. Over the past two decades, ECMO has become the standard of care in tertiary centers for refractory forms of neonatal respiratory failure, particularly in:

- persistent pulmonary hypertension of the newborn (PPHN),
- meconium aspiration syndrome,
- severe congenital diaphragmatic hernias,
- sepsis with acute respiratory failure.

I.11.5.3. Principle of Operation

Blood is drawn from the infant's venous system, passed through a membrane oxygenator, where carbon dioxide is removed and oxygen is diffused, and then reinfused into the body.

There are two main configurations:

- Venovenous (VV) ECMO: draws blood from and returns it to the venous system, providing pure pulmonary support;
- Venous-arterial (VA) ECMO: returns oxygenated blood to the carotid artery, providing complete cardiopulmonary support.

Both types use a centrifugal or roller pump, a membrane fiber oxygenator, and a heat exchanger that maintains the blood temperature at 37°C.

I.11.5.4. Indications

ECMO is indicated when there is refractory hypoxemic or hypercapnic respiratory failure, defined by the following parameters:

- Oxygenation index (OI) > 40 for > 4 hours (OI = [FiO□ × mean airway pressure × 100] / PaO□);
- PaO□ < 40 mmHg persisting despite optimal ventilation;
- pH < 7.15 due to refractory respiratory acidosis;
- FiO□ > 0.9 required to maintain oxygenation;
- No response to treatment with inhaled nitric oxide (iNO).

Main eligible diagnoses:

- Severe PPHN;
- Meconium aspiration syndrome;
- Severe neonatal pneumonia;
- Congenital diaphragmatic hernia;
- Severe sepsis with refractory pulmonary dysfunction.

I.11.5.5. Contraindications

- Weight <2 kg or gestational age <34 weeks (increased risk of cerebral hemorrhage);
- Active intracranial hemorrhage;
- Severe uncontrolled coagulopathy;
- Lethal malformations;
- Irreversible neurological damage;
- Irreversible cardiac dysfunction.

I.11.5.6. Technical Management and the ECMO Team

The ECMO procedure is complex and requires a specialized multidisciplinary team:

- neonatologist-intensivist (case coordinator);
- pediatric or cardiovascular surgeon (for cannulation);
- ECMO perfusionist (monitors the circuit and oxygenator);
- neonatal intensive care nurse (continuous monitoring);
- laboratory specialist (for gas and coagulation monitoring).

Monitoring during ECMO includes:

- Frequent arterial and venous blood gas analysis;
- Plasma lactate (indicator of tissue perfusion);
- Blood pressure, urine output, temperature;
- Circuit parameters: flow, pressure, inlet and outlet saturation;
- Neurological monitoring (periodic transfontanellar ultrasound).

I.11.5.7. Possible complications

Although life-saving, ECMO is an invasive technique with a high risk of complications, the most common of which are:

- Intracranial hemorrhage—the major complication, especially in preterm infants;
- Thrombosis or embolism in the extracorporeal circuit;
- Nosocomial infections (catheter-associated sepsis);
- Hemolysis and secondary renal dysfunction;
- Mechanical complications (line rupture, pump failure, accidental air embolism);
- Hypoxic neurological injury prior to ECMO initiation.

The overall rate of major complications is approximately 30–40%, but the overall mortality of selected patients remains below 20%.

I.11.5.8. Criteria for discontinuing ECMO

ECMO is discontinued when the child's lungs regain sufficient function to ensure adequate oxygenation with minimal support.

Discontinuation criteria:

- PaO□ > 60 mmHg at FiO□ ≤ 0.4;
- PaCO□ < 50 mmHg with pH > 7.3;
- Moderate ventilatory pressures (PIP < 25 cmH□O, PEEP 5 cmH□O);
- Chest X-ray showing good pulmonary re-expansion;
- Hemodynamic stability without high doses of vasopressors.

After weaning, the patient is maintained on conventional ventilation or HFOV, with intensive monitoring for the first 24–48 hours.

I.11.5.9. Outcomes and Prognosis

Survival after neonatal ECMO depends on the underlying etiology:

- Meconium aspiration: survival >90%;
- Idiopathic PPHN: 80–85%;
- Congenital diaphragmatic hernia: 50–60%;
- Severe sepsis: 60–70%.

Most surviving children have normal neuropsychomotor development at 1–2 years of age, although there is an increased risk of sensorineural hearing loss, fine motor coordination disorders, and subtle cognitive deficits.

I.11.5.10. Conclusions. Key points

Key points:

- ECMO is a last-resort technique, reserved for cases refractory to conventional ventilation;
- It allows for "lung rest" and the repair of severe lung injury;
- It requires a multidisciplinary team and a dedicated center;
- The main risks are cerebral hemorrhage and infections;

Self-assessment questions

- What are the main indications for ECMO in newborns?
- What distinguishes veno-venous ECMO from veno-arterial ECMO?
- What are the major risks associated with the procedure?
- What criteria are used to discontinue ECMO?
- In which neonatal conditions does ECMO yield the best results?

I.11.6. PULSE OXIMETRY

I.11.6.1. Definition

Pulse oximetry is a noninvasive, continuous, and rapid method for assessing peripheral oxygen saturation (SpO□) and pulse rate, based on the differential absorption of light by oxygenated and deoxygenated hemoglobin. It is one of the most important methods for monitoring newborns, particularly in intensive care, during resuscitation, or during oxygen and ventilation treatments.

I.11.6.2. Principle of Operation

The pulse oximeter uses two beams of light (red and infrared), transmitted through a well-perfused area (usually the finger, hand, foot, or earlobe). The sensor detects the difference in light absorption based on the ratio of oxyhemoglobin (HbO□) to deoxyhemoglobin (Hb). The result is expressed as SpO□, which reflects the percentage of oxygen-saturated hemoglobin out of the total circulating hemoglobin.

I.11.6.3. Site and Application Technique in Newborns

For measurement accuracy, the correct choice of site and sensor placement is essential:

- Full-term: the sensor is applied to the right hand (preductal measurement) or to one of the feet (postductal).
- In preterm infants: application to the sole of the foot or the ankle is preferred.

The difference between pre-ductal and post-ductal values (usually <10%) provides information about right-to-left shunts in the pulmonary circulation (e.g., in persistent pulmonary hypertension—PPHN). The sensor should be attached gently, without compressing the blood flow, and movement should be minimized to reduce artifacts.

I.11.6.4. Reference Values

In the healthy term newborn, SpO□ gradually stabilizes after birth:

- at 1 minute: approximately 60–65%;
- at 5 minutes: 80–85%;
- after 10 minutes: 90–95%.

After the transition period, normal values range from 92 to 96% in term infants and 90–94% in preterm infants. Maintaining these values is the goal of any oxygen therapy or ventilation.

I.11.6.5. Main Indications for Pulse Oximetry

- Monitoring oxygenation in all forms of respiratory distress (RDS, TTN, pneumonia, PPHN);
- Monitoring of preterm infants receiving oxygen therapy to prevent hyperoxia;
- Assessment of response to oxygen therapy and mechanical ventilation;
- Guidance for neonatal resuscitation (according to the AAP – Neonatal Resuscitation Program);
- Early detection of silent hypoxemia;
- Screening for critical congenital heart defects (difference between preductal and postductal SpO□).

I.11.6.6. Advantages

- Noninvasive and painless method;
- Allows for continuous, real-time monitoring;
- It is fast and accurate in most clinical situations;
- Can be used at the patient's bedside, including during neonatal transport;
- Provides immediate information on the effectiveness of oxygen therapy.

I.11.6.7. Limitations and Interpretation Errors

Pulse oximetry has certain limitations that must be understood to avoid misinterpretation:

- Excessive movement can generate artifacts and false readings;
- Low peripheral perfusion (hypothermia, shock) reduces the optical signal;
- Intense ambient light (surgical lights, phototherapy) can interfere with the sensor;
- The presence of fetal hemoglobin (HbF) alters the oxygen dissociation curve, resulting in slightly higher SpO□ values;
- Methemoglobinemia and carboxyhemoglobinemia (rare in neonatology) produce false-normal values.

I.11.6.8. Interpretation of Abnormal Values

- SpO□ < 88% in term infants or < 85% in preterm infants indicates severe hypoxemia and requires immediate intervention;

- A sudden drop in SpO□ may signal apnea, tube obstruction, or disconnection from the ventilator;
- Persistently low values, despite oxygen therapy, suggest a right-to-left shunt (e.g., PPHN or congenital heart disease);
- SpO□ > 96% during oxygen therapy signals a risk of hyperoxia, requiring a reduction in FiO□.

I.11.6.9. The Role of Pulse Oximetry in Clinical Management

Pulse oximetry is indispensable in all stages of respiratory care:

- At the start of oxygen therapy – to determine the minimum effective dose;
- During mechanical ventilation – to adjust FiO□;
- In neonatal resuscitation – to guide oxygen administration;
- In the follow-up of preterm infants – to prevent retinopathy of prematurity (ROP);
- In the post-ECMO or post-extubation period – for the early detection of recurrent hypoxia.

I.11.6.10. Conclusions. Key points

Key points:

- Pulse oximetry is an essential noninvasive method for monitoring the newborn;
- The SpO□ value must be interpreted in the clinical context and correlated with blood gas analysis;
- The measurement site (preductal vs. postductal) has diagnostic significance;
- Avoiding hyperoxia is just as important as preventing hypoxia;
- Signal quality and peripheral perfusion influence measurement accuracy.

Self-assessment questions

- What is the operating principle of pulse oximetry?
- What is the difference between preductal and postductal measurement?
- What clinical situations can lead to misinterpretation?
- What are the normal SpO□ values for term and preterm newborns?
- Why is it important to correlate pulse oximetry with blood gas analysis?

I.11.7. TRANSCUTANEOUS $CO_□$ MONITORING

I.11.7.1. Definition

Transcutaneous monitoring is a noninvasive method for the continuous assessment of the partial pressure of oxygen (tcPO□) and carbon dioxide (tcPCO□) in the capillary blood perfusing the skin. It is a useful alternative to repeated blood gas analyses, providing dynamic information about oxygenation and ventilation.

I.11.7.2. Principle of Operation

The method is based on the diffusion of gases through skin that has been locally heated to approximately 43–44°C. The heat causes capillary vasodilation, increasing local blood flow and allowing the measurement of the partial pressures of O□ and CO□ in the capillary blood, which reflect arterial values.

The transcutaneous sensor contains:

- a Clark cell for measuring oxygen (tcPO□);
- a Severinghaus cell for carbon dioxide (tcPCO□).

Both are connected to a monitor that displays the values in real time.

I.11.7.3. Indications

Transcutaneous monitoring is used primarily in newborns with respiratory impairment for:

- continuous assessment of ventilation during CPAP therapy or mechanical ventilation;
- monitoring oxygen therapy and avoiding hyperoxia, particularly in preterm infants;
- early detection of hypoventilation during sedation or apnea;
- monitoring unstable patients where arterial blood sampling is difficult or risky;
- monitoring the progression of PPHN (persistent pulmonary hypertension).

I.11.7.4. Location and Application Technique

The sensor is applied to a well-perfused, flat area of the body:

- the anterior chest,
- the side of the abdomen,
- inner thigh,
- scapular region.

The area must be cleaned and dried. An electrolyte gel is applied, and the sensor is secured with soft adhesive tape. To prevent skin burns, the application site is changed every 3–4 hours, more frequently in premature infants.

I.11.7.5. Advantages

- Allows for continuous and non-invasive monitoring;
- Reduces the need for arterial blood gas analysis;
- Provides real-time data on oxygenation and ventilation;
- It is useful in preterm infants, where arterial access is difficult;
- Enables early detection of hypercapnia or hypoxemia.

I.11.7.6. Limitations and Interpretation Errors

Although accurate under stable conditions, the method has some limitations:

- Excessive local heating can cause burns, especially in premature infants with fragile skin;
- Poor cutaneous perfusion (in shock, hypothermia, vasoconstriction) reduces accuracy;
- Patient movements may disrupt sensor contact;
- Falsely elevated tcPCO□ values may occur if the sensor is not calibrated or is applied for too long;
- Differences between tcPO□ and PaO□ may be significant in cases of edema or skin hypoperfusion.

Therefore, the obtained values must be periodically correlated with arterial blood gas analysis for calibration.

I.11.7.7. Interpretation of Values

In general, there is a good correlation between transcutaneous and arterial values:

- Normal tcPO□: 50–80 mmHg;
- normal tcPCO□: 35–45 mmHg.

A decrease in tcPO□ indicates hypoxemia or low perfusion. An increase in tcPCO□ indicates alveolar hypoventilation, apnea, or tube obstruction. Persistent differences from arterial blood gas analysis (>10 mmHg) require sensor verification or device recalibration.

I.11.7.8. Safety and Precautions

- The sensor temperature must not exceed 44°C;
- Avoid application to areas with skin lesions or bruises;
- The site should be inspected frequently for erythema or blisters;
- For premature infants <28 weeks, the duration of application is reduced to 2–3 hours;
- The equipment must be calibrated daily according to the manufacturer's instructions.

I.11.7.9. Clinical Role and Integration into Respiratory Management

Transcutaneous monitoring is a complementary tool to pulse oximetry and blood gas analysis:

- it provides continuous information on CO□, which pulse oximetry does not measure;
- it helps adjust ventilation in real time without invasive sampling;
- reduces stress and blood loss in preterm infants;
- it is ideal for monitoring clinical progression in moderate respiratory failure or during the weaning phase from the ventilator.

I.11.7.10. Conclusions. Key points

Key points:

- Transcutaneous monitoring is a valuable noninvasive method in neonatal respiratory care;
- It continuously measures tcPO□ and tcPCO□, reflecting arterial values;

- It requires good skin perfusion and periodic calibration;
- It does not completely replace blood gas analysis, but can significantly reduce the need for it;
- Safety depends on temperature control and regular rotation of the application site.

Self-assessment questions

- What is the physiological principle of transcutaneous monitoring?
- What parameters can be measured using this method?
- What are its advantages and limitations compared to blood gas analysis?
- What measures are taken to prevent skin burns?
- How is an increase in tcPCO□ values interpreted?

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II. CARDIOVASCULAR DISEASES

II.1. INTRODUCTION. DEFINITION

Cardiovascular disorders in the neonatal period represent a major contributor to morbidity and mortality worldwide, with a particularly significant impact in countries where access to prenatal diagnosis, neonatal intensive care, and pediatric cardiac surgery remains unequal. The most common cardiovascular conditions are congenital heart defects (CHDs), which are the leading cause of congenital anomalies in both high- and middle-income countries. Congenital heart defects are structural or anatomical abnormalities of the heart or the large intrathoracic vessels that arise during embryonic development. These defects constitute the most common congenital anomalies in humans and remain the leading cause of morbidity and mortality due to congenital defects in infants and children worldwide.

The global epidemiology of congenital heart disease (CHD) varies substantially depending on the quality of regional healthcare, access to prenatal screening, and diagnostic capabilities. In 2021, the World Health Organization estimated approximately 4.2 million prevalent cases of CHD in children globally (95% uncertainty interval: 3.6–4.8 million). This represents a 3.4% increase between 1990 and 2021, reflecting improved survival rates and detection capabilities rather than an increase in disease incidence. No major global dataset has yet published comprehensive estimates for the 2022–2024 period specifically for CHD; 2019–2021 are the most recent robust regional comparative data, and projections beyond 2021 are extrapolations based on models published to date.

II.1.1. RISK FACTORS

The development of congenital heart defects is multifactorial, with genetic factors present in 15–40% of cases and environmental/maternal factors contributing substantially.

- **Genetic risk factors**

Chromosomal abnormalities are associated with an increased risk of CHD:

- Down syndrome (trisomy 21) – CHD present in 50% of affected individuals
    - The most common chromosomal abnormality associated with CHD
    - Common cardiac defects: atrioventricular septal defect (AVSD) (40% of cardiac cases in Down syndrome), ventricular septal defect (VSD), patent ductus arteriosus (PDA), tetralogy of Fallot
- Trisomy 18 (Edwards syndrome) - CHD present in nearly 100% of cases
    - Often incompatible with postnatal survival
- Trisomy 13 (Patau syndrome) – CHD present in 80–90% of cases
- Turner syndrome (45,X or mosaic) – CHD present in 30–50% of affected individuals
- DiGeorge syndrome (velocardiofacial syndrome) – CHD present in most affected individuals.
- Williams syndrome (7q11.23 deletion) – CHD present in 75–80% of cases
- Noonan syndrome – CHD present in 50–80% of cases.
- Genetic mutations and monogenic disorders:
    - Mutations in genes that regulate cardiac development.
    - Mutations affecting the development of cardiac neural crest cells
    - Recurrent family patterns: children of mothers with CHD have a 2- to 10-fold higher risk of developing CHD compared to children of unaffected mothers
- **Maternal risk factors**
- Pre-existing diabetes (type 1 or type 2)
    - Risk: 2- to 3-fold increased risk compared to pregnancies without diabetes
    - Highest risk in the first trimester, when cardiac morphogenesis occurs
- Maternal obesity (before pregnancy and early in pregnancy)
- Maternal infections during pregnancy
    - Rubella virus
    - Cytomegalovirus

    - Parvovirus B19
- Advanced maternal age (≥35 years)
- Pre-existing hypertension
- Gestational diabetes
- Medications:
    - Anticonvulsants – phenytoin, sodium valproate
    - Lithium
    - Retinoic acid/vitamin A
    - Nonsteroidal anti-inflammatory drugs
    - Indomethacin
- **Maternal risk factors with weak evidence**
- Maternal smoking
- Maternal alcohol consumption
- Gestational hypertension

II.1.2. EMBRYOLOGICAL DEVELOPMENT. PATHOGENESIS

Understanding cardiac embryology is essential for understanding the pathophysiological mechanisms underlying various cardiac malformations.

1. Chronology of cardiac development

Cardiac development occurs at a remarkable rate during early embryogenesis:

- Days 15–16 after fertilization: Production of blood cells and blood vessels begins in the extraembryonic structures (yolk sac, chorion, connective pedicle)
- Day 18 after fertilization: Vascular development begins within the embryo
- Day 21 after fertilization: The heart begins to beat; the fetal heartbeat becomes established approximately 3 weeks after conception
- Week 4 of embryonic life: Circulatory patterns are clearly established
- Weeks 4–10: Active cardiac morphogenesis occurs, including septation and valve formation
- Week 10: The heart and vascular system are substantially developed and capable of sustaining fetal circulation.

The development of the circulatory system is based on several mechanisms. Here, we will focus only on the formation of the atrial and ventricular septa.

- Atrial septation
    - Formation of the foramen ovale: The foramen ovale is a normal physiological opening in the atrial septum that allows right-to-left shunting during fetal life, when pulmonary vascular resistance is increased.
    - Septum primum: It forms first as a tissue outgrowth from the roof of the common atrium toward the endocardial cushions.
    - Septum secundum: forms as a thicker muscular septum, with its free edge leaving a space (foramen ovale) between it and the fused endocardial cushions.
    - Valve-like action: the septum primum acts as a one-way valve against the septum secundum.
    - Postnatal closure: At birth, the reversal of pressure gradients causes the functional closure of the foramen ovale as the septum primum is pushed against the septum secundum; anatomical closure occurs over the course of weeks or months.
- Ventricular septation
    - Muscular ventricular septation:
        - Formation of the muscular septum: It develops as the ventricles expand during loop formation; growth occurs at the junction between the expanding ventricular chambers.
        - Progressive closure: The muscular septum accumulates as the ventricles bulge outward from the primitive cardiac tube.

- Membranous ventricular septation:
  - Formed from: contributions from the endocardial wall tissue, the conotruncal septum, and the muscular septum

2. Critical periods of development:

- Weeks 4–5: Coiling of the cardiac tube; formation of the atria and ventricles.
- Weeks 5–7: Atrial septation (formation of the foramen ovale).
- Weeks 5–8: Ventricular septation (formation of the muscular and membranous septa).
- Weeks 5–8: Conotruncal septation (formation of the aorta and pulmonary artery)
- Weeks 5–9: Formation of the atrioventricular valve
- Weeks 7–10: Formation of the semilunar valves (aortic and pulmonary)

Disruption during these critical periods leads to specific congenital heart defects:

- **Common arterial trunk:** Complete failure of outflow tract septation; a single arterial trunk emerges from the heart.
- **Transposition of the great vessels:** Abnormal rotation of the outflow tract; the connections of the aorta and pulmonary artery are reversed.
- **Tetralogy of Fallot:** anterior malalignment of the conotruncal septum with secondary ventricular septal defect.
- **Posterior malalignment defects:** aortic coarctation with VSD, interrupted aortic arch with VSD.
- **Right ventricle with double outlet:** both great vessels arise from the right ventricle due to malalignment
- **Atrial septal defect:**
  - Atrial septal defect (most commonly in the region of the foramen ovale) allows for a persistent left-to-right shunt at the atrial level.
  - It results from inadequate growth of septal tissue or failure of proper fusion
- **Ventricular septal defect:**
  - Deficient muscular septation (which frequently occurs in the apical muscular regions or in the perimembranous region) allows for left-to-right shunting.
  - Defects in the membranous septum lead to perimembranous VSDs, which are the most common (80% of VSDs).

II.1.3. FETAL CIRCULATION AND THE TRANSITION TO POSTNATAL CIRCULATION

Understanding normal fetal circulation is essential to understanding why certain lesions remain asymptomatic in utero and become critical after birth.

1. Fetal Circulation in the Uterus

Unique characteristics of fetal circulation: The fetus exists in a unique circulatory environment, in which the lungs are non-functional (filled with fluid), gas exchange occurs via the placenta, and three specialized vascular structures (shunts) bypass the lungs and liver.

The three main fetal shunts:

- The ductus venosus
  - Located in the liver
  - Vascular connection between the umbilical vein and the inferior vena cava
  - Allows oxygenated blood from the umbilical vein to bypass the hepatic circulation
  - Approximately 50% of umbilical venous blood flows through the ductus venosus; the remainder enters the hepatic circulation.
  - It closes functionally within a few hours after birth, when umbilical circulation ceases; it obliterates anatomically within a few weeks or months, becoming the ligamentum venosum
- Foramen ovale
  - An interatrial septal opening that allows right-to-left shunting

- Allows blood from the right atrium to bypass the non-functioning lungs and enter the left atrium
- Preferentially directs oxygenated blood (from the umbilical vein) to the left atrium, brain, and coronary circulation
- Functions as a one-way valve: the primum septum allows blood to flow from right to left but prevents flow from left to right when pressure is reversed.
- It closes functionally within seconds or minutes after birth, when left atrial pressure exceeds right atrial pressure; it fuses anatomically over the course of months or years (25–30% of the population retains a patent foramen ovale).

- Ductus arteriosus
  - A vascular connection between the main pulmonary artery and the descending thoracic aorta.
  - It diverts most of the right ventricle's output from the fluid-filled, high-resistance lungs to the systemic circulation.
  - It allows the right ventricle to perfuse the lower body, abdominal organs, and the placenta.
  - It functions via specialized smooth muscle that maintains constriction in response to high oxygen tension and prostaglandins.
  - It functionally constricts and closes within 12–72 hours after birth (usually within 24 hours); it anatomically obliterates within 2–3 weeks, becoming the arterial ligament.

2. Blood flow through the fetal circulation

- Pathway of oxygenated blood:
  - The umbilical vein carries oxygen-rich blood from the placenta to the fetus.
  - Approximately 50% enters the venous sinus → bypasses the liver → enters the inferior vena cava.
  - The inferior vena cava carries this flow preferentially to the right atrium.
  - The inferior vena cava valve directs this flow of oxygenated blood preferentially through the foramen ovale to the left atrium.
  - The left atrium receives the oxygenated blood.
  - The left ventricle pumps the oxygenated blood into the ascending aorta.
  - The ascending aorta carries blood to the upper body and the brain (the most metabolically active fetal tissues, which require the highest oxygen content).
- The blood's path to the lower body:
  - The right atrium receives deoxygenated blood from the superior vena cava (from the upper body) and the remaining 50% of the blood from the inferior vena cava.
  - The right ventricle pumps this blood to the lungs.
  - The ductus arteriosus diverts most of the right ventricle's output (because pulmonary vascular resistance is very high due to the fluid-filled lungs) to the descending aorta.
  - The descending aorta carries this blood to the lower body, the abdominal organs, and back to the placenta via the umbilical arteries for reoxygenation.

3. Postnatal Circulatory Transition

At the moment of birth, dramatic hemodynamic changes occur:

1. Clamping of the umbilical cord – eliminates placental circulation.

- Loss of low-resistance placental circulation
- Systemic vascular resistance increases dramatically
- The umbilical vein, ductus venosus, and umbilical arteries become nonfunctional

2. Respiratory expansion: the newborn's first breath expands the lungs

- Pulmonary vascular resistance drops sharply (from 11 mmHg/ml/min to approximately 2 mmHg/ml/min within a few minutes)
- The pulmonary vascular bed expands as the alveoli expand
- Oxygen tension increases dramatically in the pulmonary blood, triggering metabolic and local mechanisms that cause pulmonary vasodilation

3. Reversal of the pressure gradient:

- these hemodynamic changes reverse the pressure relationships that maintained the fetal shunt

In the postnatal period, the fetal shunts close. This is also part of the transition to extrauterine life.

1. Closure of the foramen ovale:

- Fetal state: right atrial pressure > left atrial pressure (due to high pulmonary vascular resistance) → blood shunts from right to left.
- Postnatal state: pulmonary vascular resistance decreases; pulmonary venous return to the left atrium increases dramatically; left atrial pressure > right atrial pressure → pressure reversal.
- Mechanism of functional closure: Increased left atrial pressure pushes the septum primum against the septum secundum, functionally closing the foramen ovale within seconds or minutes.
- Timing: Functional closure occurs immediately after birth; shunt patency persists in 25–30% of the population (clinically insignificant).

2. Closure of the ductus arteriosus:

- Fetal state: High prostaglandin levels and low oxygen pressure maintain ductal patency by relaxing the smooth muscles.
- Postnatal state: The dramatic increase in partial pressure of oxygen and the removal of prostaglandin sources from the placental circulation trigger constriction of the duct's smooth muscles.
- Time of closure:
    - Functional closure: Begins within 12–24 hours (may take up to 72 hours in some infants, particularly preterm infants).
    - Anatomical closure: Fibrosis and muscularization of the ductal wall occur within 2–3 weeks; it becomes the ligamentum arteriosum (tissue remnants visible on imaging)
- Clinical significance: In normal infants, the brief period of ductal shunting (the first 24–72 hours) is usually benign; it represents the normal transition from fetus to newborn.

Cardiac shunts play a crucial role in the transition to extrauterine life. For this reason, these shunts have implications for duct-dependent malformations. Many cyanotic and obstructive cardiac lesions remain relatively asymptomatic during fetal life because the ductus arteriosus maintains adequate blood flow. When the ductus arteriosus closes functionally after birth, a sudden and severe deterioration occurs. Examples of duct-dependent lesions:

- Duct-dependent systemic blood flow:
    - Critical aortic coarctation
    - Critical aortic stenosis
    - Interrupted aortic arch
    - Hypoplastic left heart syndrome
    - Critical mitral stenosis
- Duct-dependent pulmonary blood flow:
    - Tetralogy of Fallot (severe forms)
    - Pulmonary atresia
    - Critical pulmonary stenosis
    - Tricuspid atresia
    - Transposition of the great arteries (initial)

Clinical presentation: Infants with duct-dependent lesions usually appear healthy at birth, but their condition deteriorates within 24–72 hours as the ductus arteriosus closes. Emergency infusion of prostaglandin E1 is vital, maintaining duct patency until surgical or interventional therapy can be performed.

II.2. CARDIAC SIGNS AND SYMPTOMS

Cardiac signs and symptoms in newborns reflect the interaction between structural lesions, transitional circulation, and the limited compensatory capacity of the immature myocardium. Careful observation, targeted assessment of vital signs, and a structured cardiovascular examination are essential to distinguish benign transient findings from manifestations of significant congenital heart disease.

II.2.1. CYANOSIS

Cyanosis becomes clinically apparent when deoxygenated hemoglobin exceeds approximately 3–5 g/dL in capillary blood, regardless of total hemoglobin concentration. In congenital heart disease, cyanosis is usually due to right-to-left shunting (e.g., Tetralogy of Fallot, transposition of the great vessels) or complete mixing lesions, such that desaturated venous blood enters the systemic circulation without complete pulmonary oxygenation.

The hyperoxia test helps differentiate pulmonary causes from cardiac ones: in cyanotic CHD, arterial oxygen saturation or partial pressure of oxygen (PaO□) increases minimally with 100% oxygen, because the shunted blood bypasses the ventilated alveoli.

- **Clinical differentiation:**
  - Central cyanosis (tongue, oral mucosa, lips) suggests low arterial oxygen saturation and is pathological beyond the immediate postnatal transition period.
  - Peripheral cyanosis (acrocyanosis) of the hands and feet is common and usually benign in the first 24–48 hours, especially if the mucous membranes remain pink and oxygen saturation levels are normal.
  - Cyanosis that worsens with crying may indicate a cardiac lesion in which decreased systemic vascular resistance accentuates right-to-left shunting, whereas cyanosis that improves with crying may indicate an upper airway obstruction.
- **Assessment tools**
  - Assess color in good ambient light, focusing on the tongue, oral mucosa, and nail beds; in darker-skinned individuals, the mucous membranes and conjunctiva are more reliable than the skin.
  - Pulse oximetry should be measured preductal (right hand) and postductal (either foot); persistent saturations <95% or a pre-/postductal difference >3% warrant further evaluation for congenital heart disease.

Cyanosis associated with tachypnea, poor perfusion, or feeding difficulties should always prompt an urgent cardiological evaluation and consideration of duct-dependent lesions.

II.2.2. RESPIRATORY SIGNS

Respiratory failure with its clinical signs and symptoms is closely intertwined with cardiac pathology. Mechanisms of its occurrence in heart diseases:

- Increased pulmonary blood flow due to significant left-to-right shunts (e.g., VSD, PDA, complete AVSD) leads to pulmonary venous congestion, interstitial edema, and reduced pulmonary compliance, manifesting as tachypnea and increased respiratory effort.
- In cases of duct-dependent systemic obstruction or severe myocardial dysfunction, pulmonary edema may develop as left atrial pressure rises, again causing respiratory failure.

Clinical features

- Respiratory rate >60/min,
- Nasal flaring,
- Dyspnea
- Intercostal or subcostal retractions

These are typical signs of significant respiratory compromise. Unlike primary lung disease, cardiac tachypnea may present with relatively clear lung fields initially and is often disproportionate to the auscultatory findings; feeding-induced dyspnea and the need for frequent pauses are classic

features of heart failure. Recurrent lower respiratory tract infections or persistent “noisy breathing,” with poor weight gain in the first few weeks, suggest chronic pulmonary overcirculation due to significant shunt lesions.

It is necessary to distinguish this from primary pulmonary pathology. In isolated pulmonary disease, cyanosis and tachypnea tend to improve with supplemental oxygen, whereas in cyanotic CHD, oxygen saturation increases minimally despite administration of high-FiO□ oxygen. A history of prematurity, risk of perinatal infection, or meconium aspiration suggests a primary respiratory cause, but the presence of a murmur, differential pulses, hepatomegaly, or abnormal saturations in the four extremities indicates a cardiac etiology.

II.2.3. HEART FAILURE

Neonatal heart failure usually reflects volume or pressure overload caused by structural lesions (large shunts, valvular regurgitation, coarctation) or primary myocardial dysfunction (myocarditis, cardiomyopathy, arrhythmia-induced failure).

Symptoms usually appear after a decrease in pulmonary vascular resistance (a few days or weeks after birth) in the case of large left-to-right shunts, whereas ductus arteriosus-dependent systemic lesions often present abruptly, with shock, upon closure of the ductus arteriosus.

Key clinical signs:

- Feeding-related symptoms: poor feeding, prolonged feeding, sweating during feeding, and inability to finish a feeding are early and sensitive signs of heart failure in newborns.
- Failure to thrive: inadequate weight gain, despite adequate caloric intake, reflects the high metabolic cost of increased respiratory effort and increased cardiac workload.
- Tachycardia and tachypnea: Persistent tachycardia at rest with an increased respiratory rate, even in the absence of fever and in a calm state, is characteristic of decompensated heart failure.
- Hepatomegaly: an enlarged, firm, and sometimes tender liver margin palpable >2 cm below the right costal margin is a reliable sign of systemic venous congestion in infants.

Additional findings

- Peripheral edema is less pronounced in the neonatal period than in older children, but may occur periorbital or sacral; cold extremities and prolonged capillary refill indicate decreased cardiac output and peripheral vasoconstriction.
- Older infants with chronic heart failure may present with subtle signs, such as reduced activity, poor interaction, and recurrent respiratory infections.

II.2.4. HEART MURMURS

A stethoscopically audible heart murmur is a sound generated by turbulent blood flow and, in newborns, may be caused by structural heart disease, transient physiology (e.g., PDA closure), or increased flow through normal structures. Not all significant congenital lesions manifest as an audible murmur in the first days of life, especially if the shunt volume is limited by high pulmonary vascular resistance or if the lesion is primarily obstructive, without major flow turbulence.

Features suggesting a benign/transient murmur:

- weak (grade 1–2/6),
- purely systolic,
- short-lived,
- best heard along the left sternal border,
- no vibrations,
- normal oxygen saturation, normal pulse
- no signs of respiratory distress or hepatomegaly.

Features suggestive of a pathological murmur:

- diastolic or continuous murmurs,
- pansystolic/holosystolic quality,

- grade ≥3/6,
- presence of a murmur,
- rough quality,
- unusual location or radiation, and association with abnormal oxygen saturation,
- weak femoral pulses or signs of heart failure.

Typical patterns of heart murmurs:

- Pansystolic (holosystolic) murmurs: classically associated with mitral valve disease (MVD) or atrioventricular (AV) valve regurgitation; usually high-pitched and best heard at the lower left sternal border or at the apex.
- Ejection systolic murmurs: often reflect outflow tract obstruction (aortic or pulmonary stenosis) and are usually of a crescendo-decrescendo quality; most intense at the upper sternal borders and may radiate to the back or neck.
- Continuous "mechanical" murmur: characteristic of a significant PDA, often best heard in the left infraclavicular area; it may change as ductal flow changes and may be accompanied by strong pulses and a widened pulsatile pressure.
- Diastolic murmurs: rare in newborns and almost always pathological, often reflecting semilunar valve regurgitation or large left-to-right shunts with increased diastolic flow.

The clinical integration of heart murmurs is of particular importance. An isolated systolic murmur in a healthy, pink newborn with normal oxygen saturation and pulses in all four limbs may be evaluated on an elective basis, but any murmur with "alarming" features (cyanosis, abnormal pulse, differential oxygen saturation, hepatomegaly, or respiratory distress) requires urgent echocardiographic evaluation.

II.2.5. CLINICAL EXAMINATION

The approach to the general examination of a newborn with suspected cardiac pathology must be systematic: observe, then palpate, then auscultate, incorporating vital signs and pulse oximetry at both the upper and lower extremities. Examinations should ideally be performed when the infant is calm or asleep, as crying can exaggerate some findings and mask others.

1. Inspection

Assess the general appearance (alert vs. lethargic), respiratory effort, and skin color, specifically looking for central cyanosis or mottling of the skin. Inspect the precordial area to detect abnormal apical shifts, chest wall deformities, or pulsations suggestive of cardiomegaly or hyperdynamic states.

Of particular importance are vital signs and signs of tissue perfusion. Measure heart rate, respiratory rate, temperature, and blood pressure; it is recommended to measure blood pressure in all four limbs when CHD is suspected, focusing on differences between the upper and lower limbs. Check capillary refill time at the sternum or fingertip; a refill time >3 seconds indicates impaired perfusion and is typical of shock or advanced heart failure.

2. Palpation

- Pulse assessment

Simultaneously palpate the brachial and femoral pulses to detect a delayed or diminished femoral pulse, which may indicate aortic coarctation or other obstructive lesions. A strong pulse and increased pulse pressure suggest significant PDA or severe aortic regurgitation, while a weak pulse is observed in low-output states and left-sided obstructive lesions.

- Palpation of the precordial area and abdomen

Locate the point of maximum impulse (PMI); lateral or inferior displacement suggests cardiomegaly, while a hyperdynamic impulse may indicate volume overload or elevated pulmonary pressures. Palpate to detect vibrations in the precordial area and suprasternal notch; a systolic vibration in the suprasternal notch is characteristic of severe aortic stenosis or coarctation. Assess the size and consistency of the liver; a smooth, firm, and enlarged liver is a key sign of right heart failure or elevated central venous pressure.

3. Auscultation

Use both the diaphragm and the bell of the stethoscope, systematically auscultating the aortic, pulmonary, tricuspid, and mitral areas, as well as the axillae and back. Determine heart rate and rhythm (regular vs. irregular), identify S1 and S2 heart sounds, and assess the splitting of S2; a single, loud S2 may indicate elevated pulmonary artery pressure or severe cyanotic heart disease. Listen for additional sounds—third heart sound, fourth heart sound, clicks, and claps—and characterize murmurs, correlating them with the pulse, oxygen saturation, and signs of respiratory distress or heart failure.

II.3. EVALUATION OF THE NEWBORN WITH CONGENITAL HEART DISEASE

The evaluation of a newborn with suspected congenital heart disease involves several steps.

1. Systematic clinical evaluation

A structured assessment remains the starting point for evaluating any newborn suspected of having heart disease.

- History:
  - Maternal: diabetes, phenylketonuria, autoimmune diseases, teratogenic medications (lithium, antiepileptics), alcohol, smoking, infections (especially rubella), assisted reproduction, advanced maternal age.
  - Fetal: abnormal four-chamber view or outflow tracts on obstetric ultrasound, polyhydramnios/oligohydramnios, IUGR, non-immune hydrops, abnormal fetal heart rate patterns.
  - Perinatal: prematurity, perinatal asphyxia, risk of sepsis, respiratory distress at birth, delayed transition.
  - Postnatal: feeding difficulties, sweating during feeding, poor weight gain, tachypnea, discoloration (blue/gray), lethargy, episodes of collapse.
- Standardized steps of the examination
  - General observations: muscle tone, activity, dysmorphic features (e.g., Down syndrome, Turner syndrome), respiratory effort, color (central vs. peripheral cyanosis).
  - Vital signs: HR, RR, temperature, BP (in all 4 limbs, if possible), pre- and post-ductal SpO□.
  - Circulatory status: capillary refill, skin temperature, skin mottling, level of consciousness.
  - Cardiovascular examination: pulses, precordial impulse, heart sounds, heart murmurs, hepatomegaly, edema.
  - Respiratory examination: breath sounds, additional sounds, signs of pulmonary edema vs. primary lung disease.

2. Pulse oximetry screening

The pulse oximeter is essential for the early detection of critical congenital heart diseases before clinical deterioration.

Screening principles:

- Measure SpO□ in the right hand (preductal) and in either foot (postductal) after 24 hours of life (or even before discharge, if earlier).
- Ensure the infant is calm, warm, and not crying; confirm a good waveform before interpreting the readings.
- Typical pass/fail criteria (adaptable to local guidelines)
  - Pass – Preductal and postductal saturations ≥95% and absolute difference between the two ≤3%.
  - Borderline/retest – Saturation 90–94% in any limb or pre-postductal difference >3% on the first reading → repeat after 1 hour; if the result is still abnormal, treat as a failed test.

    - Failure (positive test) – Any saturation <90% in any limb at any time or a persistent difference of 90–94% or >3% after repeated measurements.
- Implications of an abnormal screening
    - Urgent clinical reevaluation and targeted investigations (chest X-ray, blood gases, screening for infections) to distinguish pulmonary causes from cardiac ones.
    - Prompt cardiology consultation and echocardiography to rule out congenital heart disease (CHD), particularly duct-dependent lesions.

3. Electrocardiography (ECG)

Although the ECG is less sensitive than echocardiography for structural lesions, it provides useful information about rhythm, conduction, and ventricular workload. When the ECG is particularly useful:

- Suspected arrhythmia (SVT, heart block, long QT).
- Infants with syndromes (e.g., Down syndrome, Noonan syndrome) in whom AVSD or hypertrophic cardiomyopathy is suspected.
- Suspected myocarditis or cardiomyopathy.

ECG Interpretation:

- Axis
    - Right axis deviation is physiological in newborns;
    - Marked left axis deviation suggests AVSD or tricuspid atresia.
- Signs of hypertrophy
    - Right ventricular hypertrophy: Tall R wave in the right precordial leads in cyanotic lesions or pulmonary hypertension.
    - Left ventricular hypertrophy: in left-sided obstructive lesions or large left-to-right shunts.
- Conduction and rhythm:
    - Narrow-complex tachycardia, without P waves or with retrograde P waves → SVT.
    - Prolonged PR interval or complete AV block in newborns with maternal anti-Ro/SSA antibodies.

The ECG is rarely normal in advanced heart failure or significant arrhythmia, but may be normal in isolated shunt lesions, so a normal ECG does not completely and definitively rule out CHD.

4. Cardiopulmonary X-ray

A chest X-ray complements the clinical examination and helps distinguish cardiac pathology from pulmonary pathology.

Systematic interpretation of a radiograph is key to a result that leads to a diagnosis.

- Technical quality and positioning
- Cardiac size and shape
    - A cardiothoracic ratio >60% (0.6) in newborns suggests cardiomegaly.
    - "Clog-shaped" heart in Tetralogy of Fallot (right ventricular hypertrophy, inverted apex).
- Pulmonary vascularization
    - Increased peripheral vascular pattern in large left-to-right shunts (VSD, PDA).
    - Marked pulmonary hypertransparency in severe outflow tract obstruction or reduced pulmonary blood flow (Tetralogy of Fallot, pulmonary atresia).
- Pulmonary parenchyma
    - Diffuse interstitial/alveolar edema vs. focal consolidation/bronchial air patterns in pneumonia or ARDS.
- Mediastinum and great vessels
    - Widened mediastinum, lateralization of the aortic arch, abnormal aortic contour suggesting aortic arch pathology.

A chest X-ray should always be interpreted in conjunction with clinical findings and oxygen saturation levels; these guide but do not confirm specific diagnoses.

5. Echocardiography

Echocardiography is the definitive diagnostic tool for congenital heart disease and is necessary whenever significant structural pathology is suspected. It offers certain advantages in the neonatal setting:

- Non-invasive, performed at the patient's bedside, and radiation-free.
- It provides real-time anatomical and functional information: septa, valves, ventricular size and function, great arteries, pulmonary veins, and the pulmonary arch.
- Color and spectral Doppler accurately demonstrate shunts, flow direction, pressure gradients, and estimated pulmonary pressures.

Essential questions regarding cardiac ultrasound, the answers to which confirm the diagnosis.

- Are the location and venous return normal?
- Are there one or two atria and ventricles, and are their connections (AV and VA) consistent?
- Are the septum intact (ASD/VSD/AVSD)?
- Are the valves normal morphologically and functionally (stenosis, regurgitation)?
- What is the relationship between the great arteries (e.g., TVM, DORV)?
- Is the aortic arch patent and unobstructed?
- What is the size and direction of the shunts (PFO, ductus, collaterals)?

The Role of Focused Neonatal Ultrasound / POCUS

Functional echocardiography performed by a neonatologist can answer specific questions (e.g., presence and size of PDA, global ventricular function, pericardial effusion) and can aid in acute hemodynamic decision-making, but it does not replace a comprehensive cardiological evaluation in cases of suspected complex CHD.

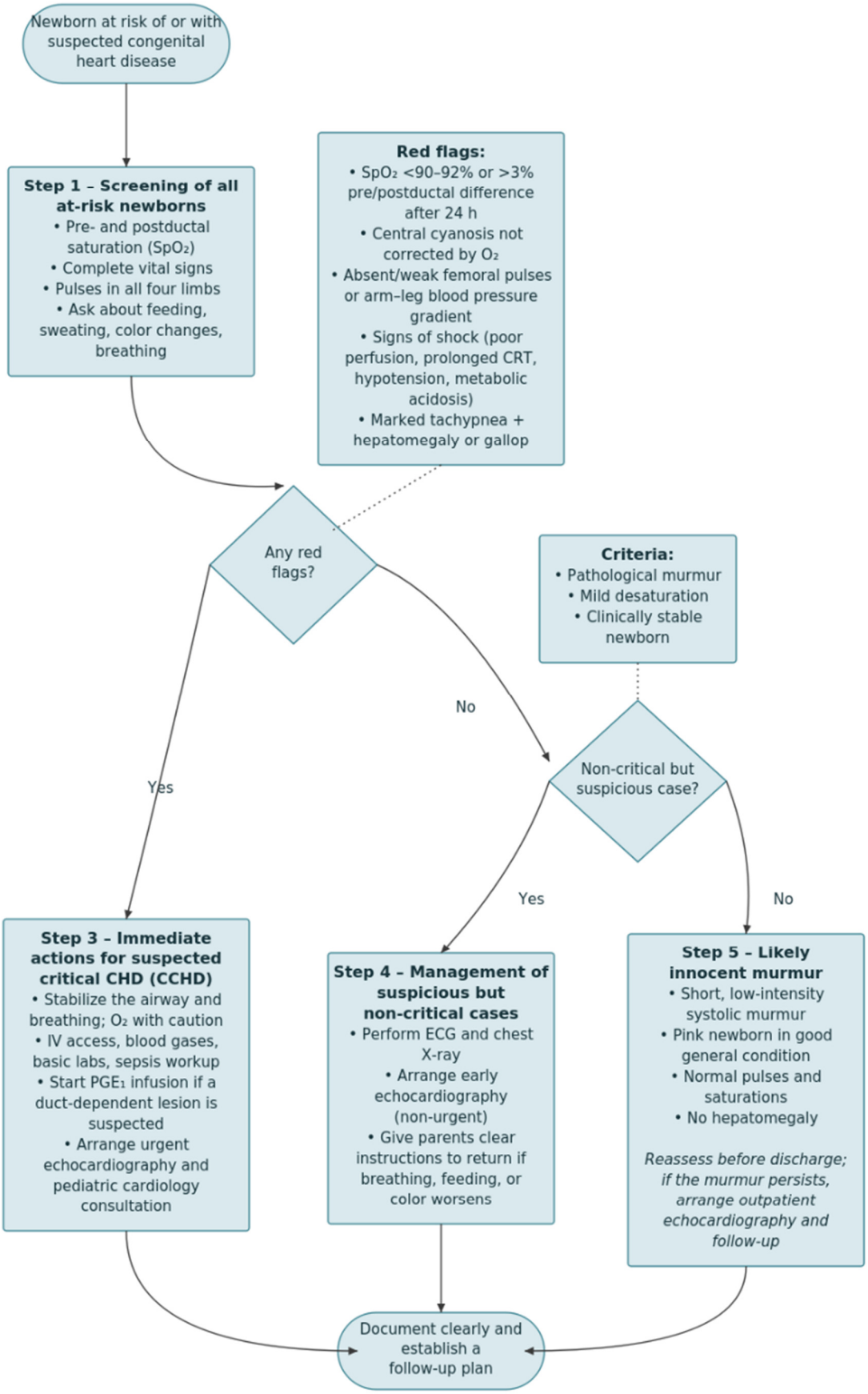

Figure 1. Diagnostic algorithm for suspected complex CHD

II.4. CARDIAC MALFORMATIONS

Congenital heart malformations are fundamentally classified based on the direction of shunting and physiological consequences:

1. Non-cyanotic heart defects (left-to-right shunts)

These are structural defects that primarily cause left-to-right shunting of blood, resulting in increased pulmonary blood flow without systemic arterial desaturation. The hemodynamic consequences of these defects are:

- Excessive pulmonary circulation: excessive blood flow to the pulmonary circulation due to left-to-right shunting.
- Pulmonary vascular stress: chronic volume overload of the pulmonary vasculature.
- Pulmonary hypertension: increased pulmonary vascular resistance develops over time.
- Pulmonary edema: Excessive pulmonary blood flow increases pulmonary venous pressure, causing interstitial and alveolar edema.
- Right ventricular volume overload: excessive pulmonary blood return increases filling of the right atrium and right ventricle.
- Left ventricular volume overload: increased pulmonary venous return to the left atrium increases left ventricular preload.
- Biventricular hypertrophy and dilation: chronic volume overload causes eccentric hypertrophy and enlargement of the ventricular cavity.
- Congestive heart failure: biventricular dysfunction develops, especially if the defect is large.
- No systemic cyanosis: arterial oxygen saturation remains normal (≥94%) because oxygenated blood from the lungs enters the systemic circulation.

Small defects often close spontaneously during childhood, as muscle growth and fibrosis narrow the shunt pathways. Moderate to large defects cause progressive symptoms, as pulmonary vascular resistance decreases in the first weeks to months of life, allowing an increasingly large left-to-right shunt.

Eisenmenger syndrome: A severe complication that can develop in the case of untreated large left-to-right shunts. Progressive pulmonary hypertension caused by chronic excessive shunting leads to irreversible pulmonary vascular remodeling. When pulmonary vascular resistance exceeds systemic vascular resistance, the shunt reverses (becomes right-to-left), leading to systemic desaturation and cyanosis.

Representative lesions:

- Patent foramen ovale (PFO)
- Atrial septal defect (ASD) – all types
- Ventricular septal defect (VSD)
- Patent ductus arteriosus (PDA)
- Atrioventricular septal defect (AVSD)
- Abnormal pulmonary venous connections (partial)
- Obstructive lesions: aortic stenosis, pulmonary stenosis, aortic coarctation

1.1.Patent foramen ovale (PFO)

- Definition: Persistence of the fetal interatrial communication when the septum primum does not completely fuse with the septum secundum.
- Epidemiology: Present in approximately 25–30% of the general population; in most cases, without clinical symptoms.
- Pathophysiology in newborns:
    - In the period immediately following birth, a small right-to-left or bidirectional shunt may persist while pressures equalize.
    - With a normal transition, left atrial pressure exceeds right atrial pressure, functionally closing the flaps; residual “catheter-patent” PFO does not cause hemodynamic compromise.

- Clinical relevance in newborns:
  - Usually an incidental echocardiographic finding.
  - Rarely contributes to significant cyanosis, unless combined with elevated right atrial pressure (e.g., persistent pulmonary hypertension) or complex heart disease.
- Management:
  - No treatment or follow-up is necessary in the case of a normal heart.
  - Important primarily as part of the anatomy in complex lesions or at older ages (paradoxical embolism, etc., outside the neonatal period).

1.2. Atrial septal defect (ASD)

- Definition: A true defect in the atrial septal tissue that allows communication between the atria, distinct from a simple PFO.
- Types:
  - Ostium secundum ASD – in the region of the foramen ovale (most common).
  - Ostium primum ASD – inferior atrial septum; part of the spectrum of AV septal defects.
  - Sinus venosus ASD – near the entrance of the superior or inferior vena cava, often with abnormal pulmonary venous return.
- Pathophysiology:
  - Left-to-right shunt at the atrial level due to higher pressure in the left atrium.
  - In newborns, the shunt is often small because atrial pressures are still similar; a significant shunt usually develops later in infancy/childhood.
- Clinical significance in newborns:
  - Often asymptomatic during the neonatal period.
  - Classic later finding: a broad, fixed second heart sound; systolic ejection murmur over the pulmonary area (increased flow across the normal pulmonary valve).
- Diagnosis:
  - Echocardiography determines the size, location, associated anomalies, and right ventricular volume load.
- Management:
  - Many small secundum ASDs close spontaneously in the first few years of life.
  - Larger defects with right heart enlargement are closed (device or surgery), usually during childhood, not in the neonatal period.

1.3.Ventricular septal defect (VSD)

- Definition: A defect in the interventricular septum that allows communication between the left and right ventricles.
- Types:
  - Perimembranous (membranous) – the most common.
  - Muscular – trabecular, inflow, or outflow muscular septum.
  - Subarterial (supracristal) – located below the semilunar valves.
- Pathophysiology:
  - When pulmonary vascular resistance decreases, blood flows from the left ventricle at high pressure to the right ventricle at lower pressure and into the pulmonary circulation.
  - Small VSDs (restrictive): high-velocity jet, minimal hemodynamic effect.
  - Moderate/large VSDs: significant left-to-right shunt → pulmonary overcirculation, left ventricular volume overload, heart failure.
- Clinical relevance in newborns:
  - The murmur may be absent or faint in the first few days, when pulmonary resistance is still high.
  - As resistance decreases (2–6 weeks), a loud pansystolic murmur appears along the left lower sternal border; signs of r heart failure may appear in cases of large VSDs (tachypnea, poor feeding, hepatomegaly, growth retardation).

- Diagnosis:
  - Clinical: harsh pansystolic murmur ± palpitations; hyperdynamic precordium with larger shunts.
  - Echocardiography: size, number, and location of defects; chamber enlargement; pressure estimation.
- Management:
  - Small VSD: observation; many close spontaneously, especially muscular types.
  - Symptomatic large VSD:
    - Medical treatment: diuretics, nutritional support, possibly ACE inhibitors and digoxin.
    - Surgical closure in early childhood to prevent pulmonary vascular disease.

1.4. Patent ductus arteriosus (PDA)

- Definition: Persistence of patency of the fetal ductus arteriosus connecting the pulmonary artery to the descending aorta beyond the expected closure period.
- Pathophysiology:
  - After a decrease in pulmonary vascular resistance, blood flows from the aorta to the pulmonary artery.
  - The degree of shunting depends on the size of the duct and the pressure gradients.
  - Large PDA: left ventricular volume overload, excessive pulmonary circulation, heart failure.
- Clinical relevance in newborns:
  - Small PDA: continuous "mechanical" murmur in the left infraclavicular area; often asymptomatic.
  - Significant PDA: strong pulses, wide pulsatile pressure, hyperdynamic precordium, tachypnea, poor feeding, hepatomegaly; in preterm infants, difficulty weaning from ventilation.
- Diagnosis:
  - Ultrasound visualizes the duct, the direction and magnitude of the flow, and the impact on chamber dimensions.
- Management:
  - Preterm newborns: fluid restriction, pharmacological closure (e.g., ibuprofen or paracetamol/acetaminophen in many protocols), or surgical ligation, if necessary.
  - Term newborns: closure is considered if the PDA is hemodynamically significant (symptoms, left ventricular dilation, pulmonary hypertension).

2. Obstructive heart defects

Usually acyanotic in the early stages, it can become critical. Obstructive lesions limit blood flow and can cause heart failure or shock when the ductus closes, even if cyanosis is minimal initially.

2.1. Aortic coarctation

- Definition: localized narrowing of the aortic lumen, usually at or immediately distal to the origin of the left subclavian artery, near the insertion of the ductus arteriosus.
- Associations: Bicuspid aortic valve, VSD, other left-sided lesions; common in Turner syndrome.
- Pathophysiology:
  - As long as the ductus is open, systemic perfusion to the lower body can be maintained by ductal flow.
  - As the duct constricts (24–72 hours), perfusion of the lower body decreases, left ventricular afterload increases sharply, leading to left ventricular failure and shock.
- Clinical relevance in newborns:
  - Initially well, then acute deterioration with poor feeding, tachypnea, pallor, cold feet, oliguria, and metabolic acidosis as the duct closes.
  - Upper extremity pulse/blood pressure relatively preserved or elevated; femoral pulse weak or absent; lower extremity blood pressure reduced or unmeasurable.

- Diagnosis:
  - Examination of blood pressure and pulses in all four limbs is essential.
  - A chest X-ray may reveal cardiomegaly and pulmonary edema.
  - Ultrasound confirms the location and severity of the narrowing and associated lesions.
- Management:
  - Prostaglandin E1 to reopen/maintain the ductus and improve perfusion of the lower body.
  - Stabilization with inotropes, diuretics, and ventilation, as needed.
  - Definitive surgical repair during the neonatal period.

2.2. Aortic valve stenosis

- Definition: narrowing of the aortic valve; may range from mild stenosis to critical "orifice" or atresia.
- Pathophysiology:
  - The left ventricle must generate high pressure to expel blood through the narrowed valve → left ventricular hypertrophy, risk of ischemia and failure.
  - In cases of critical stenosis, systemic perfusion becomes dependent on the ductus arteriosus.
- Clinical relevance in newborns:
  - Mild/moderate: often asymptomatic; faint systolic ejection murmur at the upper right sternal border, radiating to the neck.
  - Critical: poor feeding, tachypnea, weak pulse, shock; systolic murmur may be minimal; gallop rhythm, hepatomegaly.
- Management:
  - Critical: PGE1 to maintain systemic ductal flow, inotropes, urgent balloon valvuloplasty, or surgical intervention.
  - Mild/moderate: observation; intervention based on gradient and left ventricular function.

2.3. Pulmonary valve stenosis

- Definition: Obstruction at the pulmonary valve, ranging from mild stenosis to atresia.
- Pathophysiology:
  - Pressure load on the right ventricle → right ventricular hypertrophy; in severe cases, pulmonary blood flow may be dependent on the ductus arteriosus.
- Clinical relevance in newborns:
  - Mild/moderate: systolic ejection murmur at the left upper sternal border, systolic ejection click, usually well-perfused and without cyanosis.
  - Critical: cyanosis due to reduced pulmonary blood flow and right-to-left shunt at the PFO; may present with symptoms similar to other duct-dependent cyanotic lesions;
- Management:
  - Critical: PGE1, stabilization, urgent pulmonary balloon valvuloplasty.
  - Less severe: elective catheter intervention during childhood, if gradients are significant.

3. Cyanotic heart defects (right-to-left shunts)

These are structural defects that primarily cause right-to-left shunts or complete mixing of deoxygenated and oxygenated blood, resulting in systemic arterial desaturation. Hemodynamic mechanisms causing cyanosis:

- Complete mixing of circulation: anatomically, there is no separation between oxygenated and deoxygenated blood flows (e.g., persistent truncus arteriosus, heterotaxy syndromes)
- Severe obstruction of right ventricular outflow with the VSD: right ventricular pressure exceeds left ventricular pressure, forcing right-to-left shunting through the VSD (e.g., tetralogy of Fallot)

- Pulmonary atresia or severe stenosis: complete or nearly complete obstruction prevents pulmonary blood flow; the ductus arteriosus or collateral circulation provides the sole pulmonary perfusion; a right-to-left atrial shunt is necessary for any systemic circulation.
- Ventriculoarterial discordance: abnormal connections of the ventricles to the great arteries (e.g., transposition of the great arteries).
- Right or left ventricular hypoplasia: severe underdevelopment of one ventricle forces complete dependence on the contralateral ventricle for both systemic and pulmonary circulation (e.g., left cardiac hypoplasia syndrome)

Clinical features:

- Cyanosis: central cyanosis (visible on the lips, oral mucosa, and nails) due to reduced arterial oxygen saturation (usually <85–90%)
- Lack of response to supplemental oxygen: SpO usually remains <92% despite 100% oxygen (negative hyperoxia test)
- Rapid onset: The most severe defects become symptomatic within the first hours or days of life, as fetal shunts (foramen ovale, ductus arteriosus) close functionally
- Potential for rapid deterioration: Without intervention, progressive acidosis, shock, and death occur
- Ductal dependence: Many critical cyanotic defects depend on the patent ductus arteriosus for systemic or pulmonary blood flow; closure precipitates cardiovascular collapse

Unlike acyanotic defects, cyanotic lesions do not typically close spontaneously. Symptoms persist or worsen without intervention. Early diagnosis and intervention (e.g., infusion with prostaglandin E1 to maintain ductal patency, surgical or transcatheter repair) are vital.

Representative lesions:

- Tetralogy of Fallot (TOF)
- Transposition of the great arteries
- Hypoplastic left heart syndrome
- Pulmonary atresia (with intact ventricular septum and VSD)
- Tricuspid atresia
- Abnormal total pulmonary venous return
- Truncus arteriosus (persistent)
- Double-outlet right ventricle
- Heterotaxy/asplenia/polysplenia syndromes

3.1.Tetralogy of Fallot

- Components:
  - Large VSD
  - Overriding aorta (straddling the septal defect).
  - Obstruction of the right ventricular outflow tract (infundibular ± valvular pulmonary stenosis).
  - Right ventricular hypertrophy.
- Pathophysiology:
  - The degree of right ventricular outflow tract obstruction (RVOTO) determines the balance between left-to-right and right-to-left shunting through the VSD.
  - Severe obstruction: blood bypasses the lungs → cyanosis.
  - Mild obstruction: “pink” TOF with a more pronounced left-to-right shunt and signs of heart failure.
- Clinical relevance in newborns:
  - Variable: ranging from minimal early cyanosis to profound cyanosis in ductus-dependent forms.
  - Murmur: harsh systolic ejection murmur at the upper left sternal border (from RVOTO, not from the VSD), strong single M2.
- Course:
  - Cyanosis often becomes more evident over the course of weeks as RVOTO worsens.

    - Later, “cyanotic crises” in older infants/children: hypercyanotic episodes triggered by crying/exertion.
- Management:
    - If duct-dependent: PGE1 to maintain pulmonary blood flow.
    - Surgical strategy: complete repair, usually in early childhood; some may first require a palliative shunt or RVOT stent.

3.2.Transposition of the Great Arteries (TGA)

- Definition: Ventriculo-arterial discordance—the aorta arises from the right ventricle, and the pulmonary artery from the left ventricle (d-TGA in the classic form).
- Pathophysiology:
    - Two parallel circulations: systemic venous blood recirculates to the body, pulmonary venous blood recirculates to the lungs.
    - Survival depends on mixing at the atrial (PFO/ASD), ventricular (VSD), or ductal level.
- Clinical relevance in newborns:
    - Cyanosis in the first hours after birth, often severe and with poor response to oxygen.
    - Tachypnea may occur, but pulmonary auscultation may be relatively normal.
- Diagnosis:
    - Echocardiography shows the aorta arising from the right ventricle and the pulmonary artery from the left ventricle.
- Management:
    - PGE1 to maintain ductal patency.
    - Balloon atrial septostomy (Rashkind) if atrial shunting is inadequate (restrictive foramen ovale).
    - Definitive arterial switch operation in the first weeks of life.

3.3.Hypoplastic Left Heart Syndrome

- Definition: A spectrum of severe underdevelopment of the left-sided cardiac structures (left ventricle, mitral valve, aortic valve, ascending aorta).
- Pathophysiology:
    - The left ventricle cannot sustain systemic output; the right ventricle supplies both the pulmonary and systemic circulations.
    - Systemic blood flow depends entirely on the ductus (from the pulmonary artery through the PDA into the aorta).
- Clinical relevance in newborns:
    - Initially, the condition may appear stable as long as the ductus is open.
    - Rapid progression to shock, acidosis, and collapse as the duct closes (24–72 hours).
    - Weak pulse, cold extremities, tachypnea, hepatomegaly.
- Management:
    - Immediate PGE1 to maintain ductal patency.
    - Intensive care with careful balance between pulmonary and systemic blood flow.
    - Staged surgical repair (Norwood → Glenn → Fontan) or primary heart transplant in some centers.

3.4.Pulmonary atresia

- Pulmonary atresia with intact ventricular septum:
    - There is no anatomical connection between the right ventricle and the pulmonary artery; the right ventricle is often hypoplastic.
    - Pulmonary blood flow occurs through the PDA; right-to-left shunt at the atrial level.
    - Presents in the first few hours with profound cyanosis; PGE1 is essential.
- Pulmonary atresia with VSD:
    - Resembles an extreme TOF with complete RVOT obstruction.
    - Pulmonary blood flow through the ductus and/or major aortopulmonary collateral arteries (MAPCA).

- Management:
    - PGE1 to maintain the ductus arteriosus.
    - Catheter-based or surgical strategies tailored to the anatomy (RV decompression, unifocalization of collaterals, staged repairs).

3.5.Tricuspid atresia

- Definition: Absence of a direct connection between the right atrium and the right ventricle; the right ventricle is usually hypoplastic.
- Pathophysiology:
    - Systemic venous return must pass through an ASD/PFO into the left atrium.
    - Systemic outflow from the left ventricle; pulmonary blood flow through the VSD and/or PDA.
- Clinical significance in newborns:
    - Cyanosis early in life; may be duct-dependent if pulmonary blood flow is limited.
- Management:
    - PGE1 if pulmonary flow depends on the PDA.
    - Ultimately, treated with single-ventricle palliative surgery (Glenn/Fontan procedure).

3.6.Total anomalous pulmonary venous return (TAPVR)

- Definition: All pulmonary veins drain into the systemic venous circulation (SVC, coronary sinus, portal system) instead of draining into the left atrium.
- Types: Supracardiac, cardiac, infracardiac, mixed
- Pathophysiology:
    - For any systemic outflow, blood must pass through an ASD/PFO.
    - Obstructive forms (especially infracardiac) cause severe pulmonary venous hypertension and edema.
- Clinical relevance in newborns:
    - Unobstructed: mild cyanosis + heart failure due to high pulmonary flow.
    - Obstructive: severe cyanosis, respiratory distress, pulmonary edema; presents as severe pulmonary disease but with persistent cyanosis.
- Management:
    - Urgent surgical repair, especially in cases of obstructive TPA.

4. Key points

- Many significant lesions are not evident at birth and manifest as pulmonary vascular resistance decreases or the ductus closes (2–7 days or later).
- Left-to-right shunts → pulmonary overcirculation and heart failure, usually without early cyanosis.
- Left-sided obstructive lesions (coarctation, critical aortic stenosis, hypoplastic left heart syndrome) often present with shock when the ductus closes, sometimes with only subtle murmurs.
- Cyanotic lesions require a combination of ASD/VSD/PDA for mixing; deterioration after duct closure is a recurrent pattern in duct-dependent lesions.
- Echocardiography is essential for defining the anatomy and physiology; the student's clinical role is to recognize patterns that require urgent imaging and the involvement of a specialist.

II.5. CONGESTIVE HEART FAILURE

II.5.1. DEFINITION

Congestive heart failure (CHF) in newborns is a clinical syndrome in which the heart cannot provide adequate blood flow to meet the metabolic demands of the tissues without requiring high filling pressures. In this age group, CHF is almost always secondary to a structural congenital heart disease or significant myocardial dysfunction, and its presentation and physiology differ from those observed in adults and older children.

II.5.2. PATHOPHYSIOLOGY

1. Hemodynamic Mechanisms

In newborns, CHF usually arises from one or more of the following mechanisms:

- Volumetric overload
  - Large left-to-right shunts (e.g., large VSD, complete AVSD, significant PDA) increase pulmonary blood flow and venous return to the left heart.
  - The left ventricle is chronically volume-loaded, leading to eccentric hypertrophy and elevated pulmonary and left atrial pressures.
  - Pulmonary congestion and edema reduce pulmonary compliance and impair gas exchange, causing tachypnea and increased respiratory effort.
- Pressure overload
  - Obstructive lesions (critical aortic coarctation, severe aortic stenosis, severe pulmonary stenosis) force the ventricle to generate abnormally high pressure to maintain forward flow.
  - This increases the myocardium's oxygen demand, causes ventricular hypertrophy, and may ultimately impair systolic function.
- Primary myocardial dysfunction
  - Myocarditis, primary cardiomyopathy, and ischemic lesions (e.g., perinatal asphyxia) reduce contractility.
  - Even normal loading conditions cannot be managed, leading to low cardiac output with elevated filling pressures.
- Diastolic dysfunction
  - Hypertrophied or ischemic ventricles relax poorly, so filling requires higher pressures; pulmonary and systemic venous congestion follow.

2. Features specific to newborns

Compared to older children and adults, the myocardium of newborns has unique characteristics:

- Less compliant ventricle
  - The newborn's ventricle operates on a steeper portion of the Frank-Starling curve; small increases in preload produce large changes in pressure rather than in stroke volume.
  - Excess volume rapidly leads to high filling pressures and pulmonary/systemic congestion.
- Limited capacity to increase stroke volume
  - Cardiac output depends primarily on heart rate; the capacity to increase stroke volume is limited.
  - Persistent tachycardia is an early compensatory response and a key clinical sign.
- High baseline pulmonary vascular resistance (PVR) in the first few days
  - Many large left-to-right shunts remain "silent" immediately after birth because PVR is still high.
  - As PVR decreases in the first 2–6 weeks, the shunt volume increases abruptly, revealing heart failure.

II.5.3. ETIOLOGY. TIME OF ONSET

1. Early (first 24–72 hours)

Heart failure during this period usually reflects duct-dependent lesions or primary myocardial diseases:

- Hypoplastic left heart syndrome
- Critical aortic coarctation, interrupted aortic arch
- Critical aortic stenosis
- Severe pulmonary stenosis / pulmonary atresia (with volume overload on the other ventricle)
- Large arteriovenous malformations (Galen's vein, large hepatic AVMs)
- Severe myocarditis or cardiomyopathy
- Severe arrhythmias (sustained SVT, complete heart block)

Clinical deterioration often coincides with closure of the ductus arteriosus, transforming compensated circulation into decompensated low-output shock.

2. Later (after 1–2 weeks)

As PVR decreases, large left-to-right shunts become apparent:

- Large VSD
- Complete AVSD
- Significant PDA
- Truncus arteriosus
- Large aortopulmonary collaterals

The presentation is more subacute: progressive tachypnea, feeding difficulties, poor weight gain, recurrent chest infections.

II.5.4. CLINICAL DIAGNOSIS

In newborns, signs and symptoms are often nonspecific. Recognizing patterns is crucial.

1. Respiratory manifestations:

- Tachypnea (>60 breaths/min at rest)
- Increased respiratory effort
    - Flaring of the nostrils, expiratory moaning, intercostal and subcostal retractions
- Feeding-related dyspnea
    - Increased respiratory effort during feeding, frequent pauses, inability to finish feeding
- Pulmonary findings
    - Fine inspiratory crackles in pulmonary edema
    - In cases of large shunts, the lungs may sound surprisingly clear at first, despite significant tachypnea.

2. Cardiovascular manifestations

- Tachycardia
    - A persistent increase at rest (except during crying or fever) is a distinctive sign.
- Gallop rhythm
    - The presence of a third (and rarely fourth) heart sound suggests elevated filling pressures.
- Murmurs
    - Pansystolic murmur in VSD/AVSD.
    - Continuous murmur in PDA.
    - Systolic ejection murmurs in obstructive lesions.
    - Note: some critical lesions have faint or absent murmurs, despite the severity of the disease.
- Peripheral signs
    - Cold extremities and prolonged capillary refill (>3 s) indicate low cardiac output.
    - Narrow pulse pressure in low-output states; wide pulse pressure with strong pulses in high PDA or significant AR.

3. Systemic venous congestion

- Hepatomegaly
    - The most sensitive sign of systemic venous congestion in infants.
    - Smooth, firm liver margin, palpable >2 cm below the costal margin.
- Peripheral edema
    - Less pronounced than in older patients; may be periorbital or sacral in severe cases.
- Jugular venous distension
    - Difficult to assess reliably in newborns; rarely used as a primary sign.

4. Feeding and growth

- Feeding difficulties
    - Prolonged feeding time (>30 minutes), frequent pauses, refusal to feed.

- Diaphoresis during feeding
    - Excessive sweating on the forehead and scalp strongly suggests heart failure.
- Failure to thrive
    - Poor weight gain, despite adequate caloric intake, reflects a high metabolic demand and inefficient cardiac output.

5. Neurological and renal manifestations

- Irritability or lethargy
    - May reflect poor cerebral perfusion or a systemic disease.
- Oliguria
    - Decreased urine output indicates reduced renal perfusion and neurohormonal activation.

II.5.5. LABORATORY DIAGNOSIS

1. Bedside assessments

- Blood pressure and pulse in all four limbs
    - Look for gradients suggestive of coarctation or an interrupted aortic arch.
- Pre- and post-ductal saturations
    - Differential saturations indicate ductal shunting.
- Hyperoxia test
    - Minimal improvement in cyanosis on 100% oxygen suggests a cardiac cause or PPHN rather than primary lung disease.

2. Chest X-ray

- Cardiothoracic ratio
    - Cardiomegaly suggests chronic volume/pressure overload or cardiomyopathy.
- Pulmonary vascularity
    - Increased markings in large left-to-right shunts.
    - Oligemic pulmonary fields in low pulmonary blood flow (e.g., severe TOF, pulmonary atresia).
- Pulmonary edema
    - Interstitial or alveolar pattern in acute decompensation.

3. Electrocardiogram

- Assess rhythm and conduction (SVT, heart block).
- May show patterns of ventricular hypertrophy (RVH/LVH) indicating chronic overload.

4. Echocardiography

- The gold standard for defining:
    - Underlying structural lesions (shunts, valvular/arch obstruction).
    - Ventricular systolic and diastolic function.
    - Pulmonary artery pressures and shunt direction.
- Essential for guiding definitive management (surgery/intervention).

II.5.6. DIFFERENTIAL DIAGNOSIS

Several conditions mimic heart failure in newborns:

- Primary respiratory disease
    - Respiratory distress syndrome, pneumonia, meconium aspiration, transient neonatal tachypnea.
    - Typically prominent pulmonary findings; hyperoxia test improves saturation; hepatomegaly absent in the early stages.
- Sepsis
    - Tachycardia, poor perfusion, metabolic acidosis, respiratory distress.
    - Often accompanied by temperature instability, abnormal inflammatory markers.
- Metabolic disorders
    - Congenital disorders manifested by acidosis, lethargy, and food intolerance.

- Severe anemia or polycythemia
    - May strain the heart or impair oxygen transport.

To distinguish between them, careful integration of the medical history, physical examination, oxygen saturation levels, and basic investigations (blood gases, chest X-ray, ECG, echocardiography) is necessary.

II.5.7. MANAGEMENT O

The goals of management are to stabilize the infant's condition, alleviate symptoms of congestion, optimize cardiac output, and treat the underlying condition.

A. NONPHARMACOLOGICAL

1. General supportive measures

- Positioning
    - Slightly elevating the head to reduce respiratory effort.
- Thermoregulation
    - Maintain normal body temperature; both hypothermia and hyperthermia increase metabolic demand.
- Minimizing stress
    - Gentle handling, appropriate analgesia/sedation when indicated.

2. Respiratory support

- Supplemental oxygen
    - Administer to maintain adequate saturations; avoid excessive oxygen in certain duct-dependent lesions, where increased pulmonary blood flow may compromise systemic circulation.
- Noninvasive support
    - CPAP or high-flow nasal cannula may improve lung mechanics in cases of pulmonary edema.
- Mechanical ventilation
    - Indicated in cases of severe distress, exhaustion, or when balancing circulation in complex injuries; controlled ventilation may also reduce afterload in some scenarios by decreasing respiratory effort and catecholamine drive.

3. Fluid and nutritional management

- Fluid restriction
    - In infants with volume overload and pulmonary edema, moderate restriction (e.g., 100–120 mL/kg/day) helps reduce congestion.
- Nutrition
    - High-calorie-density foods (e.g., fortified breast milk or high-calorie formula) to meet energy needs while limiting volume.
    - Consider nasogastric feeding if oral intake is insufficient due to fatigue.

B. PHARMACOLOGICAL

1. Diuretics

- Loop diuretics (e.g., furosemide) are the first-line treatment for alleviating pulmonary and systemic congestion.
- Furosemide is commonly used; the dose and frequency are adjusted based on clinical response and renal function.
- Thiazides and potassium-sparing diuretics may be added in chronic treatment.

2. Inotropes

- Indicated in low-output states with poor perfusion and hypotension.
- Agents such as dopamine, dobutamine, and, occasionally, epinephrine are used in intensive care units under close monitoring.

3. Postload reduction

- ACE inhibitors (e.g., captopril/enalapril) reduce systemic vascular resistance and afterload in selected infants with good blood pressure and no critical outflow obstruction.

- They should be used with caution in newborns, especially if renal perfusion is marginal.

4. Digoxin

- It may be used in selected cases of systolic dysfunction or for symptom relief in some left-to-right shunts, provided there is no significant obstruction of blood flow or advanced conduction disease.

C. SPECIFIC MEASURES

- for duct-dependent lesions

In lesions where systemic or pulmonary circulation depends on the ductus arteriosus, prostaglandin E1 (PGE1) infusion is initiated. Initiation occurs as soon as a duct-dependent lesion is suspected (e.g., shock at 24–72 hours, differential saturations, absent femoral pulses). This maintains or reopens the duct, buying time for definitive intervention. The patient requires continuous cardiorespiratory monitoring; apnea is a common side effect and often requires ventilatory support.

- To correct precipitating factors
    - Treat sepsis aggressively with antibiotics and supportive care.
    - Correct anemia, hypoglycemia, and electrolyte imbalances (particularly potassium, calcium, and magnesium).
    - Treat arrhythmias:
        - VPS may require vagal maneuvers, adenosine, and long-term rhythm control.
        - Heart block may require cardiac pacing in some cases.
- Definitive surgical or interventional treatment

Medical therapy stabilizes but rarely cures heart failure when it is caused by significant structural heart disease.

- Large VSD / Complete AVSD
    - Early surgery once the infant is stabilized and has gained sufficient weight, usually before the onset of pulmonary vascular disease.
- Aortic coarctation, critical aortic stenosis, HLHS, TAPVR
    - Requires urgent or early surgery during the neonatal period.
- PDA
    - Pharmacological or surgical closure if hemodynamically significant.

The timing and type of intervention are determined jointly by the neonatology and pediatric cardiology/cardiac surgery teams.

D. FOLLOW-UP

Long-term follow-up includes:

- Monitoring of growth and assessment of neurological development.
- Surveillance for residual lesions, restenosis, arrhythmias, ventricular dysfunction, or pulmonary hypertension.
- Planning the transition to pediatric care and, ultimately, to adult congenital cardiology care.

II.5.8. PROGNOSIS

The prognosis depends on the underlying condition, associated abnormalities, and the timeliness of diagnosis and intervention. Many infants who receive early and appropriate treatment for CHF caused by congenital heart disease have good long-term outcomes.

II.5.9. CONCLUSIONS. KEY POINTS

Key points:

- Neonatal CHF often presents with tachypnea, feeding difficulties, sweating, hepatomegaly, and poor weight gain, rather than obvious edema.
- The timing of onset (within the first 72 hours vs. after 1–2 weeks) provides important clues: consider duct-dependent lesions in the early stage, and large shunts in the advanced stage.
- Hepatomegaly and tachypnea in a newborn, with or without a murmur, should always raise suspicion of heart failure.

- Don’t be lulled into a false sense of security by the absence of a loud murmur: some of the sickest children have faint murmurs or none at all.
- Recognize when heart failure is a manifestation of a surgical problem, not just a medical one—stabilize the patient, then promptly refer to pediatric cardiology and cardiac surgery.

II.6. SHOCK

II.6.1. DEFINITION

Shock in newborns is a life-threatening state of circulatory failure in which oxygen delivery to tissues is insufficient to meet metabolic demands, leading to cellular dysfunction and, if not corrected, to multi-organ failure. In the context of heart disease, shock is often caused by duct-dependent structural lesions, severe myocardial dysfunction, or arrhythmias, but sepsis and hypovolemia frequently coexist and must always be considered. Shock can lead to long-term morbidity, including severe neurological impairment due to cerebral ischemia and reperfusion injury. Therefore, prompt recognition of shock and initiation of goal-directed therapy that addresses its underlying pathophysiology and maintains hemodynamic stability are essential

II.6.2. PATHOPHYSIOLOGY

The pathophysiology of shock in newborns is unique because it overlaps with the physiological transition and hemodynamic changes from fetal to neonatal circulation at birth.
The main pathophysiological processes involved in the progression of neonatal shock are:

- Myocardial dysfunction
- Abnormal peripheral vasoregulation
- Hypovolemia

In short: shock = inefficient circulating blood flow → insufficient oxygen delivery → anaerobic metabolism, lactic acidosis, organ dysfunction.

In newborns, blood pressure alone is not a reliable marker; perfusion, however, is more informative, encompassing:

- mental status,
- capillary refill time,
- pulse,
- urine output, lactate levels

Cardiac output depends largely on heart rate (limited capacity for increasing stroke volume), so that bradycardia or extreme tachycardia rapidly compromise perfusion.

The determinants of oxygen transport are:

- Cardiac output (HR × stroke volume).
- Arterial oxygen content (hemoglobin concentration and saturation).

Any process that significantly reduces one or both factors or significantly increases metabolic demand can precipitate shock.

II.6.3. CLASSIFICATION OF NEONATAL SHOCK

The same general categories used in older patients apply, but their relative frequency differs in the neonatal period.

1. Hypovolemic shock

- Due to absolute loss of intravascular volume – inadequate blood volume
- Causes:
    - Intra/peripartum hemorrhage: fetomaternal hemorrhage, placental abruption, placenta previa, feto-fetal transfusion.
    - Postnatal hemorrhage: intracranial hemorrhage, pulmonary hemorrhage
    - Dehydration: inadequate intake, excessive insensible losses, osmotic diuresis (e.g., hyperglycemia).
- Hemodynamics: reduced preload, low stroke volume, compensatory tachycardia, and vasoconstriction.

2. Distributive shock
- Impaired blood flow distribution due to loss of vasomotor tone and increased vascular permeability.
- The most common cause in newborns: septic shock.
- Early phase: warm extremities, strong pulses (if cardiac output is preserved); late phase resembles hypovolemia/low output.

3. Cardiogenic shock
- Primary pump failure with reduced cardiac output, despite adequate volume.
- Causes:
    - Critical congenital heart defects (duct-dependent systemic flow, severe obstructive defects).
    - Myocarditis, cardiomyopathy.
    - Severe arrhythmias (Ventricular Tachycardia, Complete Heart Block).
- Clinical presentation: signs of heart failure (hepatomegaly, gallop rhythm), pulmonary edema, weak pulse, elevated lactate.

4. Obstructive shock
- Mechanical obstruction of cardiac output or large vessel flow.
- Causes:
    - Tension pneumothorax.
    - Cardiac tamponade.
    - Massive pulmonary embolism (rare in newborns).
    - Severe duct-dependent obstructive lesions

5. Dissociative shock
- Inadequate oxygen delivery or administration
- Causes:
    - Anemia
    - methemoglobinemia

6. Mixed shock
- Combinations are common: for example, septic shock with myocardial depression or cardiogenic shock complicated by hypovolemia.

In newborns with heart disease, it is particularly important to recognize cardiogenic, obstructive, and duct-dependent patterns.

II.6.4. CLINICAL DIAGNOSIS

Early signs may be subtle; a high index of suspicion is essential, particularly in the first days of life when ductal closure occurs.

1. General and neurological signs
- Lethargy, hypotonia, weak or high-pitched crying.
- Early irritability, progressing to decreased responsiveness.
- Poor feeding or refusal to feed.

2. Skin and peripheral perfusion
- Color: pallor, mottling, cyanosis; sometimes central cyanosis in certain cardiac or septic conditions.
- Temperature: cold extremities, with a relatively warmer trunk.
- Capillary refill time (CRT): prolonged, >3 seconds
- Peripheral pulses: weak or thready; in some circulatory conditions, initially strong.

3. Cardiovascular signs
- Heart rate: tachycardia is typical; paradoxically, a “normal” or low heart rate in a critically ill newborn is a serious sign
    - Bradycardia associated with shock is a warning sign for cardiorespiratory arrest
- Presence of a heart murmur – not mandatory

- Blood pressure: low or falling blood pressure is a late sign; diastolic hypotension is prominent in distributive shock, systolic hypotension in cardiogenic/hypovolemic shock.
- Pulse characteristics
    - The difference between pulse/blood pressure in the upper and lower extremities suggests aortic arch obstruction (e.g., coarctation, interrupted aortic arch).
    - In duct-dependent systemic lesions, the femoral pulse may be weak or absent compared to the brachial pulse.

4. Respiratory signs

- Tachypnea, increased respiratory effort.
- Apnea or irregular breathing in advanced stages.
- Signs of pulmonary edema (crackles, frothy secretions) in cardiogenic shock.

5. Renal and metabolic signs

- Oliguria (<1 ml/kg/h).
- Metabolic acidosis on blood gas analysis (increased base deficit).
- Increased lactate from anaerobic metabolism.

II.6.5. LABORATORY DIAGNOSIS

Paraclinical investigations in cases of suspected neonatal shock focus on identifying the underlying etiology of the shock based on clinical and physiological findings. Routine assessment methods used in adult and pediatric populations are often invasive and not feasible in newborns. Hence the importance of non-invasive technologies for hemodynamic monitoring in newborns. Such assessments may include bedside ultrasound to evaluate cardiac function as well as appropriate laboratory tests to assess the presence of infections, anemia, dehydration, etc.

- Laboratory Analysis
    - Blood gas analysis
    - Electrolytes
    - Serum lactate
    - Blood glucose
    - Complete blood count
    - Liver function tests
    - Renal function tests
    - Coagulation tests
    - Inflammatory markers
    - Peripheral and central cultures
- Imaging
    - POCUS ultrasounds – cardiac, transfontanellar, pulmonary, abdominal
    - Cardiopulmonary X-ray

II.6.6. POSITIVE DIAGNOSIS – INITIAL ASSESSMENT

When faced with a newborn in shock, the physician must quickly assess the situation and simultaneously begin resuscitation.

Key questions:

- Is this true shock (global hypoperfusion) or an isolated respiratory or neurological problem?
- Is the shock likely cardiac (duct-dependent, myocardial, arrhythmic) or primarily septic/hypovolemic?
- Are there signs of critical heart disease (differential saturation, absent femoral pulses, murmur, hepatomegaly)?

1. Bedside Assessment

- Airway and breathing:
    - respiratory effort, cyanosis, breath sounds.
- Circulation:

- HR, BP (preferably in all four extremities), CVR, pulses, liver size.
- Pre- and post-ductal SpO□ to assess right-to-left ductal shunt.

- History: perinatal events, known fetal cardiac anomalies, maternal conditions, time of deterioration (especially 24–72 hours).

2. Simple diagnostic criteria

- Suggest cardiac/ductal shock:
  - Sudden collapse in a previously "stable" newborn around day 2–3.
  - Weak/absent femoral pulses, arm-leg BP gradient.
  - Differential saturations (preductal higher than postductal).
  - Cardiomegaly or pulmonary edema on CXR without obvious lung disease.
  - Hepatomegaly, gallop rhythm.
- Suggests distributive/septic shock:
  - Risk of maternal infection, PROM, chorioamnionitis.
  - Fluctuating temperature, petechiae, elevated CRP/procalcitonin.
  - Extremities initially warm, with strong pulses.

II.6.7. SHOCK AND CONGENITAL HEART DEFECTS – SPECIFIC FEATURES

In cases of congenital heart defects, shock often occurs when the ductus arteriosus closes, particularly between 24 and 72 hours after birth.

1. Duct-dependent systemic circulation

- Lesions:
  - Hypoplastic left heart syndrome.
  - Critical aortic coarctation.
  - Interrupted aortic arch.
  - Critical aortic valve stenosis.
  - Severe forms of unbalanced AVSD with compromised left-sided blood flow.
- Mechanism:
  - Systemic perfusion to the lower body, as well as coronary and cerebral circulation, depends partially or entirely on right-to-left ductal flow from the pulmonary artery to the aorta.
  - Ductal closure abruptly eliminates this pathway → severe systemic hypoperfusion and left ventricular overload → cardiogenic shock.
- Clinical presentation:
  - Initially well or mildly symptomatic.
  - Sudden deterioration: tachypnea, poor feeding, pallor, cold extremities, weak or absent femoral pulses, oliguria, severe metabolic acidosis.
  - Shock is often disproportionate to the findings on chest X-ray.

2. Pulmonary circulation dependent on the ductus arteriosus

- Lesions:
  - Pulmonary atresia (± VSD).
  - Critical pulmonary stenosis.
  - Some forms of severe TOF, tricuspid atresia, and TGA with restrictive component.
- Mechanism:
  - Pulmonary blood flow depends on left-to-right ductal shunting, from the aorta to the pulmonary artery.
  - Ductal constriction causes a sudden decrease in pulmonary blood flow → severe hypoxemia and cardiovascular collapse.
- Clinical presentation:
  - Cyanosis present at birth or in the first years of life.

  Worsening desaturation and acidosis as the duct closes, sometimes with relatively preserved systemic blood pressure until late in the course.

II.6.8. MANAGEMENT

Management must begin immediately and proceed in parallel with the diagnostic steps. A useful way to remember the key areas is to think in terms of airway – breathing – circulation plus targeted therapy.

1. Airway and breathing

- Position, suction, and maintain the airway; intubate early in newborns with severe illness or those who may require PGE□ (due to the risk of apnea).
- Administer oxygen, but:
    - Avoid excessive hyperoxia in certain duct-dependent cardiac lesions, where high PaO□ may promote duct closure or increase excessive pulmonary circulation at the expense of systemic flow.
- Mechanical ventilation:
    - Reduces respiratory effort and oxygen consumption.
    - Allows for better control of PaCO□ and pH (acidosis worsens pulmonary hypertension and myocardial function).

2. Circulation: Fluids and inotropes

- Volume resuscitation
    - If hypovolemia is likely: administer a bolus of isotonic fluid (e.g., 10 mL/kg over 10–20 minutes), then reassess.
    - In cases of cardiogenic or duct-dependent shock, avoid repeated large-volume fluid boluses; even modest volumes can precipitate pulmonary edema.
- Inotropic/vasoactive support
    - The choice depends on the blood pressure pattern and the suspected mechanism:
        - Dopamine/dobutamine for low output with hypotension.
        - Adrenaline for severe hypotension with low cardiac output.
        - Norepinephrine in vasodilatory/distributive shock when diastolic pressure is very low.
    - Titrate to maintain adequate perfusion, not just “normal” values.
- Continuous monitoring:
- Heart rate
- Oxygen saturation – SpO2
- Blood pressure
- Urine output
- Lactate level
- Serial blood gas analysis.

3. Targeted therapy

- Prostaglandin E1 (PGE□) in cases of suspected duct-dependent CHD

Whenever there is a strong suspicion of a duct-dependent critical condition—and especially if the infant’s condition deteriorates around the time of the expected closure of the duct—PGE□ should be administered without waiting for definitive imaging, unless there is an obvious non-cardiac cause. The goals of prostaglandin therapy are to reopen or maintain the ductus arteriosus to restore systemic or pulmonary blood flow. Treatment begins with the standard infusion dose and is adjusted based on clinical response and side effects. In the event of apnea, early intubation and ventilation are initiated if the newborn’s condition is unstable. Once stabilized, urgent echocardiography determines the precise lesion and the definitive plan.

- Treatment of precipitating and contributing factors
    - Sepsis: broad-spectrum antibiotics pending cultures; source control, if necessary.
    - Metabolic disorders: correct hypoglycemia, hypocalcemia, and metabolic acidosis (primarily by improving perfusion; bicarbonate is reserved for severe refractory acidosis, once ventilation and circulation are optimized).
    - Anemia: transfusion in severe and symptomatic cases.

- Arrhythmias:
- Ventricular tachycardia: vagal maneuvers, adenosine, then second-line agents if necessary.
- Bradyarrhythmias (e.g., complete heart block): atropine is rarely useful; cardiac pacing may be necessary if associated with shock.

4. Follow-up

Ongoing care and definitive treatment depend on the newborn's stabilization.

- Imaging and diagnosis
  - Echocardiography to assess anatomy and function.
  - Cardiopulmonary X-ray,
  - ECG,
  - laboratory evaluation to identify concomitant pathology.
- Surgical or catheter-based intervention
- Many cardiac causes of shock require urgent or emergency procedures:
  - Repair of coarctation.
  - Balloon valvuloplasty for critical aortic or pulmonary stenosis.
  - Arterial switch for TGA.
  - Norwood procedure or equivalent palliative first-stage procedure for HLHS.
  - TAPVR repair.
- Intensive care
  - Continuous hemodynamic monitoring, ventilatory support, and titrated inotropes.
  - Nutrition and fluid balance carefully adjusted as the hemodynamic picture evolves.

II.6.9. CONCLUSIONS. KEY POINTS

- Shock during the first week of life should always prompt consideration of critical congenital heart disease, especially if the deterioration coincides with ductal closure (24–72 hours).
- In newborns, capillary refill, pulse, mental status, urine output, and lactate are more reliable than blood pressure in assessing shock.
- Absence or weakness of the femoral pulse, differential saturations, and blood pressure gradients between the arms and legs are important warning signs of left-sided obstructive lesions.
- When in doubt, and if a duct-dependent lesion is plausible, it is safer to initiate PGE□ administration and support the infant while arranging for an urgent echocardiogram than to wait for confirmatory imaging before taking action.
- The management of neonatal shock is multidisciplinary: neonatology, cardiology, cardiac surgery, anesthesiology, and intensive care must collaborate, with the junior physician's primary tasks being early recognition, prompt resuscitation, and rapid escalation.

II.7. PRACTICAL CONCEPTS IN CARDIAC PATHOLOGY

II.8. ACQUIRED HEART DISEASES

Acquired heart diseases in the neonatal period are less common than structural congenital heart diseases, but they can rapidly become life-threatening and may coexist with or mimic congenital lesions. It is essential to recognize patterns suggesting a primary myocardial, pericardial, inflammatory, or rhythm problem rather than a purely structural defect.

II.8.1. MYOCARDITIS

II.8.1.1. Definition and Etiology

Myocarditis is an inflammation of the myocardium that leads to myocyte damage, impaired contractility, and electrical instability. In newborns, the most common causes are:

- Viral: enteroviruses (particularly coxsackievirus B and echovirus), adenovirus, parvovirus B19, cytomegalovirus, and, more recently, coronaviruses.

- Bacterial: part of severe sepsis, including Group B streptococcal infections and Gram-negative infections.
- Immune-mediated or metabolic: rare in the neonatal period (e.g., maternal autoimmune diseases, congenital metabolic disorders).

Vertical transmission (in utero or peripartum) explains the very early onset in many cases.

II.8.1.2. Pathophysiology

- Viral invasion of myocytes triggers a local inflammatory reaction with lymphocytic infiltration, myocyte necrosis, and interstitial edema.
- Contractile function decreases (systolic dysfunction), and diastolic filling is impaired.
- Involvement of the conduction tissue predisposes to arrhythmias (Ventricular Tachycardia, Ventricular Tachycardia, AV Block).
- In fulminant cases, this leads to acute cardiogenic shock.

II.8.1.3. Clinical Diagnosis

- Mild to moderate disease
    - Nonspecific: poor appetite, irritability, lethargy, mild fever.
    - Tachycardia disproportionate to the temperature.
    - Signs of heart failure: tachypnea, hepatomegaly, gallop rhythm, poor peripheral perfusion.
- Fulminant myocarditis
    - Rapid-onset cardiogenic shock: severe tachycardia, hypotension, poor perfusion, cold extremities.
    - Pulmonary edema with significant respiratory distress.
    - Oliguria and lactic acidosis.
    - Arrhythmias (Ventricular Tachycardia, Ventricular Fibrillation, AV Block) may precipitate or exacerbate instability.

A recent history of maternal or perinatal viral infections may be a clue.

II.8.1.4. Laboratory Diagnosis

- Blood tests
    - Elevated cardiac biomarkers (troponin, CK-MB).
    - Elevated BNP/NT-proBNP, reflecting ventricular overload.
    - Variably elevated CRP and other inflammatory markers.
- ECG
    - Sinus tachycardia, nonspecific ST-T changes, low voltage, conduction abnormalities.
    - Supraventricular or ventricular arrhythmias in some cases.
- Chest X-ray
    - Cardiomegaly with or without pulmonary edema.
- Echocardiography
    - Global or regional systolic dysfunction.
    - Dilated chambers, particularly the left ventricle.
    - Often normal valve structure; mild to moderate mitral/tricuspid regurgitation due to annular dilation.
    - Pericardial effusion may be present.
- Cardiac MRI (for tissue characterization) and endomyocardial biopsy in selected cases—used less frequently in unstable newborns

II.8.1.5. Management

- Supportive care and intensive care
    - Stabilization of the airways and respiration; ventilation in cases of severe respiratory failure or shock.
    - Careful fluid management to avoid overload while maintaining perfusion.
- Inotropes and vasopressors
    - Dobutamine or milrinone to support contractility and reduce afterload.

    - Adrenaline when blood pressure is critically low.
- Arrhythmia management
    - Ventricular tachycardia: adenosine in acute cases; beta-blockers or amiodarone in recurrent cases.
    - Ventricular arrhythmias: amiodarone or lidocaine under specialist supervision.
    - AV block with hemodynamic compromise: temporary cardiac pacing may be necessary.
- Infection and immune modulation
    - Broad-spectrum antibiotics until bacterial infection is ruled out.
    - Antiviral therapy in specific situations (e.g., HSV).
    - IVIG is used in some centers, although evidence in newborns is limited and evolving.
- Mechanical circulatory support
    - ECMO as a bridge to recovery or transplantation in refractory cardiogenic shock.

Outcomes range from complete recovery of function to persistent cardiomyopathy or death; early aggressive support improves the chances of recovery.

II.8.2. C CARDIOMYOPATHY

True primary cardiomyopathy occurring in the neonatal period is rare but important. Two types are distinguished: dilated and hypertrophic cardiomyopathy.

II.8.2.1. Dilated cardiomyopathy (DCM)

- Etiologies
    - Genetic mutations (sarcomeric and cytoskeletal proteins).
    - Metabolic diseases (mitochondrial disorders, fatty acid oxidation defects).
    - Post-myocarditis.
- Clinical presentation
    - Progressive heart failure: tachypnea, poor feeding, growth retardation, hepatomegaly.
    - Often without significant murmur.
- Laboratory findings
    - Echocardiography – dilated LV (and frequently RV) with reduced systolic function.
- Management
    - Principles similar to those for chronic heart failure (diuretics, ACE inhibitors, inotropes, as indicated).
    - Genetic and metabolic evaluation.
    - The long-term prognosis is highly variable; some patients stabilize, while others require transplantation or die.

II.8.2.2. Hypertrophic cardiomyopathy (HCM)

- Etiologies
    - Genetic sarcomeric mutations.
    - Infants of diabetic mothers (transient hypertrophic cardiomyopathy).
    - Metabolic/storage diseases (e.g., Pompe disease).
- Pathophysiology
    - Thickened ventricular walls, often with asymmetric septal hypertrophy.
    - Outflow tract obstruction may be present; marked diastolic dysfunction.
- Clinical presentation
    - May be asymptomatic or present with tachypnea, feeding difficulties, or syncope/collapse.
    - Loud systolic murmur in cases of dynamic obstruction of left ventricular outflow.
- Management
    - Beta-blockers to reduce contractility and improve diastolic filling in obstructive forms.
    - Avoid inotropes and excessive reduction of preload in obstructive HCM.
    - Metabolic/genetic investigations, where indicated.

II.8.3. MYOCARDIAL ISCHEMIA

II.8.3.1. Definition and Etiology

Myocardial ischemia in newborns refers to an imbalance between myocardial oxygen supply and demand, leading to reversible or irreversible damage to myocytes. Unlike adults, newborns rarely suffer from atherosclerotic coronary artery disease; instead, ischemia is usually secondary: In practice, ischemic lesions are most often observed as part of multi-organ hypoxic-ischemic injury or as a postoperative complication.

- Severe systemic hypoxia or hypoperfusion (perinatal asphyxia, severe shock).
- Coronary artery anomalies (congenital or course-related anomalies, ostial stenosis, coronary occlusion following arterial switch or other surgical intervention).
- Marked anemia or polycythemia that impairs oxygen delivery or increases blood viscosity.
- Severe hypertrophy (e.g., infant of a diabetic mother) causing insufficient subendocardial perfusion when demand is high.
- Iatrogenic causes (e.g., accidental coronary injury or kinking during cardiac surgery).

II.8.3.2 Pathophysiology

- Supply side:
  - Reduced coronary perfusion pressure due to systemic hypotension, low diastolic pressure, or high left ventricular end-diastolic pressure.
  - Decreased arterial oxygen content due to hypoxemia or severe anemia.
  - Structural coronary abnormalities that limit blood flow.
- Demand side:
  - Tachycardia and increased wall stress (afterload/pressure overload).
  - Ventricular hypertrophy (e.g., HCM, infant of a diabetic mother).
  - Elevated catecholamine levels (sepsis, shock, inotropic escalation).

When supply cannot meet demand, the newborn develops subendocardial ischemia and, if prolonged, myocardial infarction with loss of contractile function and arrhythmias.

II.8.3.3. Clinical Context

Common situations in which myocardial ischemia should be considered: Clinical manifestations are nonspecific: Chest pain and the classic equivalents of angina in adults are not useful in newborns who cannot communicate verbally.

- Perinatal asphyxia / severe hypoxic-ischemic encephalopathy
  - Global hypoxia and hypotension → diffuse myocardial shock.
  - Clinical presentation: low cardiac output, hypotension, cold extremities, elevated lactate, sometimes with minimal murmurs.
- Severe duct-dependent or obstructive lesions
  - A significant increase in left ventricular pressure (critical aortic stenosis, coarctation, HLHS) can compromise subendocardial perfusion.
  - Ischemia contributes to ventricular failure and further reduces cardiac output.
- Postoperative cardiac surgery
  - Particularly procedures involving the coronary arteries (arterial switch, coronary reimplantation).
  - Sudden ST-segment changes, new regional wall motion abnormalities, and rapid hemodynamic collapse suggest acute coronary compromise.
- Infants of diabetic mothers with marked septal hypertrophy
  - Hypertrophied myocardium with relatively reduced capillary density.
  - Episodes of tachycardia, hypoxia, or hypotension can precipitate ischemia and transient left ventricular dysfunction.
- Clinical manifestations are nonspecific:
  - Unexplained low cardiac output (poor perfusion, hypotension, oliguria).
  - Tachycardia, gallop rhythm, and hepatomegaly.
  - In severe cases, arrhythmias (VT, VF, high-degree AV block) and sudden deterioration.

II.8.3.4. Laboratory Diagnosis

1. Electrocardiogram

- ST-segment depression or elevation, T-wave inversions.
- Q waves in specific leads if a myocardial infarction has occurred.
- Conduction disturbances or ventricular arrhythmias.

2. Cardiac biomarkers

- Elevated troponin and CK-MB indicate myocardial injury.
- These should be interpreted in the clinical context (levels may also be elevated in cases of myocarditis or severe sepsis).

3. Echocardiography

- Depressed global or regional systolic function.
- Regional wall motion abnormalities in a coronary territory suggest focal ischemia/infarction.
- Assessment of associated lesions (left ventricular outflow tract obstruction, coronary origins, postoperative anastomoses).

4. Advanced imaging/catheterization (specialist level)

- Coronary angiography or CT/MRI angiography to define coronary anatomy and detect stenosis or ostial occlusion.
- Used primarily postoperatively or in cases of suspected congenital coronary anomalies.

II.8.3.5. Management

Management aims to restore oxygen supply and reduce myocardial demand, while treating the underlying causes.

- General supportive care
    - Ensure adequate oxygenation and ventilation; avoid both hypoxia and significant hyperoxia.
    - Optimize hemoglobin concentration (transfusion in cases of severe anemia).
    - Correct hypotension with judicious fluid administration and vasoactive agents, balancing coronary perfusion and avoiding excessive fluid overload.
- Cardiac support
    - Inotropes (e.g., dobutamine, milrinone) to support contractility in the shocked myocardium, titrated carefully.
    - Avoid excessive tachycardia; use beta-blockers with caution in certain forms of postoperative or hypertrophic ischemia, under the guidance of a cardiologist.
- Arrhythmia management
    - Treat ventricular arrhythmias aggressively (amiodarone, lidocaine, cardioversion/defibrillation if unstable).
    - Promptly correct electrolyte imbalances (K, Mg, Ca).
- Specific etiological treatment
    - Reopen or maintain ductal patency with prostaglandin if ischemia is secondary to critical duct-dependent lesions.
    - For postoperative coronary compromise, urgent surgical or catheter-based revision may be necessary.
    - In perinatal asphyxia, management of shock and multi-organ dysfunction (plus therapeutic hypothermia if within the time window and indicated) indirectly supports the myocardium.
- Mechanical circulatory support
    - ECMO may be required in severe ischemic cardiogenic shock that does not respond to pharmacological therapy, as a bridge to recovery or further intervention.

II.8.3.6. Prognosis

Transient ischemic injuries (“shocked” myocardium), such as those occurring after perinatal asphyxia, often show substantial recovery within a few days or weeks with adequate support. True myocardial infarction (particularly due to coronary occlusion or severe structural lesions) may result in permanent regional dysfunction, predispose to ventricular aneurysm, and increase the risk of arrhythmia. Long-term follow-up with echocardiography and ECG is essential for monitoring recovery, ventricular function, and cardiac rhythm abnormalities.

II.8.4. PERICARDIAL DISEASE

Acquired heart diseases also include pericardial effusion and tamponade.

- Etiology:
  - postoperative (following cardiac procedures).
  - infection (viral, bacterial)
  - uremia, hypothyroidism, autoimmune disease (rare in newborns).
  - Chylopericardium, trauma, catheter-associated perforation.
- Clinical features
  - Tachycardia, tachypnea.
  - Muffled heart sounds (often subtle in newborns).
  - Hepatomegaly, poor perfusion.
  - Reduced pulse pressure, weak pulse.
  - In cases of tamponade: hypotension, marked tachycardia, shock.
- Diagnosis
  - Echocardiography: pericardial fluid, diastolic collapse of the right atrium/ventricle in tamponade.
- Management
  - Urgent pericardiocentesis for tamponade (life-saving).
  - Treatment of the underlying cause (infection, postoperative inflammation, metabolic disorder).
  - In cases of postoperative inflammatory effusions, NSAIDs +/- steroids may be used

II.8.5. NEONATAL ARRHYTHMIAS

Arrhythmias are common in the perinatal period; most are benign, but some cause or reflect serious heart disease.

II.8.5.1. Benign Extrasystoles

1. Premature atrial contractions (PACs)

- Very common in newborns, often incidental.
- They usually resolve spontaneously within the first few weeks.
- Important mainly because they can trigger SVT in susceptible infants.

2. Premature ventricular contractions (PVCs)

- Occasional isolated PVCs in an otherwise healthy newborn with a structurally normal heart are usually benign.
- Frequent or complex PVCs require cardiological evaluation and echocardiography.

II.8.5.2. Supraventricular tachycardia (SVT)

- Mechanism
  - Usually reentrant tachycardia via an accessory pathway (e.g., AVRT, often associated with WPW).
- Clinical features
  - Sudden-onset narrow-complex tachycardia, HR 220–300/min.
  - In early episodes, the infant may appear relatively well; prolonged SVT causes poor feeding, pallor, tachypnea, hepatomegaly, and heart failure.
- Diagnosis
  - ECG: regular tachycardia with narrow complexes; P waves are often hidden or retrograde.
- Management in the acute phase
  - Vagal maneuvers (ice on the face) under monitoring.
  - Intravenous adenosine as first-line pharmacological therapy.
  - Synchronized cardioversion if hemodynamics are unstable.
- Chronic treatment
  - Beta-blockers (e.g., propranolol) or other antiarrhythmics, as recommended by a cardiologist.

II.8.5.3. Atrial flutter

- Characteristics:
  - Rapid atrial rate (~300/min), often with 2:1 AV block (ventricular rate ~150/min).
  - May present with poor perfusion, tachypnea, or heart failure.
- Treatment:
  - Synchronized cardioversion or antiarrhythmic medications (e.g., digoxin, amiodarone), depending on stability and local protocols.

II.8.5.4. Bradyarrhythmias and heart block

- Sinus bradycardia
  - Often benign if associated with sleep or high vagal tone.
- Congenital complete heart block
  - Frequently associated with maternal anti-Ro/SSA or anti-La/SSB antibodies (neonatal lupus).
  - Heart rate is usually 40–60 beats per minute; risk of low cardiac output and intrauterine hydrops.
  - Some infants remain stable; others require pacemaker implantation.

II.8.6. THROMBOEMBOLIC DISEASE

Although rare, thrombi can form in the neonatal heart or in large vessels.

- Predisposing factors:
  - Central venous catheters (especially umbilical lines).
  - Polycythemia, sepsis, hereditary thrombophilia.
  - Postoperative conditions with low blood flow.
- Locations
  - Right atrial thrombus, left atrial/ventricular thrombus, pulmonary embolism, aortic thrombus.
- Clinical consequences
  - Pulmonary embolism with respiratory distress and hypoxemia
  - Systemic embolisms causing stroke or limb ischemia.
- Management
  - Anticoagulation (heparin) and, rarely, thrombolysis or surgical thrombectomy under specialist supervision.

II.8.7. CONCLUSIONS. KEY POINTS

Key points:

- Not all cardiac problems in newborns are structural; acquired conditions, such as myocarditis, cardiomyopathy, pericardial effusion, and arrhythmias, can present with shock, heart failure, or sudden collapse.
- Acquired disease is often suspected when:
  - The heart appears structurally normal on ultrasound, but function is impaired.
  - Arrhythmia is the dominant clinical feature.
  - There is a strong association with infection, maternal autoimmunity, or metabolic disease.
- In any sick newborn with circulatory or respiratory compromise, consider the following simultaneously:
  - Is there congenital heart disease?
  - Could it be myocarditis or cardiomyopathy?
  - Is there an arrhythmia causing or complicating the clinical picture?
- Early involvement of pediatric cardiology, careful interpretation of ECG and echocardiography, and aggressive supportive care in intensive care settings are essential for achieving good outcomes.

II.9. PHARMACOLOGY

Pharmacological management in neonatal cardiology aims to stabilize hemodynamics, optimize cardiac output, control pulmonary and systemic vascular resistance, treat heart failure and shock, and support duct-dependent circulation until definitive intervention. Responses to medications are strongly influenced by neonatal physiology (immature myocardium, developing renal/hepatic clearance, high body water content), so dosing and monitoring must be particularly careful.

II.9.1 GENERAL PRINCIPLES IN NEONATAL CARDIAC PHARMACOLOGY

- **Weight-based dosing** is mandatory, usually in micrograms (mcg) or milligrams (mg) per kg.
- **Narrow therapeutic window** for many drugs (e.g., digoxin, prostaglandin E□, antiarrhythmics); small errors can be dangerous.
- **Organ immaturity** (renal and hepatic) prolongs the half-life for many agents → the need for lower doses and longer intervals in very preterm or ill newborns.
- **Polypharmacy and drug interactions** are common in intensive care; always check for additive inotropy, vasodilation, QT prolongation, or nephrotoxicity.
- **Continuous monitoring** (ECG, blood pressure, SpO□, urine output) is essential for any vasoactive infusion or antiarrhythmic medication.

For educational purposes, medications are grouped into major functional classes:

- Inotropic and vasopressor medications
- Vascular tone-modulating medication
- Diuretic medication
- Digitalis
- Prostaglandins
- Antiarrhythmic medication

II.9.2. INOTROPIC AND VASOPRESSOR MEDICATIONS

These agents support cardiac output and blood pressure in heart failure and shock, including in cardiogenic and septic conditions and during the perioperative period.

II.9.2.1 Dopamine

- Mechanism: Dose-dependent agonist at dopaminergic, β□, and α□ receptors.
- Effects depending on the dose range (approximately):
  - Low (1–5 mcg/kg/min): primarily dopaminergic (renal/mesenteric vasodilation—effect in newborns is variable).
  - Moderate (5–10 mcg/kg/min): β□-mediated increase in contractility and heart rate.
  - High (>10 mcg/kg/min): α□-mediated vasoconstriction increases systemic vascular resistance (SVR) and blood pressure.
- Uses: First-line treatment in many units for hypotension with low perfusion; useful in mixed or septic shock.
- Advantages: Widely available, familiar, titratable; improves blood pressure and urine output in many cases.
- Risks/considerations: Tachycardia, increased myocardial oxygen demand, potential arrhythmias; high doses may worsen afterload and reduce stroke volume.

II.9.2.2. Dobutamine

- Mechanism: A synthetic catecholamine with predominantly β□ activity and some β□-agonist activity.
- Main effects: Positive inotropy with modest chronotropy; β□-mediated vasodilation somewhat reduces afterload.
- Uses: Conditions with low cardiac output and relatively high SVR (e.g., myocardial dysfunction, post-asphyxia myocardial shock).

- Advantages: Improves contractility and forward flow with less tachycardia than dopamine for an equivalent inotropic effect.
- Risks: Systemic hypotension if SVR is already low; caution in cases of distributive shock.

II.9.2.3. Adrenaline (epinephrine)

- Mechanism: β□/β□ and α□ agonist; β effects predominate at lower doses, and α effects at higher doses.
- Uses: severe hypotension with low cardiac output; resuscitation; sometimes postoperative conditions with low output.
- Effects:
  - Increases heart rate and contractility (β□).
  - At higher doses, strong vasoconstriction (α□) increases blood pressure but may impair peripheral perfusion.
- Risks: Tachyarrhythmias, increased myocardial O□ consumption, hyperglycemia, lactic acidosis; careful titration and monitoring in the ICU are required.

II.9.2.4. Noradrenaline (norepinephrine)

- Mechanism: Potent α□ with some β□ activity.
- Main effect: Potent vasoconstriction (↑SVR) with modest inotropic effect.
- Uses: Refractory vasodilatory/distributive shock (e.g., septic shock with very low diastolic pressures), usually in an intensive care unit.
- Risks: Risk of excessive vasoconstriction, peripheral/organ ischemia; requires central venous access and continuous monitoring.

II.9.2.5. Milrinone (phosphodiesterase-3 inhibitor)

- Mechanism: Inhibits PDE-3 → increases cAMP in cardiomyocytes and vascular smooth muscle → positive inotropy, lusitropy (improved relaxation), and vasodilation ("inodilator").
- Uses:
  - Low-output states with high SVR, particularly after cardiac surgery.
  - Situations where catecholamines alone are insufficient or poorly tolerated.
- Benefits: Improves cardiac output without directly stimulating catecholamine receptors; reduces afterload and pulmonary vascular resistance.
- Risks: Hypotension (due to vasodilation), arrhythmias; elimination occurs via the kidneys, so dosage must be adjusted in cases of renal insufficiency.

II.9.3. VASCULAR TONE MODULATING MEDICATIONS

II.9.3.1. Vasodilators

Used to reduce afterload (improving forward flow) or to reduce preload/pulmonary congestion.

- Angiotensin-converting enzyme inhibitors (e.g., captopril, enalapril)
  - Mechanism: blocks the conversion of angiotensin I to II → ↓SVR, ↓aldosterone.
  - Uses: Chronic treatment of left ventricular systolic dysfunction or large left-to-right shunts causing volume overload, once the infant is hemodynamically stable.
  - Precautions: Avoid in acute shock or significant renal failure; contraindicated in critical aortic stenosis or coarctation, where systemic perfusion depends on a higher afterload; monitor BP, creatinine, and potassium.
- Sodium nitroprusside
  - Potent arterial and venous vasodilator; rapid onset and offset.
  - Used for severe hypertension or significant reduction in afterload under TINN-controlled conditions.
  - Risk of cyanide/thiocyanate toxicity with prolonged use; requires careful monitoring and light-protected infusion.
- Nitroglycerin
  - Predominantly a venous vasodilator, but also arterial at higher doses.

- May be used to reduce preload and pulmonary congestion or in certain postoperative ischemic contexts.
- May influence ductal tone (potentially promoting closure) and may cause hypotension; use is highly specialized.

II.9.3.2. Pulmonary vasodilators

Important in persistent pulmonary hypertension of the newborn (PPHN) and in certain postoperative conditions.

- Inhaled nitric oxide (iNO)
  - Selective pulmonary vasodilator; reduces pulmonary arterial pressure and improves the V/Q ratio.
  - Used in PPHN and in some postoperative situations.
  - Short half-life, requires specialized delivery systems; possible rebound pulmonary hypertension if treatment is abruptly discontinued.
- Sildenafil (PDE-5 inhibitor)
  - Oral or IV; selectively dilates the pulmonary vasculature.
  - Used as an adjunct or follow-up to iNO, or for chronic pulmonary hypertension.
  - Risk of systemic hypotension, especially with other vasodilators; avoid combination with nitrates.

II.9.4. DIURETIC MEDICATION

The cornerstone of medical treatment in heart failure with volume overload and pulmonary congestion.

II.9.4.1. Furosemide

- Class: Loop diuretic (inhibits the sodium-potassium-chloride transporter in the thick ascending limb).
- Effects: Marked natriuresis and diuresis; reduces preload, pulmonary, and systemic congestion.
- Uses: Heart failure due to large shunts, LV/RV dysfunction, or postoperative fluid overload.
- Monitoring:
  - Electrolytes (Na^+ , K^+ , Cl^-), renal function, acid-base status.
  - Risk of hypokalemia, hypchloremic metabolic alkalosis, ototoxicity at high doses or with rapid intravenous administration.

II.9.4.2. Thiazides

- Less potent than loop diuretics, but useful in combination for diuretic resistance.
- Acts on the distal convoluted tubule; longer duration of action.
- Risks include hypokalemia and hyponatremia.

II.9.4.3. Potassium-sparing diuretics (spironolactone)

- Mechanism: Aldosterone antagonist; weak diuretic effect, but preserves potassium.
- Uses: Often added to loop diuretics in treatment regimens for chronic heart failure to reduce K^+ loss and counteract RAAS activation.
- Monitoring: Risk of hyperkalemia, especially with ACE inhibitors or renal dysfunction.

II.9.5. DIGITALISATION

Digitalization involves positive inotropic agents, such as digoxin.

- Mechanism: Cardiac glycoside that inhibits Na^+ /K^+ -ATPase → increases intracellular Ca^{2+} → increases contractility; also slows AV node conduction.
- Uses in newborns:
  - Selected cases of systolic heart failure.
  - Rate control in some supraventricular tachyarrhythmias (less preferred in acute cases compared to adenosine and beta-blockers).
- Dosage and safety:

- Requires careful initial and maintenance dosing, based on weight and renal function.
- Narrow therapeutic index; toxicity may cause bradyarrhythmias, AV block, ventricular ectopy, and gastrointestinal symptoms (vomiting, poor appetite).

- Monitoring:
  - Serum levels in cases of prolonged therapy or uncertain renal function.
  - ECG for conduction abnormalities.
  - Serum potassium (hypokalemia predisposes to toxicity).

II.9.6. PROSTAGLANDINS

Prostaglandin $E_1$is the main drug for duct-dependent congenital heart diseases.

- Mechanism: A vasodilator that relaxes the smooth muscle of the ductus arteriosus, maintaining or restoring patency.
- Indications:
  - Suspected duct-dependent systemic circulation (e.g., HLHS, critical coarctation, interrupted aortic arch, critical aortic stenosis).
  - Suspected duct-dependent pulmonary circulation (e.g., pulmonary atresia, critical pulmonary stenosis, some variants of TOF, TGA with restrictive mix).
- Clinical role:
  - Temporary measure to stabilize systemic oxygenation and perfusion until definitive surgery or catheter intervention.
- Adverse effects:
  - Apnea (very common; many infants require intubation and ventilation).
  - Hypotension and facial flushing (due to systemic vasodilation).
  - Fever, irritability.
- Should be initiated early when a duct-dependent lesion is suspected; it is safer to start and stop later than to delay in the case of a collapsed infant. Requires continuous cardiorespiratory monitoring and an environment capable of supporting ventilation.

II.9.7. ANTIARRHYTHMIC MEDICATION

II.9.7.1. Adenosine

- Mechanism: Transient AV nodal block; very short half-life (seconds).
- Indications: Acute termination of AV-node-dependent SVT (e.g., AVRT).
- Administration: Rapid IV bolus followed immediately by saline infusion; ECG monitoring is required.
- Effects: Transient asystole or AV block followed by restoration of sinus rhythm if the pathway is sensitive to adenosine.

II.9.7.2. Beta-blockers (e.g., propranolol)

- Mechanism: Blocks β-adrenergic receptors → reduces heart rate, contractility, and AV node conduction.
- Uses
  - Chronic suppression of SVT.
  - Management of obstructive HCM (reduces the gradient and myocardial oxygen demand).
- Precautions
  - Risk of hypoglycemia in newborns (masks adrenergic symptoms).
  - Use with caution in infants with impaired left ventricular function or bronchospasm.

II.9.7.3. Amiodarone

- Mechanism: Class III antiarrhythmic with multiple effects on channels and receptors; slows conduction and prolongs refractory period.
- Uses:
  - Refractory SVT, uncontrolled by adenosine/beta-blockers.

    - Ventricular tachycardia or fibrillation.
- Risks:
    - Hypotension (IV), bradycardia, QT interval prolongation.
    - Long-term toxicity (thyroid, liver, lungs) is more relevant in elderly patients, but still requires caution and monitoring by a specialist.

II.9.8. CONCLUSIONS. KEY POINTS

In addition to iNO and sildenafil (mentioned above), several cardiac medications indirectly modify pulmonary vascular resistance (PVR). Additionally, certain factors influence PVR, such as:

- Oxygen: Primary pulmonary vasodilator; used in PPHN, but in some duct-dependent lesions, excessive oxygenation may worsen systemic flow by increasing pulmonary shunting.
- CO□ and pH: Hypocapnia and alkalosis decrease PVR; acidosis increases PVR and depresses the myocardium. Ventilator settings and buffer therapy affect hemodynamics.
- Sedation and analgesia: By reducing stress and catecholamines, they can lower PVR and oxygen consumption, particularly in PPHN with cardiac involvement.

Regarding pharmacology in the neonatal period, as well as in infancy, there are certain considerations regarding medication safety and administration. For example:

- Double-check all weight-based calculations and infusion rates; have another physician verify calculations for narrow-range drugs (e.g., PGE□, digoxin, inotropes, antiarrhythmics).
- Renal and hepatic impairment prolong the half-life of medications; consult dosing guidelines for premature or critically ill newborns.
- Always correlate the effects of medications with the clinical response, not just with the numbers:
    - An increase in blood pressure with cold extremities and worsening lactate levels may indicate excessive vasoconstriction.
    - A decrease in heart rate with improved perfusion may be desirable; bradycardia with poor perfusion is not.
- Many cardiac medications can prolong the QT interval or interact to cause arrhythmias; ECG monitoring is crucial when using combinations.

Key points:

- Understand what each class of medication does (inotropes, vasodilators, diuretics, antiarrhythmics) and why they are chosen in specific neonatal cardiac scenarios (e.g., duct-dependent shock, heart failure due to high VSD, PPHN).
- Always think in terms of physiology: preload, afterload, contractility, heart rate, and PVR—and choose or interpret medications accordingly.
- Recognize that some medications (prostaglandin E□, inotropes, ACE inhibitors, digoxin, antiarrhythmics) pose a high risk in newborns and should be used only with continuous monitoring and clear indications.

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III. HEMATOLOGICAL DISEASES

III.1. NEONATAL HEMORRHAGIC DISEASE

III.1.1. DEFINITION

Neonatal hemorrhagic disease (NHD) is a coagulation disorder caused by vitamin K deficiency, manifested by a variable bleeding tendency, ranging from minor bleeding to major hemorrhages. It is due to the inability of the neonatal liver to synthesize, in the absence of vitamin K, coagulation factors II, VII, IX, and X, as well as proteins C and S.

The condition includes three distinct clinical forms:

- Early form (≤24 hours)—the most severe, sometimes associated with maternal medications
- Classic form (2–7 days) — the most common
- Late form (2 weeks–6 months)—often associated with exclusive breastfeeding and liver disease

In the absence of standard vitamin K prophylaxis, hemorrhagic disease is a major cause of neonatal morbidity and mortality.

III.1.2. EPIDEMIOLOGY. INCIDENCE

In countries where vitamin K is administered at birth:

- classic form – <0.01%
- late-onset form – is rare, but carries a high neurological risk
- early form – exceptionally rare

In the absence of prophylaxis:

- the incidence of the classic form can rise to 0.25–1.5%
- the incidence of late-onset forms increases up to 80-fold in the exclusively breastfed population

The incidence is higher in:

- preterm infants
- newborns with liver disease
- those whose mothers received medications that interfere with vitamin K metabolism

Epidemiological note: Breast milk protects the infant in many ways, but contains very little vitamin K.

III.1.3. PATHOPHYSIOLOGY

Vitamin K is necessary for the carboxylation of glutamic residues in factors II, VII, IX, X, and proteins C and S, allowing them to bind to platelet membranes and participate in coagulation cascades.

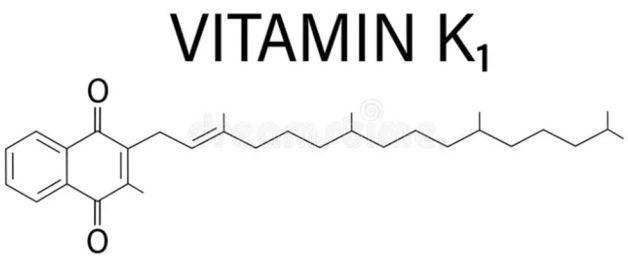

Figure 2. Structure of vitamin K

Why is the newborn vulnerable?

1. Due to reduced placental transfer of vitamin K, the fetus enters extrauterine life with minimal stores.
2. Immature gut flora: the neonatal gut does not yet produce vitamin K2.

3. Low content in breast milk: breast milk has insufficient concentrations of vitamin K to support the synthesis of clotting factors.
4. Immature liver function; production of clotting factors is limited.
5. Maternal medications, such as *anticonvulsants* and *antituberculosis drugs,* increase vitamin K catabolism or interfere with its metabolism.

The final consequence:

- prolonged prothrombin time (PT)
- elevated INR
- major bleeding risk, especially intracranial

Pathophysiological clue: no other type of neonatal hemorrhage resolves as dramatically after vitamin K administration.

III.1.4. RISK FACTORS

Maternal factors:

- treatment with anticonvulsants (phenytoin, carbamazepine)
- rifampicin, isoniazid
- warfarin
- maternal cholestasis

Neonatal factors:

- exclusive breastfeeding
- prematurity
- malabsorption syndromes
- liver diseases (biliary atresia, neonatal hepatitis)
- cystic fibrosis
- NEC or other diseases that reduce fat absorption

Nutritional factors:

- lack of vitamin K prophylaxis
- special formulas without fortification (rare)

III.1.5. CLINICAL DIAGNOSIS

Symptoms depend on the form of the disease:

1. Early form (≤24h)

- massive hemorrhages: intracranial, gastrointestinal, pulmonary
- diffuse ecchymoses
- bleeding at the site of procedures

Occurs mainly in newborns whose mothers received medications that interfere with vitamin K.

2. Classic form (2–7 days)

- umbilical bleeding
- melena
- mucosal hemorrhages
- blood in the stool
- bleeding at the puncture site

3. Late-onset form (2 weeks – 6 months)

- intracranial hemorrhage is the most characteristic
- bulging fontanelle, seizures, irritability
- cholestatic jaundice
- increased risk to life

Clinical hint: A newborn with hemorrhage and cholestatic jaundice has late-onset hemorrhagic disease until proven otherwise.

III.1.6. LABORATORY AND IMAGING STUDIES

Laboratory tests include:

- Elevated INR, often >4
- Prolonged PT (*most sensitive*)
- Normal or variable APTT
- Normal platelets
- Normal fibrinogen

In late-onset bleeding with liver involvement:

- Elevated direct bilirubin
- Elevated GGT
- Elevated transaminases

Additional investigations if intracranial hemorrhage is suspected:

- transfontanellar ultrasound
- CT or MRI

Dramatic response to vitamin K → confirms the diagnosis.

III.1.7. DIFFERENTIAL DIAGNOSIS

To establish a definitive diagnosis, the following conditions must be ruled out:

- hemophilia A/B (normal PT, prolonged APTT)
- severe thrombocytopenia
- neonatal purpura
- coagulopathies due to sepsis
- severe liver disease
- Congenital malabsorption syndromes

Differential diagnosis: a very prolonged PT + rapid response to vitamin K ≠ hemophilia.

III.1.8. MANAGEMENT

A. NON-PHARMACOLOGICAL

Non-pharmacological management of NHD depends on the presentation and involves the following steps:

- hemodynamic stabilization
- temperature maintenance
- respiratory support if bleeding is severe
- management of hemorrhagic shock
- neuroprotection if intracranial hemorrhage is suspected

B. PHARMACOLOGICAL

The main step in the pharmacological management of NHD involves the administration of vitamin K, which is the curative therapy. It is administered intravenously (IV) or intramuscularly (IM) and produces rapid improvement in PT/INR within 2–6 hours. For severe forms of NHD, blood products are used in treatment, such as:

- fresh frozen plasma (FFP) for rapid replenishment
- prothrombin complex concentrate (PCC) in critical situations
- packed red blood cells if severe anemia

In cases involving intracranial hemorrhage, management is intensive, in collaboration with pediatric neurosurgery

C. FOLLOW-UP

Monitoring and prognosis for a patient with NHD depend on:

- coagulation monitoring
- neurological follow-up

- liver function monitoring in late-onset forms
- educating parents on prevention

III.1.9. PROGNOSIS

The prognosis for neonatal hemorrhagic disease varies depending on the form of presentation, namely:

- classic forms – excellent prognosis with pharmacological treatment
- early or late forms carry a significant risk of:
    - intracranial hemorrhage
    - seizures
    - encephalopathy
    - neurodevelopmental sequelae
    - death in untreated forms

Prognostic note: a single dose of vitamin K can prevent the most severe neonatal hemorrhages.

III.2. NEONATAL THROMBOSIS

III.2.1. DEFINITION

Neonatal thrombosis is the formation of an intraluminal thrombus in a venous or arterial vessel during the neonatal period. It most commonly affects central veins (inferior vena cava, renal vein, portal vein) and vessels associated with catheters. It is a rare condition, but one with significant morbidity.

III.2.2. EPIDEMIOLOGY. INCIDENCE

- The actual incidence is underestimated because many cases are asymptomatic.
- Most thromboses are associated with central venous catheters.
- Increased risk in preterm infants and critically ill newborns in the intensive care unit.
- Renal vein thrombosis is the most common "non-catheter" thrombosis in newborns.

III.2.3. PATHOPHYSIOLOGY

Neonatal thrombosis occurs due to a combination of factors characteristic of this age group:

A. Imbalance between procoagulation and anticoagulation

The neonatal coagulation system is immature:

- low levels of antithrombin
- reduced protein C and S
- limited fibrinolytic activity

These characteristics facilitate thrombus formation under conditions of biological stress.

B. Local triggering factor

Most common: venous or arterial catheters → microtrauma to the vascular wall → thrombus nucleus.

C. Associated systemic conditions

- Sepsis
- Polycythemia
- Dehydration
- Hypoxia
- Acidosis
- Major surgery
- Massive transfusion

D. Hereditary thrombophilias

Less commonly diagnosed in the neonatal period, but can contribute significantly.

III.2.4. RISK FACTORS

- Prematurity
- central venous catheter (CVC, CAVC)
- severe sepsis
- perinatal hypoxia
- dehydration
- polycythemia
- maternal or familial thrombophilia
- cardiac or abdominal surgery

Hint: Thrombosis in the newborn is almost always secondary to a systemic stress condition or an invasive device.

III.2.5. CLINICAL DIAGNOSIS

Clinical manifestations depend on the location.

1. Renal vein thrombosis
- Hematuria
- Unilateral palpable abdominal mass
- Thrombocytopenia
- Variable hypertension
2. Vena cava or umbilical vein thrombosis
- lower limb edema
- Cyanosis or local congestion
- dilatation of subcutaneous veins
- Low tissue perfusion
3. Portal vein thrombosis
- Hepatomegaly
- abdominal distension
- late-onset risk of portal hypertension
4. Arterial thrombosis (catheter-related)
- sudden pallor of the limb
- distal cooling
- Absent pulse
- Risk of peripheral necrosis
5. Systemic forms
- Irritability
- Hemodynamic instability
- oliguria in severe forms

Clinical hint: any acute change in limb perfusion in a child with a catheter = thrombosis until proven otherwise.

III.2.6. LABORATORY AND IMAGING STUDIES

Paraclinical investigations are classified into laboratory tests and imaging studies. Additionally, thrombophilia screening is indicated in recurrent cases or those with a significant family history.
Laboratory tests:

- complete blood count (possible consumptive thrombocytopenia)
- CRP / procalcitonin (if sepsis is suspected)
- coagulation tests
- renal function in renal vein thrombosis
- assessment of hydration status

Imaging studies:

- Doppler ultrasound—the imaging modality of choice, allowing visualization of the thrombus, its extent, and blood flow.
- CT or MRI for deep locations (rare, reserved for severe cases)

Clinical tip: Ultrasound is sufficient in most cases; advanced investigations are performed only if management changes based on the results.

III.2.7. DIFFERENTIAL DIAGNOSIS

In cases of neonatal thrombosis, a differential diagnosis should be considered with the following conditions:

- neonatal compartment syndrome
- post-traumatic lymphostasis
- severe cellulitis or fasciitis
- heart failure with dependent edema
- severe renal diseases with hematuria not due to thrombosis

III.2.8. MANAGEMENT

Management requires a balanced approach: preventing thrombus extension vs. the hemorrhagic risk of anticoagulation.

A. NON-PHARMACOLOGICAL

- catheter removal if possible
- Proper positioning of the affected limb
- maintain temperature and fluid balance
- Monitoring of urine output and cardiorespiratory status
- correction of dehydration
- treating sepsis, hypoxia, or acidosis

B. PHARMACOLOGICAL

1. Unfractionated heparin – used in acute situations, with close monitoring of aPTT
2. Low-molecular-weight heparin (LMWH)

- subcutaneous administration
- anti-Xa monitoring
- frequently used in newborns due to its more stable profile

3. Antithrombin III

- Rarely indicated, in cases of severe deficiency or inadequate response to heparin

4. Thrombolysis

- reserved for critical situations (severe limb ischemia, massive thrombosis)
- major bleeding risk → decision made by a multidisciplinary team

Therapeutic tip: Newborns have a high risk of bleeding. Anticoagulation is strictly indicated in clinically significant thromboses or those at risk of spreading.

C. FOLLOW-UP

- Serial Doppler monitoring (at 48–72 h, then periodically)
- adjustment of heparin/LMWH doses based on anti-Xa levels
- assessment of renal function in renal thrombosis
- Monitoring for signs of portal hypertension in portal vein thrombosis
- Follow-up in pediatric hematology if associated thrombophilia

III.2.9. PROGNOSIS

Depends on location:

- Renal vein thrombosis: risk of unilateral renal atrophy, late-onset hypertension
- Portal vein thrombosis: risk of late-onset portal hypertension, esophageal varices
- Arterial thrombosis: risk of limb ischemia and necrosis if diagnosis is delayed
- Catheter-related thromboses: good prognosis if treated early

III.3. NEONATAL THROMBOCYTOPENIA

III.3.1. DEFINITION

Neonatal thrombocytopenia is defined as a platelet count below 150,000/µL, commonly encountered in the neonatal period, with major clinical significance when counts fall below 50,000/µL or in the presence of hemorrhagic manifestations. It results from an imbalance between platelet production, consumption, and destruction, and causes range from maternal diseases to severe fetal and neonatal pathologies.

III.3.2. EPIDEMIOLOGY. INCIDENCE

- It affects 1–5% of newborns.
- In preterm infants and those in intensive care, the incidence rises to 20–35%.
- Severe forms (<50,000/µL) account for approximately 5% of cases but are responsible for most complications.

The temporal distribution guides the diagnosis:

- <72 hours = maternal-fetal, placental, or early infectious causes
- >72 hours = sepsis, NEC, fungal infections, hematologic diseases

Epidemiological hint: any critically ill preterm infant has the potential for consumption-related thrombocytopenia.

III.3.3. PATHOPHYSIOLOGY

The main pathophysiological mechanisms are:

1. Decreased platelet production

Occurs when the bone marrow is unable to produce platelets adequately:

- intrauterine infections (TORCH)
- maternal preeclampsia (placental hypoperfusion → bone marrow hypoplasia)
- severe intrauterine malnutrition
- genetic disorders of megakaryopoiesis

2. Increased platelet consumption

The most common neonatal mechanism:

- bacterial sepsis
- necrotizing enterocolitis (NEC)
- DIC (disseminated intravascular coagulation)
- severe perinatal hypoxia
- massive hemorrhage

3. Immunological destruction

- Alloimmune thrombocytopenia (FNAIT)

The mother produces antibodies against fetal platelet antigens → severe fetal destruction.

  - Typical presentation: platelets <30,000/µL in an otherwise healthy newborn

- Maternal autoimmune thrombocytopenia

The mother's IgG antibodies with ITP cross the placenta.

4. Splenic sequestration

Rare in the neonatal period, but present in severe liver diseases and infiltrative syndromes.

III.3.4. RISK FACTORS

- prematurity
- sepsis, systemic infections
- placental pathology (preeclampsia, reduced uteroplacental blood flow)
- NEC
- polycythemia + hemodilution

- maternal autoimmune diseases
- TORCH infections
- severe hypoxia
- massive transfusion without platelet supplementation

Hint: In the first hours of life, consider "maternal causes"; after 3 days, consider "consumption + sepsis."

III.3.5. CLINICAL DIAGNOSIS

Manifestations vary depending on severity and mechanism.

1. Cutaneous and mucosal signs
- petechiae, purpura, ecchymoses
- bleeding at puncture sites
- epistaxis
2. Internal bleeding
- gastrointestinal bleeding
- pulmonary hemorrhage
- intracranial hemorrhage (maximum risk at <30,000/μL)
3. Indirect signs of the etiology
- severe jaundice → hemolysis + consumption
- hepatosplenomegaly → congenital infection
- respiratory distress → sepsis
- tender abdomen → NEC

Important observations:

- An apparently healthy infant with platelet counts <30,000/μL suggests alloimmune thrombocytopenia.
- Thrombocytopenia associated with hypothermia, apnea, and acidosis indicates acute consumption.

III.3.6. LABORATORY AND IMAGING STUDIES

Paraclinical investigations are classified into laboratory tests and imaging studies.

Laboratory tests:

1. Complete blood count
- confirms thrombocytopenia
- associated anemia → hemorrhage or sepsis
- leukocytosis / leukopenia → infection
2. Peripheral blood smear
- small or giant platelets → etiological clues
- schistocytes → DIC
- abnormal cells → leukemic infiltration (rare)
3. Coagulogram
- PT, INR, aPTT
- fibrinogen
- fibrin degradation products
4. Etiological investigations
- cultures (sepsis)
- TORCH test (congenital infections)
- anti-HPA antibodies (alloimmunity)
- liver function (cholestatic hepatitis)

Imaging studies:

1. Transfontanellar ultrasound

- mandatory in platelets <30,000/µL for hemorrhagic screening

Clinical hint: in preterm infants, severe thrombocytopenia with elevated CRP is sepsis until proven otherwise.

III.3.7. DIFFERENTIAL DIAGNOSIS

- neonatal purpura fulminans
- hemophilia (normal platelet count)
- von Willebrand disease type 3 (rare)
- sepsis with DIC
- bone marrow production defects (megablastic, aplastic)
- chromosomal syndromes with bone marrow abnormalities

III.3.8. MANAGEMENT

Management depends on severity and cause.

1. Non-pharmacological

- monitoring of vital signs
- Avoid unnecessary punctures
- Avoid maneuvers that predispose to bleeding
- gentle care (preemies are vulnerable)
- brain ultrasound screening at values <50,000/µL

2. Pharmacological

1. Platelet transfusion

Typical indications:

- <30,000/µL regardless of symptoms
- <50,000/µL in extremely vulnerable preterm infants
- <100,000/µL in active bleeding or surgery

2. IVIG (immunoglobulins)

Useful in:

- alloimmune thrombocytopenia
- severe maternal autoimmune thrombocytopenia
- inhibits immune-mediated platelet destruction

3. Antibiotics / antifungals

In cases of sepsis or fungal infections.

4. Treatment of the underlying disease

- correction of acidosis
- treatment of NEC
- treatment of liver or cholestatic diseases

Therapeutic tip: Thrombocytopenia of unknown etiology should not be treated aggressively if platelet counts are >50,000/µL and the child is stable.

3. Follow-up

- Serial blood counts (daily in severe cases)
- Serial brain ultrasound
- monitoring of response to IVIG
- Late-stage screening in immunological cases
- Hematologic evaluation if symptoms persist for >2 weeks

III.3.9. PROGNOSIS

The prognosis depends on the etiology:

- transient forms (maternal preeclampsia, prematurity): excellent
- sepsis/NEC: guarded, high risk of hemorrhage

- severe alloimmunization: risk of intracranial hemorrhage
- DIC: associated with high mortality

In the long term, most cases of neonatal thrombocytopenia resolve without sequelae.
Prognostic hint: platelet count alone is NOT sufficient; the clinical context dictates the actual severity.

III.4. NEONATAL ANEMIA

III.4.1. DEFINITION

Neonatal anemia is defined as a decrease in hemoglobin levels below the normal range for gestational age and postnatal age. Normal values are higher at birth than later on, due to the fetus's oxygen requirements and the increased concentration of fetal hemoglobin. Neonatal anemia results from three main mechanisms:

- Blood loss (acute or chronic)
- Insufficient erythrocyte production
- Hemolysis (immune or non-immune)
  This classification allows for rapid orientation in clinical diagnosis.

III.4.2. EPIDEMIOLOGY. INCIDENCE

- Anemia is common in preterm infants, especially in the first weeks of life.
- Premature infant anemia ("anemia of prematurity") is nearly universal in births <32 weeks.
- Term newborns may develop anemia in the context of perinatal hemorrhage or immunological hemolysis (ABO, Rh).
- Severe anemia (<10 g/dL at birth) is rare but associated with major pathologies (fetomaternal hemorrhage, placenta previa, twin-to-twin transfusion).

Epidemiological note: acute hemorrhage is the main cause of severe anemia in term infants; reduced erythropoiesis is the main cause in preterm infants.

III.4.3. PATHOPHYSIOLOGY

The main pathophysiological mechanisms are:

1. Blood loss

This may be:

- Antenatal: fetal-maternal hemorrhage, twin-to-twin transfusion in twin pregnancies, vasa previa rupture
- Intrapartum: placental abruption, placental rupture, obstetric trauma
- Postnatal: visceral hemorrhage (splenic, hepatic), hemorrhage during circumcision, pulmonary hemorrhage, intracranial hemorrhage

Consequence: rapid decrease in circulating volume → shock + acute anemia.

2. Insufficient production (low erythropoiesis)

Characteristic of preterm infants. Causes:

- low erythropoietin levels
- immature bone marrow response
- iron deficiency (reduced stores in preterm infants)
- congenital infections (CMV, toxoplasmosis, measles)
- rare genetic disorders (congenital aplastic anemias, Diamond–Blackfan syndrome)

This form causes progressive anemia, without jaundice or signs of hemolysis.

3. Hemolysis

It can be:

a. Immune
   - Rh isoimmunization
   - ABO isoimmunization
   - Maternal autoimmune antibodies (maternal autoimmune disease)

b. Non-immune
    - G6PD deficiency
    - rare hemoglobinopathies
    - severe infections (sepsis)
    - membrane syndromes (spherocytosis, ovalocytosis)

Hemolysis causes anemia + jaundice, sometimes severe.

III.4.4. RISK FACTORS

- prematurity
- Rh or ABO incompatibility
- monochorionic twin pregnancies
- placental complications
- severe sepsis
- maternal iron deficiency
- congenital infections
- obstetric trauma
- frequent blood draws in preterm infants

Clinical hint: The high number of daily blood tests is one of the major causes of iatrogenic anemia in neonatal intensive care units.

III.4.5. CLINICAL DIAGNOSIS

Symptoms vary depending on the severity of the anemia and the speed of its onset.

1. Acute (hemorrhagic) anemia

Rapid onset with:

- marked pallor
- tachycardia
- weak pulse
- hypotension
- respiratory distress
- low peripheral perfusion
- shock (in cases of major bleeding)

2. Progressive anemia (low production)

- Mild pallor
- moderate tachycardia
- apnea, bradycardia in preterm infants
- difficult feeding
- poor growth
- low exercise tolerance (feeding)

3. Hemolytic anemia

- early or severe jaundice
- Hepatosplenomegaly
- dark-colored urine
- Anemia + elevated indirect bilirubin

Clinical hint: jaundice + hepatosplenomegaly = hemolysis until proven otherwise.

III.4.6. LABORATORY AND IMAGING STUDIES

Paraclinical investigations are classified into laboratory tests and imaging studies.
Laboratory tests:

1. Complete blood count

- Low Hb

- MCV depending on etiology
- Elevated reticulocytes in hemolysis, decreased in reduced production

2. Reticulocytes
- Elevated values → hemolysis
- Low values → production problem / hypoplasia

3. Total and fractionated bilirubin
- increases in hemolysis
- normal in anemia due to reduced production

4. Direct Coombs test
- positive → immune hemolysis
- negative → non-immune or other mechanism

5. Iron, ferritin, transferrin saturation
- iron deficiency in preterm infants
- normal values in hemolytic anemias

6. Hemoglobin electrophoresis
- suspected hemoglobinopathy

7. G6PD test
- in enzyme deficiency

8. Kleihauer-Betke test
- suspected fetal-maternal hemorrhage

Imaging studies:

1. transfontanellar ultrasound if hemorrhage is suspected

III.4.7. DIFFERENTIAL DIAGNOSIS

- hemolytic disease of the newborn
- congenital infections
- hidden hemorrhages (splenic, hepatic, intracranial)
- liver failure
- hereditary spherocytosis
- iatrogenic dilute polycythemia
- anemia due to excessive blood draws

III.4.8. MANAGEMENT

Treatment is specific to the etiological mechanism.

A. Non-pharmacological
- Hemodynamic stabilization
- Prevention of further blood loss
- reduction in the number of blood draws (use of microtubes in preterm infants)
- monitoring of vital signs
- respiratory support if anemia is severe

B. Pharmacological

1. Red blood cell transfusions

Typical indications:
- Hb <8 g/dL with symptoms (at term)
- Hb <10 g/dL in preterm infants with respiratory instability
- Hb <12 g/dL in preterm infants on mechanical ventilation
- Acute hemorrhage

The transfusion must be precisely calculated and administered slowly.

2. Treatment of hemolysis
- IV immunoglobulin in severe immune hemolysis

- phototherapy for associated hyperbilirubinemia
- exchange transfusion in selected cases

3. Treatment of production deficiency

- oral iron (preterm infants, after stabilization)
- erythropoietin in selected situations (preterm infants requiring frequent transfusions)

Therapeutic tip: In preterm infants, transfusion is indicated not only based on Hb levels, but also on respiratory and cardiorespiratory tolerance.

C. Follow-up

- monitoring of blood counts
- assessment of iron stores
- neurological follow-up if bleeding has occurred
- Re-evaluation after treatment of congenital infections

III.4.9. PROGNOSIS

Depends on the etiology:

- anemias due to low production have a good prognosis with iron supplementation
- immune hemolysis has a favorable prognosis if treated promptly
- severe acute hemorrhages may leave neurological sequelae
- extremely premature infants are at high risk for chronic anemia and increased need for transfusions

III.5. NEONATAL POLYCYTHEMIA

III.5.1. DEFINITION

Neonatal polycythemia is defined as a hematocrit >65% or hemoglobin >22 g/dL in a venous blood sample. When an increased hematocrit leads to increased blood viscosity with impaired microvascular flow, we refer to hyperviscosity syndrome, a condition associated with neurological, respiratory, metabolic, and gastrointestinal impairment. Polycythemia is not merely a "high hemoglobin level," but a problem of microcirculatory hemodynamics that affects tissue perfusion.

III.5.2. EPIDEMIOLOGY. INCIDENCE

- Incidence in full-term newborns: 0.5–2%.
- More common in certain populations: diabetic pregnancies, post-term pregnancies, small for gestational age (SGA), twins.
- Preterm infants have a lower risk but may develop polycythemia in the context of transfusion or endocrine disorders.

Polycythemia is clinically relevant because it can compromise cerebral, renal, and intestinal perfusion.

III.5.3. PATHOPHYSIOLOGY

Neonatal polycythemia arises through one of three fundamental mechanisms:

1. Excessive blood transfer to the newborn

- delayed cord clamping (controversial, usually beneficial if properly managed)
- Uterine compression of the cord
- reverse feto-maternal transfusion
- Feto-fetal transfusion (in twins, the "recipient" twin → polycythemia)

This mechanism causes polycythemia with normal or increased plasma volume.

2. Increased erythrocyte production (primary or secondary polycythemia)

Common cause: chronic intrauterine hypoxia → increased erythropoietin stimulation.
Associated conditions:

- maternal diabetes

- placental insufficiency (preeclampsia, SGA)
- maternal smoking
- high altitude
- cyanotic congenital heart defects (rarely detected postnatally)
- congenital adrenal hyperplasia
- maternal hyperthyroidism

Small for gestational age (SGA) infants are most commonly affected.

3. Hemoconcentration

Occurs due to:

- dehydration
- increased insensible losses
- inadequate intake

In this case, the red blood cell volume is normal, but plasma volume is low.
Pathophysiological hint: true polycythemia = increased red blood cell volume; hemoconcentration = low plasma volume. Clinical manifestations may be similar.

III.5.4. RISK FACTORS

- gestational or pre-existing diabetes
- placental insufficiency
- post-term pregnancy
- monochorionic twins (feto-fetal transfusion)
- maternal smoking
- neonatal hypothermia with severe vasoconstriction
- dehydration
- uncontrolled delayed clamping
- increased erythropoiesis due to chronic hypoxia

SGA newborn + diabetic mother = the classic risk combination for polycythemia.

III.5.5. CLINICAL DIAGNOSIS

The manifestations are a consequence of hyperviscosity, not the red blood cell count itself.

1. Neurological symptoms – reduced cerebral blood flow explains these symptoms.

- lethargy
- Irritability
- tremor
- seizures
- hypotonia
- feeding difficulties

2. Respiratory signs

- tachypnea
- respiratory distress
- peripheral cyanosis
- episodes of apnea

3. Cardiovascular signs

- tachycardia
- slowed peripheral perfusion
- persistent acrocyanosis

4. Metabolic manifestations

- hypoglycemia (very common)
- hypocalcemia
- hyperbilirubinemia (due to increased erythrocyte turnover)

5. Gastrointestinal manifestations
- vomiting
- difficulty feeding
- increased risk of NEC (necrotizing enterocolitis) due to intestinal ischemia
6. Hematological signs
- Hematocrit >65% in venous blood sample
- Blood appears visibly more viscous ("thick") upon collection

Clinical hint: any infant with recurrent hypoglycemia + peripheral cyanosis should be tested for polycythemia.

III.5.6. LABORATORY AND IMAGING STUDIES

Paraclinical investigations are classified into laboratory tests and imaging studies.
Laboratory tests:

1. Venous hematocrit
- The diagnostic standard.
- Capillary hematocrit overestimates values and should not be used for therapeutic decision-making.
2. Blood glucose
- Hypoglycemia is very common.
3. Bilirubin, calcium, blood gases
- For the evaluation of secondary complications.

Imaging studies:

1. Brain and abdominal ultrasound
- Indicated if neurological or digestive disorders occur.

III.5.7. DIFFERENTIAL DIAGNOSIS

- severe neonatal hypoxia without polycythemia
- Pure dehydration (normalized Hct after rehydration)
- congenital heart disease
- neonatal sepsis
- primary familial erythrocytosis (very rare)

III.5.8. MANAGEMENT

Treatment depends on severity, symptoms, and progression.

A. Non-pharmacological
- monitoring blood glucose
- correction of hypoglycemia
- parenteral hydration (increases plasma volume and reduces viscosity)
- prevention of hypothermia
- frequent small feedings if the infant tolerates them

Metabolic stabilization is the first step.

B. Pharmacological / Procedural

1. Intravenous hydration
- An isotonic solution is used to dilute Hct in moderate cases.
2. Partial hemodilution (hTP)
- Typical indication:
    - Hct >70% with symptoms
    - Hct 65–70% + signs of hypoperfusion, recurrent hypoglycemia, or distress

In PHD, a portion of the child's blood is replaced with isotonic solution to reduce viscosity. The procedure reduces the risk of NEC, hypoglycemia, and neurological complications.

C. Follow-up
- reassess hematocrit in 6–12 hours

- 24-hour blood glucose monitoring
- Neurological assessment
- Bilirubin monitoring for jaundice
- Follow-up for neurological complications if severe symptoms were present

III.5.9. PROGNOSIS

Most cases resolve within the first 24–72 hours.
Potential complications:

- severe hypoglycemia → neurological risk
- NEC
- thrombosis
- neurological impairment in untreated cases
- severe hyperbilirubinemia

The prognosis is excellent if intervention is early.
Prognostic clue: symptoms, not hematocrit levels, determine the actual severity.

III.6. BLOOD PRODUCTS USED IN NEONATAL PATHOLOGY

III.6.1. DEFINITION

Blood products used in the neonatal period are components derived from human blood, processed to correct specific hematological deficiencies: anemia, thrombocytopenia, coagulopathies, or massive hemorrhage. Their use requires careful evaluation, as the newborn—especially the preterm infant—has a unique physiology, a small blood volume, and increased sensitivity to overcorrection, hypervolemia, and adverse reactions. The goal of using blood products is to optimize tissue oxygenation, restore hemostasis, and reduce the risk of hemorrhagic complications.

III.6.2. MAIN TYPES OF BLOOD PRODUCTS USED IN THE NEONATAL PERIOD

The following are among the blood products used in the neonatal period:

- Red blood cell (RBC) concentrate
- Platelets (platelet concentrates)
- Fresh frozen plasma (FFP)
- Cryoprecipitate
- Immunoglobulins (in hemolysis or autoimmune/alloimmune thrombocytopenia)
- Albumin (rarely used; not a volume replacement transfusion product in hemorrhage)

Each product has specific indications for newborns, which are very different from those for adults.

III.6.3. RED BLOOD CELL MASS

1. Indications

Red blood cell concentrate transfusion is used for:

- acute anemia with hemodynamic instability
- severe symptomatic anemia
- Anemia in premature infants with respiratory distress
- massive hemorrhages (postpartum hemorrhage, pulmonary hemorrhage, intracranial hemorrhage)
- fetal-maternal hemorrhage
- severe immune hemolysis (in combination with exchange transfusion, when necessary)

2. Administration guidelines

- Administer slowly over 2–3 hours
- The volume is calculated strictly per kilogram
- ABO and Rh compatibility is mandatory

- Leukoreduction is standard to reduce the risk of infection
- Continuous monitoring of temperature, pulse, and infusion

3. Risks

- Circulatory overload
- hyperkalemia
- febrile reactions
- hemolysis if the product is incompatible
- hypothermia if not warmed properly

Note: In ventilated preterm infants, transfusion is performed conservatively, for respiratory stability, not for isolated numerical values.

III.6.4. PLATELET CONCENTRATE

1. Indications

- platelet count <30,000/µL (regardless of symptoms)
- <50,000/µL in critically ill preterm infants, sepsis, NEC
- <100,000/µL in active bleeding or prior to surgical procedures
- severe alloimmune thrombocytopenia
- forms of DIC with accelerated consumption

Newborns, especially preterm infants, are at risk of intracranial hemorrhage, which is why transfusion thresholds are higher than in older children or adults.

2. Principles of administration

- Administer a transfusion at a calculated low volume per kg
- ABO compatibility
- Monitoring for transfusion reactions

3. Risks

- Allergic reactions
- alloimmunization
- transmission of infection (very rare)
- hypervolemia

Note: The platelet response is often temporary in sepsis or NEC, as consumption remains active.

III.6.5. FRESH-FROZEN PLASMA

1. Actual indications

FFP is not a volume expander and should not be used routinely.
The correct indications are:

- coagulopathy with bleeding
- congenital coagulation factor deficiency
- DIC
- after massive transfusion
- correction of severely elevated INR if associated bleeding is present

2. Incorrect indications (to be avoided)

- hypoalbuminemia
- poor nutrition
- prophylaxis of coagulopathy without bleeding

3. Risks

- Hypervolemia
- allergic reactions
- hyperammonemia
- infections (extremely rare in the era of modern screening)

Note: FFP is administered only for significant coagulopathy, not for “correcting” an isolated INR.

III.6.6. CRYOPRECIPITATE

Crioprecipitate provides fibrinogen, factor VIII, vWF, and factor XIII.

1. Indications

- fibrinogen deficiency (<100 mg/dL)
- congenital hypofibrinogenemia
- severe DIC
- massive bleeding with decreased fibrinogen

2. Administration

- The dose is calculated based on fibrinogen levels and body weight
- Administer slowly, while monitoring temperature and vital signs

3. Risks

- Allergic reactions
- minimal risk of infection
- Hypervolemia, especially in premature infants

III.6.7. IMMUNOGLOBULINS

1. Major indications in neonatology

- severe immune hemolysis (Rh isoimmunization, severe ABO)
- alloimmune thrombocytopenia
- severe autoimmune thrombocytopenia
- certain congenital viral infections (rare, selected cases)

Immunoglobulins act by reducing the destruction of blood cells coated with antibodies.

2. Administration and precautions

- slow infusion
- monitoring for adverse reactions (fever, hypotension, irritability)
- assessment of renal function in fragile newborns

III.6.8. HUMAN ALBUMIN

Albumin is NOT a product used for the treatment of bleeding or anemia.
It may be indicated in:

- severe hypoalbuminemia with refractory edema
- congenital nephrotic syndrome
- massive protein loss

It has no role in:

- correction of hypotension
- treatment of jaundice
- treatment of NEC

Tip: For volume replacement after hemorrhage, use packed red blood cells and fresh frozen plasma, not albumin.

III.6.9. GENERAL PRINCIPLES OF TRANSFUSION IN NEWBORNS

The general principles of blood product transfusion in newborns include the following:

1. Calculating volumes per kilogram

Neonatal blood volume is small (80–90 mL/kg), so any error can result in hypervolemia or hypovolemia.

2. Continuous monitoring

- pulse
- blood pressure
- oxygen saturation
- peripheral perfusion

- temperature
- blood glucose

3. Proper warming of blood products

To prevent hypothermia and bradycardia.

4. Avoiding unnecessary transfusions

Newborns, especially preterm infants, are vulnerable to overtreatment.

5. ABO and Rh compatibility always verified
6. Post-transfusion monitoring
    - Re-evaluation of complete blood count and coagulation profile
    - Blood glucose monitoring
    - clinical assessment of peripheral perfusion
    - screening for delayed reactions within the first 24 hours
    - reassessment of the need for additional treatment (RBC, platelets, FFP)

Alongside the general principles of transfusion are the general risks associated with blood products, such as:

- febrile reactions
- allergic reactions
- infections (very rare with modern screening)
- hypervolemia
- electrolyte imbalances (hyperkalemia, hypocalcemia)
- air embolism (in case of improper administration)
- hemodynamic compromise during rapid infusion
- transmission of maternal antibodies via plasma (rare, but possible)

III.6.10. CONCLUSIONS

The use of blood products in neonatology is a major intervention that requires:

- clear indication
- precise calculation
- compliance with compatibility requirements
- continuous monitoring
- close collaboration between the neonatologist, the laboratory physician, and the transfusion medicine physician

Final tip: In newborns, the decision to transfuse is a delicate balancing act—insufficient transfusion can be dangerous, but excessive transfusion is equally risky.

III.7. SPINAL TAP AND BONE MARROW ASPIRATION

III.7.1. DEFINITION

Bone marrow aspiration and bone marrow biopsy are diagnostic procedures used to obtain bone marrow material for the evaluation of hematopoietic production, cellular morphology, and pathological infiltration. They are essential in the diagnosis of hyporegenerative anemias, h , severe unexplained thrombocytopenias, and suspected congenital leukemia. In newborns, these procedures are performed only when the information obtained influences management, given their invasiveness and the limited blood volume.

III.7.2. INDICATIONS. CONTRAINDICATIONS

The actual indications are limited but important:

1. Persistent abnormalities in the blood count

- severe hyporegenerative anemia
- pancytopenia
- severe neutropenia of unknown cause

2. Suspected infiltrative disease
- congenital leukemia (rare but serious)
- metastatic infiltrations
- Congenital myeloproliferative syndromes

3. Suspected severe congenital infection
- CMV, toxoplasmosis, rubella with hematopoietic involvement
- post-infectious aplastic anemia (rare in newborns)

4. Suspected genetic disorders
- Congenital aplastic anemias (Diamond–Blackfan)
- syndromes with abnormal megakaryopoiesis
- disorders of hematopoietic stem cells

5. Neoplasms
- neuroblastoma with bone marrow metastases
- congenital myelodysplasias

Note: Most cases of neonatal thrombocytopenia and anemia do NOT require a bone marrow aspiration; the procedure is reserved for persistent, severe, or unexplained cases.

The procedure should be avoided if a diagnosis can be obtained through other laboratory tests. It is also very important to note the situations in which the procedure is not indicated, namely:

- transient thrombocytopenia in preterm infants
- thrombocytopenia due to sepsis or NEC (consumption, not production)
- hemolytic anemia (increased production, not decreased)
- anemia due to acute hemorrhage
- iron deficiency anemia in preterm infants (clinical diagnosis + ferritin)

III.7.3. PROCEDURAL STEPS

1. Practical anatomy relevant to the neonatologist

Common puncture sites in newborns:

- proximal tibia (the most commonly used site in preterm infants → safe access)
- distal femur
- anterior iliac crest (in older or term newborns)

Rationale:

- flat bones are small and more difficult to access
- the tibia and femur have active, accessible bone marrow with a low risk of complications

2. Preparation for the procedure

Clinical evaluation and technical preparation are required to prepare the patient for the procedure.

A. Clinical evaluation – the following are checked:
- hemodynamic stability
- risk of bleeding
- platelet count
- coagulation profile

If the platelet count is <50,000/μL, the procedure is performed only after a transfusion.

B. Technical preparation
- adequate analgesia (local anesthesia + minimal analgosedation as needed)
- rigorous antisepsis
- Stable positioning
- preparation for potential complications (bleeding, vagal bradycardia)

In extremely premature infants, attention to thermoregulation is critical.

3. Procedure technique (conceptual)

A. Spinal puncture
- insertion of the needle into the bone cortex

- advancement into the spinal canal
- gentle aspiration to obtain bone marrow
- rapid collection (coagulation occurs very rapidly in newborns)

B. Bone marrow aspiration

The following are obtained:

- spinal fluid smear
- material for immunophenotyping (in cases of suspected neoplasms)
- possibly culture (in rare cases of suspected infection)

C. Bone marrow biopsy

Very rare in the neonatal period due to small bone size. It is indicated only in cases of major suspicion of congenital bone marrow aplasia.

4. Post-procedural monitoring

- Light pressure on the puncture site for 5–10 minutes
- Monitor vital signs every 15 minutes for 1–2 hours
- Assessment for local hematoma
- Check blood count as needed
- interpretation of the bone marrow results together with the pediatric hematologist

Tip: In newborns, aspiration is usually sufficient; biopsy is almost always avoided.

III.7.4. SPECIFIC PATHOLOGICAL ASPECTS. COMPLICATIONS.

The following are among the particular pathological aspects in newborns:

1. Reduced megakaryopoiesis

- aplastic thrombocytopenia
- congenital infections
- rare genetic syndromes

2. Impaired erythropoiesis

- hyporegenerative anemias
- transient aplasias

3. Tumor infiltration

- Congenital leukemia (blasts)
- metastases (neuroblastoma)
- Hemophagocytic infiltration

4. Reactive changes

- severe sepsis
- systemic inflammation
- post-hemorrhagic recovery

Complications are rare if the technique is correct, but include:

1. Local bleeding – especially in severe thrombocytopenia or coagulopathies.
2. Infection – very rare with proper antisepsis.
3. Fracture – extremely rare in preterm infants if the proper technique is used.
4. Vagal reaction – bradycardia, apnea, pallor; requires discontinuation of the procedure and stabilization.
5. Failure to obtain bone marrow – bone sclerosis or improper technique → repeat at a different site.

Tip: the major risk is hemorrhage; checking platelet counts is essential.

III.7.5. CONCLUSIONS

Interpretation of results must take into account the characteristics of neonatal bone marrow:

- neonatal hypercellularity is physiological
- the myelo-erythroid ratio differs from that of adults
- the presence of precursors is normal

- fragments may be small due to the reduced volume

The final diagnosis is always integrated with clinical manifestations. Bone marrow aspiration in newborns is a valuable procedure, but it must be used under strict criteria. It plays a decisive role in the diagnosis of aplastic anemias, unexplained severe thrombocytopenias, and congenital leukemias. When performed correctly, with proper preparation and careful assessment of hemorrhagic risk, it is a safe and informative procedure.

Final tip: order a bone marrow aspiration only if the result changes the management plan.

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IV. PATHOLOGY OF THE DIGESTIVE SYSTEM

IV.1. GENERAL CONCEPTS OF EMBRYOLOGY

The formation of the digestive system begins very early, as early as the 3rd week of intrauterine life, along with the process of embryonic folding. At this stage, the primitive intestinal tube begins to take shape from the endoderm (one of the three main embryonic layers).

The digestive tract initially has a simple structure: a cylinder closed at both ends, separated from the outside by two thin membranes:

- **the buccopharyngeal membrane**—at the cranial end (toward the head),
- **the cloacal membrane** – at the caudal end (toward the future anus).

These membranes will later rupture, forming the oral and anal openings.

The primitive intestinal tube originates from a portion of the yolk sac that remains inside the embryo after it folds. The portion that remains outside the embryo's body remains connected to the intestine via a small channel called the umbilical duct.

Even at this early stage, the primitive intestinal tube can be divided into three main regions:

1. **The anterior intestine/proenteron** – from which the esophagus, stomach, first part of the duodenum, liver, pancreas, and bile ducts form.
2. **The middle intestine/mesenteron** – this will give rise to the rest of the duodenum, the entire small intestine, and part of the colon.
3. **Posterior intestine/metenteron** – this will form the rest of the colon, the rectum, and part of the urinary tract.

In addition to the endodermal layer (from which the mucosa and glands of the digestive tract develop), the surrounding mesoderm plays an essential role in the formation of the smooth muscles and supporting tissues of the future digestive system. The endoderm forms the epithelium that lines the inside (mucosa) of the digestive tract and also gives rise to specific glandular cells (parenchyma), such as hepatocytes and the exocrine and endocrine cells of the pancreas. The glandular stroma (glandular connective tissue) and the muscular, connective, and peritoneal components of the intestinal wall are formed from the splanchnic mesoderm.

Thus, as early as the end of the 3rd week and the beginning of the 4th week of embryonic development, the foundation of the digestive system takes shape, which will subsequently undergo complex and specialized transformations.

1. The anterior intestine/proenteron

The proenteron gives rise to the esophagus, the stomach, the duodenal segment located proximal to the opening of the bile duct, and the buds of the trachea and lungs. The liver, pancreas, and biliary system develop as evaginations of the endodermal epithelium corresponding to the upper portion of the duodenum. Since the upper portion of the anterior intestine is divided by a septum (the tracheoesophageal septum) into the esophagus (located posteriorly) and the buds of the trachea and lungs (located anteriorly), deviations of this septum can lead to the formation of abnormal connections between the trachea and the esophagus.

A. Esophagus

In the 4th week, the respiratory diverticulum appears in the anterior intestine, separated from the esophagus by the tracheoesophageal septum. The esophagus elongates as the neck and thoracic organs develop, with the epithelium evolving from simple to stratified and then to stratified squamous, with temporary cilia, until they are replaced by stratified squamous epithelium before birth. The surrounding mesenchyme forms esophageal glands and musculature: circular and longitudinal, striated in the upper third (innervated by the vagus nerve) and smooth in the lower third (innervated by the splanchnic plexus).

Abnormalities in esophageal development:

- Congenital atresia or obliteration—occurs due to the failure of the epithelial plug to resorb and is often accompanied by tracheoesophageal fistulas, preventing amniotic fluid from entering the fetal digestive tract and causing polyhydramnios.

- Esophageal stenosis—is congenital in nature and leads to the expulsion of ingested food through vomiting.
- Short esophagus—does not extend below the diaphragm and is associated with a partially thoracic stomach.
- Esophageal diverticula—result from abnormal separation of the pulmonary bud from the esophagus.

B. The stomach

The stomach begins to develop in the 4th week, as a spindle-shaped dilation of the anterior intestine, with cranial and caudal ends. Its shape and position change due to uneven wall growth, a 90° clockwise rotation (left side anterior, right side posterior), and the adjustment of the positions of neighboring organs. This rotation alters the vagal innervation and forms the greater and lesser curvatures. The cephalic and caudal terminal segments shift: the pylorus moves to the right and upward, the cardia to the left and downward, orienting the final gastric axis from the upper left to the lower right.

The rotation and enlargement of the stomach alter the mesogastrium: the omental bursa and greater omentum form dorsally, while the lesser omentum and falciform ligament develop anteriorly and ventrally. The spleen arises from the dorsal mesogastric mesoderm, and the pancreas, initially located in the dorsal mesoduodenum, becomes retroperitoneal through the fusion of the mesogastrium with the posterior wall. The greater and lesser omentum, associated ligaments, and the portal triad form from these structures, creating connections between the stomach, liver, duodenum, and peritoneal cavity ( ). The final position of the stomach allows for passive distension and efficient contractions during digestion.

Developmental abnormalities of the stomach

- Congenital bilocular stomach—results from uneven development of the circular muscle layer.
- Gastroschisis—characterized by a defect in the abdominal wall, usually on the right side and more common in boys, in which the organs are exposed and submerged in amniotic fluid.
- Stomach inversion—occurs as part of a general inversion of the viscera, known as *situs inversus*.
- Thoracic stomach—is due to a descent anomaly and a short esophagus, characterized by the positioning of the cardia in the posterior mediastinum of the thorax.
- Congenital pyloric atresia or stenosis, including congenital hydropic stenosis—is caused by excessive hypertrophy of the pyloric sphincter and usually manifests after birth.

C. Omental bursa

The omental bursa is a virtual space located behind the stomach, whose position is not affected by the stomach's rotation. Around the fourth week of development, small slit-like spaces appear between the cells of the dorsal mesogastric mesoderm, which subsequently merge to form a larger space—the primordium of the omental bursa.

This cavity extends transversely to the left and reaches posterior to the stomach. A cranial extension, initially called the infracardiac bursa, originates from it; its development is halted by the formation of the diaphragm. In rare cases, remnants of this bursa may persist into adulthood. The lower part of this cranial extension forms the superior recess of the omental bursa.

As the stomach develops and rotates to the right, the dorsal mesogastrium moves to the left. This change causes the omental bursa to deepen and the inferior recess to form, which extends caudally in the form of a sac. In the final fetal months, this sac covers the transverse colon and the small intestinal loop. After birth, the two layers of the sac fuse, forming a continuous structure—the greater omentum—where adipose tissue accumulates throughout life. Due to this fusion, the inferior recess is reduced in size in adults.

The greater omentum, through its posterior portion, covers the transverse mesocolon and eventually fuses with it.

The omental bursa remains in communication with the peritoneal cavity through a narrow, slit-like opening called the foramen epiploicum. This is located beneath the free edge of the hepatoduodenal ligament, a component of the lesser omentum.

D. Spleen

The spleen is a lymphoid organ that warrants study due to its relationship with the mesenteries. The splenic primordium appears at the end of the fourth week, in the mesenchyme, between the two layers of the dorsal mesogastrium, in front of the dorsal pancreatic bud. It grows rapidly, and by the second month, the initially wide connection with the dorsal mesogastrium narrows, remaining only at the level of the splenic hilum. The spleen remains an intraperitoneal organ and, upon completion of development, attaches to the posterior abdominal wall, being connected to it by the splenorenal ligament. Anteriorly, it joins the stomach via the gastrolienal ligament. Its blood supply comes from the branches of the splenic artery, a branch of the celiac trunk, located in the dorsal mesogastrium.

The spleen's final form takes shape during the third month of fetal life. In the fourth month, reticular tissue differentiates within the spleen, whose mesh is populated by lymphocytes. By the sixth month, these cells organize into lymphatic nodules of the white pulp. Also during the third and fourth months, the mesenchyme of the dorsal mesogastrium forms the splenic capsule and the internal trabeculae.

By the beginning of the seventh month, the spleen acquires a hematopoietic function. The differentiation between the white pulp and the red pulp is not fully complete until after birth.

Abnormalities in spleen development:

- Incomplete fusion of the primary lobes
- Presence of accessory spleens.

E. Duodenum

The duodenum forms from the intestinal segment that develops immediately after the pylorus, initially being included in the transverse septum. Its origin is dual: the terminal part of the anterior intestine and the cephalic part of the middle intestine. The junction between the two segments lies immediately distal to the origin of the hepatic bud. This dual origin also explains the different vascularization: the cranial half is supplied by branches of the celiac trunk, and the caudal half by branches of the superior mesenteric artery.

As the stomach rotates to the right, the duodenum undergoes the same rotation, taking on the shape of a "C"-shaped loop. The rapid growth of the pancreatic head contributes to the displacement of the duodenum from the midline to the left side of the abdominal cavity. Subsequently, the head of the pancreas and the duodenum come into contact with the dorsal wall, and the right surface of the dorsal mesoduodenum fuses with the adjacent peritoneum. The peritoneal layers disappear, and the duodenum and pancreas assume a retroperitoneal position. The dorsal mesoduodenum disappears almost completely, except for the pyloric region, where a small segment—the duodenal bulb—retains its mesentery and remains intraperitoneal. In the second month, the duodenal lumen is temporarily obliterated by the proliferation of the parietal epithelium, but it soon reopens. In the fourth month, the duodenal glands appear (as a result of epithelial differentiation), and in the sixth month, Kerckring's circular folds form. Due to its mixed origin, the duodenum has dual blood supply: cranial—from the celiac artery, and caudal—from the superior mesenteric artery.

Developmental anomalies of the duodenum

- Duodenal stenosis—occurs when the process of recanalization of the digestive tract is incomplete. It most commonly affects the horizontal and ascending portions of the duodenum. Clinically, it manifests in newborns as vomiting of bile.
- Duodenal atresia – results from the complete obliteration of the descending and horizontal segments of the duodenum, located distal to the opening of the common bile duct.

F. Liver and Biliary Tract

The hepatic parenchyma is formed from the endodermal cells of the lower end of the foregut. In this region, at the level of the ventral wall, a well-defined hepatic area appears in the third week, forming a small depression called the hepatic fossa. From this area, the following differentiate:

- a larger cranial portion—the hepatic lobe, from which the liver develops;
- a smaller caudal portion—the cystic part, from which the gallbladder and bile ducts arise.

In the middle of the third week, the hepatic diverticulum (hepatic bud) forms from the endodermal epithelium of the distal anterior intestine. Its cells proliferate rapidly and penetrate the transverse

septum, a mesodermal structure that separates the pericardial cavity from the yolk sac stalk. The connection between the diverticulum and the anterior intestine (the future duodenum) narrows and becomes the bile duct. A small ventral evagination emerges from the bile duct, which will give rise to the gallbladder and the cystic duct. Starting in the fourth month, the liver begins to secrete bile, which reaches the intestine via the bile ducts. Hepatic cells form epithelial cords that interweave with the yolk and umbilical veins, resulting in hepatic sinusoids. From these cords, hepatocytes (liver parenchyma) and the epithelial cells lining the bile ducts differentiate. Kupffer cells, hematopoietic cells, and connective tissue cells originate from the mesoderm of the transverse septum.

As the liver grows and invades the transverse septum, it becomes prominent toward the abdominal cavity. The portions of mesoderm between the liver and the duodenum, and between the liver and the anterior abdominal wall, respectively, transform into the lesser omentum and the falciform ligament. Together, these form the ventral mesentery, which connects the proenteron to the anterior abdominal wall. The mesoderm on the surface of the liver differentiates into the visceral peritoneum, with the exception of the cranial portion, which is in direct contact with the transverse septum. This region will constitute the fixed part of the liver (pars affixa). The compact portion of the transverse septum becomes the central tendon of the diaphragm.

By the 10th week, the liver accounts for approximately 10% of fetal weight, due to its abundance of sinusoids and its hematopoietic role. Between the hepatocytes and the vascular walls are numerous hematopoietic cells, responsible for the formation of white and red blood cells. This activity gradually decreases during the last two months of pregnancy, so that by birth only small hematopoietic islands remain. The weight of the liver decreases to approximately 5% of body weight.

Starting in the 12th week, hepatocytes secrete bile, which reaches the intestine via the common bile duct (formed by the union of the hepatic duct and the cystic duct). The gastrointestinal tract then takes on a dark green color. The opening of the bile duct migrates from its initial anterior position to the posterior part of the duodenum as the duodenum rotates.

Developmental abnormalities of the liver and biliary tract

- Abnormalities in lobulation and fissuring may occur during liver development. Thus, in the right lobe, an extension called Riedel's lobe may persist after birth.
- Additionally, accessory hepatic ducts may be present, into which the cystic duct may open.
- Following temporary obliteration of the bile ducts, atresia of the extrahepatic bile ducts may occur.
- A bifid or double gallbladder forms when the gallbladder bud divides partially or completely.

G. The pancreas

The pancreas is present in all vertebrates except bony fish. In the fifth week of development, it appears at the transition between the foregut and midgut, in the form of two endodermal buds: the larger dorsal bud, located in the dorsal mesentery, and the smaller ventral bud, situated near the bile duct. The C-shaped rotation of the duodenum causes the ventral bud to shift dorsally, so that it is positioned immediately inferior and posterior to the dorsal bud. The parenchyma and ductal systems of the two buds fuse, forming the definitive pancreas. The dorsal bud gives rise to the body and tail of the pancreas, as well as the cranial part of the head, while the ventral bud forms the caudal part of the head and the uncinate process.

In the seventh week, the two pancreatic primordia fuse, which alters the position and mode of drainage of the biliary and pancreatic ducts into the duodenum. The unified pancreas is initially located in the primitive dorsal mesentery, covered by the peritoneum on both sides. Subsequently, through the rotations of the stomach and duodenum, the pancreas becomes parallel to the posterior abdominal wall and fuses with it, thus becoming retroperitoneal. The main pancreatic duct (Wirsung) forms from the distal segment of the dorsal pancreatic duct and the ventral pancreatic duct. The proximal portion of the dorsal duct may be obliterated or persist as an accessory pancreatic duct (Santorini). The main pancreatic duct and the bile duct open into the duodenal at the level of the major duodenal papilla, and the accessory duct, if present, opens at the minor duodenal papilla. In approximately 10% of cases, the two ductal systems do not fuse, resulting in a double ductal system.

During the third month of fetal life, pancreatic islets (Langerhans islets) develop from the pancreatic parenchyma and are distributed diffusely. Their origin has recently been attributed to neural crest cells. Insulin secretion begins around the fifth month, and glucagon- and somatostatin-secreting cells also form from the parenchymal cells. The pancreatic connective tissue develops from the splanchnic mesoderm surrounding the pancreatic buds.

Developmental abnormalities of the pancreas

- An annular pancreas occurs when the ventral pancreatic bud does not migrate properly and remains anterior to the duodenum. In this situation, together with the dorsal bud, it encircles the duodenum, which can lead to duodenal stenosis up to complete obstruction. This malformation is more common in males.
- Sometimes, the pancreatic bud may migrate along with the hepatic bud, resulting in a pancreatic nodule or cystic structure near the gallbladder.
- Additionally, masses of ectopic pancreatic tissue may appear in the walls of the stomach, the intestine, or in relation to the spleen, a phenomenon known as an aberrant pancreas.

2. The midgut/mesentery

The midgut gives rise to the lower part of the duodenum, the jejunum, the ileum, the cecum, the vermiform appendix, the ascending colon, and the right half of the transverse colon, all of which are supplied by branches of the superior mesenteric artery. Its development involves major changes in shape and position, including the formation of the umbilical loop and its physiological detachment.

By the end of the fifth week, the mesenteron is suspended from the dorsal abdominal wall by a short mesentery and communicates with the yolk sac via the yolk duct. In adults, the midgut begins immediately distal to the entry of the bile duct into the duodenum and ends at the junction between the two proximal thirds and the distal third of the transverse colon. By the end of the first month, the umbilical loop undergoes a 90° counterclockwise rotation, placing the cranial arm on the right and the caudal arm on the left. Subsequently, the right arm of the loop elongates and forms several loops, followed by the left arm. The limited space in the trunk cavity, due to the rapid development of the primitive liver and kidneys, causes the intestine to protrude into the umbilical cord. Rotation continues clockwise to 270–300°, and the cecum initially migrates superiorly, then to the right beneath the liver, reaching the right iliac fossa. The formation of the loops establishes the segments of the large intestine.

Starting in the tenth week, the intestinal loops in the umbilical cord retract into the abdominal cavity, and the appendix forms at the distal end of the cecum. It is not until the seventh and eighth months that the appendix becomes clearly distinct from the cecum and can form its own loops. Thus, the development of the midgut involves the rapid elongation of the intestinal tube and mesentery, the formation of the primary intestinal loop, and the separation of the cephalic and caudal segments: the cephalic segment gives rise to the distal portion of the duodenum, the jejunum, and part of the ileum, while the caudal segment forms the lower ileum, the cecum, the appendix, the ascending colon, and the proximal two-thirds of the transverse colon.

A. Physiological hernia

The rapid elongation of the intestinal loops, especially the cephalic segment, and the rapid development of the liver temporarily reduce the space in the abdominal cavity. Thus, in the sixth week, the intestinal loops enter the extraembryonic cavity through the umbilical cord, a phenomenon called physiological umbilical hernia.

As the primary intestinal loop elongates, it rotates counterclockwise around the superior mesenteric artery, completing 270° by the end. The jejunum and ileum form multiple loops, while the large intestine elongates but does not twist. Rotation occurs both during the physiological hernia (approx. 90°) and during the reentry of the loops into the abdominal cavity (the remaining 180°).

By the tenth week, regression of the mesonephric kidney, slowing of liver growth, and expansion of the abdominal cavity allow the herniated intestinal loops to retract. The proximal portion of the jejunum, located on the left side, returns first, followed by the remaining loops, which move progressively to the right. The cecal primordium, which initially appeared as a small conical dilation of the caudal segment of the loops in the sixth week, is temporarily located in the right upper quadrant, beneath the hepatic lobe, and then descends into the right iliac fossa, positioning the ascending colon

and the hepatic flexure on the right side of the abdominal cavity. The distal end of the cecum forms the appendix, which, as it develops during the descent of the colon, reaches a retrocecal or retrocolic position.

Developmental abnormalities of the intestines

- Meckel's diverticulum appears on the antimesenteric margin of the ileum and may contain gastric or pancreatic tissue, which, through its secretions, can cause ulcerations and hemorrhages.
- Failure of the abdominal wall to form can lead to herniation of the viscera, which remain covered only by the amnion and peritoneum.
- Also, if the processes of intestinal migration and coalescence are not completed, the intestines remain free and suspended by a loose mesentery, which can cause them to twist (complete or incomplete volvulus) or form an internal hernia.

B. **Mesenteries**

Mesenteries are bands that attach internal organs, containing nerves, blood vessels, and lymphatic vessels, formed from two serous layers separated by connective tissue.

- **The mesentery of the primary intestinal loops** undergoes rotations and transformations during development: the dorsal mesentery twists around the superior mesenteric artery, the ascending and descending colon become retroperitoneal, and the appendix, inferior cecum, and sigmoid colon retain their free mesentery.
- **The transverse mesocolon** remains mobile, partially fusing with the greater omentum, and peritoneal recesses form in areas of incomplete insertion (e.g., the duodenal, ileocecal, and intersigmoid recesses).
- **The jejuno-ileal mesentery** acquires a new insertion from the intraperitoneal duodenum to the ileocecal junction. The mesogastrium and ventral mesoduodenum form the covering of the liver, with the area of the liver's surface representing the zone of direct contact with the diaphragm. The rotation of the stomach and intestines positions the liver to the right and the pancreas to the left.
- **The primitive dorsal mesentery** divides into the mesoesophagus, mesogastrium, dorsal mesoduodenum, and common dorsal mesentery, which attaches the jejunum, ileum, colon, and rectum to the posterior wall.

3. Posterior Intestine/Metenteron

The posterior intestine extends from the midgut to the cloacal membrane and is supplied by the inferior mesenteric artery. The flared lower end forms part of the cloaca, into which the primitive renal ducts drain.

The metenteron gives rise to the distal third of the transverse colon, the descending colon, the sigmoid colon, the rectum, and the upper portion of the anal canal, while the endoderm of the posterior intestine forms the mucosa of the bladder and urethra. The terminal portion extends into the posterior region of the cloaca (primitive anorectal canal), and the allantois into the anterior portion (primitive urogenital sinus). The cloaca is lined by the endoderm and covered ventrally by the ectoderm, and the cloacal membrane forms at the junction of the two layers.

The urogenital septum, formed from the mesoderm covering the yolk sac and surrounding the allantois, separates the two regions. As the embryo develops, caudal folding brings the tip of the septum closer to the cloacal membrane, but does not allow them to come into contact. By the end of the seventh week, the cloacal membrane perforates, forming the anal orifice and the ventral orifice of the urogenital sinus, and between them the urogenital septum forms the perineal body. The ectoderm proliferates, temporarily closing the caudal region of the anal canal, which reopens in the ninth week.

Blood supply to the anal canal: the caudal (ectodermal) segment is supplied by the inferior rectal arteries, and the cranial (endodermal) segment by the superior rectal artery, a continuation of the inferior mesenteric artery. At the junction between the two regions lies the pectineal line, which separates the cylindrical c e epithelium of the rectum from the stratified squamous epithelium of the anal canal, located immediately below the anal columns (Morgagni). Abnormalities in the size of the posterior cloaca can displace the anterior anal orifice, causing rectovaginal and rectourethral fistulas or atresias.

Anomalies of the mid and posterior intestine

These include nonrotation and malrotation of the intestine, situs inversus, duplication of intestinal segments, as well as congenital volvulus (twisting of the loops). Persistence of the vitelline duct manifests as Meckel's diverticulum, which may sometimes communicate via a fistula with the umbilical region.

Stenoses and atresias may occur in the large intestine. A more specific anomaly is congenital megacolon, caused by the absence of the intramural nerve plexus (Auerbach's plexus). Anal imperforation occurs when the cloacal membrane is not resorbed, and in some cases, rectal atresia is also present.

Self-assessment questions

1. From which embryonic layer does the intestinal epithelium originate?
2. What is the consequence of failed intestinal rotation?
3. When does physiological herniation occur?
4. What gives rise to the enteric nervous system?
5. Which neonatal pathology results from duodenal atresia?

IV.2. GENERAL CONCEPTS OF ANATOMY

The fetal digestive tract is a system in continuous development that must adapt rapidly in the immediate postnatal period to meet the nutritional and metabolic needs of extrauterine life.

1. Embryonic and Fetal Development

The formation of the digestive organs begins early, around the 3rd–4th week of gestation, and by 16–20 weeks, most components of the digestive tract exhibit incipient functional activity. At this stage:

- the sucking reflex develops,
- the salivary glands begin to produce and secrete saliva containing amylase,
- the stomach secretes pepsinogen,
- the intestine produces secretin, and swallowing amniotic fluid contributes to the formation of meconium.

During the intrauterine period, the fetus does not actively feed but receives the necessary nutrients through the placental circulation. However, the daily passage of amniotic fluid (approximately 300 ml–1 liter in a full-term fetus) represents a form of functional stimulation of the intestine. e amniotic fluid contains immunoglobulins, enzymes, growth factors, and hormones, and the fetal intestinal mucosa is capable of absorbing some of these proteins, which contributes to its maturation.

2. Structural and Functional Maturation

Although the gastrointestinal tract is fully formed morphologically around the 20th week of gestation, many functions do not mature until after 34 weeks. Consequently, the preterm newborn exhibits significant limitations in digestive function.

Even in full-term newborns, functional maturation continues postnatally; for example, pancreatic exocrine function does not reach full development until late childhood.

Some gastrointestinal functions can be initiated immediately after birth, regardless of gestational age, such as intestinal permeability. Others, however, are genetically programmed to emerge at specific postconception ages, such as the suck-swallow coordination, which develops between 33 and 36 weeks.

Fetal gastrointestinal motility follows a predictable sequence of onset:

- Swallowing – begins at 16 weeks of gestation;
- Sucking – appears around 24 weeks;
- Suck-swallow coordination – between 33–36 weeks;
- Gastric emptying – begins at 20 weeks, but is delayed in the first 12 hours after birth (in both preterm and full-term infants);
- Small intestine peristalsis – active from 16 weeks, with motor function maturing at approximately 34 weeks.

In premature infants, the intestinal muscular layer and the enteric nervous system are immature, which leads to:

- slowed intestinal transit (approximately 9 hours at 32 weeks, compared to 4 hours at 40 weeks),
- the presence of antiperistaltic waves,
- decreased secretion of intestinal hormones.

The maturation of intestinal motility can be promoted by:

- antenatal administration of corticosteroids,
- early initiation of low-calorie enteral feeding ("enteral priming").

Conversely, it may be delayed by:

- theophylline or caffeine administered to the preterm infant,
- magnesium administered to the mother during the perinatal period.

3. Postnatal adaptation

After birth, the digestive tract must transition from placental parenteral nutrition to enteral digestion and absorption. Despite the anatomical and functional dysfunctions of the preterm infant, early and gradual initiation of enteral feeding is recommended to stimulate the functional development of the digestive system. As the infant grows, the digestive organs continue to mature, and dietary diversification reflects the evolution of the gastrointestinal tract's physiological capabilities.

A. The Oral Cavity and Salivary Glands in the Newborn

The newborn's oral cavity is relatively small and adapted primarily for sucking. The maxillary alveolar processes are short and immature, and teeth are absent at birth. The hard palate is wide and flat, while the soft palate is oriented nearly horizontally, facilitating coordination between sucking and breathing.

The oral mucosa is delicate, thin, dry, and highly vascularized, with a bright red color. Bohn's epithelial nodules can be observed along the midlines, as well as mucosal folds and villi on the lower gingival surface, representing normal transitional structures. In some cases, whitish deposits may appear on the palatal mucosa, caused by Candida albicans, a condition known as candidal stomatitis.

The cheeks and lips are relatively thick and prominent due to the Bichat fat pads, which help maintain the shape of the cheeks and create the negative pressure necessary for sucking. The lips have a characteristic transverse striation, which facilitates latching onto the nipple during feeding.

B. Tongue

The newborn's tongue is large, wide, and short, with well-developed musculature. This structure allows for efficient movement during sucking, compressing the nipple and ensuring the milk is directed toward the oropharynx.

In newborns, the sucking and swallowing reflexes are well-developed from birth, being essential for survival. The act of sucking includes three main phases:

1. Sucking on the nipple and creating negative pressure in the oral cavity;
2. Compression of the nipple between the tongue and palate, with milk expression;
3. Swallowing the drawn-in milk.

During suckling, aerophagia (swallowing air) may occur, which subsequently manifests as:

- burping – the release of air after feeding;
- regurgitation – the expulsion of a small amount of unaltered milk along with air.

Anatomical features that facilitate efficient suckling include:

- transverse striations on the lips;
- gum swellings corresponding to the future canine teeth;
- Bichat fat pads;
- a voluminous and well-vascularized tongue;
- a horizontal soft palate, which prevents aspiration.

C. Salivary glands

At birth, the major salivary glands (parotid, submandibular, and sublingual) are morphologically formed but functionally immature. Saliva secretion is low or even absent in the first weeks of life, which explains the dryness of the oral mucosa and the predisposition to fissures and inflammation.

One of the causes of this inflammation is the absence of lysozyme in the salivary secretion, an enzyme with an antibacterial role. Hyposalivation in the first few months is due to the incomplete development of the central nervous system and the small size of the salivary glands.

Around 3–4 months of age, salivary secretion increases significantly, as the nerve centers mature and the trigeminal nerve (the fifth cranial nerve) becomes stimulated, as well as in response to irritation caused by developing tooth buds.

This increase in secretion causes physiological sialorrhea—the profuse salivation frequently observed between 3 and 5 months of age, when the infant is not yet able to swallow the entire volume of saliva. The parotid gland, although anatomically present at birth, intensifies its development and activity starting in the third to fourth month of life, contributing to the increase in total saliva volume.

Disorders of salivary secretion:

- Hyposalivation may occur in children with nutritional disorders, febrile states, dehydration, or diarrhea.
- Pathological hypersalivation is observed in stomatitis, conditions with swallowing disorders (retropharyngeal abscesses, epiglottitis, esophageal stenosis), as well as in brain lesions, encephalitis, or brainstem tumors.

Saliva plays multiple roles in postnatal digestive adaptation:

- it moistens the oral mucosa, facilitating sucking and swallowing;
- it contains salivary amylase (ptyalin), which plays a role in the initial digestion of starch;
- it has antibacterial action (via lysozyme and secretory IgA);
- it contributes to the development of taste and the maturation of the oral mucosa.

D. The Esophagus

The esophagus is the first part of the digestive tract proper, responsible for transporting the bolus from the pharynx to the stomach. It is a tubular organ whose length and structure vary with the child's age. In newborns, the esophagus is well-developed, shaped like a double funnel—widened at both the upper and lower ends—which facilitates the flow of milk into the stomach.

The length of the esophagus increases progressively with age:

Age	**Length of the esophagus**
Newborn	10–11 cm
1 year	12 cm
5 years	16 cm
10 years	18 cm
Teen	20–25 cm
Adult	25–32 cm

Another formula used to estimate length is Bischof's formula:

Esophageal length (cm) $= \frac{1}{5} \times$ height (cm) + 63

In newbornsand infants, the esophagus has a narrow lumen (0.8–0.9 cm at 2 months, 1.2–1.5 cm at 9–18 months) and extends from the C6 vertebra (at the level of the lower margin of the cricoid cartilage) to the cardia—the opening into the stomach, located at the level of the T11 vertebra.

Anatomically, three segments are distinguished:

- Cervical, located posterior to the trachea;
- Thoracic, located in the posterior mediastinum;
- Abdominal, short, before joining the stomach.

The esophagus has three physiological narrowings:

1. The cricoid constriction—at the beginning of the esophagus;
2. The bronchoaortic constriction – where the esophagus is compressed by the aorta and the left main bronchus;
3. The diaphragmatic constriction – located at the passage through the esophageal hiatus.

The wall of the esophagus consists of four layers:

1. The mucosa – lined with stratified squamous epithelium, resistant to mechanical trauma; at the terminal portion, it transitions into a single-layered columnar epithelium, a transition marked by the Z-line (visible endoscopically).

2. Submucosa – rich in elastic fibers and tubulo-alveolar glands that secrete mucus, facilitating the passage of the bolus.
3. Muscular layer – composed of an inner layer of circular fibers and an outer layer of longitudinal fibers; in newborns, the musculature is poorly developed, which explains the reduced propulsive forces and the tendency toward regurgitation.
4. Outer layer (adventitia) – composed of loose connective tissue, continuing into the mediastinal tissue.

The esophagus is richly innervated, with:

- Intrinsic innervation, provided by the Auerbach's myenteric plexus, located between the two muscle layers and responsible for coordinating peristaltic contractions;
- Extrinsic innervation, consisting of:
    - the vagal parasympathetic nerve, which stimulates peristalsis and relaxes the lower esophageal sphincter (LES);
    - the thoracic sympathetic nervous system, which inhibits peristalsis and causes the LES to contract.

The main function of the esophagus is swallowing, a complex reflex process by which the bolus is transported from the oral cavity to the stomach. Swallowing comprises three successive stages:

1. Oral phase – passage of the bolus through the oropharyngeal isthmus (≈0.3 seconds);
2. Pharyngeal phase – passage through the pharynx (≈0.2 seconds);
3. Esophageal phase – transport through the esophagus (≈6–7 seconds in adults).

In newborns and infants, the duration of liquid food passage through the esophagus is much shorter (0.5–1.5 seconds), due to the narrow lumen and rapid relaxation of the lower esophageal sphincter. However, the reduced tone of the LES allows gastric contents to reflux into the esophagus, explaining the frequent physiological regurgitations in the first months of life.

The transport of the bolus is ensured by:

- primary peristaltic waves, triggered by the act of swallowing and propagating along the entire length of the esophagus;
- secondary peristaltic waves, independent of swallowing, occurring in response to esophageal distension or the presence of local irritants.

These waves ensure esophageal clearance and prevent gastroesophageal reflux.

Cardia closure and reflux prevention are ensured by several factors:

- the abdominal segment of the esophagus, with positive intra-abdominal pressure;
- the Hiss angle, an acute angle between the esophagus and the stomach which, if it becomes obtuse, promotes reflux;
- the tone of the lower esophageal sphincter, regulated by neurohormonal control.

Clinical and functional aspects

- Physiological regurgitation is common in infants, due to the functional immaturity of the LES and the increased volume of liquid food.
- Motility disorders may occur in premature infants or those with neurological impairment, manifesting as dysphagia, aspiration, or gastroesophageal reflux.
- With age, neuromuscular maturation of the esophagus leads to efficient coordination of peristalsis and increased propulsive forces.

E. The Stomach

The stomach is a hollow organ located in the supramesocolic region of the peritoneal cavity, occupying the epigastric region and the left hypochondrium. Anatomically, it is situated between the xiphoid process and the umbilicus, adjacent to the liver on the right and the spleen on the left. The position of the stomach varies with the child's age and development: in the newborn, it is arranged horizontally; in the infant, it becomes slightly oblique; and after the age of 7–8 years, it assumes the vertical position characteristic of adults. When full, the stomach is cylindrical or slightly oval in shape. The cardia is located on the left side at the level of the 10th thoracic vertebra, and the pylorus projects onto the midline corresponding to the 12th thoracic vertebra.

The volume of the stomach increases progressively with age. In newborns, the physiological volume is approximately 7 ml, and the anatomical volume is 30–35 ml. By the 4th day of life, stomach capacity reaches 40–45 ml, and by the 10th day it rises to about 80 ml, increasing approximately 11-fold from the initial volume. During the first year of life, gastric volume increases by approximately 25–30 ml per month, reaching 250–300 ml by age one. At older ages, stomach capacity is as follows:

- 3–5 years: 500 ml
- 8–10 years: 1000–1200 ml
- 12–15 years: 1300–1500 ml

According to Filatov's formula, stomach volume up to 1 year of age can be calculated as follows: **V = 30 ml + 30 × n**, where *n* represents age in months.

Knowing the gastric volume is of practical importance in performing gastric lavage and in determining the optimal amount of food to be administered to infants.

Topographically, four regions are described:

1. the cardiac portion,
2. the fundus of the stomach,
3. the gastric body,
4. the antral-pyloric region.

The gastric wall consists of four layers, arranged from the inside out: the mucosa, submucosa, muscular layer, and serosa.

The stomach lining in newborns is relatively thick and well-vascularized, but poor in elastic and muscle tissue. The mucosal fold at the entrance to the stomach does not fully develop until 8–9 months of age. The gastric canal is well-defined. The gastric folds allow the stomach to adapt to the volume of ingested food—when full, they flatten, and when the stomach is empty, they rise again.

The gastric mucosal epithelium is a single layer, composed of columnar cells that secrete mucins, which protect against the action of hydrochloric acid. The lamina propria contains three types of gastric glands:

1. Cardiac glands—located around the cardia, covering an area of 2–3 cm; they secrete neutral mucins.
2. Fundic glands – distributed throughout the body and fundus of the stomach; they contain four types of cells:
    - *Mucous/parietal cells* – secrete hydrochloric acid, water, and electrolytes;
    - *Main cells* – secrete pepsinogen, the precursor of pepsin;
    - *Endocrine cells* – A cells (glucagon), D cells (somatostatin), D1 cells (intestinal vasoactive polypeptide);
    - *Chromaffin cells* – secrete motilin, histamine, and kallikrein.
3. Pyloric glands – located in the antrum-pylorus region; they contain exocrine cells that secrete neutral mucins and endocrine cells, particularly G cells (gastrin) and D cells (somatostatin).

Gastric mucus, secreted by epithelial cells and mucous glands, has an alkaline pH and acts as a protective barrier against the acidic action of gastric juice. It consists of acidic and neutral glycoproteins, whose negative electrical charge contributes to the formation of the mucosal barrier.

The submucosa contains loose connective tissue, elastic fibers, and a nerve plexus (Meissner). The muscularis layer consists of three layers:

1. longitudinal (outer),
2. circular (middle),
3. oblique (inner).

At birth, the oblique layer is poorly developed, but its thickness and fiber density triple during the first months of life. The circular layer, especially in the pyloric region, is well developed and forms a strong sphincter—the pyloric sphincter. In contrast, the cardiac sphincter is underdeveloped in young children, which explains the predisposition to regurgitation and postprandial vomiting. The serous layer is represented by the visceral peritoneum, which completely covers the stomach.

The stomach is supplied by branches of the celiac trunk—the gastric coronary artery, the right and left gastro-epiploic arteries, the pyloric artery, and the short gastric vessels. The veins of the stomach drain into the portal system.

The stomach's innervation is provided by the autonomic nervous system:

- *Parasympathetic* – via the vagus nerves, which stimulate gastric secretion and motility;
- *Sympathetic* – via the solar plexus, which inhibits gastric secretion and contractility.

The gastric glands secrete gastric juice, consisting of water (99.4%) and organic and inorganic substances—hydrochloric acid, pepsinogen, mucus, and electrolytes. The daily volume of gastric juice is 2–3 liters in adults, but much lower in children. In newborns, secretion is constant, approximately 1 ml/kg/hour, and by the age of 1–2 years, it reaches 2–3 ml/kg/hour.

The acidity of gastric juice is approximately 0.5 g% HCl, with a pH of 2.5–5, depending on the type of diet. In breastfed infants, acidity is lower (pH 4.5–3.8), gradually increasing with age and reaching values of 2–2.5 in older children.

Acid secretion is controlled by nervous and hormonal factors and occurs in three phases:

- Cephalic phase – initiated by visual, olfactory, and gustatory stimuli; accounts for approximately 50% of postprandial secretion;
- Gastric phase – triggered by the presence of food in the stomach; regulated reflexively and humoral via gastrin;
- Intestinal phase – occurs upon contact of gastric chyme with the duodenal mucosa; stimulates the release of gastrin and secretin.

Secretin, glucagon, and the gastrointestinal inhibitory polypeptide exert inhibitory effects on gastric secretion. Pepsinogen, secreted by chief cells, is converted to pepsin at an optimal pH of 1.5–2, where it exerts its maximum proteolytic activity.

The motor function of the stomach is relatively immature at birth. It includes three main processes: relaxation, contraction, and gastric emptying. Relaxation predominates in the proximal region, allowing the stomach to adapt to the volume of food, while peristaltic contractions are more intense in the distal region, facilitating the fragmentation and propulsion of the contents toward the duodenum.

The emptying of food from the stomach depends on its consistency and type. In the case of natural feeding, breast milk is digested in approximately 2 hours, while cow's milk (formula) takes 3–4 hours. In infants, gastric juice accounts for approximately 10–15% of the volume of ingested milk, while in formula-fed infants this proportion increases to 35%, due to more abundant secretion and higher acidity.

F. The Liver and Bile Ducts

The liver is the body's largest parenchymal organ, located in the supramesocolic region of the abdominal cavity, within the subdiaphragmatic and thoracoabdominal hepatic fossa. In newborns, the liver accounts for approximately 4% of body weight (approx. 120–150 g) and occupies nearly half of the abdominal cavity, highlighting its vital metabolic role from the very first days of life. Liver growth is progressive: by age two, it doubles in weight; by age three, it triples; and by puberty, it can reach ten times its initial weight.

The lower margin of the liver in a newborn is palpable 2–3 cm below the costal margin, and from 1 to 3 years of age, approximately 1.5 cm below. After the age of 3, under physiological conditions, the liver is no longer palpable. The liver is divided into two main lobes, the right and left, and has two surfaces: the diaphragmatic (superior) and the visceral (inferior). On the visceral surface, the quadrate lobe and the caudate lobe are distinguishable, as well as impressions for the neighboring organs: the stomach, the right colon, the duodenal flexure, the right adrenal gland, and the right kidney. Glisson's capsule, a subperitoneal fibrous capsule, follows the course of the vessels and divides the hepatic parenchyma into lobules, constituting the functional unit of the liver.

The hepatic lobule is pyramidal, with its base toward the surface of the liver and its apex inward, numbering up to 100,000 lobules. These are formed of hepatocytes arranged in thin layers, separated by sinusoidal capillaries ( ). Intralobular bile canaliculi form between the hepatocytes, transporting the exocrine secretion of the hepatocytes. At the periphery of the lobules, Hering's canaliculi become perilobular and then interlobular bile canaliculi, connecting to the intrahepatic canalicular system. In the spaces of Disse, between the sinusoidal capillaries and the hepatic laminae, lie the lymphatic capillaries. Stellate cells and Kupffer cells, components of the reticuloendothelial system, are present in the sinusoids.

The liver has a dual circulation:

- Nutrient supply comes from the branches of the hepatic artery, delivering oxygenated blood to hepatocytes and interlobular structures.
- Functional blood supply comes from the portal vein, carrying blood rich in nutrients absorbed from the intestine. The sinusoidal vessels drain into the hepatic veins and then into the inferior vena cava. In shock situations, the lack of vasodilation can lead to a reduction in hepatic blood flow, causing necrosis.

The liver is innervated by the celiac plexus (sympathetic) and the vagus nerves (parasympathetic), which coordinate autonomic functions.

The liver performs multiple vital roles:

- Bile secretion, essential for the digestion of lipids.
- Detoxification, through the filtration and metabolism of toxins.
- Phagocytosis, acting as an immune barrier against bacteria.
- Synthesis of vitamins and plasma proteins.
- Storage of glycogen, lipids, proteins, iron, and vitamins.

G. Gallbladder

The gallbladder is located in the gallbladder fossa, on the inferior surface of the right hepatic lobe, serving as a reservoir and concentrator of bile. In newborns, it is situated deep within the hepatic parenchyma, and by three months of age, it reaches the inferior margin of the liver. The increase in gallbladder volume is progressive: 3 cm^3 at 3 months, 9 cm^3 at 1 year, 35 cm^3 at 10 years, and 40–50 cm^3 in adults. The structure of the gallbladder includes the fundus, body, infundibulum, and neck, each composed of three layers: mucosal, muscular, and serosal.

The functions of the gallbladder include:

- Concentration of bile through passive water absorption and active transport of electrolytes, increasing the concentration of bile components by 5–10 times.
- Secretion, carried out by the mucous glands of the cystic duct, of substances such as glucosamine, galactosamine, chlorides, and carbonates, regulated by hormonal and neural mechanisms. Contraction of the gallbladder and the sphincter of Oddi is mediated by the parasympathetic nervous system, while the sympathetic nervous system exerts an inhibitory effect.

The common bile duct is divided into four anatomical segments: supraduodenal, retroduodenal, intrapancreatic, and intraduodenal. The cystic duct connects the gallbladder to the common bile duct and contains the Lutkens sphincter, which is neurohumorally regulated along with the sphincter of Oddi.

- **Bilirubin Metabolism**

Bilirubin derives mainly from the breakdown of aged erythrocyte hemoglobin (≈80%), with the remainder coming from unused hemoglobin and heme enzymes (≈15%). Heme is converted to biliverdin and then, under the action of biliverdin reductase, to unconjugated bilirubin. This circulates bound to albumin and cannot cross the blood-brain barrier. In hepatocytes, unconjugated bilirubin is converted through conjugation with glucuronic acid, becoming water-soluble and secreted into bile. In the intestine, bacteria convert bilirubin glucuronide into urobilinogen; part of it is excreted in the feces (stercobilin), and the rest re-enters the enterohepatic circulation or is eliminated in the urine.

Types of bilirubin:

- **Unconjugated**: fat-soluble, can cross the blood-brain barrier, implicated in neonatal jaundice.
- **Conjugated**: water-soluble, can be excreted in the urine, indicating conjugated hyperbilirubinemia.

In newborns, reduced glucuronyltransferase activity in the first few days can cause transient physiological jaundice, which is more pronounced in preterm infants.

H. The Pancreas

The pancreas is a mixed gland, both exocrine and endocrine, located retroperitoneally in a horizontal position at the level of the first two lumbar vertebrae, attached posteriorly to the abdominal wall by Treitz's fascia (right) and Toldt's fascia (left). In newborns, the pancreas weighs between

2–3.6 g, with a length of 4–6 cm and a width of 1–2 cm. By the age of 2–2.5 years, the weight reaches approximately 20 g, and between 10–12 years it can reach 30 g.

The structure of the pancreas includes four main sections:

- The head (cephalic region), embedded in the duodenal loop;
- The isthmus, which connects the head to the body;
- The body, located centrally;
- The tail, which is mobile, supported by the pancreatico-splenic ligament, and extending to the splenic pedicle.

The pancreas has two excretory ducts:

1. The Wirsung duct—the main duct—runs through the organ from tail to head and opens into the duodenum at the ampulla of Vater, where it joins the common bile duct;
2. The Santorini duct—an accessory duct—branches off from the Wirsung duct and opens into the duodenum above the ampulla of Vater.

The pancreas has a mixed blood supply: arterial branches originate from the celiac trunk and the superior mesenteric artery; additionally, the body and tail receive blood from the splenic artery. The superior mesenteric vein, the splenic vein, and the portal vein provide venous drainage. Lymph drains to the splenic, pancreatico-splenic, hepatic hilum, mesocolic, and mesenteric lymph nodes. Innervation is provided by the vagus nerve (parasympathetic) and the splanchnic nerves (sympathetic).

The islets of Langerhans account for 1–2% of pancreatic tissue and contain four types of cells:

- B cells – secrete insulin, a hypoglycemic hormone that increases peripheral glucose utilization, decreases glycogenolysis and hepatic gluconeogenesis, and promotes glycogen storage in the liver and muscles.
- A cells – secrete glucagon, which stimulates glycogenolysis and hepatic gluconeogenesis, activates glucagon-sensitive lipase and hepatic proteolysis, and has an anti-anabolic effect.
- D cells – secrete somatostatin, inhibiting the secretion of insulin, glucagon, and pancreatic polypeptide; they reduce gastroduodenal and gallbladder motility, ensuring paracrine regulation of insulin and glucagon.
- F cells – secrete pancreatic polypeptide (PP), inhibiting exocrine secretion and slowing the absorption of digestive products.

The exocrine portion of the pancreas consists of serous acini, arranged in clusters and connected to excretory ducts. Pancreatic juice is a colorless, alkaline liquid (pH 8–8.4) with a density of 1007–1012, consisting of 98.6% water and 1.5% dry residue, which includes inorganic substances (Na^+, K^+, Ca^{2+}, HCO_3^-, Cl^-, PO_4^{3-}) and organic substances. Pancreatic secretion is triggered by food intake and regulated neurohumorally:

- Via the bloodstream – duodenal secretin;
- Neurally – via viscero-cortical and cortico-visceral connections.

The volume of pancreatic juice varies with age:

- Newborn – 450 ml/day;
- Older children and adults – 1500–4000 ml/day (4.5–5 ml/min).

The concentration of cations is constant, while that of anions varies inversely proportional to the secretory flow, maintaining ionic balance. Ductal cells carry out hydro-electrolytic secretion via active ion transport mechanisms, with water transferred passively, explaining acid-base disturbances in massive losses of duodenal fluid.

Pancreatic enzymes are:

a. Proteolytic: ensure protein digestion and are divided into:

- Endopeptidases:
    - Trypsin (activated by enterokinase)
    - Chymotrypsin
    - Elastase
- Exopeptidases:
    - Carboxypeptidase A and B (cleave amino acids at the ends of polypeptides)

b. Lipolytic enzymes: digestion of lipids, including:
- Pancreatic lipase – hydrolyzes triglycerides into monoglycerides and fatty acids;
- Cholesterol esterase – esterifies cholesterol with fatty acids;
- Phospholipase A2 – activated by trypsin, hydrolyzes lecithins into lysolecithins.

c. Glycolytic: digestion of carbohydrates:
- Pancreatic amylase – acts on starch and glycogen, producing maltose and dextrins. Amylase is absent at birth and becomes active in the first months of life.
- Lactase and maltase – hydrolyze lactose and maltose.

d. Nucleolytic: ribonucleases and deoxyribonucleases hydrolyze nucleic acids.

Proteolytic enzymes are secreted in an inactive form (zymogens) and activated in the duodenum to prevent self-digestion. Antiprotease enzymes (antitrypsin) inhibit trypsin accidentally produced by acinar or ductal cells.

I. The Intestine

The intestine in newborns and infants exhibits anatomical and functional characteristics that differ significantly from those of adults. The small intestine, the segment between the pylorus and the ileocecal valve, consists of the duodenum, jejunum, and ileum. In infants, the length of the intestine exceeds six times the body length, compared to four times in adults, which allows for predominantly parietal digestion and ensures complete nutrient absorption.

a. **The duodenum** is the only fixed portion of the intestine, located retroperitoneally, having a ring-shaped form at birth that gradually evolves into a horseshoe shape, opening to the left to encircle the head of the pancreas. It is divided into four segments: superior, descending, horizontal, and ascending. The length of the duodenum increases significantly in the first years of life, from approximately 8–10 cm in a newborn to 25–30 cm in an older child.

b. **The jejunum and ileum** are the mobile portions of the small intestine, with a total length of 2.5–3 meters: the jejunum accounts for approximately three-fifths, and the ileum for two-fifths. The jejunal loops are arranged horizontally, predominantly in the left colic region, while the ileal loops are arranged vertically in the right iliac fossa. Their position varies depending on the fullness or emptiness of the colon and the child's age. The mesentery is very long, which ensures increased mobility but also increases the risk of intestinal volvulus.

The structure of the intestinal wall consists of four layers: mucosa, submucosa, muscularis, and serosa. In newborns and infants, the layers are of similar thickness; structural differences emerge with growth, when the muscular layer becomes dominant. The mucosa is thin, richly vascularized, and——forms circular folds called **Kerckring valves**, covered with intestinal villi. These increase the absorption surface area by approximately 600 times and contain a chorion with blood vessels, lymphatic vessels, and solitary lymphatic follicles, which in the distal jejunum and ileum form Peyer's patches, essential for local immunity. The epithelium of the villi consists of:

- **Enterocytes**, cylindrical cells with microvilli that form the brush border, involved in the digestion and absorption of nutrients.
- **Glandular cells**, which secrete mucus, protecting the mucosa, lubricating the intestine, and participating in the regulation of immunity through the synthesis of secretory IgA.
- **Endocrine cells**, part of the APUD system, which regulate intestinal functions through endocrine and paracrine mechanisms.

The submucosa consists of loose connective tissue, blood and lymphatic vessels, nerves, and lymphoplasmacytic cells. This is where Brunner's glands are located in the duodenum. The muscularis layer has two smooth layers, an inner circular layer and an outer longitudinal layer, between which lies the Auerbach plexus, responsible for coordinating intestinal motility. The serosa, represented by the visceral peritoneum, lines the small intestine, with the exception of the retroperitoneal portions of the duodenum.

Digestion and absorption in the small intestine occur in several interdependent stages:

- The luminal stage, within the lumen, where pancreatic juice and bile partially hydrolyze nutrients.
- The membrane stage, or contact digestion, occurs at the brush border, where intestinal enzymes complete the breakdown of nutrients.

- The intracellular stage, within enterocytes, where cytoplasmic and lysosomal enzymes complete hydrolysis, with the exception of chylomicrons.

The final products of digestion that are absorbed are: amino acids from proteins, monosaccharides from carbohydrates, and fatty acids, mono- and diglycerides from lipids. Absorption occurs through active and passive transport, as well as through macromolecular transport, endocytosis, and exocytosis.

c. **The large intestine**, consisting of the cecum, colon, rectum, and appendix, has a total length approximately equal to the length of the body. The cecum in the newborn is small and conical, and the appendix is 4–10 cm long, with a wide lumen and increased mobility. The lymphatic follicles of the appendix develop gradually, reaching maturity during adolescence. The ascending colon is immobile, the transverse and sigmoid colons are more mobile due to the mesocolon, and the descending colon is less mobile and may be palpable. The rectum is longer than in adults, lacking the ampullary portion, and the poorly attached mucosa and submucosa predispose to rectal prolapse. The anal sphincter is incompletely developed, which explains the high frequency of bowel movements in the first weeks of life.

The colon mucosa is smooth, without villi, but with large and numerous Lieberkühn glands. The crypts are not fully developed, reducing fecal propulsion and promoting constipation and inflammation. At birth, the intestine is sterile, and the intestinal microflora establishes itself gradually: bifidobacteria predominate in natural feeding, and colibacteria in artificial feeding. The intestinal microflora provides:

- A barrier function against pathogenic bacteria.
- Fermentation of undigested carbohydrates and proteins.
- The synthesis of essential vitamins (B, PP, K).

Digestion in the proximal colon is carried out by non-pathogenic aerobic flora, while in the distal colon, anaerobic putrefactive flora acts, breaking down unabsorbed proteins and amino acids and generating toxic substances, which are subsequently neutralized by the liver. Absorption in the large intestine occurs primarily for water and electrolytes, with nutrients being absorbed almost exclusively in the small intestine.

Thus, the infant's and newborn's intestine is adapted for the efficient digestion and absorption of nutrients, but it has specific vulnerabilities: susceptibility to poisoning, constipation, rectal prolapse, and the importance of the microflora in the development of immunity and efficient digestion.

Self-assessment questions

1. What is the capacity of the stomach at birth?
2. Why are preterm infants prone to NEC?
3. What is the mechanism of neonatal gastroesophageal reflux?
4. What are the consequences of liver immaturity?
5. What role does the microbiota play during the neonatal period?

IV.3. NEONATAL JAUNDICE

IV.3.1. DEFINITION

Neonatal jaundice is the yellow discoloration of the skin and sclera caused by serum bilirubin levels exceeding normal values for postnatal and gestational age. It results from an imbalance between production, hepatic metabolism, and excretion. It can be physiological or pathological, unconjugated or conjugated, benign, or neurologically threatening.

Clinical tip: we do not treat the color; we treat the child + bilirubin levels + age in hours + biological context.

IV.3.2. EPIDEMIOLOGY. INCIDENCE

- ~60% of full-term newborns develop jaundice in the first few days
- 80% of preterm infants develop jaundice
- Severe jaundice requiring intervention ~1–2 per 1,000 full-term newborns

- Preterm infants have a significantly higher risk of bilirubin encephalopathy
- Cholestatic jaundice is rare, but always pathological

Clinical hint: Jaundice <24h = pathological until proven otherwise.

IV.3.3. PATHOPHYSIOLOGY

1. Bilirubin metabolism
   a. Hemolysis → unconjugated bilirubin (fat-soluble)
   b. Albumin-bound transport
   c. Hepatic uptake
   d. Conjugation via UGT1A1 (immature enzyme in newborns)
   e. Biliary excretion
   f. Fecal excretion; some is reabsorbed (enterohepatic circulation)
2. Neonatal characteristics
   - short-lived red blood cells
   - Low hepatic enzyme activity
   - Initially absent intestinal flora
   - Increased intestinal β-glucuronidase → ↑ reabsorption
3. Bilirubin neurotoxicity

Unconjugated bilirubin diffuses into the CNS, affecting the basal ganglia and brainstem → bilirubin encephalopathy → kernicterus if untreated.

Pathophysiological note: blood-brain barrier permeability is higher in preterm infants, sepsis, hypoxia, acidosis → increased risk even at moderate levels.

IV.3.4. RISK FACTORS

Risk factors include:

- prematurity
- ABO/Rh incompatibility
- G6PD deficiency, hemoglobinopathies
- obstetric trauma (cephalhematoma, hemorrhages)
- perinatal infections
- ineffective breastfeeding / dehydration
- family history of severe jaundice
- children of diabetic mothers
- hypoxia, acidosis, hypothermia
- drugs that displace bilirubin from albumin (rare, but relevant)

Clinical hint: prematurity + infection = maximum risk of bilirubin encephalopathy.

IV.3.5. CLINICAL DIAGNOSIS

We evaluate:

- onset (key to diagnosis)
- cranio-caudal extent
- muscle tone, reflexes, sucking
- signs of dehydration
- hepatosplenomegaly
- bruises/cephalhematoma
- stool color (acholic = alarm!)
- urine color (hyperchromia in cholestasis)

Neurological warning signs

- lethargy or irritability
- poor sucking
- hypotonia or alternating hypo- and hypertonia

- apnea, seizures

Clinical hint: "The jaundiced infant who sleeps too well" = warning sign.

IV.3.6. LABORATORY AND IMAGING STUDIES

Basic tests

- total and direct bilirubin
- hemoglobin, hematocrit
- reticulocytes
- mother/child blood group, direct Coombs test

Targeted tests

- G6PD, smear
- CRP/procalcitonin, blood culture (suspected sepsis)
- liver enzymes (GGT ↑ in cholestasis)
- Liver & biliary tract ultrasound
- TSH/T4 (hypothyroidism screening)
- metabolic tests as needed

Key interpretation:

- Elevated direct bilirubin → cholestasis → urgent investigation
- increase >5 mg/dL/24h → pathological
- Positive Coombs test → immune hemolysis

IV.3.7. DIFFERENTIAL DIAGNOSIS

The differential diagnosis of neonatal jaundice depends on its form, namely unconjugated or conjugated bilirubin jaundice.

A. Unconjugated jaundice
   - physiological jaundice
   - breastfeeding jaundice (insufficient intake)
   - breast milk jaundice (increased enterohepatic circulation)
   - immune/non-immune hemolysis
   - prematurity
   - polycythemia
   - congenital hypothyroidism

B. Conjugated (cholestatic) jaundice — *always* pathological
   - biliary atresia
   - neonatal hepatitis
   - TORCH infections
   - galactosemia, tyrosinemia
   - cystic fibrosis
   - choledochal cyst

Clinical hint: Jaundice + pale stools = cholestasis → refer urgently to a doctor.

IV.3.8. MANAGEMENT

A. Non-pharmacological
   - encourage effective, supervised breastfeeding
   - Adequate hydration (breast milk ≫ oral glucose)
   - temperature monitoring
   - educating the mother to recognize warning signs

B. Pharmacological and interventional

1. Phototherapy
   - first-line treatment for unconjugated hyperbilirubinemia

- Effect: conversion of bilirubin into soluble isomers
- Proper application:
    - Maximum skin surface area exposed
    - protection of the eyes and external genitalia
    - monitor temperature + hydration
- Premature infants, sepsis, hypoxia → lower therapeutic thresholds.

2. IV immunoglobulins
    - immune hemolysis with rapidly rising bilirubin
    - reduces the need for exchange transfusion
3. Exsanguination transfusion
    - indicated when bilirubin approaches the neurotoxic threshold or neurological signs appear
    - performed in specialized centers
4. Etiological treatment
    - antibiotics for sepsis
    - specific metabolic treatment when indicated
    - Discontinuation of breastfeeding only in rare situations (e.g., galactosemia)

Practical tip: Treatment of jaundice = prevention of brain damage, not correction of skin color

C. Follow-up
- Reassessment of bilirubin levels after phototherapy
- Monitoring of nutrition and growth
- Neurodevelopmental follow-up in severe cases
- liver function monitoring if cholestatic jaundice

IV.3.9. PROGNOSIS

- Physiological/breastfeeding jaundice: excellent
- Properly treated immune hemolysis: very good
- severe prematurity, sepsis, acidosis: risk of encephalopathy
- Untreated cholestasis: liver fibrosis, liver failure

Self-assessment questions

1. What are the criteria that define pathological jaundice?
2. Why is jaundice lasting <24 hours considered an emergency?
3. What is the difference between jaundice from breastfeeding vs. jaundice caused by breast milk?
4. What sign indicates urgent cholestasis in a newborn?
5. When do we prescribe immunoglobulins?
6. What are the guiding principles of phototherapy?

IV.4. HEMOLYTIC DISEASE

IV.4.1. DEFINITION

Hemolytic disease of the newborn (HDN) is the accelerated destruction of fetal red blood cells resulting from maternal sensitization and the transplacental transfer of maternal IgG antibodies, which bind to the infant's red blood cells, causing hemolysis.

It is a severe form of immune hemolytic anemia, with a high risk of:

- severe fetal anemia
- severe early-onset jaundice
- fetal heart failure
- fetal hydrops
- postnatal bilirubin encephalopathy

IV.4.2. EPIDEMIOLOGY. INCIDENCE

- ABO incompatibility is the most common, but often milder
- Rh (D) incompatibility is rarer but potentially catastrophic
- The incidence of Rh HDN has decreased dramatically due to immunoprophylaxis, but cases persist due to:
    - failure to administer prophylaxis
    - immunization prior to pregnancy
    - rare isoimmunizations (anti-C, anti-E, anti-Kell, etc.)

Clinical hint: Jaundice in the first few hours + anemia = hemolysis until proven otherwise.

IV.4.3. PATHOPHYSIOLOGY

1. Immunological mechanism

- The Rh-negative mother is exposed to Rh-positive red blood cells (childbirth, bleeding, transfusions, procedures)
- Produces anti-D antibodies
- In the next pregnancy, IgG antibodies cross the placenta
- They bind to fetal red blood cells → immune-mediated hemolysis
- The following occur:
    - progressive fetal anemia
    - extramedullary erythropoiesis
    - hepatosplenomegaly
    - fetal hydrops (generalized edema, ascites, pleural effusion)

2. ABO incompatibility

- Mother blood type 0, child A/B
- Maternal anti-A/anti-B antibodies (IgG) can cause hemolysis of fetal red blood cells
- Usually milder than Rh

Pathophysiological note: Anti-Kell inhibits erythropoiesis — may cause severe anemia without pronounced jaundice.

IV.4.4. RISK FACTORS

Risk factors include:

- Rh-negative mother → Rh-positive fetus
- lack of anti-D prophylaxis
- previous transfusion with Rh-positive blood
- fetal-maternal hemorrhage
- invasive procedures (amniocentesis, CVS)
- suggestive obstetric history (previous newborn with severe jaundice)

IV.4.5. CLINICAL DIAGNOSIS

Signs of hemolytic disease may appear during the prenatal period, which suggests a severe form of the disease. However, hemolytic disease may also develop after birth.

- Postnatal signs
    - jaundice within the first 24 hours
    - pallor
    - lethargy, poor feeding
    - tachycardia
    - Hepatosplenomegaly
    - edema (severe residual hydrops)
- Severe prenatal signs
    - fetal hydrops (edema + ascites + pleural effusion)

- polyhydramnios
- fetal cardiomegaly

Clinical hint: Jaundice appearing in the first hours of life = immune hemolysis until proven otherwise.

IV.4.6. LABORATORY AND IMAGING STUDIES

To establish the diagnosis using paraclinical investigations, laboratory tests and imaging are required.

Laboratory tests:

- Total and direct bilirubin: rapid increase
- Hemoglobin: low
- Reticulocytes: elevated (except in anti-Kell cases)
- Direct Coombs test: positive in immune hemolysis – detects antibodies attached to red blood cells
- Mother/child blood type
- Smear: spherocytes in ABO sometimes

Imaging studies:

- Prenatal fetal ultrasound (hydrops)

Paraclinical clue: Positive Coombs test + early jaundice + anemia = diagnosis practically established.

IV.4.7. DIFFERENTIAL DIAGNOSIS

The differential diagnosis can sometimes be complex. The following should be considered:

- G6PD deficiency
- hereditary spherocytosis
- other non-immune hemolytic anemias
- congenital infections
- massive neonatal hemorrhage
- polycythemia with subsequent hyperbilirubinemia

IV.4.8. MANAGEMENT

A. Non-pharmacological

- early intensive monitoring (first few hours)
- assessment of neurological status
- adequate nutrition, hydration
- support for breastfeeding (not contraindicated, except in rare metabolic cases)

B. Pharmacological & interventional

1. Early phototherapy

- indicated at thresholds lower than physiological jaundice
- purpose: prevention of bilirubin encephalopathy

2. IV immunoglobulins

- in rapidly rising bilirubin levels
- reduces the need for exchange transfusion

3. Exchange transfusion

- Replaces sensitized red blood cells + rapidly reduces bilirubin
- in critical jaundice or neurological signs
- performed in specialized centers

4. Blood transfusion

- in severe anemia without extreme hyperbilirubinemia or after acute treatment

5. In utero treatment (in obstetrics)

- Fetal intrauterine transfusion in severe cases diagnosed prenatally

Practical tip: Rapid intervention saves the brain—we do not wait for clinical deterioration.

C. Follow-up

- Monitoring of bilirubin and hemoglobin
- Neurological and developmental follow-up
- Breastfeeding support
- Hematologic evaluation if necessary
- Parent education regarding warning signs

IV.4.9. PROGNOSIS

- With screening and appropriate treatment: excellent
- Without prophylaxis / delayed treatment:
    - risk of hydrops
    - bilirubinic encephalopathy
    - fetal/neonatal death
- Anti-Kell: more guarded prognosis (suppression of erythropoiesis)

Quick reference guide:

- <24h jaundice + anemia + positive Coombs test = HDN
- ABO = common, Rh = severe
- Intrauterine TT if hydrops
- Postnatal: phototherapy → IVIG → exchange transfusion if necessary

Hemolytic disease is one of the most dramatic neonatal emergencies—but also one of the most preventable.

Self-assessment questions

1. What is the mechanism of HBD?
2. Why is ABO incompatibility usually milder?
3. What is the role of the direct Coombs test?
4. When is phototherapy indicated?
5. What role do immunoglobulins play in immune hemolysis?
6. What major intrauterine complication can occur?
7. Why can anti-Kell cause severe anemia with only moderate bilirubin levels?

IV.5. ACUTE DIARRHEAL DISEASE

IV.5.1. DEFINITION

Acute diarrheal disease in the newborn is characterized by frequent stools (≥3/day) with a watery or altered consistency, with or without systemic signs (fever, vomiting, dehydration, altered muscle tone, and feeding difficulties). In newborns, distinguishing between normal stools, accelerated transit, and pathological diarrhea is essential, as this age group has limited physiological reserves and is at high risk for:

- dehydration
- electrolyte imbalances
- acute malnutrition
- sepsis

Clinical tip: Any newborn with frequent stools + poor feeding = immediate medical evaluation.

IV.5.2. EPIDEMIOLOGY. INCIDENCE

- Acute diarrheal disease is less common in newborns than in infants, but much more dangerous.
- Most cases occur in association with:
- bacterial or viral infections
- poor nutrition
- early antibiotic treatment

- poor sanitary conditions
- Necrotizing enterocolitis (NEC) is a major differential diagnosis; we do not automatically classify diarrhea as simple gastroenteritis.

Epidemiological clue: An exclusively breastfed newborn has the lowest incidence of infectious diarrhea.

IV.5.3. PATHOPHYSIOLOGY

Diarrhea results from an imbalance in the intestinal environment between:

- water and electrolyte absorption
- intestinal secretion
- motility
- mucosal integrity
- protective intestinal flora

In newborns:

- the intestinal mucosa is immature
- intestinal permeability is increased
- immune barriers are reduced
- the gut flora is developing (especially in preterm infants)

These characteristics increase the risk of bacterial translocation and sepsis.

IV.5.4. RISK FACTORS

- prematurity
- formula feeding
- poor feeding hygiene
- use of improperly prepared formula
- maternal/perinatal infections
- neonatal or maternal antibiotics around the time of birth
- immunodeficiencies (rare but severe)
- prolonged hospitalization / intensive care

Helpful tip: Diarrhea + fever + poor feeding = prompt investigation → the risk of sepsis is real.

IV.5.5. CLINICAL DIAGNOSIS

Main manifestations

- watery or mucoid-watery stools ≥3/day
- change in color, odor
- vomiting
- fever or hypothermia
- refusal to eat
- irritability or lethargy
- weight loss
- signs of dehydration (sunken fontanelle, crying without tears, skin turgor barely visible in newborns)
- diaper rash, perianal irritation

Signs of severity

- extreme lethargy/irritability
- hypotonia
- significant decrease in feeding
- bloody stools
- bile-stained vomit
- apnea/thermal instability

- signs of shock

Clinical hint: Bilious vomiting = suspected surgical cause, not gastroenteritis.

IV.5.6. LABORATORY AND IMAGING STUDIES

Tests are tailored to the severity.

- Complete blood count, CRP/procalcitonin
- Electrolyte panel (Na, K, Cl), blood glucose
- Urea, creatinine
- stool culture if an infection is suspected
- fecal cytology
- blood culture if sepsis is suspected
- blood gas analysis in severe cases
- viral tests if available

Laboratory note: Hyponatremia and metabolic acidosis can develop rapidly in preterm infants.

IV.5.7. DIFFERENTIAL DIAGNOSIS

- Necrotizing enterocolitis (NEC)
- Congenital malabsorption (glucose/galactose, CF—rare in neonates, but may present)
- Cow's milk protein intolerance (less common in newborns)
- Rare metabolic disorder
- Neonatal sepsis with gastrointestinal involvement
- Intestinal obstruction (bilious vomiting, abdominal distension)

Differential diagnosis tip: If the abdomen is distended, the child is lethargic, and the stools contain blood → immediately consider NEC, not "gastroenteritis."

IV.5.8. MANAGEMENT

A. Non-pharmacological

- Mandatory hospitalization for newborns with significant diarrhea
- Monitor hydration, weight, and urine output
- Breast milk supplementation (the best treatment)
- Assisted lactation for mothers with difficulties

B. Pharmacological and supportive

1. Rehydration

- Oral rehydration with breast milk or appropriate ORS solutions, if well tolerated
- Parenteral rehydration if:
    - persistent vomiting
    - moderate-to-severe dehydration
    - altered general condition
- Excess IV fluids may worsen metabolic status.

2. Antibiotics are NOT routinely administered; they are administered only if:

- suspected sepsis
- blood in the stool
- persistent fever
- premature infant with altered general condition
- severe nosocomial onset

3. Probiotics may be considered in some clinical protocols following medical evaluation—do not administer empirically to vulnerable newborns.
4. Etiological treatment:

- correction of improper feeding
- avoid incorrect formula preparation

- discontinuation of inappropriate medications
- treating systemic infection if present

Therapeutic tip: the best "medicine" for a newborn's gut is breast milk.

C. Follow-up

- Daily monitoring of weight and urine output
- assessment of food tolerance
- post-discharge follow-up for preterm infants

IV.5.9. PROGNOSIS

- Most mild cases resolve with nutritional support and hydration
- Premature infants may develop severe dehydration, electrolyte disturbances, and sepsis
- Severe untreated cases → shock, renal failure, neurological disorders

Prognostic hint: The course depends on the prompt recognition of warning signs.

Mental algorithm

- Newborn + diarrhea ≠ "gastroenteritis" → evaluation
- Feeding? Temperature? Abdomen? Tone?
- Bloody stools / green vomit / lethargy → urgent
- Continue breastfeeding + judicious rehydration
- Antibiotics only if signs of infection/sepsis

Self-assessment questions

1. What is the definition of diarrhea in a newborn?
2. What are the most important signs of severity?
3. When are antibiotics indicated?
4. Why is breast milk a natural protection?
5. What are the major differential diagnoses?
6. Which clinical sign suggests a surgical condition rather than simple diarrhea?

IV.6. NECROTIZING ENTEROCOLITIS (NEC)

IV.6.1. DEFINITION

Necrotizing enterocolitis (NEC) is an acute inflammatory lesion of the distal small intestine and frequently of the proximal large intestine. Surgical pathology reveals segmental coagulative necrosis of the mucosa with the presence of focal hemorrhages, indicative of ischemia. Other features include pneumatosis (intramural air bubbles) and degradation of the mucosa, submucosa, and muscularis mucosae, which contrasts with the intact mucosa seen in spontaneous intestinal perforation.

IV.6.2. EPIDEMIOLOGY. INCIDENCE

NEC is the leading cause of gastrointestinal tract involvement in the neonatal period. The pathogenesis is complex and multifactorial, and the etiology remains unclear. Despite advances made in recent decades, mortality and morbidity associated with necrotizing enterocolitis remain high.

Its incidence is estimated at 1–3 cases per 1,000 live births, with more than 90% occurring among preterm infants. The frequency of NEC varies among maternity wards, with no correlation to season or geographic location. Outbreaks of NEC appear to follow an epidemic pattern, suggesting an infectious etiology, although no causative microorganism has been isolated. Furthermore, cases tend to cluster, suggesting an environmental component to the pathophysiology.

The mortality rate is 10–50% in VLBW (very low birth weight) newborns, depending on disease severity, and 0–20% in newborns weighing more than 2,500 grams. ELBW (early low birth weight) newborns are particularly vulnerable, with mortality rates ranging from 40 to 100%. Mortality in term newborns is approximately 5% compared to 12% in preterm newborns.

Survivors may experience long- or short-term complications. Patients with mild disease require fasting to facilitate resolution of the intestinal inflammatory process, while severely affected patients may require intestinal resection during the acute phase of the disease. Others may develop strictures

as part of the healing process, which may ultimately require surgical resection. In extremely severe cases of severe NEC, the entire intestine may be affected. Depending on the location and extent of the removed intestine, long-term complications may include the need for an ileostomy and/or colostomy, repeated surgeries, prolonged parenteral nutrition, short bowel syndrome, malabsorption syndrome, and multiple and prolonged hospitalizations.

IV.6.3. PATHOPHYSIOLOGY

The pathogenesis of necrotizing enterocolitis stems from the immaturity of the gastrointestinal tract. Immunological immaturity allows the digestive tract to be colonized by the bacterial flora present in the Neonatal Intensive Care Unit. Antibiotics frequently administered in the treatment of respiratory distress syndrome suppress the native flora, which provides some protection against the growth of pathogenic microorganisms.

Enteral feeding with powdered milk formulas provides a carbohydrate substrate for bacterial proliferation, without supplying any of the immunoglobulins contained in breast milk. Bacteria attack the mucosa, migrating directly through it or through breaks in its integrity.

The resulting inflammatory response releases cytokines and other cellular inflammatory mediators, which in turn damage the mucosa and can extend into the deeper layers of the intestinal wall, leading to necrosis throughout the entire thickness of the wall and subsequent perforation.

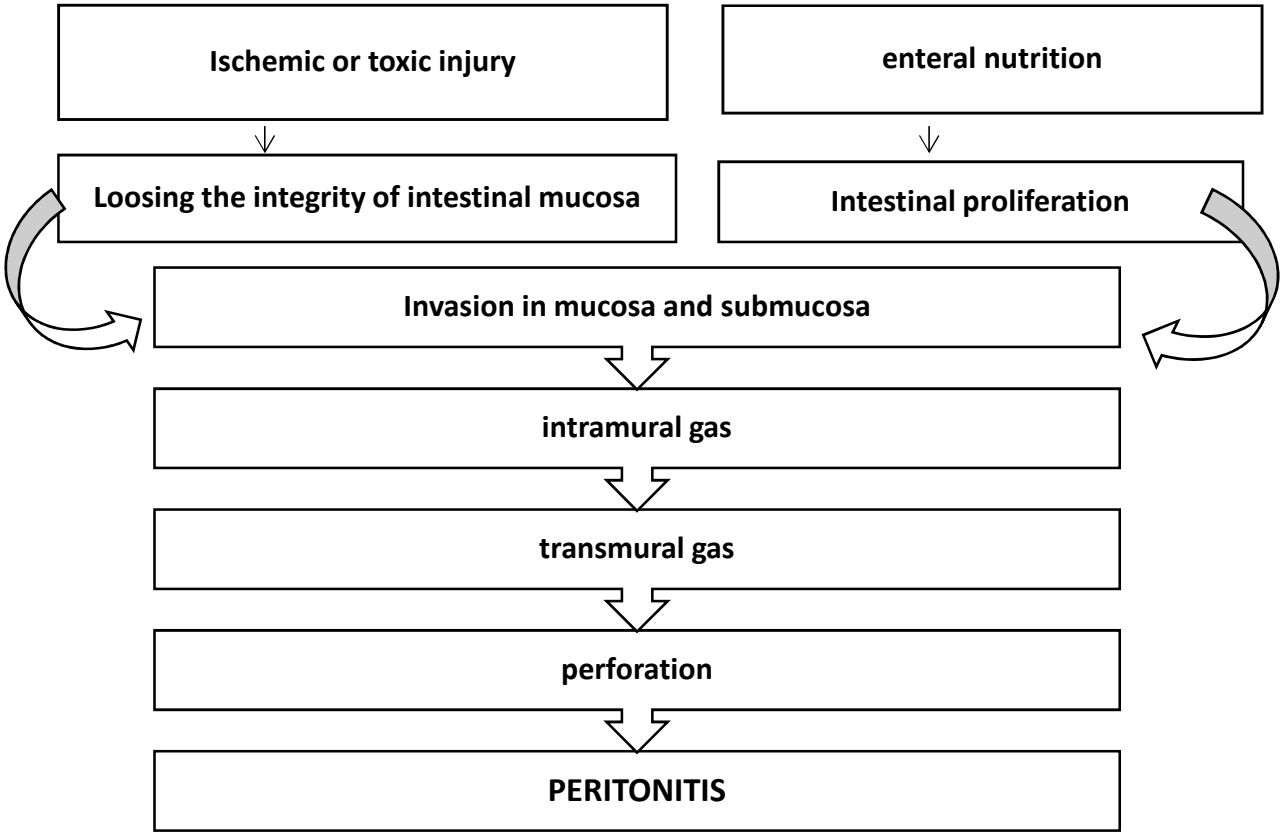

Figure 3. Pathogenesis of NEC

IV.6.4. RISK FACTORS

Table 1. NEC risk factors

Prenatal (maternal) risk factors	Postnatal risk factors
1. Preeclampsia/toxemia	1. Prematurity
2. Maternal hemorrhage	2. Enteral feeding
3. Placental abruption	3. Intestinal mucosal injury
4. Antenatal detection of zero or reversed diastolic flow on Doppler examination of the umbilical artery	4. Ischemia
5. Chorioamnionitis	5. Bacteria

6. Preterm birth	6. Immaturity of the intestinal barrier function
7. Lack of antenatal prophylaxis with corticosteroids	7. Red blood cell concentrate transfusion
8. Antenatal administration of Coamoxiclav in cases of preterm birth or RPPA	8. Umbilical venous catheter
9. Use of tocolysis with indomethacin	9. Patent ductus arteriosus

Prenatal risk factors 1–4 lead to reduced mesenteric blood flow in the infant (hypoperfusion), thereby contributing to the development of NEC, whereas risk factors 5–7 increase NEC-related morbidity by increasing the intestinal tract's susceptibility to inflammatory mediators. Inflammatory cytokines have been detected in both the mother and the fetus in cases of maternal chorioamnionitis, preterm birth, and PAPP (premature rupture of the amniotic sac). The fetal inflammatory response may be responsible for inducing preterm birth and is also responsible for neonatal morbidity, including NEC. Antenatal use of corticosteroids reduces the risk of developing necrotizing enterocolitis. Antenatal administration of indomethacin for tocolytic purposes (48 hours before delivery) is associated with a risk of developing NEC.

Although NEC can occur in infants who have not received enteral feeding, 90–95% of cases occur after the initiation or resumption of enteral feeding.In addition to the direct damaging osmotic effect on the intestinal mucosa, enteral feeding can affect mesenteric blood flow and increase the risk of mucosal ischemia by increasing local oxygen demand in areas of hypoperfusion. Infants fed formula have a higher risk of developing NEC compared to those fed breast milk.

IV.6.5. CLINICAL DIAGNOSIS

Early diagnosis of NEC can be an important factor in determining the prognosis. There is a wide spectrum of disease manifestations. The clinical features of NEC can be divided into systemic and abdominal signs. Most newborns present with a combination of both, although abdominal signs usually predominate.

Table 2. Signs and symptoms of NEC

Systemic Signs and Symptoms	Gastrointestinal signs and symptoms
• Lethargy • Tachycardia • Apnea or respiratory distress • Thermal instability • The newborn appears to be "looking unwell" • Acidosis (metabolic and/or respiratory) • Glucose instability • Fluid imbalance or shock • DIC syndrome • Blood culture may be positive	• Abdominal distension • Abdominal tenderness and rigidity on palpation • Increased abdominal circumference • Food intolerance • Gastric residue • Vomiting • Occult or visible blood in the stool • Change in stool consistency (diarrhea/constipation) • Erythema of the anterior abdominal wall • Palpable mass in the abdomen • Ileus with diminished bowel sounds

IV.6.6. LABORATORY AND IMAGING STUDIES

The diagnosis is suspected based on clinical manifestations, but must be confirmed by radiography, surgery, and necropsy. Laboratory tests are not specific for NEC; however, some of them are valuable in confirming the suspected diagnosis.

Imaging studies:

1. Abdominal radiography will most often reveal an abnormal gas pattern consistent with ileus. Both anteroposterior and transverse views, as well as views in the left lateral decubitus

position, should be included. These may reveal intestinal wall edema, a loop with a fixed position on serial images, the appearance of a mass, the presence of air in the portal or hepatic vein (presence of free portal or hepatic gas), pneumobilia, or pneumoperitoneum with the appearance of gas below the diaphragm. However, the distinctive radiological sign used to confirm the diagnosis is intestinal pneumatosis. Intramural air bubbles represent gas produced by bacteria in the intestinal wall. The amount of gas is not correlated with the severity of the disease. There are two types of pneumatosis: the cystic form and the linear form. The cystic form appears foamy due to submucosal air accumulation and is usually observed first. The linear form is due to subserosal air accumulation. Intestinal pneumomatosis is not specific to NEC; it also occurs in Hirschsprung's disease, severe diarrhea, or carbohydrate intolerance.

2. Abdominal ultrasound may be a more sensitive method for detecting intramural air and free gas in the portal space. Doppler imaging can confirm intestinal necrosis by demonstrating the absence of blood flow. These techniques are particularly useful for radiologically confirming the presence of intestinal pneumatosis in apparently well newborns with feeding intolerance.

Laboratory tests:

1. Complete blood count – should be repeated every 6 hours if the clinical condition remains poor and may indicate changes in white blood cell counts. As concerning as elevated white blood cell counts may be, leukopenia should be of greater concern. Although elevated counts of mature or immature neutrophils are not optimal indicators of sepsis after the first 3 days of life, an absolute neutrophil count lower than 1,500/mm³ indicates sepsis. Elevated hemoglobin or hematocrit levels indicate hemoconcentration due to fluid accumulation in the extracellular space, but the newborn may be anemic if massive gastrointestinal bleeding has occurred, and consumption coagulopathy may be objectively d by a marked decrease in hematocrit. Thrombocytopenia appears to be a reaction to Gram-negative microorganisms and endotoxins that worsens if associated with a consumption coagulopathy. This is characterized by prolonged prothrombin time and activated thromboplastin time, decreased fibrinogen, and increased concentrations of fibrinogen degradation products. Values below 50,000/mm³ indicate the need for a platelet transfusion.
2. C-reactive protein—represents another nonspecific change among acute-phase reactants. It increases in advanced stages of the disease and decreases rapidly upon initiation of antibiotic therapy.
3. Blood cultures should be collected before starting antibiotic treatment in any patient with signs of systemic infection. Although they are positive in only 40% of cases, sepsis is one of the most likely differential diagnoses and must be ruled out.
4. Serum electrolytes may undergo characteristic changes and should be repeated every 6 hours for dynamic monitoring. These changes are accompanied by metabolic acidosis, characterized by a decrease in serum bicarbonate, which is a marker of intestinal ischemia, hypoperfusion, hypovolemia, and intestinal necrosis. Hyponatremia is a concerning sign that accompanies fluid extravasation into the extracellular space.
5. Arterial blood gases can help determine the need for ventilatory support. Hypoventilation and frank apnea are commonly seen in NEC. Lactic acidosis results from low cardiac output and leads to decreased peripheral perfusion and tissue necrosis.
6. Stool occult blood testing has been used to identify newborns with NEC based on changes in intestinal integrity. Although the presence of abundant blood in the stool may indicate enterocolitis, stool testing for occult blood has no diagnostic value for NEC. Approximately 60% of newborns will have stools that test positive for occult blood at some point during hospitalization, without any evidence of NEC.

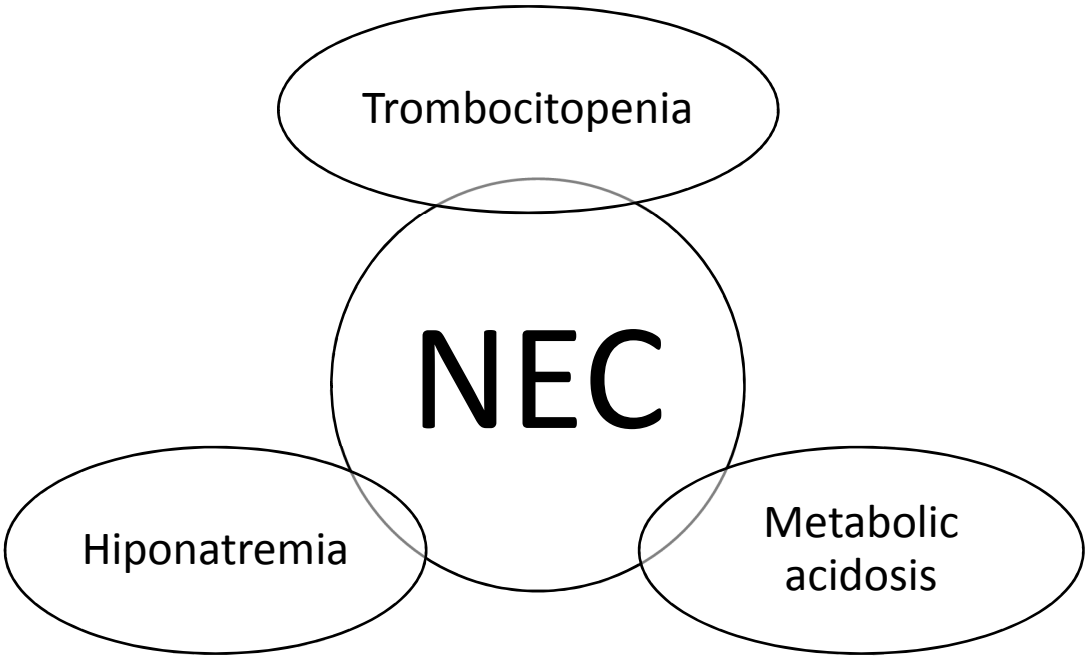

Figure 4. The Specific Triad in NEC

Thrombocytopenia, persistent **metabolic acidosis,** and severe refractory **hyponatremia** constitute the most common triad of signs and help confirm the diagnosis.

IV.6.7. DIFFERENTIAL DIAGNOSIS

- Pneumonia and sepsis are commonly and frequently associated with intestinal ileus. The abdominal distension, color changes, and tenderness characteristic of NEC should be absent.
- Major surgical abdominal emergencies include malrotation with intestinal volvulus, intussusception, ulcer, gastric perforation, and mesenteric vascular thrombosis. The clinical presentation of these conditions may overlap with that of NEC.
- Spontaneous intestinal perforation is a distinct clinical entity that occurs in 2% of ELBW newborns. It frequently presents as the absence of gas in the abdomen or as asymptomatic pneumoperitoneum, although other clinical or laboratory abnormalities may be present.
- Infectious enterocolitis is rare in this population but should be considered when diarrhea is present.
- Feeding intolerance is a common but poorly defined problem in preterm infants. Despite adequate gastrointestinal tract function in utero, some preterm infants will experience episodes of gastric residue and abdominal distension associated with the progression of feeding. Differentiating this problem from NEC can be difficult.
- Other conditions with which a differential diagnosis can be made include: metabolic or respiratory acidosis, apnea of prematurity, bacteremia, candidiasis, enteroviral infections, gastroesophageal reflux, Hirschsprung's disease, and nosocomial infections.

IV.6.8. MANAGEMENT

Treatment of NEC depends on the degree of intestinal involvement. The objective staging criteria, developed by Bell and modified by Kliegmann and Walsh, have been widely adopted and help tailor treatment to the severity of the disease.

- **STAGE I – Suspected disease**
- **I A**
    - mild, nonspecific systemic signs (lethargy, apnea, bradycardia, temperature instability)
    - mild gastrointestinal signs (gastric residue, vomiting, mild abdominal distension)
    - Normal abdominal radiograph or with mild abdominal distension

- **Stage I B**
  - The same signs as in Stage I A, plus occult hematochezia.
- **STAGE II – Established disease ("medical" stage)**
- **Stage II A**
  - slightly altered general condition
  - intestinal signs include those from Stage I, with the addition of abdominal dullness and distension
  - Radiological signs include ileus, intestinal wall edema, persistent rigid fixed bowel loops, or intestinal pneumatosis
- **II B**
  - altered general condition
  - moderate metabolic acidosis, mild thrombocytopenia
  - abdominal distension accompanied by tenderness, erythema of the abdomen, palpable mass in the lower outer quadrants, gross hematochezia
  - Abdominal radiography shows air in the portal vein, with or without ascites.
- **STAGE III – Advanced disease (surgical stage)**
- **III A**
  - severely impaired general condition, but without perforation
  - Systemic signs are required for diagnosis: hypotension, bradycardia, apnea, respiratory failure, severe metabolic acidosis, coagulopathy, signs of septic shock—neutropenia
  - abdominal examination reveals marked distension with signs of generalized peritonitis, massive gastrointestinal hemorrhage
  - Abdominal X-ray shows clear signs of ascites
- **III B**
  - all signs of stage III A but with pneumoperitoneum

NEC is a neonatal emergency requiring complex multidisciplinary management. The goals of drug therapy are:

- Eradication of systemic and intestinal infection;
- Reduction of inflammation and tissue necrosis;
- Hemodynamic and metabolic stabilization;
- Prevention of complications (perforation, sepsis, shock, multiple organ failure).

A. NON-PHARMACOLOGICAL

In cases of suspected NEC, enteral feeding should be suspended, nasogastric decompression performed, central or peripheral venous access established, and parenteral nutrition initiated. Optimal intravenous nutrition should provide approximately 120 kcal/kg/day. Low-volume, low-concentration enteral feeding may be resumed 7–10 days after the abdominal X-ray returns to normal in cases of non-surgical NEC. Once feeding is resumed, the newborn's stools should continue to be checked for occult blood, abdominal distension, and vomiting, and feeding should be stopped again if any of these occur.

Resuming feeding in newborns who have undergone surgery may be delayed and depends on the extent of the resected intestinal segment, the resumption of intestinal motility, the timing of anastomosis, and the surgeon's preferences.

B. PHARMACOLOGICAL

1. Antibiotic Therapy

Pharmacological treatment is the cornerstone of NEC management. Antibiotics are administered empirically, immediately upon suspicion of NEC (particularly Bell stage $\geq$ II). Broad-spectrum antimicrobial agents are used in combination. The combination of Ampicillin + Gentamicin + Metronidazole/Clindamycin is typically used, but this must be adapted based on the nosocomial pathogens in each ICU-NICU. In cases of suspected stage III NEC, antibiotics covering the anaerobic spectrum should be indicated.

2. Vasopressors

Vasopressors (Dopamine, Dobutamine, Epinephrine) are used to maintain adequate tissue perfusion and oxygenation when the newborn has severe hypotension that does not respond to fluid administration. In severe necrotizing enterocolitis (Bell stage III), systemic inflammation and sepsis can lead to: generalized vasodilation (distributive shock), decreased cardiac output, tissue hypoperfusion → additional intestinal ischemia. In these cases, vasopressors are vital to maintain minimal cerebral, renal, and intestinal perfusion until the infection is controlled.

Table 3. Vasopressors used in SHS

Pathology	Vasopressor agent	Action
Hypotension with low cardiac output	**Dobutamine**	Stimulates contractility
Predominantly vasodilatory hypotension (septic shock)	**Dopamine→Adrenaline/Norepinephrine**	Increases systemic vascular tone
Catecholamine-refractory hypotension	**Vasopressin**	Restores sensitivity to catecholamines
Post-shock cardiac dysfunction	**Milrinone**	Inotropic effect + moderate vasodilator
SEPSIS with septic shock	**Dopamine (initially) ± Epinephrine/Norepinephrine**	Maintenance of vital perfusion

3. Pain management

Analgesics such as morphine or fentanyl are administered to control abdominal pain and discomfort or to reduce metabolic stress and oxygen consumption. Nonsteroidal anti-inflammatory drugs (NSAIDs) are avoided as they may exacerbate intestinal ischemia.

4. **Antifungal therapy**

Antifungal medication, such as Fluconazole or Amphotericin B, is considered in cases of prolonged antibiotic therapy (over 10 days) or in cases of enterocolitis with negative blood cultures.

5. Supportive adjunctive drug therapies include:

- Lactoferrin – a natural glycoprotein with antibacterial, anti-inflammatory, and immunomodulatory effects. It is used prophylactically to reduce the risk of NEC and sepsis (not as primary treatment). Some studies show benefits in prevention, but there is limited evidence for its use as an adjunctive treatment.
- Probiotics such as *Lactobacillus rhamnosus GG*, *Bifidobacterium breve*, and *Saccharomyces boulardii* are microorganisms that produce lactic acid (which acidifies the intestinal contents and inhibits the growth of certain pathogenic bacteria) and aim to restore beneficial gut microbiota.
- Growth factors and experimental cytokines**:** Epidermal Growth Factor (EGF), GLP-2, secretory IgA, arginine — under investigation for their protective role in the intestinal mucosa. They are not approved for standard clinical treatment.

C. SURGICAL

Surgical treatment of necrotizing ulcerative enterocolitis is an essential component in advanced forms of the disease (Bell stage III), where medical therapy is no longer sufficient. The goal of surgical treatment is to remove necrotic or perforated intestinal segments, control intra-abdominal sepsis, maintain digestive continuity (if possible), and preserve as much viable intestine as possible to prevent short bowel syndrome.

Indications for surgery may include:

a. Absolute (clear, urgent):

- Pneumoperitoneum (free air below the diaphragm → radiologically confirmed perforation)
- Clinical peritonitis (hard, fixed abdomen with parietal erythema)
- Rapid deterioration of general condition despite appropriate medical therapy (within 24–48 h)
- Severe refractory metabolic acidosis

- Progressive thrombocytopenia / uncontrolled sepsis
- Fixed abdominal masses suggestive of extensive necrosis or abscess

b. Relative:

- Progressive abdominal distension unresponsive to decompression
- X-ray showing fixed loops and signs of parietal necrosis
- Failure to restore bowel transit > 10–14 days

Table 4. Main types of surgical procedures

Type of intervention	Indications	Advantages	Disadvantages
Exploratory laparotomy + intestinal resection + stoma	Perforation, limited necrosis	Direct visualization of lesions, drainage of sepsis	Requires reoperation to restore continuity
Laparotomy with resection and primary anastomosis	Limited necrosis, viable proximal/distal intestine	Preserves intestinal continuity	Increased risk of dehiscence and fistula
Primary peritoneal drainage	Premature infants <1000 g or critically ill, inoperable	Minimally invasive, decompression effect, and partial control of sepsis	May subsequently require laparotomy (≈50%)
Laparoscopy (in specialized centers)	Uncertain diagnosis / limited extent	Accurate diagnosis, minimally invasive	Technically difficult in newborns <1.5 kg

Postoperative management in necrotizing enterocolitis consists of:

- Hemodynamic stabilization and correction of metabolic imbalances
- Control of sepsis and prevention of nosocomial infections
- Ensuring adequate nutrition (parenteral and subsequently enteral)
- Maintaining the integrity of the remaining intestine and preventing mechanical complications
- Close monitoring of vital signs and clinical progress

Postoperative nutrition involves several stages, such as:

- **Phase I – Total Parenteral Nutrition (TPN):**
  - Initiated immediately postoperatively.
  - Administered via a central venous catheter (preferably percutaneous).
  - Provide:
    - Glucose 6–10 mg/kg/min
    - Amino acids 2–3 g/kg/day
    - Lipids 2–3 g/kg/day
    - Electrolytes, trace elements, and vitamins adjusted daily.
- **Phase II – Resumption of enteral feeding:**
  - Begins after 7–14 days, when there are signs of resumed bowel movement (gas through the stoma, bowel sounds).
  - Breast milk is the food of choice.
  - Gradually increase the volume (1 ml/kg/hour → progressively).
  - Hydrolyzed formulas may be used if breast milk is unavailable.
  - Monitor gastric residues and stool appearance.

An important aspect of postoperative management is stoma care:

- Daily check of viability (pink color, normal flow).
- Protect the peristomal skin with hydrocolloid paste/barrier.
- Monitoring output (ileostomies may have significant fluid and electrolyte losses).
- Compensatory rehydration (Na^+ , K^+ , bicarbonate).
- Monitoring for signs of stenosis, retraction, or prolapse.

Surgical complications of NEC are a major cause of late neonatal mortality. They require multidisciplinary management: surgeon, neonatologist, nutritionist, infectious disease specialist. Parenteral nutrition and careful progression of enteral feeding are key to recovery, and early diagnosis of strictures and short bowel syndrome is essential for prognosis.

Table 5. Postoperative complications and management

Complication	Time of onset	Management
Anastomotic dehiscence / fistula	3–7 days postoperatively	Drainage, antibiotic therapy, possible reoperation
Intra-abdominal abscess / persistent sepsis	5–10 days	Ultrasound / CT, surgical or percutaneous drainage
Short bowel syndrome	Late	Prolonged parenteral nutrition, high-calorie diet, possibly reconstructive surgery
Electrolyte disturbances (hyponatremia, acidosis)	Early	Careful fluid management
Recurrence of NEC	late (after resumption of feeding)	Reassessment of feeding, probiotics, lactoferrin
Growth delay	chronic	Long-term nutritional monitoring

Consequently, therapeutic management depends on the stage of ulcerative necrotizing enterocolitis. The following summarizes treatment and progression based on staging.

- **STAGE I – suspected NEC**

Signs: food intolerance, abdominal distension, bilious vomiting, without obvious pneumatosis.
Treatment:

- Total digestive rest (NPO)
- Gastric decompression (orogastric tube with continuous suction)
- Total parenteral nutrition (TPN)
- Empirical antibiotic therapy:
    - **Ampicillin + Gentamicin** (10 days)
    - Add **Metronidazole** if anaerobes are suspected
- Continuous monitoring: BP, urine output, serial X-rays
- Correction of fluid, electrolyte, and acid-base balance

Course: if symptoms resolve within 48–72 hours → gradual resumption of feeding; if they worsen → Stage II.

- **STAGE II – Confirmed NEC**

Signs: intestinal pneumatosis, air in the portal system, abdominal tenderness, leukocytosis/leukopenia.
Treatment:

- Complete digestive rest
- Permanent gastric decompression
- Broad-spectrum antibiotic therapy:
    - Ampicillin + Gentamicin + Metronidazole (covers Gram-positive, Gram-negative, and anaerobic bacteria)
    - Alternatively: Cefotaxime + Metronidazole
    - If MRSA risk: add Vancomycin
- Duration of therapy: 10–14 days (depending on clinical course)
- Intravenous fluid support: isotonic fluids, correction of acidosis, transfusion if Ht <30%
- TPN until bowel movements resume
- Monitoring: abdominal X-rays every 6–12 hours, blood cultures, inflammatory markers

Course: if stabilized → gradual tapering of antibiotics; if distension, acidosis, or pneumoperitoneum persists → Stage III.

- **STAGE III – Advanced/Complicated NEC**

Signs: peritonitis, pneumoperitoneum, hypotension, metabolic acidosis, oliguria, severe thrombocytopenia.

Treatment:

- Broad-spectrum antibiotic therapy:
  - Piperacillin–Tazobactam or Meropenem (complete coverage of Gram+/– bacteria and anaerobes)
  - +/Vancomycin if MRSA risk
  - +/Fluconazole (prophylactic antifungal, especially with central catheters)
- Hemodynamic support: Dopamine / Dobutamine
- Metabolic correction + total parenteral nutrition
- Controlled analgesia / sedation
- Urgent surgical evaluation:
  - Confirmed pneumoperitoneum
  - Clinical deterioration despite optimal therapy
  - Palpable masses or peritonitis

Postoperative: continue antibiotics for 10–14 days after surgery; adjust based on intraoperative cultures.

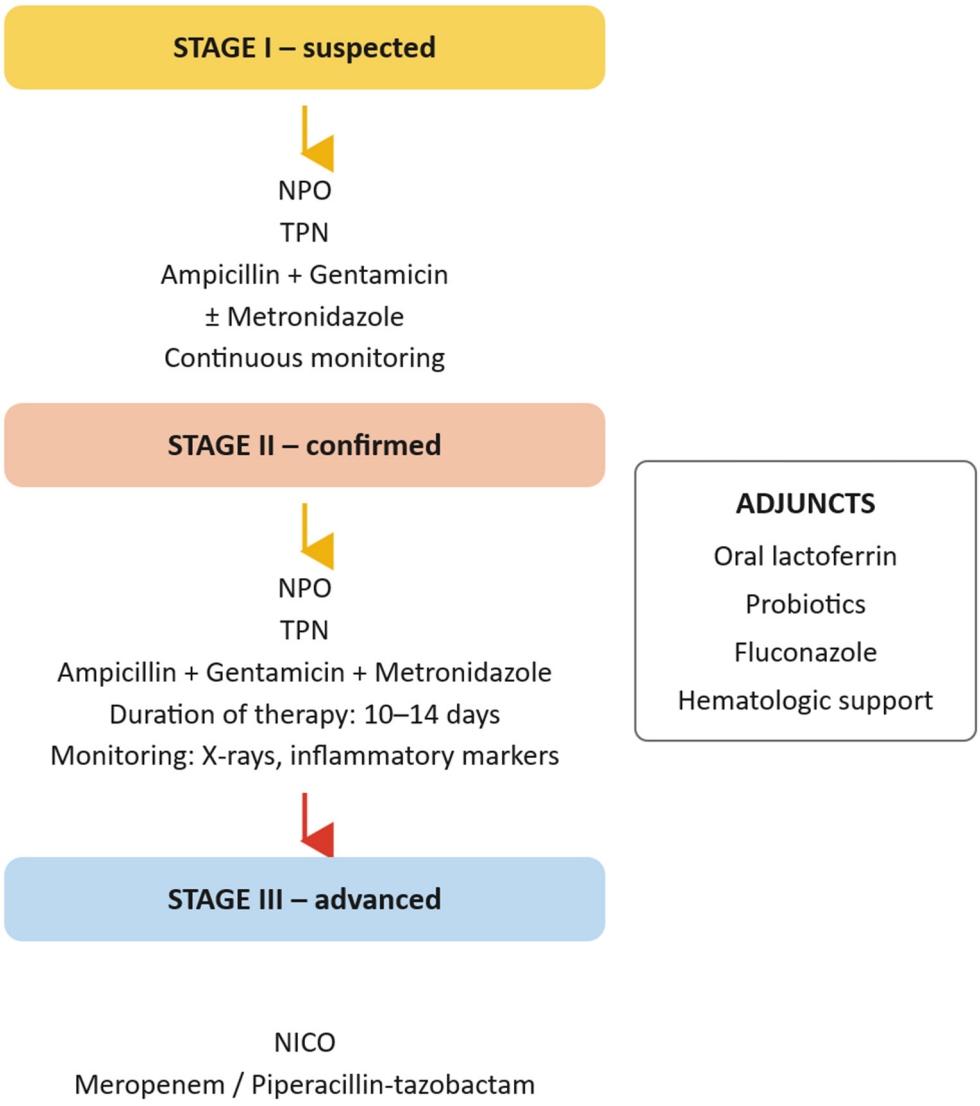

Figure 5. Drug therapy according to NEC stages

IV.6.9. PROGNOSIS

Approximately 75% of NEC patients survive, but among those requiring surgical treatment during the acute phase of the disease, survival is reduced. Of the survivors, 50% develop long-term complications, the most common being intestinal strictures and short bowel syndrome.

With the advancement of neonatal intensive care, including mechanical ventilation, anesthetic techniques, and total parenteral nutrition, the survival rate of newborns with NEC has improved slowly but steadily over the years. Although the mortality rate remains high, some studies have shown survival rates of 70–80% in newborns who underwent surgical treatment for NEC.

Efforts to reduce the incidence of NEC should focus on controlling nosocomial infections in neonatal intensive care units, improving the immune mechanisms of the preterm infant, promoting gastrointestinal tract maturation, inhibiting inflammatory mediators, and reducing the enteral bacterial load.

IV.7. SURGICAL DIGESTIVE DISORDERS OF THE NEONATAL PERIOD

Neonatal surgical digestive disorders represent a group of malformations or acute pathologies that require rapid evaluation and surgical intervention to prevent severe complications such as intestinal ischemia, perforation, sepsis, severe malnutrition, and mortality. These situations require a multidisciplinary neonatology–pediatric surgery approach, initial stabilization, and prompt surgical decision-making.

Clinical hint: bilious vomiting in a newborn = surgical emergency until proven otherwise.

IV.7.1. ESOPHAGEAL ATRESIA

- **Definition**

A congenital malformation characterized by an interruption in the continuity of the esophagus, with or without abnormal communication between the esophagus and the trachea.

- **Epidemiology**
  - ~1/3000 births
  - Frequently associated with other malformations: VACTERL (vertebral, anorectal, cardiac, tracheoesophageal, renal, limb)
- **Pathophysiology**

The esophagus does not form completely → saliva and milk cannot reach the stomach; if a fistula is present, air enters the stomach → distension, risk of aspiration.

- **Risk factors**
  - Chromosomal abnormalities
  - Genetic syndromes
  - Maternal polyhydramnios (common prenatal sign)
- **Clinical diagnosis**
  - Excessive salivation, foamy mouth
  - Cyanosis during feeding
  - Difficulty inserting the nasogastric tube → it stops "up high"

Prenatal sign: polyhydramnios + small or absent stomach on ultrasound

- **Laboratory findings**
  - X-ray showing the tube stuck in the esophagus
  - Gastric air present in cases with fistula
- **Differential diagnosis**
  - Esophageal atresia without fistula (stomach without air)
  - Upper gastrointestinal obstructions
- **Management**
- Initially:
  - Antireflux position

    - Continuous suction of saliva
    - Withhold food
    - IV fluids
- Definitive: surgical reconnection
- **Prognosis**

Excellent with early diagnosis; guarded if severe associated malformations are present.
Clinical hint: Salivation + cyanosis + inability to pass the tube = AO until proven otherwise.

IV.7.2. HYPERTROPHIC PYLORIC STENOSIS

- **Definition**

Progressive thickening of the pyloric muscle → gastric obstruction → repeated vomiting.

- **Epidemiology**
    - Typical onset: 2–6 weeks
    - More common in boys (4:1)
- **Pathophysiology**

Pyloric hypertrophy → narrowed lumen → impaired gastric emptying → hypchloremic metabolic alkalosis.

- **Risk factors**
    - Male
    - Family history
    - Possible association with early macrolide administration
- **Clinical**
    - Projectile vomiting, non-bilious
    - No bile (the obstruction is proximal to the ampulla of Vater)
    - Weight loss
    - Classic sign: palpable “pyloric olive” (not always evident)
- **Laboratory**
    - Abdominal ultrasound (the test of choice)
    - Hypchloremic metabolic alkalosis
- **Differential diagnosis**
    - severe gastroesophageal reflux
    - Allergy to cow's milk protein
- **Management**
    - Correction of fluid and electrolyte imbalances
    - Surgery (pyloromyotomy)
- **Prognosis**

Excellent with treatment.
Clinical hint: Vomiting + hunger immediately afterward = pyloric obstruction until proven otherwise.

IV.7.3. INTESTINAL MALROTATION AND VOLVULUS

- **Definition**

Abnormal intestinal positioning → risk of acute mesenteric torsion (volvulus) → severe ischemia.

- **Epidemiology**
    - It often occurs in the first few days or weeks
    - Volvulus = life-threatening
- **Pathophysiology**

Malrotation → short, mobile mesentery → volvulus → ischemia, necrosis.

- **Clinical**
    - Bile-stained vomiting (cardinal sign)
    - Variable distension
    - Lethargy, hemodynamic instability

- **Laboratory**
  - X-ray, ultrasound, possibly contrast
  - Immediate surgical intervention if strongly suspected
- **Management**
  - Rapid stabilization
  - Emergency surgery (*Ladd* procedure)
- **Prognosis**

Excellent if treated before ischemia; poor if delayed.

IV.7.4. INTESTINAL ATRESIA

- **Definition**

Absence of the intestinal lumen (jejunal/ileal/duodenal), congenital cause of obstruction.

- **Clinical presentation:**
  - vomiting (bile-stained if beyond the papilla of Vater)
  - abdominal distension
  - absence of meconium passage
- **Management:** Stabilization + surgery.

Hint: Absence of bowel movements + bilious vomiting = severe obstruction.

IV.7.5. HIRSCHSPRUNG'S DISEASE

- **Definition**

Absence of enteric ganglion cells (aganglionosis) → spastic colon, obstruction.

- **Clinical presentation:**
  - delayed passage of meconium >24–48 hours
  - distension, vomiting
  - episodes of severe enterocolitis

Hint: Newborn without meconium = Hirschsprung's disease until proven otherwise.

- **Diagnosis**: Rectal biopsy (standard)
- **Management**: Surgical (pull-through).

IV.7.6. GASTROSCHIZIS AND OMAFOLCEL

- Gastroschisis: Protrusion of intestinal loops through a parietal defect, without a membrane
- Omphalocele: herniation covered by a membrane, frequently associated with malformations

Clinical: The organs are visible externally at birth.

Management:

- Sterile draping, prevention of hypothermia
- Fluids, respiratory support
- staged surgery

Tip: Gastroschisis = exposed intestine → risk of infection & fluid and electrolyte loss.

IV.7.7. SPONTANEOUS INTESTINAL PERFORATION

Important distinction from NEC, especially in ELBW preterm infants.

- Earlier onset
- No marked pneumatosis
- Associated with steroids, indomethacin
- Treatment: drainage ± surgery

IV.7.8. CONCLUSIONS

A short mnemonic for neonatal surgical pathology:

- Saliva + cyanosis + feeding tube that does not pass = esophageal atresia
- Non-bilious vomiting + immediate hunger = pyloric stenosis

- Bile-stained vomiting = emergency surgery!
- No meconium + distension = Hirschsprung's disease
- Intestines protruding = gastroschisis/omphalocele

Self-assessment questions

1. What is the cardinal sign of high intestinal obstruction?
2. Why does delayed meconium passage suggest Hirschsprung's disease?
3. What distinguishes gastroschisis from omphalocele?
4. How do you recognize pyloric stenosis?
5. Why is bilious vomiting a medical emergency?

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V. PATHOLOGY OF THE RENAL-URINARY SYSTEM

V.1. GENERAL CONCEPTS OF EMBRYOLOGY

A. Embryonic origin of the urinary system

The urinary system originates in the intermediate mesoderm, at the level of the nephrogenic crest. From this structure, three paired renal systems develop successively, corresponding to different stages of embryonic development, reflecting a progressive process of differentiation and specialization.

B. Transitional Embryonic Renal Systems

The first two renal systems—the pronephros and the mesonephros—are temporary and of limited functional importance in humans.

- **The pronephros** appears early but regresses rapidly, without a significant functional role.
- **The mesonephros** is active for a limited period and subsequently participates in the development of the reproductive system:
    - In males, the mesonephric duct and tubules (Wolffian ducts) contribute to the formation of the efferent ducts of the epididymis, the vas deferens, the ejaculatory ducts, and the seminal vesicles;
    - in females, these structures regress almost completely, persisting only as embryonic vestiges (epophoron and parophoron).

C. Metanephros – the definitive kidney

The metanephros constitutes the definitive kidney and begins to develop around the 5th week of gestation. It results from the interaction of two distinct embryonic components:

- **the ureteric bud**, which will give rise to the collecting system (ureter, renal pelvis, and calyces);
- **the metanephric blastema**, from which the nephrons differentiate.

The pyelocaliceal system is well defined by weeks 13–14 of gestation, and nephrogenesis continues until approximately weeks 34–36. The final number of nephrons ranges from 300,000 to 1,800,000 per kidney, with an average of approximately 900,000; these nephrons lack the ability to regenerate. Renal excretory activity begins around the 12th week of intrauterine life. The kidneys reach their definitive lumbar position around the eighth week of gestation.

Stages of Nephron Development

Nephron development proceeds through four successive stages:

1. the appearance of the renal vesicle;
2. its transformation into a comma-shaped structure;
3. the capillary loop stage;
4. complete maturation of the nephron, including the proximal and distal tubules, the loop of Henle, the juxtaglomerular complex, and a portion of the afferent arteriole.

During this stage, the renal interstitium also differentiates into cortical and medullary structures. Any disruption of these processes can lead to a reduction in the number of nephrons. After birth, pathological factors can only further reduce the existing number of nephrons.

D. Development of the lower urinary tract

The development of the kidneys is closely linked to the formation of the lower urinary tract:

- in the 5th week, the mesonephric duct opens into the cloaca and allantois;
- in the 6th week, the urorectal septum forms, separating the posterior digestive compartment from the urogenital sinus;
- in the 7th week, distinct ureterovesical orifices appear;
- the allantois regresses, forming the urachus, which contributes to the formation of the upper portion of the bladder;
- the bladder trigone originates from the remnants of the Wolffian duct.

Sexual differentiation results in:

- in females, the development of the Müllerian structures, which will form the vaginal vestibule, vagina, and cervix;

- in males, the regression of the Müllerian system and its contribution to the formation of the prostatic urethra.

Disorders occurring at any stage of development can lead to congenital anomalies, such as renal agenesis, renal hypoplasia, renal ectopia, renal dysplasia, or cystic kidney diseases.

E. Functional development of the kidney

At birth, the kidneys take over the placenta's role in maintaining fluid and electrolyte homeostasis and in eliminating metabolic waste products. This transition is marked by a progressive increase in renal blood flow, glomerular filtration rate (GFR), and the maturation of tubular functions. For this reason, renal function correlates more closely with postnatal age than with gestational age.

1. Renal blood flow

During intrauterine life, renal blood flow accounts for only 2–3% of cardiac output. After birth, it increases rapidly, reaching 15–18%, as a result of decreased renal vascular resistance, increased systemic blood pressure, and the progressive redistribution of blood flow to the renal cortex. The renal artery enters through the renal hilum, near the medulla. 90% of arterial blood is directed to the cortical glomerular capillaries, and only 10% to the medulla. The cortical arteries have extensive branching, particularly afferent arterioles around the glomeruli. The glomerular arterioles have high-resist, allowing for filtration of ~125 mL/min. The peritubular capillaries have high oncotic pressure, reabsorbing solutes and fluids from the glomerular filtrate

2. Glomerular filtration

Glomerular filtration begins with the appearance of the first nephrons and increases proportionally with somatic and renal development. At birth, the glomerular filtration rate (GFR) is low, especially in preterm infants, but it increases progressively. In full-term newborns, GFR doubles in the first two weeks and reaches adult levels around one year of age.

Reference values for GFR:

- extremely preterm (24 weeks): ~0.5 mL/kg/min
- term newborn: 20–30 mL/min/1.73 m²
- progressive increase to values close to adult levels by 1–2 years

3. Tubular function

- **Sodium regulation**

The capacity for tubular sodium reabsorption begins to develop after 24 weeks of gestation, becoming effective after 34 weeks. At this stage, up to 99% of filtered sodium is reabsorbed, with a sodium excretion fraction of less than 1%.

- **Water regulation**

Newborns have a limited ability to concentrate urine, due to the low concentration of urea in the renal interstitium. Thus, the maximum urine osmolarity is approximately 500 mOsm/L in preterm infants and 800 mOsm/L in full-term newborns.

- **Potassium Regulation**

Preterm infants have a reduced capacity for potassium excretion due to decreased sensitivity to aldosterone, reduced Na^+ /K^+ -ATPase activity, and reduced GFR. This explains the slightly elevated serum potassium levels compared to older children.

- **Acid-base balance regulation**

Acidity control is limited by the low threshold for bicarbonate reabsorption in the proximal tubule. Preterm infants frequently present with a mild form of proximal tubular acidosis, which improves as tubular function matures.

Serum bicarbonate:

- preterm: 16–20 mEq/L
- full-term newborn: 19–21 mEq/L

- **Calcium and phosphorus metabolism**

Phosphate reabsorption increases progressively with gestational age, from approximately 85% at 28 weeks to 98% at term. Urinary calcium excretion is reduced in preterm infants and subsequently increases p . Neonatal stress and certain therapies can exacerbate urinary calcium losses, promoting hypocalcemia or nephrocalcinosis.

4. Fetal Urine and Amniotic Fluid

In the first half of pregnancy, the contribution of fetal urine to amniotic fluid volume is minimal, but it increases significantly thereafter. Oligohydramnios or polyhydramnios may signal renal developmental abnormalities or other fetal pathologies.

In the first days of life, renal function is relatively immature, characterized by low GFR, limited concentrating ability, and incomplete electrolyte regulation. The newborn exhibits reduced renal efficiency relative to metabolic needs, which requires caution in the administration of fluids and medications with renal elimination. Careful monitoring of weight, fluid balance, and electrolyte levels is essential, particularly in preterm infants, who are prone to fluid and electrolyte disturbances, including non-oliguric hyperkalemia.

V.2. GENERAL ANATOMY

1. General Considerations

In the newborn, the kidneys are a pair of morpho-functionally immature organs, adapted to extrauterine life, with anatomical and structural features distinct from those of adults. Structural renal development is complete at birth, but functional maturation continues during the first years of life.

2. Location and Anatomical Relationships

The newborn's kidneys are located retroperitoneally, on either side of the spine, but are positioned lower than in adults.

- The upper poles are located approximately at the L1–L2 level.
- The right kidney is situated slightly lower than the left.
- The kidneys are more mobile due to the reduced amount of perirenal adipose tissue.

3. Dimensions and External Appearance

- The average length of the kidney in a newborn is 4–5 cm.
- The weight of each kidney is approximately 10–12 g.
- The renal surface is lobulated, reflecting the persistence of fetal lobulation, which is normal at this age.

4. Internal structure – cortex and medulla

- The renal cortex is relatively thin compared to the medulla.
- The medulla is well developed, and the renal pyramids are prominent.
- The corticomedullary ratio differs from that of adults, which influences the ability to concentrate urine.

5. Pyelocaliceal system

- The calyces and renal pelvis are relatively wide and compliant, a feature that may promote transient dilations.
- This characteristic explains the increased frequency of physiological pyeloectasis in newborns.

6. The nephron

- At birth, the kidney contains the final number of nephrons (≈ 1 million/nephron/kidney).
- However, the nephrons are functionally immature, particularly at the level of the tubules.
- Glomerular filtration rate is reduced immediately after birth and increases progressively during the first few weeks.

7. Renal Vascularization

- Renal blood flow is relatively low at birth.
- Blood flow is initially distributed primarily to the medulla, with a progressive increase in cortical perfusion.
- This characteristic explains the newborn's susceptibility to renal ischemia.

8. Innervation and lymphatic drainage

- Renal innervation is predominantly sympathetic and immature.
- Lymphatic drainage occurs to the lumbar lymph nodes, similar to that in adults.

V.3. URINARY TRACT INFECTION

V.3.1. DEFINITION

Urinary tract infection (UTI) in the newborn is defined as the presence and multiplication of pathogenic bacteria in the urinary tract (kidneys, ureters, bladder, or urethra), confirmed by a positive urine culture obtained from a properly collected specimen, with or without clinical signs of systemic infection.

In newborns, UTI is often a severe bacterial infection with the potential for hematogenous spread, which is why it is frequently considered a form of neonatal sepsis.

V.3.2. EPIDEMIOLOGY. INCIDENCE

- Overall incidence: UTIs affect approximately 1% of term newborns and 3% of preterm infants (5–10% in very low birth weight [VLBW] preterm infants).
- Male newborns are affected 5 times more frequently, especially if uncircumcised.
- The condition may be the first manifestation of genitourinary malformations or vesicoureteral reflux (VUR).

V.3.3. PATHOPHYSIOLOGY

Neonatal urinary tract infection occurs via: ascending (from the bladder) (most common) or hematogenous spread.

- **Bacterial infections**

Escherichia coli is responsible for approximately 75% of infections. The remaining cases are caused by other Gram-negative bacilli (Klebsiella, Enterobacter, Proteus) and Gram-positive cocci (Enterococci, Staphylococcus epidermidis, Staphylococcus aureus). Enterococcus, a Gram-positive coccus, is the third most common causative agent, with an incidence of 10–16%.

The underdeveloped neonatal immune system not only increases the newborn's risk of infection but also makes them susceptible to a wider range of microorganisms compared to older children. In newborns with UTIs, Group B Streptococcus is more common than in older children.

- **Fungal infections**

Candida can be a causative agent of UTI, with a reported incidence of 25–42% in preterm infants admitted to neonatal intensive care units (NICUs).

V.3.4. RISK FACTORS

Risk factors for the development of UTIs include:

- immunological immaturity,
- vesicoureteral reflux,
- urinary stasis,
- urinary catheters.

The risk of UTI is determined by:

- the bacterial antigen—its quantity and virulence

Normal defense against UTIs, which includes:

- maintaining adequate urine flow
- complete bladder emptying.

Risk factors:

- prematurity;
- male gender (uncircumcised);
- urinary catheterization;
- neonatal sepsis
- maternal history of UTI

In newborns, host factors are often related to anatomy and include urogenital malformations, such as:

- posterior urethral valves,
- vesicoureteral reflux (VUR),
- phimosis,
- ureteropelvic junction obstruction,
- neurogenic bladder dysfunction secondary to spinal dysraphism

V.3.5. CLINICAL DIAGNOSIS

The diagnosis of UTI in newborns differs from that in older children. The initial evaluation should include:

1. **Detailed history**:

- birth and family history
- results of prenatal investigations, if performed

2. Signs and symptoms of urinary tract infection in newborns

The signs and symptoms of urinary tract infection (UTI) in newborns differ from those seen in older children. Nonspecific manifestations are described, such as:

- general malaise ("not feeling well")
- abdominal distension
- diarrhea
- vomiting
- failure to thrive
- temperature instability or fever > 38·0°C
- signs associated with bacteremia: respiratory distress or focal infection: omphalitis, cutaneous-mucosal candidiasis
- association with neonatal jaundice

Neonatal jaundice, especially when it begins after the 8th day of life, has been associated with neonatal urinary tract infections.

- In febrile newborns with UTI, 20–30% present with bacteremia
- For this reason, comprehensive investigations for sepsis are recommended in all febrile newborns

V.3.6. LABORATORY AND IMAGING STUDIES

Paraclinical diagnosis is based on laboratory tests and imaging studies.

A. Laboratory tests:

- Urine culture (diagnostic standard): $>10^3$ CFU/mL for invasive collection.
- Urinalysis: leukocyturia, nitrites, bacteriuria.
- Complete blood count: leukocytosis
- Blood culture: mandatory, risk of bacteremia 30–40%.
- CRP, procalcitonin: frequently elevated.
- Glomerular filtration rate (estimated based on creatinine).

Collecting urine samples from newborns

The simplest method: using sterile plastic collection cups.

- It carries a high risk of contamination, with a 75% false-positive rate for urine culture.
- Its true value lies only in ruling out UTI in the event of a negative result.

Superior methods:

1. Urethral catheterization

- Sensitivity: 95%
- Specificity: 99% for urine culture
- Catheterization may not be recommended in newborns:

- risk of urethral stricture in boys
- frequent contamination of cultures in girls

2. Suprapubic aspiration (more accurate, but more invasive)

- Contamination rate: 1%
- Recommended especially for:
  - boys with severe phimosis
  - girls with labial adhesions
- Topical anesthetics may be used to reduce pain associated with the procedure

Microscopic analysis

- Complements the simple analysis by counting white blood cells, red blood cells, and bacteria

B. Renal imaging:

- Bladder-kidney ultrasound
  - In the acute phase of UTI, it is the first-line imaging investigation in newborns.
  - Advantages: safe, noninvasive, inexpensive, and widely available.
  - RBUS should be performed routinely to assess urinary tract abnormalities, including:
    - Obstructions
    - renal structural abnormalities
    - stones or calcifications
    - perirenal abscesses or abdominal masses
  - A delayed vesicorenal ultrasound is also recommended after resolution of the UTI, for a more accurate assessment of anatomy and to avoid false positives due to edema
  - Renal ultrasound — mandatory after the acute episode (ideally within the first 48–72 hours).
- Other additional investigations:
  - Voiding cystourethrogram (VCUG)
    - The degree of reflux is determined by VCUG
    - Urine must be sterile prior to performing the VCUG
  - Renal scintigraphy
  - CT scan
    - Assessment of renal scarring and lesions
  - Voiding cystography — only if ultrasound indicates reflux or after 2 episodes of infection.

V.3.7. MANAGEMENT

A. NONPHARMACOLOGICAL

- mandatory hospitalization;
- monitoring of vital signs;
- correction of fluid and electrolyte imbalances;
- treatment of the infection should begin immediately after specimen collection

B. PHARMACOLOGICAL

1. Empirical antibiotic therapy (after culture collection)

Empirical therapy with broad-spectrum antibiotics should be initiated without delay, after collecting blood, urine, and CSF cultures. The goal of early treatment: prevention of urosepsis and renal scarring.

Choice of antibiotics:

- It is recommended to consider local resistance patterns and the mother's antibiotic history
- After cultures are obtained, adjust the antibiotic according to the sensitivity of the isolated organism
- Full-term newborn: Ampicillin + Gentamicin administered parenterally
- Preterm / suspected malformation: Cefotaxime ± Aminoglycoside

- Third-generation cephalosporins: excellent coverage for Gram-negative bacteria, without the nephrotoxicity of aminoglycosides.
- Alternatively (according to the European Association of Urology): ampicillin + ceftazidime
- Late-onset infections (>7 days) in hospitalized newborns
    - Vancomycin is recommended instead of Ampicillin to cover nosocomial organisms until final culture results are obtained

Duration of treatment:

- pyelonephritis: 10–14 days;
- lower urinary tract infection: 7–10 days.

C. FOLLOW-UP

If fever persists >48 hours → repeat imaging, suspicion of structural abnormality or pyogenic renal focus. Follow-up urine culture 3 days after completion of antibiotics. Many specialists recommend antibiotic prophylaxis until significant reflux or an anatomical abnormality is ruled out.

Prophylaxis:

- Amoxicillin 20 mg/kg/day until VCUG is performed
- If VUR is present, continued prophylactic treatment is recommended

D. SPECIAL SITUATIONS

- **Neonatal candiduria and candidemia**
    - Occur primarily in neonatal intensive care units
    - Associated with significant mortality and neurodevelopmental impairment in extremely low birth weight newborns (<1000 g)
    - In EBLW infants or those in the NICU, candiduria requires further investigation:
        - Blood culture
        - Lumbar puncture
        - Abdominal ultrasound
    - Treatment: amphotericin B or fluconazole

Inadequate treatment, particularly in the presence of urological anomalies, can lead to renal scarring, with a risk of developing hypertension and loss of renal function.

V.4. CONGENITAL NEPHROTIC SYNDROME

V.4.1. DEFINITION

Congenital nephrotic syndrome (CNS) is a rare form of nephrotic syndrome that occurs within the first 3 months of life, characterized by massive proteinuria, edema, hypoalbuminemia, hypogammaglobulinemia, a hypercoagulable state, and hyperlipidemia.

V.4.2. EPIDEMIOLOGY. INCIDENCE

CNS can be primary or secondary:

- Primary (genetic)
    - Most cases are caused by genetic defects in structural or regulatory proteins involved in the function of the glomerular basement membrane and/or podocytes.
    - The most common cause is mutations in the NPHS1 gene, which encodes the nephrin protein and is responsible for Finnish-type congenital nephrotic syndrome—the most common form in newborns
    - Other genes involved in the pathogenesis of congenital nephrotic syndrome include NPHS2 (which encodes podocin), WT1 (Wilms Tumor Protein 1), PLCE1, and LAMB2.
    - Genetic abnormalities in these genes lead to impaired podocyte function, which is why these conditions are classified as podocytopathies.
- Secondary
    - Caused by congenital/perinatal infections or underlying metabolic disorders. Congenital infections with: human immunodeficiency virus (HIV), cytomegalovirus (CMV), hepatitis B virus, rubella virus, congenital syphilis, congenital toxoplasmosis

- Metabolic diseases: rare tubulopathies, Fanconi syndrome, nephrogenic diabetes insipidus
- Maternal systemic lupus erythematosus, mercury poisoning, renal vein thrombosis, neonatal alloimmunization

Most cases of congenital nephrotic syndrome have a genetic etiology, being caused by monogenic defects in the structural proteins that make up the renal glomerular filtration barrier.

The most common cause is Finnish-type congenital nephrotic syndrome. This form is named for its high incidence in Finland and is inherited in an autosomal recessive manner.

Finnish-type congenital nephrotic syndrome is caused by a mutation in the NPHS1 gene, which encodes nephrin, one of the essential structural proteins of the glomerular filtration barrier. Because NPHS1 is expressed exclusively in renal podocytes, Finnish-type congenital nephrotic syndrome does not present with extrarenal manifestations.

Incidence of congenital nephrotic syndrome:

- 1–3 cases per 100,000 live births.
- Congenital nephrotic syndrome of the Finnish type (CNF) is common in Finland (incidence—1 case per 8,200 births).

V.4.3. PATHOPHYSIOLOGY

In Finnish-type congenital nephrotic syndrome, the primary defect consists of excessive protein loss at the renal level. This form of congenital nephrotic syndrome is caused by a mutation in the NPHS1 gene, located on chromosome 19, which encodes nephrin, one of the essential structural proteins of the glomerular filtration barrier. The impairment of the filtration barrier's integrity allows high-molecular-weight molecules, including plasma proteins, to pass into the urinary space, leading to massive proteinuria, a hallmark of congenital nephrotic syndrome.

Proteinuria leads to albuminuria, hypoalbuminemia, and edema. Hyperlipidemia occurs as a result of increased lipoprotein synthesis, secondary to hypoalbuminemia, which promotes platelet aggregation and thrombosis. The loss of minerals and vitamins predisposes to malnutrition and infections.

Hypothyroidism develops as a result of the loss of thyroid hormone-binding globulin in the urine.

The most characteristic histological change in Finnish-type congenital nephrotic syndrome is irregular microcystic dilation of the proximal tubule. The glomeruli are usually normal or may show matrix expansion and mesangial hypercellularity.

The Finnish type is suspected in cases of:

- fetal hydrops, accumulation of free extracellular fluid in the cavities and fetal tissue edema
- placental edema,
- a placenta weighing more than 25% above normal
- marked increase in alpha-fetoprotein.

Onset—in utero—marked increase in alpha-fetoprotein levels.

V.4.4. CLINICAL DIAGNOSIS

The clinical diagnosis is based on both family history and clinical manifestations.

1. **Clinical manifestations:**

- **Prenatal**
  - Enlarged placenta
  - Elevated amniotic alpha-fetoprotein
  - Possible hydronephrosis or fetal polyuria
  - In severe cases, fetal edema or ascites may be detected.
- **Postnatal**
  - Massive proteinuria (>1.5 g/m²/day)
  - Hypoalbuminemia (<2.5 g/dL)
  - Edema: due to decreased oncotic pressure; may be exacerbated by fluid overload or tubular deficits.

- Signs of generalized edema, including:
  - Pericardial effusions
  - Pleural effusions
  - Ascites
- Microscopic hematuria (sometimes)
- Common complications: thrombosis (10% of cases), severe bacterial infections, hypothyroidism, refractory anemia, vitamin and mineral deficiencies.
- Delayed growth and development without nutritional supplementation

2. History

- **Prenatal and perinatal history**
  - Placental weight less than 25% of the newborn's weight
  - Increased prenatal nuchal translucency
  - Fetal edema
  - Elevated alpha-fetoprotein in amniotic fluid
  - Oligohydramnios
- **Family history**
  - History of congenital nephrotic syndrome
  - Consanguinity
  - Ethnicity (relevant for genetic forms)
  - Early infant deaths
  - History of neurological disorders and kidney disease in childhood

V.4.4. LABORATORY AND IMAGING STUDIES

A positive diagnosis is based on paraclinical investigations beginning in the prenatal period and continuing into the postnatal period.

- **Prenatal**
  - Amniocentesis: elevated alpha-fetoprotein levels
  - Fetal ultrasound: enlarged placenta, large kidneys, or hydronephrosis
  - Congenital Finnish-type nephrotic syndrome can be diagnosed prenatally by measuring maternal serum alpha-fetoprotein in the second trimester, with values elevated more than 2.5 times the normal mean.
- **Postnatal**
- **Main investigations:**
  - Albumin <2.5 g/dL (usually <2 g/dL)
  - Massive proteinuria (urine protein-to-creatinine ratio >200 mg/mmol).
  - Hyperlipidemia, elevated LDL
  - Microscopic hematuria (25–30% of cases).
  - Variable C3/C4 complement levels (low in immune-mediated forms)
  - Genetic testing (NPHS1/NPHS2/WT1 mutations)
  - A renal biopsy is not indicated in the first few months if the genetic mutation is confirmed—major bleeding risk.
- **Thyroid evaluation**
  - TSH (thyroid-stimulating hormone): may be normal initially, but usually rises in the first month of life
  - Free T4 (free thyroxine): low
- **Blood chemistry**
  - Complete blood count
  - Serum levels: sodium, chloride, magnesium, protein, albumin, creatinine, urea, cholesterol, triglycerides (fasting), glucose
- **Other relevant tests**
  - Serum IgG level
  - Serum levels of: phosphate, ionized calcium, 25(OH)D3, alkaline phosphatase, PTH
  - Serum urea and creatinine levels: variable; renal function is often normal in the first months of life

- **Serum and Urine Tests**
  - Hypoalbuminemia (<2.5 g/dL) and low thyroid hormone levels
  - Urinalysis: severe proteinuria (>2000 mg/L), hematuria, leukocyturia, with negative urine culture
- **Imaging studies**
  - Renal ultrasound: normal-sized or enlarged kidneys, hyperechoic renal cortex.
  - Echocardiography: to assess left ventricular regurgitation and mass
- **Genetic diagnosis**
  - The method of choice for definitive confirmation of CNF is genetic testing, through detection of mutations in the NPHS1 gene
  - First-line genetic screening: NPHS1, NPHS2, WT1, PLCE1, LAMB2
  - Importance: establishes the etiology, enables genetic counseling, prevents complications (e.g., Wilms tumors for WT1 mutations).

V.4.5. MANAGEMENT

A. NON-PHARMACOLOGICAL

Nutrition is an important factor in non-pharmacological management and involves a high-calorie, high-protein diet, salt restriction, and supplementation with vitamins and minerals.

- High-calorie diet: 130 kcal/kg/day
- Fluid requirement: 100–130 mL/kg/day
- High-protein diet: 3–4 g/kg/day
- Breast milk and infant formula are used; supplemental protein is casein-based.
- Lipid supplementation: a mixture of rapeseed and sunflower oil

B. PHARMACOLOGICAL

The CNS does not respond to immunosuppressants.

- Objectives:
  - Maintain intravascular volume
  - Minimizing protein loss
  - Adequate nutritional support
  - Maintaining electrolyte balance
  - Preventing CNS-related complications

Supportive therapy

1. Intravenous albumin infusion – replaces lost proteins and stabilizes intravascular volume.
2. Increased protein intake (3–4 g/kg/day);
3. Diuretics (furosemide) – combined with albumin to reduce edema, with close monitoring. (Albumin injection 1 g/kg over 3–4 hours + diuretic).

Typical dose: 3–4 g/kg/day of 20% albumin, administered together with an intravenous bolus of furosemide (0.5 mg/kg).

4. Anti-proteinuric medication:
   - Angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers – to reduce proteinuria
   - Nonsteroidal anti-inflammatory drugs (NSAIDs), selective or non-selective—to reduce glomerular perfusion and intraglomerular pressure
5. Nutrition: high-calorie, high-protein diet, salt restriction, vitamin and mineral supplementation.
6. Monitoring for complications: thrombosis, infections, hypothyroidism, anemia, hypocalcemia, vitamin D deficiency.

Treatment is complex and multidisciplinary.

C. SURGICAL

Surgical procedures:

- Unilateral or bilateral nephrectomy: in cases of severe complications or when conservative therapy is insufficient.
- Kidney transplant: the definitive treatment, usually at 6–12 months of age, when the child reaches the appropriate weight (~10 kg).

D. FOLLOW-UP

Complications

- **Acute:** hypovolemia, hypervolemia, severe infections, thrombosis, intermittent hypertension
- **Chronic:** chronic kidney disease, dyslipidemia, osteodystrophy, hypothyroidism (due to urinary loss of thyroid hormone-binding proteins), growth and developmental delay
- **Post-transplant:** recurrence of proteinuria in cases of NPHS1 mutations (Fin-major)

Monitoring:

- daily weight;
- blood pressure (risk of hypertension);
- urinary protein;
- renal function (urea, creatinine);
- repeat ultrasound every 3–6 months.
- periodic evaluation by a pediatric nephrologist.
- Multidisciplinary monitoring (nephrologist, nutritionist, cardiologist, endocrinologist, psychologist) is mandatory.

V.3.9. PROGNOSIS

- The course of Finnish-type congenital nephrotic syndrome (CNF) is progressive, usually leading to end-stage renal disease by the age of 2–3 years.
- The prognosis is more guarded in patients with mutations in the NPHS1 gene compared to those with mutations in NPHS2.
- Without treatment, severe CNF can be fatal within the first few months of life.
- With conservative management and kidney transplantation, most children achieve growth and survival rates comparable to those with chronic kidney disease caused by other factors.
- The course of the disease depends on the genetic type and the severity of proteinuria.
- Secondary forms are reversible if the causative agent is treated.
- Conservative treatment prolongs survival, but progression to transplantation is usually predictable.
- Well-controlled congenital nephrotic syndrome allows the child to develop until the optimal time for transplantation. Without early management, neonatal mortality exceeds 60%.

Kidney transplantation is, in most cases, the only curative treatment.

- Renal transplant outcomes are **very good**
  - **5-year survival:** >90%
  - **Graft survival:** >80%

V.5. ACUTE KIDNEY FAILURE

V.5.1. DEFINITION

Neonatal acute renal failure (ARF) is a sudden decline in renal function, characterized by reduced glomerular filtration, impaired excretion of nitrogenous metabolic products (urea, creatinine), and the inability to regulate water, electrolyte, and acid-base homeostasis.

The term “acute kidney injury” (AKI) describes the entire spectrum, ranging from mild renal dysfunction to complete renal failure with anuria.

- **Diagnostic criteria for newborns**:
- Serum creatinine >1.5 mg/dL (132.6 μmol/L) in the context of normal maternal renal function, regardless of age or urine output,
- ARF/AKI can be classified as follows:
  - **Anuric**: absence of urine output for up to 24–48 hours
  - **Oliguric**: urine output <1 ml/kg/hour
  - **Non-oliguric**: urine output between 1–5 ml/kg/hour
  - **Polyuric:** urine output > 5 ml/kg/hour

- Anuric and oliguric ARF account for 40% of all forms of ARF in newborns.
- **Important characteristics**:
- Newborns may present with ARF/AKI even with normal urine output (e.g., in perinatal asphyxia).
- Normal urine output is approximately 1–5 mL/kg/hour, with most newborns urinating within the first 24 hours.
- **Interpretation of serum creatinine**:
- At birth, this reflects maternal renal function, so it is not an immediate indicator of neonatal renal function.
    - In term newborns, creatinine gradually decreases to 0.4–0.6 mg/dL around 2 weeks of age.
    - In preterm infants, this decline is slower, and initial values may be higher.
- Warning signs:
    - Increase in serum creatinine from baseline
    - Creatinine >1.5 mg/dL with normal maternal function
    - Decreased urine output is common in prerenal failure, hypoxic-ischemic injury, or cortical necrosis
    - Nephrotoxic renal injuries may have normal urine output

V.5.2. EPIDEMIOLOGY. INCIDENCE

- Overall incidence: 1–3% in term newborns.
- In VLBW preterm infants: 8–24%, and in those with severe sepsis or hypotension: up to 50%.

Neonatal ARF is almost always secondary to another critical condition (sepsis, asphyxia, NEC, hypotension). In some studies, up to 24% of newborns admitted to neonatal intensive care units exhibit some degree of renal failure. The prerenal form is the most common in newborns, being identified in up to 85% of cases. Intrinsic renal failure has an incidence of 6–8%, and the postrenal form of 3–5%. Mortality associated with neonatal ARF exceeds 40% if left untreated and 20% even with optimal treatment.

V.5.3. PATHOPHYSIOLOGY

There are numerous causes of renal failure in the newborn. These are usually classified into prerenal causes, intrinsic renal disorders (including vascular lesions), and obstructive uropathies.

Most factors causing acute renal failure (ARF) in newborns are prerenal in nature (e.g., hypoxia, hypovolemia, hypotension); primary intrinsic renal diseases and obstructive uropathy are much rarer. Neonatal ARF can be:

1. **Prerenal (70–80%)**

- caused by renal hypoperfusion without structural renal damage;
- reversible by restoring perfusion;
- the most common form of acute renal failure in the newborn.
- **Decrease in effective intravascular volume**
    - Hemorrhage
    - Dehydration
    - Inadequate fluid intake
    - Gastrointestinal losses (vomiting, diarrhea)
    - Hypoalbuminemia (congenital nephrotic syndrome, protein-losing enteropathies)
    - Renal or adrenal disorders with salt loss (tubular nephropathies, congenital adrenal insufficiency)
    - Diabetes insipidus (central or nephrogenic)
    - "Third-space" losses (neonatal sepsis, necrotizing enterocolitis, traumatized tissues)
- **Decrease in effective intravascular blood volume**
    - Congestive heart failure, congenital heart disease

- Pericarditis, cardiac tamponade
- Perinatal asphyxia with myocardial dysfunction

- **Increased renal vascular resistance**
  - Neonatal polycythemia
  - Indomethacin / Ibuprofen (ductus arteriosus closure)
  - Vasopressor drugs (dopamine, norepinephrine – high doses)
- **Hypoxia / asphyxia**
  - Important: if hypoxia is severe or prolonged → it may progress from prerenal to intrinsic renal failure (acute tubular necrosis).

2. Renal (intrinsic) (parenchymal) (10–20%)

- **Severe and/or prolonged renal hypoperfusion,** progressing to **acute tubular necrosis**
- **Congenital renal anomalies**
  - Renal agenesis
  - Renal hypoplasia/dysplasia
  - Polycystic kidney disease
- **Thromboembolic disorders**
  - Bilateral renal vein thrombosis
  - Bilateral renal artery thrombosis
- **Nephrotoxins**
  - Aminoglycosides, amphotericin B
  - Radiographic contrast agents
  - Maternal use of **captopril** or **indomethacin**

3. Postrenal (5–10%)

- **Urethral obstruction**
  - Posterior urethral valves
  - Urethral diverticulum
  - Strictures
  - Prune Belly Syndrome
- **Ureterocele**
- **Pyeloureteral / Ureterovesical Obstruction**
- **Extrinsic tumors**
- **Neurogenic bladder**
- **Megacystis-megaureter syndrome**

Prerenal renal failure occurs due to decreased renal perfusion in a structurally normal kidney. Early treatment of the underlying cause usually results in complete recovery of renal function. Severe or prolonged hypoperfusion can progress to intrinsic renal failure. The transition from the prerenal to the intrinsic form is gradual, due to the presence of compensatory mechanisms. Acute tubular necrosis (ATN) occurs when ischemic injury is severe or prolonged. The prognosis for ATN is generally good, except in severe cases (cortical necrosis). Recovery of renal function takes from a few days to several weeks. The recovery phase may be accompanied by polyuria, requiring careful monitoring of fluid and electrolyte balance.

In newborns, renal failure may be:

- congenital (renal dysplasia, obstructive uropathy, genetic disorders);
- acquired postnatally, most commonly due to asphyxia or sepsis.

Perinatal asphyxia is the leading cause of acute renal failure in term newborns. Sepsis is the most common cause in preterm infants. The risk of renal impairment is increased in newborns with r congenital heart defects; exposure to nephrotoxic medications (aminoglycosides, NSAIDs, contrast agents). Indomethacin can cause reversible renal dysfunction in preterm infants. Renal thrombosis causes renal failure if it is bilateral or occurs in a single kidney.

- Associated manifestations may include:
  - oliguria,

- hematuria,
- hypertension,
- thrombocytopenia.

V.5.4. CLINICAL DIAGNOSIS

A. Medical History

- **Family** history – family history of kidney or urinary tract disorders, kidney malformations, hypertension, other children with kidney disorders or who died during the neonatal period)
- **Perinatal History**
- Pregnancy history – identification of maternal risk factors
  - Maternal diabetes
  - Abnormal prenatal ultrasounds
  - Maternal medication, particularly those with nephrotoxic potential
  - Oligohydramnios
    - Renal agenesis or hypoplasia
    - Lower urinary tract obstruction (e.g., posterior urethral valves)
  - Polyhydramnios (VACTERL syndrome, Bartter syndrome)
- **Neonatal history**
  - Gestational age
  - Birth conditions: asphyxia, prematurity, shock, acute or chronic fetal distress
  - Fetal heart rate monitoring
  - Need for resuscitation at birth
- **Postnatal events:**
- episodes of hypotension
- administration of nephrotoxic medications

B. Clinical assessment of volume status

- **Signs of volume depletion / hypovolemia**
  - Cold extremities
  - Prolonged capillary refill time
  - Tachycardia
  - Oliguria (<1 mL/kg/hour) or anuria
- **Signs of hypervolemia / volume overload**
  - Tachypnea
  - Edema
  - Excessive weight gain
  - Elevated blood pressure
  - Gallop rhythm
  - Hepatomegaly

C. Clinical examination

- **Decreased or absent urine output**:
  - is often the primary presenting sign
  - most newborns urinate within the first 24 hours of life
  - the absence of urine output after 48 hours suggests an increased risk of renal abnormalities
- **Abdominal mass**, possibly present in:
  - distended bladder
  - polycystic kidneys
  - hydronephrosis
  - abdominal tumors
- **Potter's facies** – associated with renal agenesis
- **Myelomeningocele** – associated with neurogenic bladder

- **Pulmonary hypoplasia** – secondary to severe oligohydramnios
- **Prune Belly Syndrome**:
    - abdominal wall muscle hypoplasia
    - cryptorchidism
    - dilatation of the upper urinary tract

V.5.5. LABORATORY AND IMAGING STUDIES

In the immediate postnatal period, serum creatinine is influenced by maternal renal function and, consequently, is not a reliable marker of renal function in the newborn. Therefore, the interpretation of serum creatinine as a marker of renal failure must be performed in correlation with gestational age, postnatal age, as well as certain maternal factors.

In term newborns, the glomerular filtration rate increases rapidly after birth, leading to a progressive decrease in serum creatinine to levels between 0.4 and 0.6 mg/dL in approximately two weeks.

In preterm infants**,** this decrease occurs at a slower rate, reflecting renal functional immaturity.

An increase in serum creatinine of more than 0.3 mg/dL per day, associated with an increase in blood urea nitrogen (BUN) of more than 10 mg/dL per day, is a classic criterion suggestive of acute renal failure. Other criteria used include the persistence of plasma creatinine levels above 1.5 mg/dL for a duration of 24–48 hours, in the context of normal maternal renal function, or the maintenance of creatinine levels above maternal levels for a period of 5–7 days postnatally.

It is important to note that non-protein nitrogen levels can be influenced by extrarenal factors, such as hydration status and the degree of catabolism, aspects that must be taken into account when evaluating neonatal renal function.

A. Blood tests

- Complete blood count (CBC) with evaluation of erythrocyte morphology—may reveal thrombocytopenia (in cases of sepsis or renal vein thrombosis)
- Coagulation tests
- Serum electrolytes:
    - Na – usually hyponatremia. Elevated sodium is observed only in prerenal azotemia and severe dehydration
    - K – hyperkalemia frequently occurs in:
        - hypoxic-ischemic injury,
        - renal disorders associated with low urine output,
        - obstructive uropathies.
- Total protein, albumin, magnesium
- Blood gases
- Blood culture and C-reactive protein (CRP)
- Uric acid – elevated, especially post-asphyxia
- Blood urea nitrogen (BUN): 15–20 mg/dL suggests dehydration or renal failure.
- **Creatinine**: normal values in newborns:
    - Day 1: 0.8–1.0 mg/dL
    - Day 3: 0.7–0.8 mg/dL
    - Day 7: <0.6 mg/dL
    - In low-birth-weight newborns, <1.6 mg/dL may be considered a normal value.
    - General rule: a doubling of creatinine suggests a loss of ~50% of renal function.

B. Urinalysis:

- Hematuria (renal vein thrombosis, tumors, DIC, renal malformations)
- Pyuria (suggests urinary tract infection)
- Proteinuria: rare in newborns
    - protein excretion varies with gestational age
    - normal 0.15 mg/kg/hour, after the 3rd postnatal day

- (massive proteinuria = congenital nephrotic syndrome)
- Leukocyturia -> 2–5 cells/field – suspected urinary tract infection
- Glucosuria – tubular dysfunction
- Urinary osmolality – determine urine osmolality, urinary and serum sodium, and urinary and serum creatinine.
- Urine culture with antibiotic susceptibility testing
- Urinary electrolytes
- Urinary protein-to-creatinine ratio (from a spontaneous sample)

The following is calculated:

- **Fractional excretion of sodium (FENa):** may be of limited use in preterm newborns

$$\textbf{FENa (\%)} = \frac{\text{Na urinar} \times \text{creatinină plasmatică}}{\text{Na plasmatic} \times \text{creatinină urinară}} \times 100$$

- **Renal Failure Index (RFI)**
  - Note: values may be influenced by diuretics (e.g., furosemide).

$$\textbf{RFI} = \frac{\text{Na urinar} \times \text{creatinină plasmatică}}{\text{creatinină urinară}}$$

Table 6. Urinary indices in newborns used in the evaluation of acute renal failure / acute kidney injury

Index	Prerenal	Renal
Urinary osmolality (mOsmol/kg water)	≥ 400 mOsm/L	< 400 mOsm/L
Urinalysis	Normal	> 5 red blood cells/field of view
Urinary sodium (mmol/L)	31 ± 19	63 ± 35
Urinary/plasma creatinine ratio	29 ± 16	10 ± 4
Renal Insufficiency Index (RII)	< 3	≥ 3
Fractional Na excretion (%)	< 2.5	≥ 2.5

C. Imaging studies

- Abdominal/renal **ultrasound**
  - Identifies: hydronephrosis, dilated ureters, abdominal masses, distended bladder, renal vein thrombosis, presence of congenital anomalies of the kidneys and urinary tract.
  - In the case of an umbilical artery catheter (UAC): abdominal X-ray to verify the position of the catheter tip; avoid positioning near the L1 vertebra (origin of the renal arteries)
- **Abdominal X-ray**
  - May reveal: spina bifida, absent sacrum (associated with neurogenic bladder), displaced intestinal loop (space-occupying mass).
- **Renal scintigraphy**
  - Assesses renal parenchymal function, but accuracy is limited in newborns due to incomplete renal maturity.

D. Water loading test

- In the absence of volume overload or congestive heart failure:
  - Administer saline or colloid solution, 5–10 mL/kg IV, repeated if necessary.
  - If there is no response, administer furosemide 1 mg/kg IV.
  - If anuria/oliguria persists: investigate for obstruction above the bladder via ultrasound.
  - If there is no obstruction and the patient does not respond, the likely cause is intrinsic renal failure.

E. Monitoring

Table 7. Monitoring of parameters

Area	Parameters / Assessments	Frequency / Observations
Weight and vital signs	Weight, Blood pressure	Every 12 hours
Heart monitor	Arrhythmia detection	Continuous
Fluids	Strict documentation of fluid intake and output	Continuous / daily – cumulative balance
Medication	Medication assessment, monitoring of drug levels	Daily
Urine	• Dipstick: proteinuria, sediment (blood, casts, tubular debris) • Leukocytes and nitrites (infection) • Microscopy and culture • Electrolytes, urea, creatinine, osmolality	At each collection / as per protocol
Blood	• Urea, creatinine, Na, K (monitoring and blood gases if possible) • Blood gases and pH • Glucose • Calcium, phosphate, magnesium, albumin, complete blood count	• Urea, creatinine: every 12 hours • Blood gases, pH: every 4–8 hours • Glucose: every 4 hours • Others: daily

Clinical notes:

- Increased urine output: an early sign of improvement.
- Monitoring electrolytes during the polyuric phase
- Creatinine estimates may be misleading in the first few days; after 48–72 hours, they can be used, but the trend in values is more relevant than the absolute concentration
- Urea is influenced by tissue breakdown or reduced protein intake

V.5.6. MANAGEMENT

Assessment to determine the underlying cause of rising creatinine levels or decreased urine output is essential in the management of acute kidney injury (AKI).

A. Prophylactic

- Fluid intake
    - It is essential to ensure optimal fluid intake, particularly in very preterm infants, who are at risk of increased transepidermal water loss.
- Temperature control
    - Extra caution is recommended when using radiant heaters, compared to the increased humidity provided by the incubator, to prevent fluid and thermal imbalances.
- Maintaining blood pressure
    - Maintaining a safe blood pressure, appropriate to the newborn's clinical condition, should be monitored to protect renal perfusion and vital organ function.
    - Avoid administering nephrotoxic medications (aminoglycosides, NSAIDs).

B. Curative

Treatment should focus on:

1. treating the underlying cause,
2. preventing further kidney damage,
3. managing the consequences of impaired renal function

Doses of concomitantly administered medications should be adjusted based on estimated renal function.

1. **General**

- Supportive care with fluid and electrolyte balance, acid-base balance, and nutritional support
- blood pressure control
- treatment of the underlying cause (asphyxia, infections)
- optimization of cardiac output
- maintaining protein intake below 2 g/kg/day, while ensuring an adequate caloric intake from non-protein sources.
- It is recommended to place a urinary catheter for therapeutic purposes and to monitor renal function.

a. Prerenal renal failure

- Treatment consists of administering fluids to increase and restore renal perfusion, as well as correcting the underlying cause.
- Correct hypovolemia, taking care to avoid fluid overload in established renal failure.
- IV fluid administration: 0.9% sodium chloride – 10–20 mL/kg.
- Known or suspected bleeding: red blood cell transfusion, 10–20 mL/kg.
- Hypotension without fluid deficit: initiate inotropic infusion
- Duct-dependent circulation in congenital heart disease: maintain the ductus arteriosus open
- Sepsis: administer antibiotics according to protocol.

b. Postrenal renal failure

- Surgical approach for obstructive uropathy,
- Acute management involves removing the obstruction:
    - postrenal obstruction (e.g., posterior urethral valves) can be temporarily relieved with a urinary catheter until definitive surgical treatment is considered.
    - via percutaneous drainage (nephrostomy), depending on the level of obstruction.
- Prophylaxis of urinary tract infections may be indicated.

c. Intrinsic kidney disease

- Objective: to prevent worsening of renal damage.
- Management: correction of fluid and electrolyte imbalances and hypertension (hypertension may occur, especially in renal artery or vein thrombosis).
- **Medication:** Discontinue or adjust doses of renally excreted medications, if possible:
    - by extending the dosing interval
    - by reducing doses and monitoring blood levels of the drug
- **Diuretic therapy:** Furosemide (1–2 mg/kg/dose) may increase diuresis and support fluid management, but studies show that it does not alter the course of renal injury.
    - If the newborn does not respond to therapy, increased doses of the diuretic are not warranted.
    - The use of continuous infusion appears to be more effective and less toxic than bolus administration
- **Low-dose dopamine:** 2–5 mcg/kg/min may increase renal perfusion.
- **Biochemical monitoring:** Monitor for the frequent occurrence of:
    - hyponatremia,
    - hyperkalemia,
    - hyperphosphatemia,
    - hypocalcemia,
    - metabolic acidosis.
- **Consultation:** A consultation with a pediatric nephrologist is recommended.
- **Prognosis:** In most cases, renal function recovers within 24–48 hours.

2. **Fluid balance**

Monitor intake and output

- In cases of hypovolemia or hypotension, it is essential to correct these conditions before initiating fluid restriction.
- If signs of fluid overload appear, furosemide may be administered.

- Restrict fluid intake to the minimum volume necessary for maintenance.

Calculation of maintenance fluids

- Maintenance fluids are calculated as follows:

Fluide de întreținere = pierderi insensibile + diureză + pierderi gastrointestinale +20% for newborns cared for under a radiant heater

- **Insensible losses** (if the newborn is cared for in an incubator):
  - <1000 g: 60–80 mL/kg/day
  - 1000–1500 g: 40–60 mL/kg/day
  - 1500 g: 20 mL/kg/day
  - For newborns in a well-humidified incubator or receiving humidified respiratory support, the lower value is used.
- Administration of maintenance fluids: 10–20% glucose solution without electrolytes.
- If there is ongoing electrolyte loss (e.g., diarrhea, fistula), appropriate electrolytes should be added.
- Weighing: twice daily.
  - Changes in body weight are the best indicator of changes in hydration status.
  - A stable weight may indicate fluid overload, requiring a reduction in intake.
  - Goal: a daily weight loss of approximately 1% of body weight.

3. Management of complications:

A. Hyperkalemia

General principles

- Potassium (K^+) intake is stopped or reduced.
- Use low-K^+ milk formulas or K^+-free IV solutions.
- Treatment of hyperkalemia (K^+ ≥6 mEq/L) is performed as follows:
- Calcium
  - Administration: 10% calcium gluconate, 1–2 mL/kg IV, over 2–4 minutes, for cardiac protection.
  - Monitoring: Continuous ECG.
- Sodium bicarbonate
  - Administer 1 mEq/kg IV over 5–10 minutes.
  - Effect: shifts K^+ into cells, temporarily lowering serum potassium by ~1 mEq/L
- Glucose and insulin
  - Mechanism: shifts K^+ into cells, temporarily reducing serum K^+.
  - Frequent monitoring: blood glucose.
  - Maintain a ratio of 1–2 units of insulin to 4 g of glucose.
- Furosemide
  - May be administered for kaliuresis and natriuresis if volume expansion is present.
  - Dose: 1 mg/kg intermittently.
- Salbutamol
- Ion-exchange resins (Kayexalate)
  - Administered rectally at a dose of 1–1.5 g/kg (dissolved in normal saline at a concentration of 0.5 g/mL) or orally at a dose of 1 g/kg (dissolved in 10% glucose- e solution), as needed, to reduce serum potassium levels. The use of Kayexalate should preferably be avoided in low-birth-weight newborns due to the increased risk of intestinal perforation. Administration of a 1 g/kg dose of Kayexalate results in the elimination of approximately 1 mEq/L of potassium. Not routinely used
- Dialysis
  - Indication: hyperkalemia uncontrolled by drug therapy.
  - Methods:
    - Hemodialysis (HD) – the most effective method for removing K^+.
    - Peritoneal dialysis (PD) or continuous veno-venous hemofiltration (CVVH) – alternatives if HD is not feasible.

B. Hypokalemia – is rare, occurring during the resumption of diuresis and as a side effect of furosemide administration.

C. Acidosis

- Usually mild, except in cases of:
  - significant tubular dysfunction, with reduced bicarbonate reabsorption capacity,
  - increased lactate production due to low perfusion in heart failure or volume loss from bleeding
- pH is monitored at 4–8-hour intervals.
- If metabolic acidosis is present with a pH <7.2 or HCO^-_3 <12 mmol/L, administer sodium bicarbonate.

D. Hyponatremia

- A decrease in sodium is more commonly a sign of fluid overload, not sodium deficiency.
- In the absence of signs of dehydration, treatment consists of fluid restriction and maintaining sodium intake at 2–3 mmol/kg/day.
- If severe (Na <120 mmol/L), correction is performed:
- Required sodium intake: $\text{Na necesar} = (\text{Na dorit} - \text{Na actual}) \times 0{,}6 \times \text{greutate (kg)}$
- Serum sodium is corrected cautiously (maximum 8–10 mmol/L per day) to avoid neurological complications.

E. Calcium–phosphate imbalance

- Hyperphosphatemia and hypocalcemia are common complications in newborns.
- Symptomatic hypocalcemia is corrected with 10% calcium gluconate, 0.5–1 mL/kg IV, administered over 5 minutes, under ECG monitoring.
- Hyperphosphatemia is corrected by restricting phosphate in parenteral nutrition or milk formulas. Oral calcium carbonate may be administered as a phosphate-binding agent

F. Hypertension

- In ARF with hypertension—fluid and electrolyte management, dialysis.

4. Nutrition

- Nutritional monitoring is essential to prevent excessive catabolism.
- If the infant tolerates oral feeding: renal formula with reduced sodium and phosphate.
- Newborns who tolerate oral feeding: breast milk or formulas with low phosphorus and potassium, with reduced renal load
- If oral feeding is not tolerated: parenteral nutrition with 50 kcal/kg/day and 1–2 g protein/kg/day.
- Essential for the newborn's growth.

5. Dialysis

- Consultation with the pediatric nephrology team is recommended.
- Indications: when conservative management does not correct:
  - severe fluid overload,
  - hyperkalemia
  - severe acidosis,
  - uremia.
- Severe fluid restriction that limits nutrition in anuric newborns is a relative indication for dialysis.
- Due to the technical complexity and requirements for supportive care, the procedure must be performed in centers with experience in dialysis for infants and newborns.
- Peritoneal dialysis is the most commonly used method in newborns.

V.5.7. PROGNOSIS

- The prognosis for acute kidney injury depends on the underlying cause and the degree of kidney damage.
- In cases where kidney damage is caused by exposure to toxins or acute tubular necrosis, kidney function may partially recover over time

- Chronic kidney disease may develop, as newborns with ARF are at increased long-term risk.
- Prerenal forms – reversible with early treatment.
- Structural forms – risk of progression to chronic kidney disease.
- Extremely preterm infants + sepsis = maximum risk of mortality.

Complete recovery is possible if intervention occurs before severe tubular damage sets in. The long-term prognosis must be managed by a multidisciplinary team: neonatologist, nephrologist, geneticist, radiologist. Mortality and morbidity are elevated in infants with multiple organ failure.
Factors that increase mortality include:

- hypotension,
- the need for mechanical ventilation,
- dialysis,
- use of vasopressors,
- hemodynamic instability,
- multiple organ failure.

V.6. RENAL-URINARY MALFORMATION

V.6.1. DEFINITION

Renal-urinary malformations represent a group of congenital anomalies of the kidneys and urinary tract (calices, renal pelvis, ureters, bladder, urethra), resulting from disturbances in embryonic development.
They can be:

- structural (shape, position, number),
- functional (obstruction, reflux),
- or combined (dysplastic kidney, multicystic kidney).

During the neonatal period, these malformations manifest as:

- prenatal/postnatal ultrasound abnormalities,
- urinary tract infections,
- acute or chronic renal failure,
- growth disorders and hypertension (later on).

Any neonatal urinary tract infection or any unexplained oliguria = suspicion of a renal-urinary malformation until proven otherwise.

V.6.2. EPIDEMIOLOGY. INCIDENCE

Urinary tract malformations are the most common ultrasound-detectable congenital anomalies (≈1–2% of pregnancies). Antenatal hydronephrosis (dilatation of the pyelocaliceal system) — the most common
Renal malformations are a major cause of:

- chronic kidney disease in childhood,
- secondary hypertension.

The actual incidence is likely higher, as many mild forms remain asymptomatic or clinically silent for years.

V.6.3. PATHOPHYSIOLOGY

Malformations result from:

- Induction defects between the ureteric bud and the metanephric blastema
  - renal agenesis, hypoplasia, dysplastic kidney, multicystic kidney.
- Branching abnormalities of the ureteric bud
  - double collecting system, double ureter, ectopic ureter.
- Disorders of renal migration
  - ectopic kidney (pelvic, thoracic), horseshoe kidney.
- Defects in the drainage or outflow of the urinary tract

    - pyeloureteral junction (PUJ) obstruction, urethrovesical junction (UVJ) obstruction, posterior urethral valves.
- Defects in ureteral insertion into the bladder
    - vesicoureteral reflux (VUR).

In short, any anomaly of the two main "players"—the ureteric bud and the metanephric blastema—results in a structural or functional malformation.

V.6.4. CLASSIFICATION

Congenital anomalies of the kidney and urinary tract

Table 8. Classification of Renal-Urinary Malformations

Type of anomaly		Definition
Number of kidneys	**Renal agenesis**	Unilateral or bilateral; the kidneys and urinary tract do not form
Kidney size and morphology	**Renal hypoplasia**	Unilateral or bilateral; the shape of the kidneys is normal, but they are smaller in size, with a reduced number of nephrons
	Renal dysplasia	Unilateral or bilateral; the shape of the kidneys and tissue differentiation are abnormal, with a reduced number of nephrons
	Multicystic renal dysplasia	Multiple cysts within a dysplastic kidney, giving it an abnormal shape
Position of the kidneys	**Horseshoe kidney**	The kidneys are fused posteriorly, forming a horseshoe-shaped structure
	Ectopic kidney/pelvis	Abnormally located kidneys, usually in the pelvis
Outflow abnormalities	**Ureteropelvic junction obstruction (UPJO)**	Unilateral or bilateral; the junction between the kidney and the ureter is obstructed, preventing urine from draining from the renal pelvis
	Vesicoureteral reflux (VUR)	Unilateral or bilateral; the junction between the ureter and the bladder is defective, causing urine to flow back into the ureter
	Duplex collection system	Unilateral or bilateral; duplication of the ureter and renal pelvis; may be associated with duplicated kidneys; the urinary tract may exhibit reflux or obstruction
	Megaureter	Unilateral or bilateral; dilation of the ureter alters urinary flow
	Posterior urethral valves	A membrane that forms in the urethra, preventing bladder emptying; occurs exclusively in males

V.6.5. CONGENITAL HYDRONEPHROSIS

Congenital hydronephrosis is the dilation of the renal pyelocaliceal system caused by an anatomical or functional obstruction in the upper urinary tract.

Traditionally, the term hydronephrosis has been used to describe this condition; however, due to its imprecise nature and the potential for confusion with other obstructive uropathies, the term pyeloureteral junction syndrome (PUJS) is currently preferred, as it more accurately reflects the pathogenic mechanism.

Pyeloureteral junction obstruction is the most common and most severe cause of congenital hydronephrosis in newborns. It is characterized by dilation of the renal pelvis and calyces in the absence of ureteral or bladder dilation, a feature that distinguishes it from other obstructive malformations of the urinary tract.

Most cases are diagnosed antenatally, with ureteropelvic junction syndrome being one of the most common urological anomalies identified during the fetal period.

Postnatal clinical manifestations

In the absence of prenatal diagnosis, congenital hydronephrosis may become apparent postnatally through:

- urinary tract infections, which may be the first clinical sign and require further investigation;
- hematuria,
- renal trauma to a hydronephrotic kidney,
- hypertension, possibly associated with concomitant renal artery stenosis.

Laboratory and imaging studies

After birth, the primary objective is to determine the obstructive nature of the dilatation. The investigations used include:

- Isotopic renogram with MAG3, the method of choice for evaluating urinary drainage and renal function due to superior tracer uptake, particularly useful in newborns and infants;
- Renal scintigraphy with DMSA-Tc99, indicated for assessing renal morphology and differential function;
- Intravenous urography, of limited value

Management:

Management of congenital hydronephrosis is individualized and depends on the severity of dilation, symptoms, and the progression of renal function.

- **Conservative treatment**

In most cases diagnosed antenatally and confirmed postnatally, close monitoring is recommended, consisting of:

- periodic clinical evaluations,
- serial ultrasounds,
- investigations

Many cases remain stable or resolve spontaneously; clinical observation may be extended up to 2–2.5 years in asymptomatic patients.

- **Indications for surgery**

Surgery is necessary in a limited percentage of cases and is indicated in the presence of:

- recurrent urinary tract infections,
- progressive deterioration of renal function.

An initial therapeutic intervention may be percutaneous nephrostomy, which allows for decompression of the renal pelvis and assessment of the renal parenchyma's potential for recovery, particularly in cases of an apparently non-functioning kidney.

Definitive surgical treatment: the standard surgical procedure is the Hynes–Andersen pyeloplasty, which involves resection of the stenotic segment of the pyeloureteral junction and restoration of pyeloureteral continuity through a reconstructive technique.

Minimally invasive alternatives include:

- endopyelotomy,
- laparoscopic or robotic procedures,

which are generally reserved for older children. Endopyelotomy has proven particularly effective as a salvage procedure following the failure of classic pyeloplasty.

V.6.6. CONGENITAL URETEROHYDRONEPHROSIS – PRIMARY OBSTRUCTIVE MEGAURETER

The term megaureter is a vague term that refers to a heterogeneous group of congenital malformations of the urinary tract**,** characterized by abnormal dilation of the ureter**,** with or without impaired renal function. It does not define a single clinical entity, as it is used to encompass conditions with different etiopathogenic mechanisms**.** Among the clinical forms described**,** primary obstructive megaureter is of the greatest relevance in the neonatal and **infant** periods, due to its potential to compromise renal function.

- **Etiopathogenesis**

Primary obstructive megaureter is caused by an obstruction in the distal segment of the ureter, located near the ureterovesical junction. This obstruction may be functional or anatomical in nature.

The consequence of this structural anomaly is impaired ureteral peristalsis, which prevents efficient drainage of urine to the bladder. Over time, progressive dilation of the proximal ureter occurs, followed by ureterohydronephrosis, with varying degrees of renal parenchymal involvement.

- **Prenatal Diagnosis**

Antenatal ultrasound is the primary method for detecting primary obstructive megaureter and may reveal:

- dilatation of the pyelocaliceal system,
- dilatation of the ureter,
- thinning or atrophy of the renal parenchyma in severe cases.

- **Postnatal diagnosis**

After birth, an abdominal ultrasound confirms the presence of ureterohydronephrosis and allows for monitoring of its progression.

Additional investigations:

- Voiding cystourethrography, mandatory to rule out vesicoureteral reflux (not characteristic of primary obstructive megaureter);
- Diuretic renogram, indicated especially in newborns with bilateral involvement or a palpable abdominal mass, to assess the degree of obstruction.

- **Course**

The prognosis is often favorable, with a gradual tendency toward spontaneous regression of hydronephrosis in the first years of life. This regression is observed predominantly in mild and moderate forms (grades I–III), usually within 36 months.

In contrast, severe forms, characterized by:

- grade IV–V ureterohydronephrosis,
- a retrovesical ureter diameter >1 cm, present a significant risk of progressive deterioration of renal function and require, in most cases, surgical treatment.

- **Treatment**

In asymptomatic, mild, and moderate forms, a conservative approach is recommended, which includes: periodic clinical and ultrasound monitoring, serial assessment of renal function, and prevention of urinary tract infections.

- Surgical treatment

Surgery is indicated in the following situations:

- the presence of significant clinical symptoms,
- recurrent urinary tract infections,
- progressive deterioration of renal function, defined as a decline of >5% over a 6-month period.

The standard surgical procedure consists of:

- resection of the stenosed distal segment of the ureter,
- reimplantation of the ureter into the bladder, with or without ureteral tapering,
- temporary placement of a ureteral stent, which helps maintain anastomotic patency and facilitates postoperative healing.

V.6.7. LOWER OBSTRUCTIVE UROLOGICAL DISORDERS – POSTERIOR URETHRAL VALVE

- **Definition and epidemiology**

Posterior urethral valves (PUV) are the most common cause of subvesical obstruction in newborns and infants

- **Incidence**

Approximately 1 case per 5,000 births, accounting for nearly 10% of antenatally diagnosed obstructive uropathies. The condition is exclusively male and causes a variable degree of obstruction of urine flow upon bladder emptying, with significant impact on the upper urinary tract, as well as on renal and pulmonary development.

- **Prenatal diagnosis**

It is diagnosed by ultrasound, beginning in the second trimester of pregnancy.
Suggestive ultrasound findings include:

- bilateral hydronephrosis,
- persistent bladder distension,
- oligoamnios, as an indication of impaired fetal renal function.

- **Anatomical classification**

According to the Young classification, there are three types, all with obstructive potential:

- Type I – the most common form (approximately 90% of cases); consists of two mucosal folds originating proximal to the veru montanum and extending distally and anteriorly toward the anterior wall of the urethra at the level of the urogenital diaphragm.
- Type II – a rare form, characterized by mucosal folds extending from the veru montanum toward the bladder neck and the internal urethral sphincter, usually associated with severe obstruction.
- Type III – characterized by an incomplete urethral diaphragm, located distal to the veru montanum, with an obstructive effect of varying intensity.

Type I is the most common type of valve (90%). The most severe obstruction is caused by Type II valves.

- **Clinical Presentation**

It is heterogeneous and depends on the degree of obstruction. Manifestations may include:

- significant bladder distension (bladder globe),
- acute urinary retention, commonly seen in infants,
- recurrent or persistent urinary tract infections,
- delayed growth and development,
- urinary ascites, due to urine leakage,
- persistence or reopening of the ureter.

In severe cases, systemic complications may occur, such as acute or chronic renal failure and significant fluid and electrolyte imbalances.

- **Paraclinical investigations**

Postnatal evaluation includes a set of imaging and laboratory tests:

- Renal and pelvic ultrasound, to assess the degree of hydronephrosis and evaluate the integrity of the renal parenchyma;
- Voiding urethrocystography, the test of choice for confirming the diagnosis, highlighting urethral obstruction and any associated vesicoureteral reflux;
- Assessment of renal function and fluid and electrolyte status.

- **Initial management**

The goals of emergency treatment are:

- prompt drainage of the bladder via urethral catheterization,
- correction of fluid and electrolyte imbalances,
- treatment of acute renal failure and dehydration.

- **Surgical treatment**

Definitive treatment consists of endoscopic ablation of the urethral valves. In cases of severe systemic condition or severe metabolic imbalances, temporary urinary diversion procedures, such as cystostomy or pyelostomy, may be used for urine diversion and decompression of the upper urinary tract.

- **Prognosis**

Severe forms of posterior urethral valves may be associated with:

- pulmonary hypoplasia secondary to severe oligohydramnios,
- limb deformities resulting from intrauterine compression,
- a poor prognosis, with an increased risk of chronic kidney disease.

A favorable prognostic factor is a serum creatinine level <0.8 mg/dL approximately one month after urinary diversion, correlated with better long-term renal function. Posterior urethral valves can

lead to a wide range of long-term urological complications. Over 50% of patients develop varying degrees of chronic kidney disease. Regular assessment of renal function, identification and management of bladder dysfunction, and prevention of urinary tract infections are necessary.

V.6.8. MULTICYSTIC DYSPLASTIC KIDNEY

- **Definition**

Multicystic dysplastic kidney is a congenital anomaly of the kidney characterized by the complete replacement of normal renal parenchyma with multiple non-functional cysts.

- **Incidence**

It is estimated to occur in approximately 1 in 4,000 live births. The condition is most commonly unilateral, although bilateral cases have been reported, though these are much rarer.

- **Diagnosis**
- Prenatal: ultrasound
- Postnatal
    - Renal ultrasound confirms the presence of multiple cysts and the absence of functional parenchyma.
    - A renal scintigraphy shows that the multicystic dysplastic kidney is non-functional.

In approximately 25% of cases, the healthy kidney exhibits associated anomalies, such as:

- obstruction of the pyeloureteral junction
- vesicoureteral reflux.

- **Course and Management**
- In recent decades, management has become predominantly conservative and non-surgical.
- Serial ultrasounds show regression of the multicystic dysplastic kidney:
    - approximately one-third by age 2,
    - half by age 5,
    - two-thirds by age 10.
- Surgery (nephrectomy) is indicated only if the kidney does not decrease in size or if complications arise.

Regular monitoring is recommended for the contralateral kidney, renal function, and blood pressure.

V.6.9. RENAL AGENESIS

- **Definition**

Renal agenesis is the congenital absence of one or both kidneys, caused by the failure of the ureteric bud to induce kidney development. This condition may be caused either by defects in the ureteric bud or by abnormalities in the developing renal tissue.

- **Unilateral renal agenesis**
    - Often asymptomatic if the contralateral kidney is normal.
    - The ipsilateral ureter is absent or partially atresic.
    - Requires exclusion of an ectopic kidney via renal scintigraphy (DMSA).
    - Incidence 1:1000 – 1:1500 newborns
    - More common in males
    - The contralateral kidney may be ectopic or malrotated in 15% of cases; associated vesicoureteral reflux in 37% of cases.
- **Bilateral renal agenesis (Potter syndrome)**
    - Incidence 1:4,000 newborns
    - More common in males
    - Prenatal diagnosis via ultrasound: oligohydramnios and absence of the kidneys.
    - The ureters are absent or hypoplastic.
    - Approximately 10% of cases present with testicular absence, but the vas deferens is usually present.
    - Prognosis: fatal; complete renal failure.

- **Laboratory diagnosis**
  - Prenatal ultrasound: reveals absence of the kidneys and oligohydramnios.
  - DMSA scintigraphy: detects functional renal tissue, particularly useful for unilateral agenesis.
  - Associated urogenital evaluation: contralateral malrotated or ectopic kidney; absent ipsilateral ureters.
  - Laboratory: monitoring of renal function of the contralateral kidney, if present.
- **Complications**
  - Unilateral agenesis: the present kidney may develop compensatory hypertrophy.
  - Bilateral agenesis: associated with Potter syndrome, severe oligohydramnios, pulmonary hypoplasia, and limb deformities. Differential diagnosis: involuted bilateral multicystic dysplastic kidneys. Bilateral agenesis may be familial, suggesting a genetic component.

V.6.10. ECTOPIC KIDNEY

- **Definition**

An ectopic kidney is a congenital malformation characterized by abnormal positioning of the kidney, caused by defects in renal migration (ascent) and/or renal fusion. The diagnosis is suspected when the kidney is not located in the normal position and is confirmed by renal ultrasound and, if necessary, DMSA scintigraphy to assess functional renal tissue.
Ectopic kidneys can be classified into the following forms:

1. Simple ectopic kidney
2. Horseshoe kidney
3. Crossed ectopic kidney

1. Simple ectopic kidney

The most common location is the pelvis, accounting for approximately 60% of cases. It is generally unilateral, with a slight preference for the left kidney, but can be bilateral in about 10% of cases. The pelvic kidney is often small and irregularly shaped. Other locations include the space between the pelvis and the normal position of the kidney ( ), and very rarely, the kidney may be located in the chest. The ectopic kidney may be associated with contralateral genital and renal malformations, including:

- Absence of the vagina
- Retrocaval ureter (behind the inferior vena cava)
- Bicornuate uterus
- Supernumerary kidney
- Contralateral ectopic ureter

The diagnosis is established through imaging, particularly ultrasound and DMSA scintigraphy, to assess kidney function. Treatment is necessary only if the ectopic kidney causes clinical complications, such as urinary tract obstruction or recurrent infections.

2. Horseshoe kidney

The incidence of horseshoe kidney ranges from 1 in 400 to 1 in 1,800 births and is more common in males. In 95% of cases, the lower poles of the two kidneys are joined by a bridge of renal tissue, which may be normal, dysplastic, or fibrous. In approximately 40% of cases, the isthmus is located at the L4 level, immediately below the origin of the inferior mesenteric artery. In 20% of cases, the isthmus is situated in the pelvis, and in the remaining cases, at the level of the lower poles of the normally positioned kidneys. Rarely, fusion may occur at the upper poles of the kidneys. The ureters pass anteriorly over the isthmus, which may explain the relatively high incidence of pyeloureteral anomalies (20%) associated with horseshoe kidney. Horseshoe kidney is frequently associated with other congenital malformations, which may involve:

- The central nervous system,
- The gastrointestinal tract,
- The skeletal system,

- The cardiovascular system.

3. Crossed ectopic kidney

A crossed ectopic kidney is a congenital malformation in which a kidney crosses the midline and is located on the opposite side of the body. This anomaly may occur with renal fusion (~80% of cases) or without fusion. In most cases, the left kidney crosses to the right side, where the upper pole of the crossed kidney fuses with the lower pole of the normal kidney. It is slightly more common in boys. Most cases are asymptomatic and discovered incidentally during imaging studies. Treatment is not necessary unless there are significant clinical complications: vesicoureteral reflux, obstruction of the pyeloureteral junction. In the absence of these problems, management is conservative, with periodic monitoring.

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VI. NEUROLOGICAL PATHOLOGY

VI.1. GENERAL CONCEPTS OF ANATOMY AND EMBRYOLOGY

VI.1.1. INTRODUCTION

The human brain emerges from a small population of embryonic cells, but over the course of the 280 days of gestation, it becomes the most complex organ. In a full-term newborn, there are trillions of neurons and glial cells arranged and interconnected in an extraordinary three-dimensional network. However, minor changes in the formation processes have major implications for postnatal development and function.

VI.1.2. INTRAUTERINE DEVELOPMENT

The intrauterine development of the CNS comprises three important stages:

1. **The embryonic period** corresponds to the first trimester of intrauterine life. The first structure to appear is the neural tube, from which the cerebral hemispheres, the cortex with some convolutions, the subcortical nuclei, the internal capsule, the thalamus, the cerebellum, and the vascular system with the choroid plexuses progressively develop. Schematically, during this period, these structures develop as follows:
    - in the 3rd week of intrauterine life, the neural tube appears, from which the three major vesicles on the anterior side subsequently derive.
    - The anterior and posterior vesicles then divide in half, resulting in the five well-known vesicles: the telencephalon, diencephalon, mesencephalon, metencephalon, and myelencephalon.
    - The telencephalon gives rise to the hemispheres and lateral ventricles; the diencephalon gives rise to the diencephalic region and the third ventricle of the brain;
    - The mesencephalon develops into the midbrain and the aqueduct of Sylvi,
    - The metencephalon gives rise to the pons, the cerebellum, and the fourth ventricle,
    - Myelencephalon – the medulla oblongata, the spinal cord, and the central spinal canal.

The first vascular plexuses appear in the first month, from which cerebrospinal fluid (CSF) is secreted; then, during the second month, the cerebral hemispheres and subcortical ganglia develop. The embryonic period is the most vulnerable period in neurological development, as harmful factors of any kind acting on the fetus cause developmental disorders in these structures.

2. **The fetal period** spans 4 to 6 months and is characterized by the following aspects:
    - intensified differentiation of brain structures.
    - maturation of the choroid plexuses and CSF secretion.
    - the appearance of the Sylvian fissure in the 4th month, and the central fissure in the 5th month
    - differentiation of the cerebral cortex convolutions
    - the fourth ventricle appears with the foramen of Majandi and two lateral foramina of Luksa.
    - The cerebral cortex differentiates intensively: the layers of cortical cells and functional fields appear.
    - Development of the vascular system
3. **Late fetal period** – the development process continues, the myelination process proceeds unevenly. The myelination period **begins in the second trimester of pregnancy**, but the most rapid period of myelination continues during the first two years of life until adulthood. The myelination process is complex. The proliferation, migration, and differentiation of oligodendrocytes continue, and they then align along the axons, forming the myelin sheath. Myelin is initially deposited in all areas of white matter, with the last area to become myelinated being the intracortical fibers of the cerebral cortex.

Disorders in the myelination process cause several brain conditions

- Cerebral white matter hypoplasia
- Cerebral white matter injuries in preterm infants – WMI - PVL
- Metabolic and nutritional disorders
- Leukodystrophy

The **main stages of development** can be summarized as follows

- Primary neurulation – 3–4 weeks of gestation
- Prosencephalic cleavage – 2–3 months of gestation
- Neuronal proliferation – 3–4 months of gestation
- Neuronal migration – 3–5 months of gestation
- Organization process – 5 months of gestation – postnatal years
- Myelination process – birth – postnatal years

VI.1.3. DEVELOPMENTAL CHARACTERISTICS

During the process of complete development and maturation from conception to birth, several factors intervene that can disrupt normal development:

- Premature birth alters the temporal-spatial progression of brain structures—including migration, organization, differentiation, and myelination—and modifies brain architecture. Depending on the gestational age, postnatal visual, auditory, tactile, and vestibular-proprioceptive changes may occur—compared to full-term newborns
- The CNS of newborns in the high-risk group is frequently exposed to maternal infections, hypoxic-ischemic encephalopathies, intraventricular hemorrhages, or periventricular leukomalacia.
- A gestational age of less than 28 weeks, regardless of other exogenous and endogenous factors, increases the risk of CNS disorders
- Various somatic conditions can exacerbate the risk of neurological complications: extracranial and intracranial trauma, respiratory disorders, infections, hypoxic-ischemic encephalopathy, and intrauterine growth restriction.

VI.2. PERINATAL HYPOXIC-ISCHEMIC ENCEPHALOPATHY

VI.2.1. DEFINITION

Perinatal **hypoxic-ischemic encephalopathy** (PHIE) is characterized by impaired neurological function in the early neonatal period. It manifests through a variety of neurological symptoms, ranging from difficulties in initiating and maintaining respiration, decreased muscle tone and reflexes, to altered consciousness and, in severe cases, seizures. Depending on the severity of the hypoxic injury and the affected area—specifically the degree of neurological maturity—the impairment may be isolated or involve multiple organs, with lesions grouped under **the post-asphyxial syndrome**, particularly in severe forms of the disease.

VI.2.2. EPIDEMIOLOGY. INCIDENCE

The incidence of perinatal hypoxic-ischemic encephalopathy is estimated at 2–4 per 1,000 live births in developed countries. Death or severe neurological sequelae may occur in 0.5–1 per 1,000 live births.

VI.2.3. PATHOPHYSIOLOGY

Depending on the severity of the insult, perinatal asphyxia may be accompanied by hypoxia, hypoxemia, hypercapnia, and metabolic acidosis. Initially, in response to asphyxia, cerebrovascular autoregulation occurs with an increase in cerebral blood flow, serving to maintain cerebral blood flow. Since the limits of autoregulation are narrow in the newborn, as systemic blood pressure drops, the adaptive mechanism is overwhelmed.

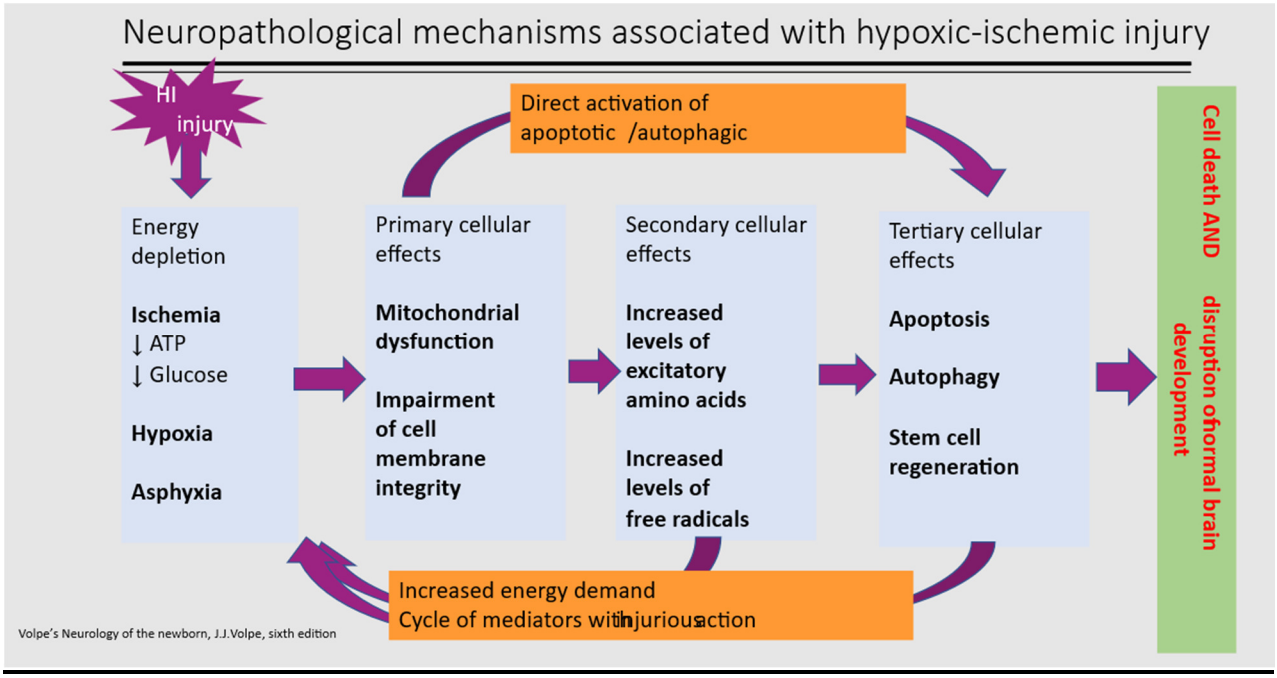

Figure 6. Neuropathological mechanisms of hypoxic-ischemic injury.

Brain injury is a progressive process that begins during the "injury" phase and continues into the recovery period following resuscitation (the reperfusion interval).
"Injury" or tissue damage is described according to 5 basic patterns:

1. selective neuronal necrosis,
2. marmorization of the basal ganglia and thalamus,
3. parasagittal cerebral lesion,
4. focal and multifocal ischemic cerebral necrosis,
5. PVL (premature infants).

These lesions often coexist, with one tending to be predominant depending on the dominant nature of the "injury" (hypoxia or ischemia) and the gestational age of the infant. The mechanism of neuronal damage involves the participation of circulatory, cellular metabolic, and biochemical factors, leading to neuronal destruction. The areas of brain injury correlate topographically with the progression of myelination and with the brain's metabolic activity at that time, with white matter being more susceptible to hypoxic injury. Regional vulnerability to asphyxia, however, depends on gestational age. Thus, in preterm infants, the periventricular white matter is much more vulnerable, whereas in term newborns, it is the area between the territories supplied by the large cerebral arteries.
The mechanisms of injury are described as follows:

- localized infarction in neurons in the immediately adjacent area (the penumbra) triggers a process of necrosis or apoptosis (programmed cell death).
- Cerebral hypoxia-ischemia at the cellular level leads to a cascade of biochemical events: the replacement of oxidative metabolism with anaerobic metabolism (glycolysis), which causes the accumulation of NADH (nicotinamide adenine dinucleotide), FADH (flavin adenine dinucleotide), lactic acid, and hydrogen ions.
- Anaerobic glycolysis cannot meet cellular energy needs and, as a result, leads to a depletion of ATP reserves
- transcellular ion transfer is reduced, leading to intracellular accumulation of sodium, calcium, and chloride ions and water (cytotoxic edema).
- Hypoxia-ischemia contributes to the release of excitatory amino acids (glutamate) at the axon terminals, which activate glutamate receptors on the cell surface, causing an influx of Na and Ca
- into the cytosol—where the following accumulate: AGL—which subsequently undergoes peroxidation; calcium, necessary to increase the influx across the plasma membrane; and nitric oxide, which is generated upon calcium activation in selected neurons and diffuses into adjacent cells susceptible to its toxicity.

The combined effects of cellular energy failure, acidosis, glutamate and nitric oxide neurotoxicity, free radical formation, lipid accumulation, and lipid peroxidation lead to the destruction of the cell's structural components and ultimately cell death

The predominant neurological lesion in preterm infants is periventricular leukomalacia (PVL), the cause of cognitive, motor, and sensory disabilities and impairments in this group of infants.

The term white matter injury (WMI) is increasingly used in place of PVL. This denotes diffuse damage to the cerebral white matter, extending beyond the periventricular regions, as defined in neuropathological and ultrasonographic studies. This condition has also been reported in term newborns, particularly those with congenital heart disease.

Encephalopathy of prematurity, a term proposed by Volpe, is not widely used in the literature and, in addition to white matter injury, encompasses the fact that preterm infants suffer brain damage affecting gray matter structures as well as the cerebral white matter.

VI.2.4. RISK FACTORS

Several factors are implicated depending on the period in which they occur:

1. antenatal factors (20%)
2. intrapartum factors (35%)
3. postnatal factors (10%)
4. unknown etiology or combinations (35%)

Table 9. Risk factors associated with perinatal hypoxia

Maternal conditions	Labor and delivery	Fetal conditions
Diabetes mellitus	Forceps	Prematurity
High blood pressure	Abnormal presentations	Acidosis
Chronic kidney disease	Cephalopelvic disproportion	Meconium aspiration
Anemia (Hb < 10 g/dL)	Cesarean section	Oligohydramnios and polyhydramnios
Rh and ABO isoimmunization	Umbilical cord prolapse	Macrosomia
Placenta previa	Umbilical cord knots	Congenital malformations
Drugs, narcotics	Precipitous labor	Fetal hydrops
Heart disease	Prolonged labor	
Fever		
Rupture of the amniotic membranes		
Age under 16 or over 35		
Pregnancy toxemia		
Malnutrition		

VI.2.5. CLINICAL DIAGNOSIS

Depending on the time of onset and the intensity of symptoms, three clinical stages of severity are described according to Sarnat:

- **Stage I, mild form**: characterized by irritability, tremors, myoclonus, normal muscle tone, weak sucking reflex, pronounced Moro reflex, mydriasis, tachycardia, and normal EEG. The subsequent course is favorable.
- **Stage II, moderate form**: characterized by lethargy, moderate hypotonia, myoclonus, weak or absent sucking reflex, incomplete Moro reflex, miosis, bradycardia, profuse secretions, and low-voltage EEG. Seizures are present. 20% of children are at risk for subsequent sequelae, especially when seizures last longer than 5 days.
- **Stage III, severe form:** characterized by lack of response to physical stimuli (stupor, coma), generalized hypotonia, and areflexia (sucking, swallowing, grasping, Moro).

The following may be present:

- seizures, usually generalized and resistant to conventional treatment.
- cerebral edema, evidenced by bulging of the anterior fontanelle
- severe respiratory depression with irregular, shallow breathing, severe pulmonary hypertension, pulmonary hemorrhage, and pulmonary edema
- cardiac arrhythmias, reduced myocardial contractility, severe arterial hypotension, cardiomegaly, tricuspid regurgitation.
- Renal impairment—leading to acute failure with oliguria initially, followed by polyuria, which causes fluid and electrolyte imbalances.
- intestinal lesions manifested by digestive intolerance

The clinical diagnosis involves several steps:

- **Medical history –** which provides information about:
    - the presence of any of the causes in the patient's history
    - parameters of fetal distress at birth:
        - delayed onset of spontaneous breathing,
        - a low Apgar score,
        - the need for resuscitation,
        - acidosis (determined by the Astrup micro-method of measuring pH in blood from the fetal scalp and umbilical cord).
        - Acute fetal distress, even if the newborn exhibits "depression" of consciousness at the time of delivery, *does not always* indicate cerebral distress with EHIP.
        - Only in the presence of abnormal neurological manifestations during the first days of life should EHIP be considered.
- **Clinical examination**: clinical manifestations—often nonspecific—are similar to those associated with metabolic, infectious, or malformative conditions acting prenatally, which may be masked in preterm infants and term newborns who have received muscle relaxants (pancuronium) to facilitate mechanical ventilation.

Systemic manifestations to be monitored: myocardial ischemia indicating persistent systemic hypoperfusion and refractory hypoxemia. Renal impairment with oliguria and azotemia, hypoglycemia—caused by depletion of glycogen stores, hypocalcemia.

VI.2.6. LABORATORY AND IMAGING STUDIES

1. Biochemical **laboratory tests**:

- Scalp pH,
- umbilical cord pH,
- HLG,
- TGO,
- TGP,
- Bilirubin
- Renal tests
- Coagulation profile
- LDH
- Hypoxanthine,
- Lactic acid in blood and CSF,
- Cerebral fraction of CPK in blood and CSF.

2. **Electroencephalogram**
3. **Brain imaging:**

- transfontanellar ultrasound,
- computed tomography,
- magnetic resonance imaging

Since **transfontanellar ultrasound** is the method of choice for definitive diagnosis, and the images vary depending on the neuropathogenic lesion, we offer the following clarifications. **Periventricular leukomalacia is** a common condition in extremely preterm infants, second in frequency only to germinal zone hemorrhage, characterized by ischemic necrosis of the periventricular white matter. It is located near the external angles of the lateral ventricles; this region represents a true "watershed" toward which the terminal branches of the main vessels converge. Incidence—7–26% in autopsy studies, and the frequency in preterm infants with a birth weight (<) of 1,500 g and a history of severe hypoxia or ischemia is 80–90%. Other risk categories include newborns from difficult deliveries, accompanied by head trauma, and cardio-respiratory conditions during the neonatal period (heart failure, patent ductus arteriosus, recurrent apnea episodes, sepsis).

The primary lesion is coagulative necrosis, followed by the proliferation of astrocytes and macrophages. After a period of 5–7 days, phagocytosis of the necrotic tissue begins, which is completed in approximately 2 weeks when single or multiple cavities appear.

Cystic lesion – may exist as such, may communicate with the ventricular system, and in 28% of cases presents with associated hemorrhages—subependymal, intraventricular, or subarachnoid.

- **Transfontanellar ultrasound** allows for early diagnosis of lesions and their monitoring as long as the fontanelle size permits.
    - In the first stage, *a broad band of echogenicity* is visualized, *located laterally to the anterior horns and the left lateral ventricles. This is* an early sign, appearing within the first 2 weeks of life.
    - In the second stage, cystic formations appear—transsonic, heterogeneous images—2–3 weeks after the onset of increased echogenicity, at which point a definitive diagnosis of PVL can be established. These cysts are described as follows: multiple transsonic, thick-walled, homogeneous, well-defined formations ( ) with no connection to the ventricular system.
    - In stage III**,** cystic PVL may progress to generalized cerebral atrophy: widening of the interhemispheric fissure and varying degrees of ventriculomegaly
- **Computed tomography** has difficulty detecting ischemic lesions due to the physiological hypodensity of the periventricular white matter. Microcavities are generally undetectable; only large cystic formations and ventriculomegaly are detected.
- **MRI** ( ) is a useful diagnostic method in the early stages of the disease and after the age of 16 months to 2 years, when normal myelination is complete. It can reveal the irregular, pathognomonic dilation of the lateral ventricles and volume loss in the white matter.

VI.2.7. DIFFERENTIAL DIAGNOSIS

Focal or diffuse ischemic lesion. It affects full-term newborns more than preterm infants, with an incidence of 15–20% among newborns with EHIP. This type of lesion accounts for 10–15% of neonatal seizures.

Cerebral infarction is associated with extensive necrosis of brain tissue and the formation of a single cavity (porencephalic) or multiple cavities (multicystic encephalomalacia or hydrocephalus).

Focal lesions occur in the territory supplied by one of the major cerebral arteries, the middle cerebral artery—in 50% of cases. Ischemic lesions associated with intrauterine factors occur in the territory supplied by the anterior cerebral artery

Diffuse lesions – initial cellular dysfunction manifests as extensive necrosis of brain tissue (cerebral infarcts), which, as the condition progresses, leads to: cerebral atrophy, mild ventricular dilation, parenchymal calcifications, or multicystic encephalopathy

Hemorrhagic necrosis of the basal ganglia and thalamus. This is a rare lesion that occurs in both preterm and term newborns. It is characterized by a marbled appearance of the caudate nucleus, putamen, globus pallidus, and thalamus, due to neuronal destruction, astrogliosis, and hypermyelination. The most common causes are perinatal asphyxia and thrombosis due to meningitis.

VI.2.8. MANAGEMENT

A. NONPHARMACOLOGICAL.

- The most important preventive measure is the prevention of preterm birth.
- Preventing a drop $_{in\ pCO}$ below 35 mmHg through careful monitoring of arterial blood gases
- Diagnosis and treatment of chorioamnionitis
- Administration of betamethasone between 24 and 31 weeks of gestation
- Administration of magnesium sulfate during labor—no significant results
- Postnatal – avoidance of arterial hypotension and fluctuations in blood pressure
- Hypothermia – reduces the risk of neurological impairment in term newborns; not sufficiently evaluated in preterm newborns
- Prevention of pre-oligodendroglial destruction by free radicals and inflammatory mediators. Administration of antioxidants and glutathione precursors such as N-acetylcysteine may inhibit the action of pro-inflammatory cytokines on the CNS and the destruction of immature oligodendrocytes (under study)
- Identification of drugs that exert trophic effects exclusively on premyelinized oligodendrocytes and immature neurons, thereby enhancing their resistance to oxidative and inflammatory processes. Erythropoietin—counteracts the toxic effects of free radicals, cytotoxins, and pro-inflammatory factors

B. PHARMACOLOGICAL.

Curative treatment does not involve a specific therapy; it is primarily based on the prevention of complications.

- Correction of arterial hypotension
- Judicious use of mechanical ventilation and avoidance of hypocapnia
- Treatment of apnea and bradycardia
- Follow-up program and multidisciplinary teams including pediatricians, neurologists, psychotherapists, ophthalmologists, and physical therapists
- Prevention of delayed neuronal death. Administered within the 6–12-hour therapeutic window following the acute episode, during which the administration of neuroprotective agents can reduce or prevent brain damage.
- Vitamin E – antioxidant, free radical scavenger, 20 mg/day for 7–14 days.
- Vitamin B6, which plays *a role in neurotransmitter synthesis and amino acid (serotonin) metabolism* – 20 mg/day
- Vitamin C – *glucocorticoid and neurotransmitter synthesis, cellular antioxidant – 30 mg/kg/day*
- *Coenzyme Q10* – reduces carbohydrate metabolism, circulatory insufficiencies due to oxidative disorders, 8 mg/kg (oxygenation enzyme)
- *Etamsylate* – stabilizes fragile vessels in the germinal matrix, inhibits prostaglandin synthesis, ↓ basal cerebral blood flow, 12.5 mg/kg every 6 hours for 3 to 7 days

Treatment is individualized based on the stage of the disease. In the mild stage, the therapeutic approach is minimal, focused on maintaining normoxia and normocapnia, as well as keeping blood pressure and blood glucose within normal limits. In the moderate and severe stages, control of seizures and management of acute cerebral edema are added

Preventing complications is one of the major goals of treatment, with the most important measures being:

- Phenobarbital
- Calcium channel blockers: interrupt the cascade of events leading to neuronal death. Nicardipine, Flunarizine, and Nimodipine
- Magnesium sulfate – conflicting results
- Oxygen free radical inhibitors – Allopurinol and Oxipurinol – at a dose of 20 mg/kg IV 4 hours after birth and a second dose 12 hours after the first administration, inhibit xanthine oxidase and neutralize free radicals

- Indomethacin – prevents brain damage by inhibiting phospholipase and cyclooxygenase.
- The "21-amino-steroids" class – prevent iron-dependent lipid peroxidation by neutralizing peroxyl radicals
- Excitotoxic amino acid antagonists – antagonists of NMDA and AMPA/QA receptors or of the ion channels controlled by them (research phase): phencyclidine, dextromethorphan, ketamine, MK-801, NBQX.
- Inhibitors of nitric oxide (NO) production. At high concentrations, NO can act as a neurotoxic agent. Experiments in adult animals have demonstrated that NO-mediated neuronal death following cerebral ischemia, and the severity of neuronal injury, can be reduced by the prophylactic administration of NO synthase inhibitors.
- Controlled hypothermia – reduces the release of excitatory neurotransmitters, alterations in ion flux, EHIP-induced apoptosis, and vascular permeability

Inclusion criteria: ≤ 36 weeks of gestation, pH≤ 7.0, BE≥ 16 mEq/L, clinical seizures or signs of cerebral encephalopathy

- Neural stem cell transplantation into the cerebral ventricles. 28 days after transplantation—improvements in motor development and mental development.

C. FOLLOW-UP

Follow-up care for newborns with perinatal and neonatal hypoxic-ischemic lesions is provided through existing follow-up services to prevent complications and neurological sequelae . Follow-up care is provided by a multidisciplinary team—neonatologist, pediatrician, pediatric neurologist, physical therapist, radiologist, and nutritionist. It is very important to monitor:

- weight curve—newborns with severe asphyxia experience feeding difficulties and have an increased risk of growth failure.
- Monitoring of head circumference – a predictive factor for the development of complications
- neurological evaluation – through specialist consultations, dynamic EEG , and dynamic transfontanellar ultrasounds. Warning signs to watch for: persistent irritability; persistent tremors; seizures; feeding difficulties;

VI.2.9. PROGNOSIS

Clinical factors for determining the prognosis include the severity of the disease, gestational age and birth weight, associated risk factors, early onset of the convulsive syndrome, and response to treatment. Perinatal asphyxia can lead to increased neonatal morbidity and mortality. The mortality rate in stage I is less than 1%, with newborns generally having normal neurological development. In stage II, 20–37% of children die or have neurological sequelae. In stage III, mortality is high (50%) and neurological disabilities are severe: cerebral palsy, mental retardation, recurrent seizures; lower IQ; impaired cognitive abilities with worsening neuropsychological outcomes; behavioral problems; infantile cerebral palsy (spastic diplegia/tetraplegia); hearing disorders up to deafness; visual disorders up to blindness due to optic nerve atrophy.

Negative prognostic factors

- Obstetric complications followed by a 5-minute Apgar score < 5 and signs of EN,
- umbilical cord pH < 7,
- Low birth weight,
- Microcephaly at birth,
- Apgar score < 3 at 5 minutes and thereafter,
- Early-onset, persistent, or difficult-to-treat neonatal seizures,
- MRI abnormalities,
- Oliguria > 36 hours.

EEG—*suppression-burst* patterns (alternating bursts of sharp theta waves and periods of inactivity) and inactive patterns (isoelectric, flat).

VI.3. INTRACRANIAL HEMORRHAGE

During the neonatal period, there are four major categories of cerebral hemorrhage:

- Peri-/intraventricular hemorrhage
- Subarachnoid hemorrhage
- Subdural hemorrhage
- Cerebellar hemorrhage

VI.3.1. PERI/INTRAVENTRICULAR HEMORRHAGE

VI.3.1.1. DEFINITION

Peri/intraventricular hemorrhage refers to bleeding within the ventricular system that can extend throughout the cerebral parenchyma, depending on the severity of etiopathogenic factors and the degree of neurological maturation.

VI.3.1.2. EPIDEMIOLOGY. INCIDENCE

This type of hemorrhage occurs almost exclusively in preterm infants, with an incidence of 40% in very preterm infants with a gestational age < 32 weeks and a birth weight < 1500 g. Recent studies show that its frequency is inversely proportional to birth weight. In infants with a birth weight < 1000 g, the incidence is 50–60%, and in infants weighing 1000–1500 g, the incidence is 10–20%.

Depending on the presence of intraparenchymal hemorrhage, several classification criteria have been used. In the most widely recognized classification, intraparenchymal hemorrhage is the most severe form. In this classification, hemorrhage is divided into 4 grades of severity:

- Grade I – hemorrhage limited to the subependymal matrix;
- Grade II – intraventricular hemorrhage without ventricular dilation;
- Grade III – intraventricular hemorrhage with ventricular dilation;
- Grade IV – intraventricular hemorrhage accompanied by intraparenchymal hemorrhage.

Grade 1 and 2 hemorrhages are considered mild forms, grade 3 hemorrhage is a moderate form, and grade 4 hemorrhage is a severe form of the disease. The frequency of these forms, by severity group, is: mild—70% (40% grade 1, 30% grade 2); moderate—20%; severe—10%.

VI.3.1.3. PATHOPHYSIOLOGY

The pathogenesis of PVH/IVH is multifactorial and consists of a combination of intravascular, vascular, and extravascular factors. Commonly associated intravascular factors include:

- Variations in cerebral blood flow.
- Increased cerebral blood flow.
- Increases in cerebral venous pressure.
- Decreases in cerebral blood flow leading to damage to the vessels of the germinal matrix.
- Platelet and coagulation disorders.

VI.3.1.4. RISK FACTORS

- Vascular factors – affect the blood vessels of the germinal matrix.
- Extravascular factors refer specifically to the space surrounding the germinal matrix.

The primary lesion, the point of origin of the lesion, is the germinal matrix, located at the junction of the head of the caudate nucleus with the choroid plexus on the floor of the lateral ventricles, at the level of the foramen of Monro. The germinal matrix is a highly vascularized structure; it is present in preterm infants (clearly visible at 26–32 weeks of gestation) and absent in term newborns. Its structure contains pluripotent cells that will develop into cortical neurons, astrocytes, and oligodendrocytes. Neuronal precursors migrate from the matrix by 24 weeks of gestation, but glial cells may be found in the germinal matrix until term. It rapidly regresses between 26 and 32 weeks of gestation.

Peri- and intraventricular hemorrhage occurs during this period of involution, originating in the vessels of the germinal matrix due to their specific characteristics: they are thin-walled vessels relative to their large size, lacking a muscular layer, with immature interendothelial junctions and basement membranes, and often lacking direct contact with perivascular glial structures, which effectively results in diminished extravascular support. The vascular structures within it consist of a single layer of endothelial cells, which are fragile and easily damaged. In mild cases, the hemorrhage

may be limited to the germinal matrix (40% of cases), with a favorable course and prognosis. In approximately 60% of cases, the lesion extends along the ependyma, extending beyond it, leading to intraventricular hemorrhages (Volpe 1997). Bleeding in the germinal matrix may also extend to the parenchyma, leading to areas of encephalomalacia as the condition progresses.

VI.3.1.5. CLINICAL DIAGNOSIS

There are 3 types of clinical manifestations, outlined as follows:

- Catastrophic syndrome, characterized by dramatic clinical deterioration within minutes to hours, manifested by:
  - stupor or coma, apnea,
  - generalized tonic seizures,
  - decerebrate posture and fixed pupils.
  - decreasing hematocrit,
  - bulging of the anterior fontanelle,
  - hypotension,
  - bradycardia
  - metabolic acidosis.
- Jumping syndrome: the presentation is subtle, develops over hours or even days, and is characterized by altered level of consciousness, hypotonia, and subtle seizures.
- Clinically silent syndrome: in approximately 50% of cases, there are no clinical manifestations.

VI.3.1.6. LABORATORY AND IMAGING STUDIES

Paraclinical data useful in establishing the diagnosis include:

- complete blood count, blood type, Rh
- electrolytes, blood glucose, urea, creatinine
- Astrup, blood gases,
- TGO, TPG, LDH, CPK, lactate, coagulation profile
- bacteriological tests: blood culture, peripheral cultures useful for assessing the risk of infection
- Cardiac ultrasound, chest X-ray: differential diagnosis
- Serial cranial ultrasound for the detection, monitoring, and assessment of complications
- CT, MRI.
- EEG

Ultrasonography is the technique of choice; in 97% of cases, hemorrhage begins in the first days of life and can be diagnosed by ultrasound.

VI.3.1.7. DIFFERENTIAL DIAGNOSIS

Although the clinical and ultrasound diagnosis is relatively easy to establish, a differential diagnosis with the following conditions is required:

- Perinatal hypoxic-ischemic encephalopathy
- Convulsive syndrome
- Certain cerebral malformations
- Congenital toxoplasmosis
- Congenital CMV infection
- Neonatal sepsis
- Severe MCC
- Severe RDS
- Pneumothorax, etc.

VI.3.1.8. MANAGEMENT

A. Preventive treatment

Prevention of preterm birth: early identification of at-risk women, education on the causes of preterm birth, early diagnosis, and aggressive tocolytic therapy for preterm labor. In-utero transport of infants to a perinatal center specializing in high-risk births. Antenatal administration of

corticosteroids induces fetal lung maturation, thereby reducing the incidence of RDS and reducing the incidence of PVH/IVH. This evident protective effect of prenatal corticosteroid administration is likely secondary to the maturation of blood vessels in the lung or the inhibition of prostaglandin synthesis. Prenatal administration of vitamin K to women in preterm labor. Prenatal administration of phenobarbital—did not result in a significant reduction in the incidence of hemorrhage.

Optimal management of labor and delivery: the optimal mode of delivery for high-risk preterm infants for PVH/IVH. Since many hemorrhages occur within the first 24 hours after birth, a correlation has been established with the characteristics of labor and delivery. The factors evaluated are labor, presentation, and mode of delivery—with no influence on the incidence and severity of the disease.

B. Curative treatment

- **Neonatal resuscitation**.

Recent advances in neonatal care have been associated with a decrease in the incidence of PVH/IVH. Aggressive resuscitation, with avoidance of hypercapnia, rapid volume infusions, and the use of hypertonic solutions, may increase the incidence of PVH/IVH.

- **Correction or prevention of major hemodynamic disturbances**.

Cerebral circulation in a sick preterm infant is pressure-dependent, and changes in systemic blood pressure are directly reflected in changes in cerebral blood flow. Prevention of hypertension associated with excessive manipulation, suctioning, and rapid infusion of blood or colloid solutions; maintenance of adequate ventilation to minimize apnea, pneumothorax, and hypercapnia.

- **Correction of coagulation disorders**.

Administration of fresh frozen plasma—reduces the overall incidence of PVH/IVH, but had no effect on the incidence of severe IVH. Platelet transfusions in preterm infants with thrombocytopenia did not ensure success in preventing PVH/IVH.

- **Postnatal administration of phenobarbital**

Phenobarbital reduces the incidence and severity by mitigating increases in blood pressure (associated with motor activity, handling, and tracheal suctioning) and decreases cerebral metabolism.

- **Etamsylate**

It likely acts by stabilizing fragile vessels in the germinal matrix and inhibits the synthesis of prostaglandins (PG), which reduces basal cerebral blood flow. The dose is 12.5 mg/kg intramuscularly every 6 hours for 3 to 7 days.

- **Vitamin E**, with antioxidant properties, eliminates free radicals and protects the endothelial cells of the germinal matrix from hypoxic injury. Recommended doses: 20 mg/day for 7 to 14 days.
- **Indomethacin**. Cerebral blood flow is partially controlled by prostaglandins (PGs) synthesized in cerebral vessels. Indomethacin is an inhibitor of PG synthesis via the cyclooxygenase pathway, and its hemodynamic effects appear to be directly mediated by a decrease in prostacyclin (a vasodilator) production. It may be administered prophylactically to premature newborns with a birth weight of 500–1250 g, starting 6–11 hours after birth. The dose is 0.1 mg/kg IV—repeated every 24 hours for two additional doses. An echocardiogram must be performed prior to administering the first dose to rule out a patent ductus arteriosus-dependent cardiac lesion.

C. Treatment of the complication – posthemorrhagic hydrocephalus

Treatment of hydrocephalus differs between cases of progressive hydrocephalus (increased intracranial pressure) and cases in which ventriculomegaly is secondary to cerebral atrophy (normal or low intracranial pressure).

- Slowly progressive ventriculomegaly. Clinical and ultrasound monitoring of ventricular size is sufficient; in 2/3 of cases, the condition spontaneously resolves or stabilizes.
- Progressive ventriculomegaly requires serial lumbar punctures every 1–3 days—10–15 mL CSF/kg until the time of intervention. Measurement (via Doppler ultrasound) of the resistance index (RI) in the ACM and systolic blood flow velocity is recommended.

- Medications that reduce CSF production, such as acetazolamide ± furosemide, are also recommended. Complications of this therapy include metabolic acidosis, hypercalciuria, and nephrocalcinosis.
- If ventricular size is stable on two consecutive TEE examinations and the increase in intracranial pressure is normal, no further examinations are necessary.
- Surgical indications depend on ventricular size (which does not decrease after 4 weeks of medical treatment) and the rapid progression of ventriculomegaly.

In non-communicating forms, the following are recommended: temporary ventricular shunting (➔ -week periods), implantation of a subcutaneous shunt, or external ventricular drainage. Temporary drainage is preferred in infants weighing less than 1500 g until they gain weight. Permanent ventricular drainage is recommended if severe progressive hydrocephalus develops, and placement of a ventricular reservoir, ventriculostomy, or ventriculo-peritoneal shunt is indicated.

VI.3.1.9. PROGNOSIS

The prognosis depends on the mechanisms of brain injury, namely hypoxic-ischemic injury, posthemorrhagic hydrocephalus, and periventricular hemorrhagic infarction. The short-term prognosis is determined by the severity of the hemorrhage

Table 10. Correlation of PVH/IVH severity with mortality and hydrocephalus

Severity of PVH/IVH	Mortality	Hydrocephalus
Grade I–II	0%	0%
Grade III	10%	20
Grade IV	50–60%	65–100%

- The long-term prognosis depends on concurrent or prior hemorrhagic or nonhemorrhagic (hypoxic-ischemic) brain lesions.
- Preterm infants with Grade I and II hemorrhage have a prognosis similar to that of infants of the same gestational age without hemorrhagic lesions.
- Stabilized ventriculomegaly carries an increased risk of neuropsychological impairment in approximately 50% of cases. The risk rises to 75% in those with ventricular drainage.
- The prognosis is difficult to estimate in those with intraparenchymal hemorrhage. Mortality is high, 59% in those with extensive lesions; 86% develop spastic hemiplegia or tetraplegia, as well as cognitive impairments.

Complications of peri- and intraventricular hemorrhage

1. **Destruction of the neural crest**

The initial hemorrhagic lesion leads to the destruction of the germinal matrix and glial precursors. This can undermine the development of the normal relationship between neuronal and glial cells in the cortex. The hemorrhage causes the formation of a cyst that is visible on CT for an extended period.

2. **Posthemorrhagic hydrocephalus**

- *The acute form* is characterized by rapid enlargement of the lateral ventricles and cranial circumference within 2 weeks of the onset of the hemorrhagic process. The causes are: obstruction of the Sylvian aqueduct or other drainage pathways by a clot or its debris; impaired CSF absorption at the level of the arachnoid villi; or both.
- *Insidious hydrocephalus*—usually develops over weeks; CSF flow obstruction occurs due to obliterative arachnoiditis in the posterior fossa. In general, ventriculomegaly occurs in 30% of newborns with intraventricular hemorrhage. The incidence increases with the severity of the hemorrhage—rare in grades I and II hemorrhage (5%–10%). It occurs in 75% of moderate and severe cases (grades III and IV).

Preterm infants weighing less than 1500 g may present a unique situation:

- 50% do not develop ventricular dilatation
- 25% present with stabilized ventriculomegaly
- 25% develop progressive ventriculomegaly

3. **Periventricular hemorrhagic infarction**

- occurs in 10% of surviving infants. Parenchymal hemorrhages are accompanied by severe intraventricular hemorrhage in 85% of infants. The hemorrhagic infarct is asymmetrical in the most cases, and parenchymal hemorrhage usually occurs on the same side as the intraventricular lesion.

4. **Multicystic encephalomalacia**

The cystic formations have a heterogeneous appearance and vary in size; they are often a mixture of heterogeneous cysts, overlapping with irregular margins and shapes, found primarily in the middle cerebral artery territory. This may constitute an intermediate stage toward hydranencephaly. The cysts may extend to the cortex but do not involve the molecular layer, which is thickened as a result of gliosis. Following asphyxia with asystole or profound bradycardia, the lesion may be localized in the periventricular white matter, symmetrically. A particular form of polyporencephaly may occur following hemorrhage with an intrauterine onset (diffuse cerebral localization) and in autoimmune thrombocytopenia (localized in the temporal lobe).

Lesions associated with PVH/IVH:

1. **Periventricular leukomalacia (PVL**) is an ischemic lesion of the periventricular white matter, more common in deceased newborns with severe hemorrhage. The frequency of PVL among children with hemorrhage is difficult to determine because current noninvasive cranial imaging techniques have difficulty distinguishing between the two lesions.
2. **Pons neuronal necrosis** may be observed in association with hemorrhage and reflects associated hypoxic-ischemic injury.

VI.3.2. SUBARACHNOID HEMORRHAGE

VI.3.2.1. PATHOPHYSIOLOGY

There are two forms of hemorrhage:

- The traumatic form occurs in term newborns
- The post-asphyxia form occurs with normal labor in preterm infants.

The primary form of subarachnoid hemorrhage is hemorrhage that is not secondary to the spread of a subdural, intraventricular, or parenchymal hemorrhage. The most common causes are: rupture of small arachnoid vessels due to the use of forceps or vacuum extraction, or asphyxia in cases of prolonged labor.

The secondary form occurs through distant diffusion in the case of intraventricular hemorrhage.

VI.3.2.2. CLINICAL DIAGNOSIS

If the hemorrhage is isolated, the following may be present on the first day: irritability, generalized hypertonia, and a shrill cry. In the form associated with cellular injury (EHIP), the following are present: generalized hypotonia, hyporeflexia, and hyporeactivity, which progressively worsen until the onset of apnea episodes. It is very difficult to determine which symptoms are due to hemorrhage, as the lesions are h nd often associated with trauma, hypoxia, and other forms of intracranial hemorrhage. Three major syndromes have been defined:

- Grade I: the most common—minor hemorrhage without clinical signs, and it is more common in preterm infants.
- Grade II: characterized by the onset of seizures on the second day of life; otherwise, the newborn is in good general condition (a well-functioning infant with seizures), and the course is normal in 90% of cases.
- Grade III: rarer, this is massive subarachnoid hemorrhage with rapid progression. These newborns have most often suffered severe asphyxia, sometimes with birth trauma. Few of them have a major vascular lesion, such as aneurysms and vascular malformations.

VI.3.2.3. LABORATORY AND IMAGING STUDIES

Confirmed by lumbar puncture and CT scan. The CSF appears different depending on the degree of hemorrhage, ranging from pale pink to deep red. CT scans reveal discrete hyperechoic areas in the subarachnoid spaces.

Treatment is symptomatic.

VI.3.3. SUBDURAL HEMORRHAGE

VI.3.3.1. DEFINITION

It is defined as a thin layer of blood or a hematoma in the virtual space between the dura mater and the arachnoid membrane. It is almost exclusively a traumatic injury in newborns.

VI.3.3.2. EPIDEMIOLOGY. INCIDENCE

The incidence is low, accounting for 5–10% of all intracranial hemorrhages, due to improvements in obstetric practice and a corresponding decrease in obstetric trauma. It can be localized: supratentorial—at the level of the cerebral hemispheres—or subtentorial—at the level of the cerebellum. It occurs mainly in full-term newborns and less frequently in preterm infants. The relationship between head size and the diameter of the birth canal is implicated in the pathogenesis in newborns. Other factors involved include: rigidity of the birth canal, duration of labor, and maneuvers during delivery.

VI.3.3.3. CLINICAL DIAGNOSIS

- onset is early, immediately after birth
- neurological signs: irritability, seizures, high-pitched crying, disturbances of consciousness, reflexes, and muscle tone;
- signs of acute anemia: pallor, tachycardia, hypotension;
- signs of ICH (bulging of the anterior fontanelle, suture dehiscence, increased head circumference) occurring in 50% of cases.
- rigidity or opisthotonos, which may be initial diagnostic signs.
- As the clot grows larger, the coma deepens, the pupils become fixed and dilated, and ultimately respiratory arrest with death may occur.

Subdural hemorrhage located above the cerebral convexity is associated with at least 3 clinical grades:

- Grade I**:** minor hemorrhage without apparent clinical signs,
- Grade II: signs of brain injury may appear, particularly seizures that may be focal and are often associated with hemiparesis, with the eyes deviating toward the side of the hemiparesis or a "doll's eye" appearance.
- Grade III**:** the clinical presentation may be characterized by the onset of a subdural hemorrhage in the neonatal period, with few clinical signs (tachypnea, distress in the infant), which progresses to chronic subdural effusions over the following months.

VI.3.3.4. LABORATORY AND IMAGING STUDIES

Confirmation and localization of the hemorrhage rely exclusively on ultrasound and MRI. Lumbar puncture reveals bloody CSF; the EEG may be altered depending on the location.

VI.3.3.4. MANAGEMENT

- Puncture of the hematoma and evacuation through the external angle of the fontanelle.
- Treatment of hydrocephalus—surgical.

VI.3.3.5. PROGNOSIS

- Progression to death or severe neurological sequelae when associated with severe EHIP.
- The prognosis for a newborn with major tentorial or cerebral peduncle damage is poor.
- Death occurs in 45% of cases, and survivors mostly present with hydrocephalus or other neurological sequelae.
- Newborns with mild, small subdural hemorrhages have a 50% chance of normal neurological development. A factor contributing to severity is the association with hypoxic-ischemic lesions.

VI.3.4. CEREBELLAR HEMORRHAGE

VI.3.4.1. EPIDEMIOLOGY. INCIDENCE

It occurs in premature newborns with an incidence of 12–15% in those with a gestational age of less than 32 weeks and/or a birth weight of less than 1,500 g. A lower incidence is reported in term newborns. The most common causes are:

- skull deformities and occipital diastasis with damage to the cerebellum, large vessels, or the sulcus;
- massive intraventricular or subarachnoid hemorrhage;
- severe EHIP;
- cerebrovascular autoregulatory disorders;
- In preterm infants—perinatal asphyxia or severe RDS.

VI.3.4.2. CLINICAL DIAGNOSIS

In preterm infants, onset occurs within the first three weeks of life (especially within the first 2 days) with severe deterioration of general condition, apnea, bradycardia, and decreased hematocrit. In term newborns, signs of brainstem compression appear, including stupor or coma, cranial nerve abnormalities, apnea, bradycardia, and opisthotonos.

VI.3.4.3. LABORATORY AND IMAGING STUDIES

The following investigations are of choice:

- Computed tomography (CT)
- Magnetic resonance imaging (MRI)

VI.3.4.4. MANAGEMENT

Treatment is conservative. In severe cases with extensive brain lesions, surgical evacuation of the hemorrhage is performed.

VI.3.4.5. PROGNOSIS

The prognosis is poor, with major neurological sequelae in survivors: spastic tetraparesis, hemiparesis, and mental retardation.

VI.4. NEONATAL SEIZURES

VI.4.1. DEFINITION

Neonatal seizures are the most common manifestation of neurological diseases in the neonatal period and also the most reliable indicator of this type of condition.

VI.4.2. EPIDEMIOLOGY. INCIDENCE

The incidence of seizures varies depending on several factors; the latest data estimate an incidence of 1.5–5 per 1,000 among full-term newborns. In preterm infants, it depends on the degree of neurological maturity: in infants weighing between 1,500 and 2,500 g, the incidence is estimated at 4.4 per 1,000; in those weighing less than 1,500 g, the incidence is 5.5; and in extremely immature preterm infants weighing less than 1000 g, the incidence can rise to 6.4 per 1000 newborns

VI.4.3. PATHOPHYSIOLOGY

Neonatal seizures occur, in most cases, in the context of neurological disorders of the perinatal period, with the timing and mode of delivery being very important. The pathophysiological mechanisms depend on the underlying condition.

- Perinatal hypoxic-ischemic encephalopathy is the cause of seizures in 50–70% of cases.
- Cerebral hemorrhage—15%.
- Metabolic seizures are common in newborns, especially in premature infants or those with intrauterine growth restriction.
    - hypoglycemic (below 40 mg/dL),
    - hypocalcemic (below 7 mg/dL),
    - hyponatremic,

- hypernatremic,
- hypomagnesemic,
- maple syrup urine disease.

- Pyridoxine-dependent seizures.
- Infectious seizures: meningitis, congenital and postnatal meningoencephalitis caused by streptococcus, E. coli, Listeria, CMV, Coxsackie virus, herpes simplex.
- Drug-induced seizures: respiratory analeptics, alcohol, barbiturates.
- The most commonly involved CNS malformations are:
  - cranio-cerebral dysraphism,
  - Arnold-Chiari malformation,
  - Dandy-Walker malformation,
  - arachnoid cysts,
  - Galen's vein malformation, corpus callosum agenesis

VI.4.4. RISK FACTORS

The risk factors for neonatal seizures are varied and somewhat common to perinatal hypoxic-ischemic or hemorrhagic conditions.

- **Antepartum risk factors**
  - Extreme maternal age, mothers who are minors or over 40 years old,
  - Insulin-dependent diabetes mellitus
  - Endocrine or metabolic disorders
  - Gestational toxemia
  - Placental disorders
  - Bleeding during pregnancy
  - Maternal fever
- **Intrapartum risk factors**
  - Premature rupture of membranes
  - Maternal infections: chorioamnionitis, other maternal infections,
  - Apgar score below 5, requiring resuscitation at birth
  - Postterm pregnancy (over 42 weeks)
  - Precipitous or prolonged labor
  - Chronic intrauterine fetal distress
  - Fetal-pelvic disproportion
  - Umbilical cord entanglement, umbilical cord prolapse
  - Abnormal presentations
  - Forceps delivery
  - Obstetric trauma

VI.4.5. CLINICAL DIAGNOSIS

Clinical signs, specifically seizures, present differently depending on the type of seizure:

- ***frustrated seizures*** are seizures with a distinct character, usually occurring in premature newborns. They can manifest in various forms:
  - apnea episodes,
  - chewing movements,
  - sucking, eye movements (horizontal deviation, staring).
  - when they occur in a full-term newborn, they are not accompanied by convulsive EEG activity.
- ***Clonic seizures***.
  - There are two types:
    - focal or localized to one part of the body, which may spread to one half of the body

        - multifocal, which are less common than focal seizures and often migrate from one side of the body to the other.
    - Clonic seizures are most often followed by vasomotor disturbances or apnea and are accompanied by EEG changes, with the appearance of spikes or slow waves in different areas of the brain.
- ***Tonic seizures***—occur at the same rate as clonic seizures and have the following characteristics:
    - They are followed by apneic episodes.
    - They may be localized to one part of the body,
    - or they may be generalized.
    - EEG – high-voltage slow waves
    - sometimes pseudo-alpha rhythms with a flat trace.
- ***Myoclonic seizures*** manifest as single or repetitive flexion movements of the extremities. They can be focal, multifocal, or generalized, with or without EEG changes. In general, they have a better prognosis.
- ***Convulsive states*** – these are prolonged subclinical seizures with the following characteristics:
    - they recur several times a day
    - manifest as localized clonic movements (or clonic contractures), eye movements, nystagmus, apneic episodes, etc.
    - During a seizure, consciousness is lost.
    - Between seizures, symptoms such as:
        - hypo- or hypertonia,
        - absence of spontaneous motor activity
        - fixation of the eyeballs,
        - hypo-reactivity to painful stimuli

VI.4.6. LABORATORY AND IMAGING STUDIES

- **Investigations**
    - Complete blood count, platelets, white blood cell differential
    - Blood type, Rh
    - Blood glucose
    - Serum calcium, serum magnesium, serum electrolyte panel (sodium, potassium)
    - ASTRUP
    - Urea, serum creatinine
    - Bilirubin
    - Urinalysis
    - CSF examination (cytology, chemistry, bacterial cultures)
    - Blood culture, peripheral cultures
    - Protein electrophoresis
    - Guthrie test
    - Screening for toxins in blood and urine
    - lumbar puncture,
    - bacteriological investigations,
    - tests to rule out hereditary metabolic disorders (determination of serum levels of lactate, pyruvate, ammonia, urinary organic acids, and aminoacidemia),
    - cytogenetic analysis.
- **EEG, aEEG, videoEEG –** are useful for
    - initiating and monitoring anticonvulsant therapy
    - formulating the immediate and long-term prognosis
    - monitoring the duration of seizures and their response to treatment, as well as assessing the baseline brain electrical activity

- **Brain imaging studies**
    - **Transfontanellar ultrasound (TFU)**. This is a rapid, non-invasive diagnostic method that can be performed at the patient's bedside. It is particularly useful for peri- and intraventricular hemorrhages, fluid collections, cystic formations of various etiologies, ventriculomegaly, hydrocephalus, and certain cerebral malformations.
    - **Magnetic resonance imaging (MRI) is** the most sensitive **method** of diagnostic imaging for neurological pathology in newborns.
    - **Cranial computed tomography (CT) has** good sensitivity and specificity, especially for cerebral hemorrhages and calcifications, bone lesions, and neonatal infections.

VI.4.7. DIFFERENTIAL DIAGNOSIS

1. **benign sleep movements** in the newborn
- may occur during sleep (especially in preterm infants)
- are not influenced by sensory stimuli,
- are not accompanied by sensory stimuli, motor activity, or EEG activity
- They diminish during wakefulness and disappear after a few months of life.

2. **benign myoclonus** in infants – begins between 3 and 9 months
- myoclonic spasm episodes;
- EEG activity is normal.
- They occur almost exclusively while awake
- Last for a period of 1–2 years.

3. **tremors (gitteriness or neonatal clonus)**
- are triggered by stimuli,
- disappear or diminish with a change in posture;
- are not accompanied by oculomotor or autonomic phenomena;
- disappear by 2 months.

4. **stimulus-induced myoclonus** – severe neurological lesions (metabolic, CNS malformations).
5. **congenital rigidity syndrome** (hyperreflexia, startle syndrome)
- Clinical features:
    - rigidity,
    - severe hypertonia,
    - apnea attacks,
    - bradycardia;
- The EEG shows no abnormalities.

VI.4.8. MANAGEMENT

A. NONPHARMACOLOGICAL
- Placement in a servo-controlled incubator
- Temperature monitoring
- Clinical and laboratory monitoring**:** color, heart rate, blood pressure, pulse oximetry, and blood gas analysis.
- Establishment of an intravenous line in any newborn presenting with neonatal seizures
- Prompt initiation of neonatal resuscitation measures
- Providing respiratory, cardiovascular, and metabolic support

B. PHARMACOLOGICAL

Anticonvulsant treatment must be initiated rapidly, as seizure control is a medical emergency. The most commonly used medications are:

- *Phenobarbital*
    - the drug of choice
    - 20 mg/kg body weight per day IV—up to 40
    - Maintenance dose: 5 mg/kg/day.

- *Phenytoin.*
  - The loading dose is 20 mg/kg/day
  - Maintenance dose: 5 mg/kg/day.
- *Diazepam*
  - may also be used as first-line therapy.
  - The loading dose is 0.1–0.3 mg/kg IV
  - The maintenance dose is 0.1 mg/kg/day.
- *Lorazepam*
  - is administered at a dose of 0.05 mg/kg IV slowly.
- *Primidone*
  - may be used as an adjunctive treatment.
  - The loading dose is 15–25 mg/kg/day.
  - The maintenance dose is 10 mg/kg/day.
- *Paraldehyde*—an adjunctive therapeutic agent.
  - In PEV—150 mg/kg/hour for three hours.

Specific treatment:

- hypoglycemic seizures
  - 5% or 10% glucose solution via IV - 6 mg/kg/minute.
  - severe forms – a mini-bolus of 200 mg/kg 10% glucose over one minute, followed by continuous infusion at→ .
- hypocalcemic seizures
  - IV calcium gluconate – 1 ml/kg/day
- Hypomagnesemic seizures
  - 50% magnesium sulfate solution, 0.1–0.2 ml/kg/day.
- pyridoxine-dependent seizures
  - 100 mg pyridoxine IV

C. FOLLOW-UP

Follow-up care for newborns with neonatal seizures is provided through existing follow-up services to prevent complications of both the seizure syndrome and those caused by anticonvulsant therapy. Follow-up is conducted by a multidisciplinary team—neonatologist, pediatrician, pediatric neurologist, and physical therapist. Therapy and anticonvulsant dose adjustments are monitored. EEG and ultrasound monitoring are also necessary.

VI.4.9. PROGNOSIS

The prognosis depends on the etiology of the seizures and the degree of maturity, and is much more guarded in premature infants.

- 20–25% die within the first 2 weeks of life.
- 25–30% of children develop neurological sequelae (mental retardation, recurrent seizures, cerebral palsy).
- 50% may recover without neurological sequelae.

Factors associated with a poor prognosis include:

- Apgar score below 6 at 5 minutes
- need for positive ventilation beyond 5 minutes
- early seizures
- tonic or myoclonic seizures
- seizures lasting longer than 3 days
- status epilepticus
- prolonged hypotonia.

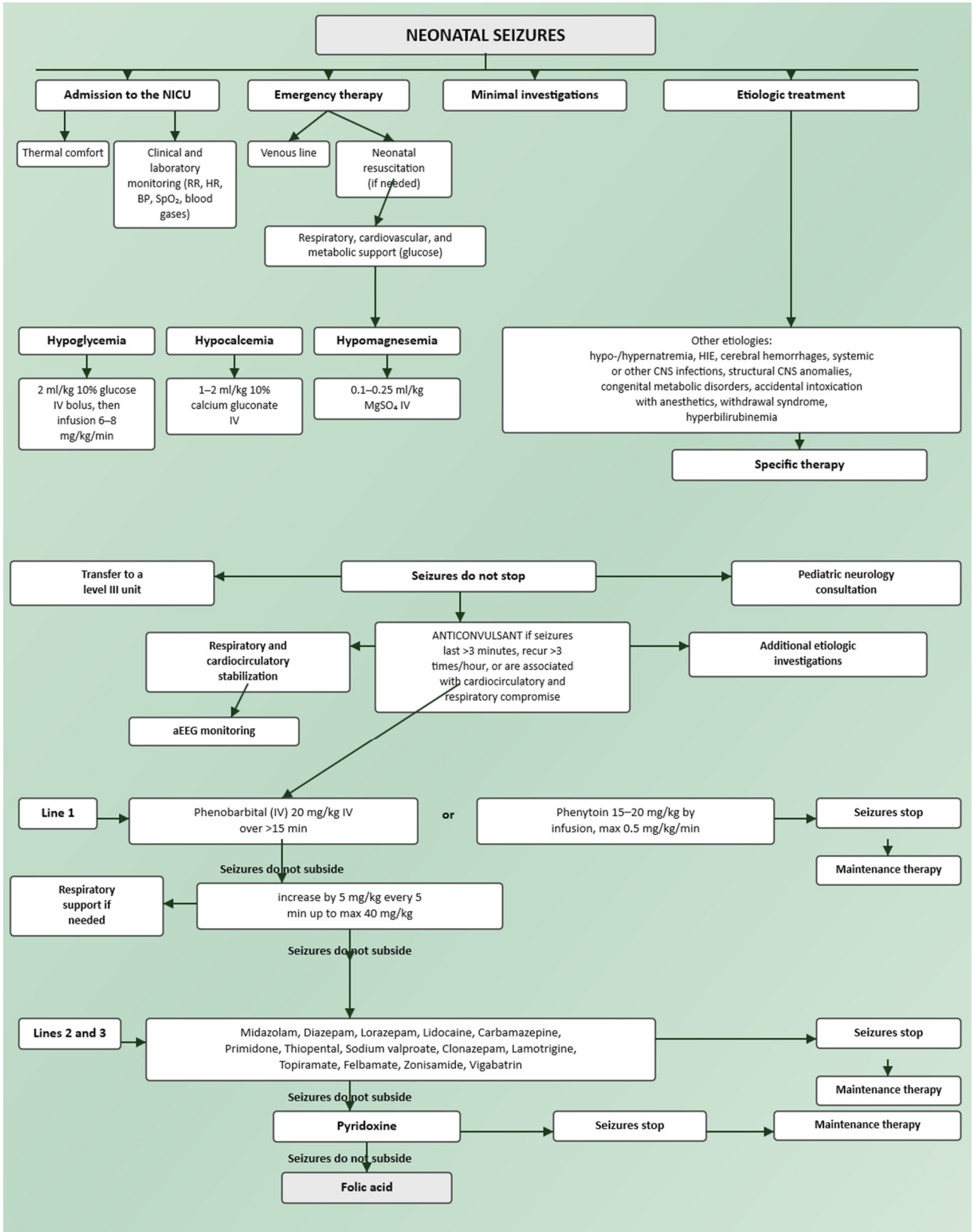

Figure 7. Management of neonatal seizures (GUIDE: Management of Seizures in Newborns and Infants Diagnosis and Treatment of Neonatal Seizures Revision 1/2020 Guide No. 04 – COLLECTION OF CLINICAL GUIDELINES FOR NEONATOLOGY)

VI.5. BRAIN MALFORMATIONS

VI.5.1. INTRODUCTION

Cerebral malformations cause increased morbidity and mortality both in the neonatal period and during infancy and early childhood. Immediate and long-term complications depend primarily on the type of malformation, its severity, and the degree of cerebral maturity.
Several factors are involved in the pathogenesis: genetic factors, congenital infections, radiation, chemical agents, drug use, and nutritional deficiencies.

VI.5.2. CLASSIFICATION OF BRAIN MALFORMATIONS

- Neural tube defects
- Diverticulation disorders
- Disorders of cell proliferation and neuronal migration
- Neuronal migration disorders
- Complex cerebral anomalies
- Encephaloclastic lesions

1. Neural tube defects

- *Anencephaly*—occurs due to failure of the anterior neural tube to close. It is one of the most severe malformations of the CNS. Due to the absence of bony structures, the face has a characteristic, frog-like appearance. It can be detected in utero as early as 12 weeks of gestation. The prevalence is 1 in 2,000 births, the risk of recurrence is 4%, and it is usually accompanied by other malformations such as adrenal hypoplasia, myelomeningocele, clubfoot, cleft palate, and umbilical hernia.
- *An encephalocele* occurs when intracranial structures herniate in a sac-like formation through defects in the frontal or occipital skull bones. Occipital encephaloceles may be accompanied by: microcephaly, motor, visual, and auditory impairments; if associated with Sylvius aqueduct stenosis or Dandy-Walker syndrome, hydrocephalus may develop. Anterior encephaloceles can have multiple locations—nasal, orbital, etc.; those with basal locations (sphenoidal, nasal sinuses, or deep within the orbits) may not be visible and have a good long-term prognosis.
    - *Myelomeningocele* is a neural tube defect that occurs after the caudal neural pore has closed (26 days) and is frequently associated with hydrocephalus and Chiari II malformation. Vertebral defects located in the lumbosacral region occur in 80% of cases because this is the last portion to close. Clinically, they are associated with motor deficits up to paresis, loss of skin sensation, and bowel motility disorders. Depending on the location of the anatomical defect, myelomeningocele is accompanied by hydrocephalus. In occipital, cervical, thoracic, or sacral lesions, the incidence of hydrocephalus is 60%. In thoracolumbar or lumbosacral lesions, the incidence is 90%. During the neonatal period, 10% of children with myelomeningocele present with hydrocephalus. The onset of hydrocephalus following myelomeningocele is similar to the development of hydrocephalus following intraventricular hemorrhage. The most common time for hydrocephalus associated with myelomeningocele to present with clinical signs is the 2nd or 3rd week after birth. More than 80% of children who develop hydrocephalus do not present clinical signs for the first 6 weeks of life.

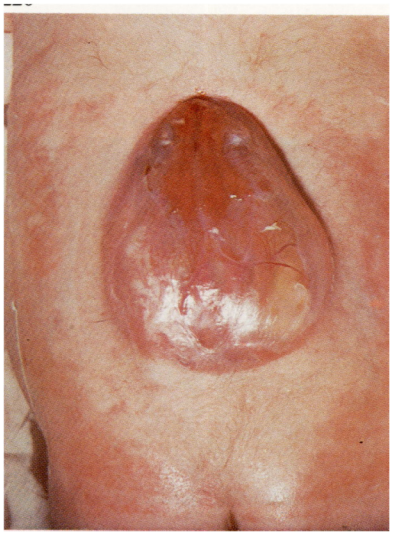

Figure 8. Thoracolumbar myelomeningocele.

- *Arnold-Chiari malformation (ACM)* – characterized by cerebellar hypoplasia, herniation of the cerebellar vermis into the foramen magnum with posterior displacement of the cerebellum, and varying degrees of cerebellar dysplasia. Three types of ACM are described:
    - Type I – downward displacement of the cerebellar tonsils and the lower cerebellum, without involvement of the spinal cord and the fourth ventricle;
    - Type II – downward displacement of the lower cerebellum, tonsils, pons, medulla, and fourth ventricle into the upper region of the spinal canal. It is almost always associated with myelomeningocele.
    - Type III – displacement of the medulla, the fourth ventricle, and the entire cerebellum into a cerebral or occipital encephalomeningocele.

  Specific ultrasound findings include:
    - Lower displacement of the cerebellum,
    - Difficulty visualizing the fourth ventricle,
    - Obliterated cisterna magna,
    - Dilated third ventricle with enlarged intermediate mass,
    - Lateral ventricles with dilated posterior horns.
    - Classically, the anterior and inferior extension of the frontal horn gives the characteristic "bat wings" appearance

Hydrocephalus in Arnold-Chiari malformation is caused by: cerebellar malformation leading to obstruction of the fourth ventricle and impeded CSF flow into the posterior fossa. Aqueductal stenosis causes hydrocephalus in 75% of cases.

2. Diverticulation disorders

- **Holoprosencephaly.** It occurs due to the absence of prosencephalic cleavage into the telencephalon and diencephalon; this process of ventral separation occurs during the fifth week of intrauterine life. The frequency is 1 in 10,000 live births, with an incidence 60 times higher in aborted embryos. De Myer's classification based on the degree of differentiation and severity is as follows:
    - **Alobar holoprosencephaly**: this is the most severe form, characterized by the complete absence of separation, with a single ventricle along the midline, continuing into a dorsal sac. The thalamus is spindle-shaped and the parenchyma is undifferentiated. The anterior, posterior, and temporal horns of the lateral ventricles do not differentiate; the third ventricle is small or absent; the fourth ventricle, cerebellum, and brainstem are usually normal. It may be associated with partial or total agenesis of the corpus callosum.
    - **Semilobar holoprosencephaly** has the following characteristics:
        - A single ventricle with a fused thalamus,
        - SIE present but partially developed, especially in the posterior region,
        - Small or absent third ventricle,
        - Ventricles IV, cerebellum, and brainstem—usually normal,
        - Total or partial agenesis of the corpus callosum may sometimes be present.
    - **Lobar holoprosencephaly** presents the following characteristics: absence of the septum pellucidum, the bodies of the lateral ventricles are fused along the midline, the posterior horns are separated. The posterior SIE and thalamus appear normal. The anterior SIE is incompletely developed. The long-term neurological prognosis is related to the form of the disease. Neurological signs are present from the neonatal period. The course in severe forms is unfavorable, leading to death.
- **Absence of the septum pellucidum** is an incomplete form of midline anomaly. It is usually associated with: holoprosencephaly, septo-optic dysplasia, schizencephaly, and corpus callosum agenesis. Severe hydrocephalus and progressive holoprosencephaly can cause destructive lesions of the septum pellucidum.
- **Septo-optic dysplasia** is characterized by the absence of the septum pellucidum, optic nerve hypoplasia, and pituitary gland dysfunction.It is associated with other cerebral malformations

such as corpus callosum agenesis, schizencephaly, and cortical dysfunctions. Clinically, it is a severe condition manifested by decreased visual acuity, endocrine dysfunction, cholestasis, and mental retardation.

3. **Disorders of cell proliferation and neuronal migration**

- **Microcephaly** (microcrania) is defined as a head circumference 2 standard deviations below that of children of the same age and sex. It is usually associated with microencephaly.Two forms are described: Primary form – not associated with other malformations, may be of genetic origin (true microcephaly). In autosomal recessive forms, it is present at birth, and children continue to have microcephaly throughout their growth. It is accompanied by disturbances in neural proliferation with a reduction in the number of neurons. Secondary microcephaly – has an intrauterine onset or appears within the first two years of life. Causes include genetic factors (chromosomal or genetic aberrations), environmental factors (radiation, drugs, chemical agents), congenital infections (rubella, CMV, toxoplasmosis), and chronic intrauterine ischemia.
- **Megalencephaly** is characterized by diffuse neuroepithelial proliferation, which leads to increased cerebral cell density. It may be associated with genetic syndromes: SOTO syndrome (cerebral gigantism), Fragile X syndrome, autism, and neurocutaneous syndromes.It may be seen in certain metabolic disorders—Tay-Sachs disease, Canavan disease, Alexander disease.

4. Neuronal Migration Disorders

Neuronal migration occurs from 40–41 days of gestation until approximately 6 months of embryonic development, when neuroblasts from the neural crest migrate radially toward the cerebral cortex, cerebellum, and spinal cord. Neuronal migration disorders are characterized by disorganization of the cortical brain structure due to gaps and a lack of neurons, leading to changes in cerebral cytoarchitecture.

- **Lysencephaly** – impaired neuronal migration resulting in a cerebral cortex with few or absent gyri ("smooth brain"),
- **Polygyria** – reduction in the size of sulci and gyri, occurring concurrently with lissencephaly. Clinically, it presents with growth disorders, severe neurological retardation, and severe forms of epilepsy.
- **Schizencephaly.** It is characterized by unilateral or bilateral septation of the cerebral hemispheres, resulting in fissures of variable, irregular sizes that extend from the lateral ventricles to the cerebral cortex. It occurs due to defective migration of neuroblasts from the germinal matrix, leading to localized cortical agenesis or hypoplasia. Clinically, it is accompanied by microcephaly, motor delay, seizures, hyper/hypotonia, epilepsy, and developmental disorders.
- **Corpus callosum agenesis.** The corpus callosum is a fibrous structure located between the two cerebral hemispheres. It begins to develop between the 6th and 8th week of gestation and continues until 18–20 weeks of gestation. Etiologically, infectious factors (congenital rubella), inborn errors of metabolism, and genetic syndromes are implicated. Approximately 50 syndromes are associated with corpus callosum agenesis (chromosomal abnormalities—trisomy 8, 18). The prevalence is 0.1–0.7% and rises to 2.3% in cases of severe disability. Agenesis may be partial, when only the posterior portion is missing, or total, when the corpus callosum is entirely absent.

5. Encephaloclastic lesions

- **Hydrocephalus.** This is a severe condition characterized by the flattening or absence of the cerebral hemispheres, leading to the formation of a thin-walled, membranous sac filled with cerebrospinal fluid (CSF). The structure of the midbrain and cerebellum may be intact, while the brainstem may be atrophic. The condition results from intrauterine destruction, with pathogenic factors (ischemia, infection, vascular disorders) acting during the period when liquefactive necrosis occurs (20–27 weeks). Infectious factors involved include toxoplasmosis, syphilis, CMV, and herpes simplex. The diagnosis is established by ultrasound and cerebral transillumination. The neurological course is severe, with epilepsy, flexion spasms, respiratory failure, and death.

- **Porencephaly** is a focal congenital or acquired cavity located in the cerebral parenchyma. It may communicate with the subarachnoid space (external porencephaly), with the lateral ventricles (internal porencephaly), or with the midline (central porencephaly). Classification:
    - **Embryonic porencephaly** or schizencephaly has the following characteristics:
        - Bilateral defect in the cerebral parenchyma
        - Communication between the lateral ventricles and the subarachnoid space.
        - Occurs during neuronal migration (7th week of gestation),
        - Acquired following vascular damage in the glyconeuronal matrix
    - **Early fetal porencephaly** occurs at approximately 24 weeks of gestation and is characterized by:
        - well-defined, regular margins, involving the cortex and white matter,
        - communication with the lateral ventricles
        - accompanied by polymicrogyria.
    - **Perinatal porencephaly** is characterized by cystic lesions of vascular or infectious etiology, single or multiple, with irregular walls. It occurs after 20 weeks of gestation and during the perinatal period. It may be secondary to peri- or intraventricular hemorrhage, periventricular leukomalacia, or severe cerebral infections
- **Dandy-Walker malformation**

The classic form is characterized by:

- Complete or incomplete agenesis of the cerebellar vermis,
- Cystic dilation of the posterior fossa communicating with the fourth ventricle,
- Abnormalities of the tentorium with widening of the posterior fossa.

The fundamental abnormality of the posterior brain is related to the malformation of the cerebellar vermis and the roof of the fourth ventricle. The starting point is the total or partial obstruction of the foramen of Magendie, leading to CSF accumulation and dilation of the fourth ventricle. Subsequent opening of the Luschka foramen leads to persistent cystic dilation of the fourth ventricle and impaired CSF drainage.

- **The Dandy-Walker variant** is characterized by moderate hypoplasia of the cerebellar vermis, a less developed tentorium, and dilation of the posterior fossa. Neurological impairment is less severe and also depends on associated lesions. Megacisterna magna may sometimes be present. In the absence of cerebral anomalies, the prognosis is good.
- **Joubert syndrome.** A complex autosomal recessive disorder characterized by:
    - Cerebellar vermis hypoplasia,
    - Thickening and elongation of the cerebellar peduncles,
    - Deepening of the interpeduncular fossa.

Clinically, it manifests as marked hypotonia, episodes of apnea, or tachypnea. The prognosis is guarded, with the most common complications being psychomotor retardation, ataxia, nystagmus, and recurrent seizures.

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VII. METABOLIC AND ENDOCRINE DISEASES

VII.1. CONGENITAL METABOLIC DISORDERS

Metabolic and endocrine disorders in the newborn constitute an essential chapter in neonatology, due to the major impact that biochemical and hormonal imbalances can have on adaptation to extrauterine life. During the neonatal period, the immaturity of metabolic and endocrine regulatory mechanisms can lead to early clinical manifestations, which are sometimes nonspecific but have the potential to be severe if not promptly recognized and treated. Understanding the pathophysiological characteristics of these conditions, neonatal screening methods, and the principles of diagnosis and management is fundamental, playing a decisive role in preventing short- and long-term complications.

Screening is the initial, "mass" examination that consists of applying a set of investigative procedures and techniques to a population for the purpose of presumptive identification of a disease, abnormality, or risk factors.

VII.1.1. DEFINITION

Congenital metabolic disorders (CMDs), also known as inborn errors of metabolism, represent a heterogeneous group of genetic conditions caused by the total or partial deficiency of enzymes, cofactors, transporters, or proteins involved in metabolic pathways, leading to the accumulation of toxic metabolites, cellular energy deficiency, or the body's inability to synthesize essential products.

VII.1.2. EPIDEMIOLOGY. INCIDENCE

Although each condition is rare, the estimated incidence is between 1 in 800 and 1 in 3,000 live births (depending on the region and screening programs). Many IEMs manifest during the neonatal period, often with a severe, nonspecific clinical presentation that can mimic sepsis, liver failure, or neurological disorders. Due to the nonspecific nature of neonatal symptoms, these disorders are often underdiagnosed, which is why **neonatal screening** plays a crucial role in early detection. The inheritance of IEM is predominantly autosomal recessive, but there are also X-linked forms (e.g., ornithine transcarbamylase deficiency, adrenoleukodystrophy) or mitochondrial forms.

The etiology of IEM can be categorized based on the affected metabolic pathway:

A. Carbohydrate metabolism disorders:
- Glycogen storage diseases
- Galactosemia
- Hereditary fructose intolerance
- Glucose-6-phosphate dehydrogenase deficiency

B. Amino acid metabolism disorders:
- Phenylketonuria
- Maple syrup urine disease
- Homocystinuria
- Tyrosinemia

C. Organic acid metabolism disorders:
- Methylmalonic acidemia
- Propionic acidemia
- Isovaleric acidemia

D. Fatty acid oxidation disorders:
- Medium-chain acyl-CoA dehydrogenase deficiency
- Long-chain fatty acid oxidation disorders
- Carnitine deficiency syndromes

E. Urea cycle disorders:
- Ornithine transcarbamylase deficiency

- Citrullinemia
- Arginine succinic aciduria

F. Lysosomal storage diseases:

- Gaucher disease (deficiency of an enzyme called glucocerebrosidase)
- Tay-Sachs disease (deficiency of the enzyme hexosaminidase A)
- Mucopolysaccharidoses
- Niemann-Pick disease (deficiency of the enzyme sphingomyelinase or defects in lipid transport)

G. Mitochondrial disorders:

- MELAS syndrome (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes)
- MERRF syndrome (myoclonic epilepsy with ruffled red fibers)
- Leigh syndrome (subacute necrotizing encephalopathy)

H. Peroxisomal disorders:

- Zellweger syndrome
- Adrenoleukodystrophy

VII.1.3. PATHOPHYSIOLOGY

The pathophysiological impact on the newborn is severe because their metabolism is in a postnatal transition phase, with reduced energy reserves and increased dependence on certain metabolic pathways. IEMs can arise, from a functional perspective, through:

- **Disorders caused by accumulation of toxic substrates**
  - Enzyme deficiency leads to the overproduction of a toxic metabolite (e.g., ammonia in urea cycle defects, organic acids in organic acidoses).
- **Disorders due to end-product deficiency**
  - The lack of enzymatic activity prevents the production of necessary metabolites.
- **Energy production disorders**
  - Imbalanced energy production affects organs with high energy consumption (brain, heart, muscles).
- **Disorders due to activation of alternative pathways**
  - When the primary pathway is blocked, substrates can be metabolized via minor pathways, producing abnormal metabolites.

VII.1.4. RISK FACTORS

- family history of IEM or unexplained neonatal death, sudden death,
- consanguineous parents,
- siblings with developmental delay or metabolic encephalopathy,
- suggestive maternal symptoms (e.g., inherited food intolerances),
- geographic origin from populations with a high prevalence of certain mutations,
- abnormal results in prenatal or neonatal screening.

VII.1.5. CLINICAL DIAGNOSIS

Symptoms are often **nonspecific** and appear after a latency period of several hours to days after birth, upon the initiation of feeding. Many IEMs present with **an acute onset** in a newborn who was initially well. Manifestations that may occur include:

- feeding difficulties, vomiting,
- lethargy, hypotonia, irritability,
- seizures, apnea,
- unusual odor (sweaty feet, maple syrup, mold),
- respiratory distress,
- cardiomyopathy, arrhythmias, cardiac arrest,

- hepatomegaly, jaundice, liver failure,
- developmental regression.

Some metabolic disorders have **a delayed onset** with:

- developmental delay,
- hepatosplenomegaly,
- skeletal abnormalities,
- neurological impairment,
- metabolic crises triggered by illness, fasting, or stress.

Symptoms suggestive of disease groups:

- hypoglycemia → defects in fatty acid oxidation, glycogenolytic disorders,
- hyperammonemia → urea cycle defects,
- metabolic acidosis with elevated anion gap → organic acidoses,
- jaundice + liver failure → galactosemia, fatty acid oxidation defects,
- distinctive odor → maple syrup urine disease (the body cannot properly break down certain amino acids: leucine, isoleucine, and valine):
    - urine, sweat, and sometimes breath may smell like mice or mold (phenylketonuria),
    - urine, sweat, and sometimes breath have a sweaty feet/cheese odor (isovaleric aciduria).

VII.1.6. LABORATORY DIAGNOSIS

Diagnosis is based on **early clinical suspicion** and urgent **biochemical testing**. Early diagnosis and initiation of appropriate treatment are essential to prevent complications and death.

A. Emergency tests:

- blood glucose,
- blood gases, lactate,
- serum ammonia,
- electrolytes,
- complete blood count,
- CRP (to rule out sepsis),
- urea, creatinine,
- transaminases, bilirubin,
- urine: pH, urinary ketones.

B. Specific tests:

- plasma and urinary amino acids,
- urinary organic acids,
- plasma carnitine and acetylcarnitine,
- galactose and galactose-1-phosphate uridyltransferase in galactosemia,
- molecular genetic testing – etiological confirmation,
- liver/muscle/skin biopsy in selected cases,
- ECG, EEG.

C. Imaging

- brain MRI (changes in the basal ganglia in mitochondrial diseases),
- abdominal ultrasound (hepatosplenomegaly),
- echocardiography (cardiomyopathy in respiratory chain defects, fatty acid oxidation disorders, Pompe disease),
- skeletal X-ray (storage disorders).

D. Neonatal screening

In Romania, the national metabolic screening program conducted in all maternity wards currently includes testing of all newborns for:

- Phenylketonuria,

- Congenital hypothyroidism,
- Cystic fibrosis.

Extended neonatal screening allows for the detection of over 40–50 metabolic disorders as early as the first days of life, reducing morbidity, but it is applied selectively to newborns.

VII.1.7. DIFFERENTIAL DIAGNOSIS

The nonspecific symptoms of IEM will require a differential diagnosis with:

- neonatal sepsis,
- hypoxic-ischemic encephalopathy,
- severe hemoglobinopathies,
- hemolytic disease of the newborn,
- brain malformations,
- endocrine disorders (congenital hypothyroidism, congenital adrenal hyperplasia),
- feeding errors / severe dehydration.

VII.1.8. MANAGEMENT

The treatment of IEM has two objectives: **acute stabilization** and **prevention of recurrence**. General principles of IEM management:

- IEM constitutes **a neonatal metabolic emergency**;
- Goal: to prevent irreversible neurological damage and death;
- treatment must be initiated as soon as the diagnosis is suspected, without waiting for final confirmation.

A. NON-PHARMACOLOGICAL

- temporary cessation of protein intake in cases of suspected protein metabolism defect;
- feeding with special formulas (low in the implicated amino acids or galactose-free);
- adequate hydration to correct acidosis and prevent catabolism;
- temporary low-calorie diet in fatty acid oxidation defects (avoid fasting),
- genetic counseling for the family.

B. PHARMACOLOGICAL

1. Acute (emergency) treatment

- cessation of protein intake (in protein catabolism disorders) for 24–48 hours;
- aggressive IV hydration with 10–15% glucose, 8–10 mg/kg/min, to which insulin may be added if hyperglycemia occurs → halting catabolism;
- correction of acidosis and hypoglycemia (bicarbonate, glucose);
- removal of toxic metabolites:
    - hemodialysis/hemofiltration in severe hyperammonemia;
    - ammonia-binding agents: sodium benzoate, phenylbutyrate, arginine;
- administration of metabolic cofactors: carnitine, biotin, thiamine, vitamin B12, riboflavin;
- correction of electrolyte imbalances and hypothermia;
- antibiotics in cases of confirmed or suspected infections;
- management of complications: anticonvulsants, treatment for liver or heart failure.

2. Specific treatment following confirmation of the diagnosis.

- Phenylketonuria
    - low-protein diet, replacement with special phenylalanine-free formulas, tyrosine supplementation;
- Leucinosis (maple syrup urine disease)
    - diet low in branched-chain amino acids (leucine, isoleucine, valine);
- Hyperammonemia (urea cycle defects)
    - restriction of protein intake, sodium benzoate/phenylbutyrate, arginine, dialysis in severe cases;

- Galactosemia
    - elimination of galactose and lactose from the diet;
- Fatty acid oxidation disorders
    - Avoid fasting; glucose supplementation in cases of hypoglycemia; carnitine;
- Tyrosinemia type I
    - Nitisinone (4-hydroxyphenylpyruvate dioxygenase inhibitor) + tyrosine-restricted diet;
- Mitochondrial disorders
    - Energy support, coenzyme Q10, L-carnitine (variable effect).

3. Organ transplantation

- Liver transplant: curative for certain hepatic enzyme deficiencies (maple syrup urine disease, certain urea cycle disorders, glycogen storage diseases).
- Bone marrow/stem cell transplant: for certain storage disorders (Hurler syndrome).

C. FOLLOW-UP

- Multidisciplinary monitoring (neonatology, neurology, nutrition and metabolism, genetics) and follow-up at **specialized metabolic disease centers**;
- adjustment of the dietary regimen throughout childhood;
- periodic metabolic monitoring: amino acids, acylcarnitines, liver function;
- monitoring of growth and neuropsychological development;
- psychological support for the family and education regarding the early recognition of metabolic decompensation;
- prevention of crises through regular meals and appropriate supplementation during periods of stress or illness;
- family genetic counseling and prenatal diagnosis, where possible. Genetic counseling is mandatory for all families with an affected child, as the risk of recurrence is 25% for autosomal recessive disorders. Prenatal diagnosis and preimplantation testing are possible in most cases.

VII.1.9. PROGNOSIS

A. PROGNOSIS

The prognosis varies depending on the type of disease, the severity of the mutation, and the speed with which treatment is initiated:

- highly recommended for conditions detected through screening before symptoms appear;
- reserved for severe fatty acid oxidation defects and urea cycle defects with onset in the first hours of life;
- forms treated early (e.g., phenylketonuria, galactosemia) may allow for normal development;
- forms diagnosed late may lead to intellectual disability, liver failure, cardiomyopathies, or death;
- early detection and rapid intervention reduce mortality and long-term disability.

B. COMPLICATIONS

BMCs can cause severe complications in the neonatal period with multisystem involvement.

- acute metabolic complications (severe hypoglycemia, metabolic acidosis, electrolyte imbalances, ketoacidosis);
- neurological involvement (treatment-resistant seizures, cerebral edema, tone and coordination disorders, neuropsychological developmental delay, intellectual disability);
- liver dysfunction (acute or chronic liver failure, liver cirrhosis, cholestasis, hepatic steatosis, secondary coagulopathy);
- cardiac and muscular impairment (hypertrophic or dilated cardiomyopathy, heart failure, arrhythmias, muscle hypotonia, rhabdomyolysis);
- secondary respiratory failure
- nutritional and growth disorders (protein-calorie malnutrition);
- renal dysfunction (tubulopathies, renal tubular acidosis, severe dehydration, ARF).

VII.2. CONGENITAL HYPOTHYROIDISM

VII.2.1. DEFINITION

Congenital hypothyroidism (CH) is an endocrine disorder present at birth, characterized by a deficiency in the production, secretion, or action of thyroid hormones. It is one of the most common preventable causes of intellectual disability.

Through **universal newborn screening**, early diagnosis, and treatment, the irreversible neurological consequences associated with this disease have been dramatically reduced.

VII.2.2. EPIDEMIOLOGY. INCIDENCE

- The average incidence is 1 in 2,000 to 1 in 4,000 live births
- The incidence is higher in preterm infants, multiple pregnancies, and populations with iodine deficiency
- It is more common in females (F:M = 2:1)
- In 80–85% of cases, the condition is primary (thyroid-related); 10–15% are hereditary forms (dishormonogenesis); <5% have a central cause (pituitary/hypothalamic).

Etiological classification of CH:

1. **Primary congenital hypothyroidism**

- *Thyroid dysgenesis* (sporadic):
  - thyroid aplasia
  - thyroid hypoplasia
  - thyroid ectopia
- *Dishormonogenesis* (hereditary, most commonly autosomal recessive):
  - iodine uptake defect
  - organification defect
  - defect in the coupling of iodotyrosines
  - hormone release defect
- *Transient causes*:
  - maternal treatment with antithyroid drugs
  - maternal iodine excess/deficiency
  - maternal antithyroid antibodies that block the TSH receptor
  - prematurity

2. **Central congenital hypothyroidism (secondary/tertiary)**

- *Pituitary defects* (low TSH)
- *Hypothalamic defects* (low TRH)
- Genetic *abnormalities* or malformations of the central nervous system
- *Panhypopituitarism.*

VII.2.3. PATHOPHYSIOLOGY

Thyroid hormones play an essential role in brain maturation (myelination, synapsogenesis), energy metabolism, somatic growth, and neuropsychological development, acting during the prenatal and neonatal periods to regulate the development of the central nervous system.

The anterior pituitary secretes thyroid-stimulating hormone (TSH), which acts on the thyroid and stimulates the secretion of thyroid hormones. TSH, in turn, is regulated by thyrotropin-releasing hormone (TRH) produced by the hypothalamus. This regulatory pathway is known as the hypothalamic-pituitary-thyroid axis. There are two active thyroid hormones: thyroxine (T4) and triiodothyronine (T3). Circulating T3 and T4 are bound to serum proteins, with a small portion of these hormones remaining unbound—free T3 and free T4—which are biologically active.

A deficiency of thyroid hormones in the early neonatal period causes:

- a slowing of the general metabolism,
- impaired bone growth,
- delayed brain maturation and myelination.

VII.2.4. RISK FACTORS

- a family history of congenital hypothyroidism or thyroid disease,
- consanguinity (increases the risk of dyshormonogenesis),
- maternal autoimmune diseases (anti-TSH antibodies),
- maternal treatment with antithyroid drugs,
- iodine exposure (excess or deficiency),
- prematurity and low birth weight (in transient forms),
- chromosomal abnormalities: Down syndrome, Turner syndrome,
- mother with untreated or inadequately treated hypothyroidism.

VII.2.5. CLINICAL DIAGNOSIS

Most newborns with CH are **asymptomatic at birth** due to transplacental maternal T4, which is why screening is essential. Symptoms appear progressively:

1. **Early signs—**appear in the first 2–4 weeks and include:

- prolonged jaundice (>14 days),
- lethargy, drowsiness, hypotonia,
- feeding difficulties, slow weight gain,
- constipation,
- persistent hypothermia.

2. **Late signs—**appear after 4–6 weeks and include:

- an expressionless "doll-like" face, macroglossia,
- wide fontanelles,
- umbilical hernia, distended abdomen,
- dry, cold, pale skin,
- hoarse voice,
- neuropsychomotor delay.

3. **In the absence of early treatment, the following will develop:**

- irreversible intellectual disability,
- stunted growth,
- coordination and speech disorders.

VII.2.6. LABORATORY AND IMAGING STUDIES

1. **Neonatal screening:**

Neonatal screening for CH is performed in most developed countries. In Romania, neonatal screening is a public health program designed to evaluate infants shortly after birth for conditions that are treatable but clinically inapparent during the neonatal period.
Sampling is performed 48–72 hours after birth by collecting a few drops of capillary blood from the newborn's heel onto a filter paper card ("Guthrie test"). TSH is measured (in some programs, total or free T4 is also measured).

2. **Confirmatory diagnosis:**

Abnormal screening results require confirmation of the diagnosis through thyroid function testing (measurement of thyroid hormones in venous blood).
Primary hypothyroidism:

- Elevated TSH,
- Low FT4.

Central hypothyroidism:

- Low/normal TSH,
- Low FT4.

3. **Additional tests:**
- determination of anti-TSH receptor antibodies,
- evaluation of the pituitary axis if a central form is suspected (ACTH, STH, prolactin),
- metabolic tests if there is prolonged jaundice or other associated signs,
- genetic testing is recommended in familial cases or cases of persistent, unexplained forms.

4. **Imaging:**
- thyroid ultrasound – identifies thyroid absence/ectopia/hypoplasia, as well as the size and location of the gland,
- thyroid scintigraphy – highlights iodine uptake and the location of functional thyroid tissue.

VII.2.7. DIFFERENTIAL DIAGNOSIS

Differential diagnosis primarily involves determining the type of CH: transient, primary, or central. Differentiation will be made from:

- Down syndrome (slightly elevated TSH without hypothyroidism),
- metabolic disorders with prolonged jaundice (galactosemia, hypopituitarism),
- neurological disorders with hypotonia (encephalopathy, cerebral hemorrhages).

VII.2.8. MANAGEMENT

A. GENERAL PRINCIPLES
- Treatment of CH can be considered **an endocrinological emergency** and should be initiated immediately upon confirmation of the diagnosis, without waiting for complete etiological investigations;
- The goal of treatment is the rapid restoration of T4 levels to normal.

B. NON-PHARMACOLOGICAL
- Educating the family on the importance of continuous treatment,
- psychological and social support, especially in severe cases,
- close monitoring of neuropsychological development,
- instructing parents on avoiding iodine supplements or drug interactions.

C. PHARMACOLOGICAL

Treatment of choice: **Levothyroxine (L-T4):**
- It should be administered as early as possible, ideally before 14 days of age**,**
- recommended initial dose: 10–15 μg/kg/day**,** orally, once daily (tablets are administered as a powder),
- avoid soy-based formulas, iron, and calcium when taking L-T4 (they reduce absorption),
- adjust doses based on TSH and FT4 levels and the child's weight.

D. FOLLOW-UP
- hormone monitoring (TSH, FT4): 2 weeks after starting treatment, then monthly for up to 6 months, subsequently every 2–3 months, at 6 months, and annually,
- assessment of growth parameters,
- assessment of neuropsychomotor development.

VII.2.9. PROGNOSIS

The prognosis is **very good** with normal neuropsychological development if treatment begins within the first 2 weeks. Delaying treatment increases the risk of:

- intellectual disability,
- learning difficulties,
- attention disorders,
- motor disorders.

Severe untreated forms can lead to **severe intellectual disability**, an irreversible neurological impairment. In some cases (transient form), the need for treatment can be reassessed at 3 years by discontinuing L-T4 for 4 weeks and performing a hormonal reassessment.

Complications without adequate treatment or in cases of late diagnosis:

- severe intellectual disability,
- failure to thrive,
- microcephaly,
- sensorineural hearing loss,
- motor disorders (ataxia, persistent hypotonia),
- cardiomyopathy,
- anemia,
- severe constipation,
- myxedema,
- impaired puberty (delayed puberty),
- behavioral and learning disorders.

Treatment complications:

- excessive doses → tachycardia, irritability, sweating, weight loss, accelerated bone maturation, and risk of iatrogenic hyperthyroidism.

VII.3. HYPOGLYCEMIA AND HYPERGLYCEMIA

Glucose is the primary source of energy for the newborn's brain. The transition from intrauterine to extrauterine life causes changes in blood glucose levels. During fetal life, glucose is continuously supplied from the mother via placental transfer, maintaining fetal blood glucose at approximately 70–80% of maternal levels. At birth, this continuous supply is abruptly interrupted, triggering a cascade of metabolic adaptations:

- an immediate drop in plasma glucose levels within the first 1–2 hours of life,
- activation of glycogenolysis to mobilize hepatic glycogen stores,
- initiation of gluconeogenesis from amino acids, lactate, and glycerol,
- increased secretion of counterregulatory hormones (glucagon, cortisol, growth hormone, epinephrine),
- decreased insulin secretion.

VII.3.1. HYPOGLYCEMIA

VII.3.1.1. DEFINITION

Neonatal hypoglycemia is defined as a decrease in plasma glucose concentration below the levels necessary to maintain optimal metabolic and neurological functions in the newborn. There is no single universally accepted value. It is necessary to know the exact age of the newborn (hours of life, days) to interpret blood glucose levels and diagnose hypoglycemia.

According to the American Academy of Pediatrics (AAP), hypoglycemia is defined as:

- **<47 mg/dL (2.6 mmol/L)** in the first 24–48 hours of life.

The AAP acknowledges that there is physiological variability in blood glucose levels during the first hours/days and that lower values may be transient and adaptive, but **≤47 mg/dl** is used in practice as the level at which hypoglycemia is considered potentially pathological and requiring treatment to prevent potential neurological consequences.

- After 48–72 hours of life, blood glucose levels should be **>55–60 mg/dL**.
- Physiological drops (e.g., **~30 mg/dl** in the first 1–2 hours) are common and normalize if feeding is early and adequate.

VII.3.1.2 EPIDEMIOLOGY. INCIDENCE

Neonatal hypoglycemia is one of the most common metabolic disorders in newborns, with an estimated incidence of **5–15%** in the general population. The incidence increases in high-risk groups, reaching up to **30–50%**.

From an etiological perspective, it can be classified as **transient** or **persistent**.

1. **Transient neonatal hypoglycemia**

This is the most common form and occurs within the first 24–72 hours of life, being linked to postnatal metabolic adaptation.

- **Insufficient glucose intake**
  - Delayed initiation of feeding
  - Insufficient enteral intake
  - feeding difficulties (prematurity, neurological impairment)
- **Low glycogen stores**
  - preterm newborn
  - SGA
  - IUGR
- **Increased glucose consumption**
  - Perinatal asphyxia
  - neonatal sepsis
  - shock
  - hypothermia
  - respiratory distress
  - polycythemia
- **Transient hyperinsulinism**
  - Newborn of a mother with diabetes mellitus (pre-existing or gestational)
  - maternal tocolytic therapy with beta-sympathomimetic agents (Terbutaline)
  - in utero exposure to hyperglycemia
  - sudden discontinuation of glucose infusion
  - perinatal stress

2. **Persistent neonatal hypoglycemia**

Persists beyond 72 hours of life and requires thorough etiological investigation.

- **Persistent hyperinsulinism**
  - Congenital hyperinsulinism (genetic forms): gene mutations in the coding of adenosine triphosphate (ATP)-sensitive potassium channels
  - associated syndromes (e.g., Beckwith–Wiedemann)
  - Insulin-producing tumors (nesidioblastosis, islet adenoma, islet cell dysmaturity).
- **Hormonal Deficiencies**
  - Hypopituitarism
  - growth hormone deficiency
  - adrenal insufficiency (cortisol deficiency)
  - Glucagon deficiency
- **Inborn errors of metabolism**
  - disorders of glycogenolysis (e.g., glycogen storage diseases)
  - gluconeogenesis disorders
  - fatty acid oxidation defects
  - galactosemia
  - hereditary fructose intolerance
  - defects in amino acid metabolism: maple syrup urine disease, tyrosinemia, propionic acidemia, methylmalonic acidemia
- **Liver disorders**
  - neonatal hepatitis
  - congenital liver failure
  - metabolic diseases with liver involvement

3. **Associated maternal and perinatal factors**

- maternal diabetes
- maternal treatment with insulin, beta-blockers (Labetalol, Propranolol), or oral antidiabetics
- preeclampsia
- Cesarean delivery
- acute or chronic fetal distress

VII.3.1.3. PATHOPHYSIOLOGY

Clamping the umbilical cord at birth abruptly cuts off the newborn's maternal source of glucose, resulting in the first 2–3 hours of life after birth in a rapid, physiological drop in blood glucose levels (down to 30 mg/dL), followed by a gradual rise. After the interruption of maternal glucose supply, the newborn must respond rapidly to maintain adequate blood glucose levels through glycogenolysis of hepatic stores, induction of gluconeogenesis, and utilization of exogenous nutrients from the diet.

Pathological hypoglycemia occurs when:

- hepatic synthesis is inadequate (glycogen depletion);
- peripheral consumption is increased (hyperinsulinism);
- alternative energy production (ketones, fatty acids) is insufficient.

VII.3.1.4. RISK FACTORS

- preterm birth (especially <34 weeks),
- SGA,
- macrosomia,
- newborn of a diabetic mother,
- perinatal asphyxia,
- hypothermia, infections,
- delayed or insufficient feeding,
- polycythemia,
- maternal medications (insulin, oral hypoglycemic agents, β-blockers).

VII.3.1.5. CLINICAL DIAGNOSIS

The symptoms of hypoglycemia do not correlate with blood glucose levels. Some healthy newborns may remain **asymptomatic** despite extremely low blood glucose levels during the period of transient hypoglycemia. Others may present with **nonspecific** clinical manifestations**,** such as:

- *neurological* signs: tremor, irritability, lethargy, hypotonia, seizures, apnea, weak or high-pitched crying, coma,
- *cardiopulmonary* signs: tachypnea, cyanosis, arrhythmias, bradycardia,
- *gastrointestinal* signs*:* refusal to feed, difficulty feeding, vomiting,
- *General* signs: hypothermia, pallor, sweating.

VII.3.1.6. LABORATORY DIAGNOSIS

A. Blood glucose measurement

Screening*:* blood glucose measurement using a glucometer on capillary blood—for guidance; performed 30–60 minutes after birth and before each feeding in at-risk newborns. The blood glucose value from capillary blood will be 15% lower than that from plasma. Any blood glucose level < 47 mg/dL on capillary testing will require a plasma blood test (laboratory method) as well; however, there is no justification for delaying therapeutic intervention until the result is known.

Mandatory confirmation: plasma blood glucose from venous or arterial blood.

B. Additional investigations in cases of persistent/severe hypoglycemia:

- *diagnosis of hyperinsulinemia*: insulin, cortisol, ketone bodies, lactate, beta-hydroxybutyrate, free fatty acids;
- if *insulin levels are normal*, additional testing is performed for defects in carbohydrate and amino acid metabolism, and endocrine disorders:
    - STH,
    - ACTH,
    - T4 and TSH,
    - glucagon,
    - plasma and urinary amino acids,
    - urinary ketone bodies
    - urine reducing substances,
    - organic acid in urine,
    - genetic testing.

VII.3.1.7. DIFFERENTIAL DIAGNOSIS

The differential diagnosis of hypoglycemia is initially approached etiologically, by identifying the causal factors and mechanisms involved. However, the nonspecific nature of the symptoms of neonatal hypoglycemia requires differential diagnosis with:

- sepsis,
- neurological disorders,
- metabolic disorders (hypocalcemia, hypo-/hypernatremia, hypomagnesemia, pyridoxine deficiency),
- adrenal insufficiency,
- heart, liver, or kidney failure.

VII.3.1.8. MANAGEMENT

A. GENERAL PRINCIPLES

- Goal: maintain blood glucose > 47 mg/dL,
- anticipating and preventing hypoglycemia in at-risk newborns.

B. NONPHARMACOLOGICAL

- Preventive: early feeding within the first 30–60 minutes of life for all newborns who can be fed,
- **oral feeding** with breast milk or low-lactose formula for stable newborns without hypoglycemic risk factors, with blood glucose levels between 25–47 mg/dL; monitoring blood glucose until normalization,
- increase the frequency of feedings (ideally breast milk),
- maintaining normal body temperature,
- monitoring blood glucose in at-risk groups according to protocols: at 1, 2, 4, 6, 12, 24 hours, or more frequently depending on the course of the condition.

C. PHARMACOLOGICAL

1. Intravenous glucose therapy

Indicated in cases of:

- blood glucose < 25 mg/dL (first few hours),
- neurological symptoms

IV bolus: 2 ml/kg of 10% glucose over 1–2 minutes, followed by continuous administration via IV infusion.

Continuous IV infusion: glucose infusion rate of 4–6 mg/kg/min

May be gradually increased to 8–12 mg/kg/min if hypoglycemia persists.

2. Specific treatment (severe/persistent cases)

- **Hydrocortisone**:
  - dose: 10 mg/kg/day, divided every 12 hours, IM or IV;
  - use: in cases of suspected adrenal insufficiency.
- **Diazoxide**:
  - dose: 8–15 mg/kg/day, divided every 8–12 hours, orally;
  - use: for hyperinsulinism.
- **Octreotide**:
  - dose: 5–20 µg/kg/day, SC or IV, divided every 6–8 hours;
  - use: for hyperinsulinism if diazoxide is not effective.
- **Glucagon**:
  - dose: 0.2–0.3 mg/kg IV or IM if venous access is difficult;
  - use: limited to prolonged hypoglycemia, in emergency situations when venous access is difficult, until IV glucose can be administered.

In cases of refractory congenital hyperinsulinism, surgical intervention with **partial pancreatectomy** is required.

D. FOLLOW-UP

- monitor blood glucose levels until they stabilize,

- blood glucose levels will be checked until at least one value is **> 45 mg/dL**,
- periodic neurological evaluation,
- screening for metabolic disorders in persistent cases,
- monitoring of neuropsychomotor development during the first year of life.

VII.3.1.9. PROGNOSIS

The prognosis depends on the severity and duration of hypoglycemia, the promptness of treatment, and etiology. Promptly treated **transient** hypoglycemia has an **excellent** prognosis**. Severe** (<25 mg/dL), recurrent, or prolonged hypoglycemia is associated with an increased risk of complications. These include:

- permanent neurological damage,
- developmental delay,
- recurrent seizures, intellectual disability,
- visual disturbances,
- learning and behavioral disorders,
- long-term neurodevelopmental disabilities, cerebral palsy, and death.

VII.3.2. HYPERGLYCEMIA

VII.3.2.1. DEFINITION

Neonatal hyperglycemia is defined as an increase in plasma glucose concentration above the values considered normal for newborns.

- Blood **glucose > 125 mg/dl (6.9 mmol/l)** in whole blood
- **Blood glucose > 150 mg/dl (8.3 mmol/l)** in plasma

VII.3.2.2. EPIDEMIOLOGY. INCIDENCE

Hyperglycemia is most common in **preterm infants <32 weeks**, with an incidence of **40–80%** in ELBW infants (<1000 g). Term newborns rarely develop hyperglycemia, except in cases of major stress or metabolic disorders.

The etiology is **multifactorial** and includes:

1. **Excessive exogenous glucose intake (iatrogenic):**

- intravenous infusion at a rate >8–10 mg/kg/min,
- administration of medications in glucose-containing solutions,
- administration errors, defective pumps.

2. **Metabolic immaturity:**

- variable response to insulin, immaturity of glycogenolysis enzyme systems (ELBW preterm infants),
- stress-induced insulin resistance,
- reduced peripheral glucose utilization.

3. **Stressful conditions and associated diseases:**

- sepsis,
- shock, hypoxia, perinatal asphyxia,
- intracranial hemorrhage,
- necrotizing enterocolitis,
- surgical procedures.

4. **Medications**

- corticosteroids,
- methylxanthines (caffeine, theophylline),
- phenytoin,
- diazoxide.

5. **Endocrine or genetic causes (rare):**

- transient or permanent neonatal diabetes,
- mutations in KCNJ11, ABCC8, INS.

6. **Ingestion of hyperosmolar formula:**
- improper dilution of the milk formula → transient hyperglycemia.
7. **Lipid infusion**
8. **Pancreatic lesions**
- pancreatic aplasia,
- hypoplasia, or absence of pancreatic beta cells.

VII.3.2.3. PATHOPHYSIOLOGY

Neonatal hyperglycemia results from an imbalance between glucose **production**, **delivery,** and **utilization**:

- **increased hepatic production** (gluconeogenesis stimulated by stress, catecholamines, cortisol);
- **reduced peripheral utilization** due to immaturity of pancreatic β-cells, insulin resistance, and glucose transporter deficiency;
- **low insulin secretion**, particularly in preterm infants;
- **lack** of **fine-tuning** of glucose tolerance in newborns, as hormonal mechanisms are still immature.

Hyperglycemia causes an increase in serum osmolarity, and when this exceeds 300 mOsm/L, osmotic diuresis occurs, with subsequent dehydration potentially developing rapidly in preterm infants with low birth weight.

VII.3.2.4. RISK FACTORS

- extremely preterm infants (<1000 g),
- PN with carbohydrate intake > 8–10 mg/kg/min,
- systemic stress: sepsis, asphyxia, respiratory distress, surgery,
- treatment with steroids, catecholamines, caffeine, theophylline,
- polycythemia,
- rare endocrine disorders (transient neonatal diabetes),
- brain injuries (intracranial hemorrhage, hypoxic-ischemic injury).

VII.3.2.5. CLINICAL DIAGNOSIS

Hyperglycemia may be **asymptomatic**; clinical manifestations, when present, may include:

- polyuria (osmotic diuresis),
- dehydration, weight loss,
- difficulty eating,
- tachycardia, tachypnea,
- lethargy, irritability,
- in severe cases: hyperosmolarity, seizures, stupor, risk of intracranial hemorrhage.

Neonatal diabetes mellitus is a rare disorder that can occur in the first days to weeks of life. There are two types:

- **transient neonatal diabetes**—it resolves within the first few weeks but carries a risk of recurrence in the second or third decade of life.
- **permanent neonatal diabetes**—many of those with permanent ND have mutations in Kir6.2 or Sur1.

Newborns exhibit the following clinical and laboratory findings:

- blood glucose levels ranging from 240 to 2300 mg/dL,
- polyuria with marked glycosuria,
- acidosis,
- mild or absent ketonuria,
- severe dehydration,
- no weight gain,
- reduction in subcutaneous tissue.

VII.3.2.6. LABORATORY AND IMAGING STUDIES

1. **Laboratory:**

- blood glucose >125 mg/dL in 2 consecutive measurements,
- glucosuria,
- elevated plasma osmolarity,
- electrolytes (risk of dilutional hyponatremia, K^+disorders)
- blood gases: metabolic acidosis in severe cases,
- complete blood count with differential, blood culture, urine culture (suspected sepsis),
- Serum insulin,
- genetic testing for the diagnosis of transient neonatal diabetes.

2. **Chest and abdominal X-rays** are necessary in cases of respiratory distress, suspected sepsis, or NEC.

VII.3.2.7. DIFFERENTIAL DIAGNOSIS

The differential diagnosis of hyperglycemia in the newborn is made among various etiological causes:

- false-positive results (improperly collected samples, glucose infusions via the same venous line),
- neonatal diabetes (transient or permanent),
- acute perinatal stress,
- severe infections,
- administration of medications (steroids, caffeine, theophylline),

but it also extends to other metabolic conditions such as:

- congenital metabolic disorders,
- neonatal hyperthyroidism,
- genetic syndromes associated with pancreatic beta-cell dysfunction.

VII.3.2.8. MANAGEMENT

A. NONPHARMACOLOGICAL

- anticipation and prevention of hyperglycemia in at-risk newborns,
- reduction of the glucose infusion rate:
    - gradual reduction by 1–2 mg/kg/min to a minimum of 4–6 mg/kg/min, the amount necessary for cerebral metabolism,
    - re-evaluate blood glucose levels at 30–60 minutes.
- correction of precipitating factors:
    - treatment of sepsis,
    - temperature regulation, stress minimization, pain control,
    - adjusting TPN.
- Ensuring adequate hydration, avoiding hyperosmolarity.
- Increasing enteral nutrition:
    - early initiation of minimal enteral nutrition when appropriate,
    - gradual advancement based on tolerance.

B. PHARMACOLOGICAL

1. **Insulin therapy**

Indications:

- persistent hyperglycemia >200–250 mg/dL despite reduction in infusion rate,
- inability to provide adequate nutrition due to glucose intolerance,
- osmotic diuresis with dehydration and electrolyte imbalances.

Dosage:

- initially administered as a *bolus*, 0.05–0.1 IU/kg, every 4–6 hours;
- if, after 3 doses, blood glucose remains above 200 mg/dL, administer *continuous IV* insulin at 0.05–0.2 IU/kg/h
- *Subcutaneous* insulin, rarely used, except in neonatal diabetes.

2. **Therapy with oral sulfonylureas,** administered long-term in cases of Kir6.2 and Sur1 defects.

C. FOLLOW-UP

- Check blood glucose every 30–60 minutes until it stabilizes to adjust the PRG.
- A too-rapid drop in blood glucose can induce **rebound hypoglycemia**.
- Nutritional reassessment,
- monitor neurodevelopment in preterm infants with severe episodes,
- in cases of suspected neonatal diabetes: consult a pediatric endocrinologist and perform genetic testing.

VII.3.2.9. PROGNOSIS

Depends mainly on:

- gestational age (extremely preterm infants have a guarded prognosis),
- the duration and severity of hyperglycemia,
- associated complications (sepsis, intracranial hemorrhage).

Transient hyperglycemia generally has **a good prognosis** if corrected promptly. Persistent hyperglycemia can affect growth, neurological status, and reduce survival in ELBW infants.

Complications:

- severe dehydration due to osmotic diuresis,
- hyperosmolarity, risk of seizures and intracranial hemorrhage,
- complications of insulin therapy (hypoglycemia, hypokalemia),
- suboptimal weight gain,
- increased risk of infections in preterm infants with poor glycemic control (hyperglycemia impairs neutrophil function),
- increased mortality in ELBW preterm infants with prolonged severe hyperglycemia,
- retinal lesions, neurological impairment in preterm infants.

VII.4. HYPONATREMIA AND HYPERNATREMIA

Sodium (Na^+), also known as sodium, is the primary extracellular cation and the major determinant of plasma osmolarity. Regulation of sodium homeostasis involves the balance between intake, loss, and distribution between intracellular and extracellular compartments, controlled by the kidneys, antidiuretic hormone (ADH), aldosterone, and atrial natriuretic factor (ANF).

In newborns, sodium regulatory mechanisms are immature due to:

- immature renal function (limited capacity for urine concentration and dilution),
- increased permeability of the skin and mucous membranes,
- increased total body water content (75–80% of body weight at birth),
- incomplete regulation of ADH and aldosterone secretion.

Normal values:

- full-term newborn: 135–145 mmol/L (mEq/L)
- preterm: 130–145 mmol/L (mEq/L)

VII.4.1. HYPONATREMIA

VII.4.1.1. DEFINITION

Hyponatremia is defined as a serum Na^+level <135 mmol/l and reflects a relative excess of water relative to sodium. It can be true (dilutional or depletive) or false (pseudo-hyponatremia due to hyperproteinemia or hyperlipidemia). In newborns, even moderate decreases in serum sodium levels can cause neurological dysfunction due to cerebral vulnerability.

VII.4.1.2. EPIDEMIOLOGY. INCIDENCE

Hyponatremia is frequently encountered in neonatal intensive care units, particularly in preterm infants. Estimated incidence: 5–15% of hospitalized newborns. Preterm infants are at increased risk due to renal salt loss and variable fluid intake.

Hyponatremia can have several underlying causes:

1. **Hyponatremia due to increased Na^+loss (hypovolemic)** – concurrent loss of $Na^+$and water, but Na^+loss > water loss:

- gastrointestinal losses: vomiting, diarrhea;
- renal losses: diuretics, salt-wasting nephropathies;
- cutaneous losses: in very low birth weight preterm infants, burns;
- losses in the third space: omphalocele, gastroschisis, NEC, peritonitis;
- adrenal insufficiency: steroid deficiency, obstetric trauma.

2. **Dilutional (hypervolemic) hyponatremia** – concurrent retention of water and Na^+, but water retention > Na^+retention:

- excess of IV fluids;
- liver, kidney, or heart failure;
- sepsis.

3. **Isovolemic hyponatremia** – excess water without Na^+retention:

- SIADH (elevated ADH);
- CNS involvement (asphyxia, intracranial hemorrhage, meningitis);
- lung involvement (infections, pneumothorax, positive-pressure ventilation);
- surgical stress;
- severe congenital hypothyroidism.

4. **Hyponatremia due to impaired transplacental transfer:**

- newborns with excessive maternal fluid intake during labor;
- newborns of mothers with preeclampsia.

5. **Hyponatremia due to inadequate sodium intake:**

- failure to meet daily oral or IV requirements.

6. **Drug-induced hyponatremia:**

- diuretics cause sodium loss;
- indomethacin causes water-salt retention;
- opioids and barbiturates may cause SIADH;
- Mannitol or hypertonic glucose infusion can cause hyperosmolarity with salt loss.

7. **Pseudohyponatremia:**

- significant hyperlipidemia, hyperproteinemia, and hyperglycemia.

VII.4.1.3. PATHOPHYSIOLOGY

Hyponatremia causes a decrease in plasma osmolarity with water shifting into the intracellular space, which can lead to cerebral edema with the onset of seizures, apnea episodes, and altered general condition. It develops easily in newborns because they have:

- a high body water content,
- immature kidneys with Na^+loss and reduced urine concentration capacity, and immature hormonal regulation (ADH, aldosterone).

VII.4.1.4. RISK FACTORS

- prematurity,
- administration of hypotonic fluids,
- perinatal asphyxia, intracranial hemorrhage, meningitis,
- lung diseases (pneumonia, BPD),
- diuretics (Furosemide),
- congenital adrenal hyperplasia (salt wasting),
- severe urinary tract infections (secondary pseudohypoaldosteronism).

VII.4.1.5. CLINICAL DIAGNOSIS

Clinical manifestations are **nonspecific**, with symptoms depending on the rate of onset and the severity of hyponatremia.

- *Mild hyponatremia* (130–135 mmol/L): is often **asymptomatic**;
- *Moderate hyponatremia* (125–130 mmol/L): lethargy, hypotonia, difficulty feeding;

- *Severe hyponatremia* (<125 mmol/L): seizures, coma, apnea, cerebral edema, irritability, hyporeflexia, death. Severe hyponatremia is a neonatal **medical emergency**.

Other signs:

- signs of hypovolemia: weight loss, cold skin, pallor, decreased skin turgor, sunken anterior fontanelle, weak pulse, tachycardia, hypotension;
- signs of fluid retention: edema, rapid weight gain, bulging anterior fontanelle, low urine output (in SIADH).

VII.4.1.6. LABORATORY DIAGNOSIS

- Serum Na^+<135 mmol/l
- Urinary Na^+:
  - <20 mmol/l indicates extrarenal loss (diarrhea, dehydration);
  - >20 mmol/l indicates renal loss (SIADH, diuretics, renal failure);
- plasma osmolarity <275 mOsm/kg – true hypotonic hyponatremia;
- urinary osmolarity >100 mOsm/kg – SIADH;
- serum potassium, chloride, urea, and creatinine;
- blood glucose (pseudohyponatremia);
- hormones: ACTH, aldosterone, renin, TSH;
- urine culture, renal ultrasound (suspected pseudohypoaldosteronism).

VII.4.1.7. DIFFERENTIAL DIAGNOSIS

The differential diagnosis of neonatal hyponatremia is **based on the etiological mechanism**, by distinguishing it from **neonatal conditions in which decreased serum sodium levels occur as a secondary biochemical manifestation**.

- conditions with Na^+loss: digestive, renal, and cutaneous losses,
- conditions with free water retention: SIADH, severe neurological conditions, water overload,
- Endocrine disorders: adrenal insufficiency,
- Renal conditions: acute renal failure (ARF), chronic kidney disease (CKD), congenital tubulopathies,
- asphyxia, sepsis, shock.
- pseudohyponatremia: severe hyperlipidemia, hyperproteinemia.

VII.4.1.8. MANAGEMENT

A. GENERAL PRINCIPLES:

- Hyponatremia should be corrected slowly: 0.5–1 mmol/L/h,
- maximum 10–12 mmol/L/24 h;
- the cause should be determined and etiological treatment indicated.

B. NONPHARMACOLOGICAL

- monitoring of body weight (weight loss/gain),
- monitoring urine output (low urine output is associated with SIADH),
- calculating daily fluid intake,
- adjustment of enteral sodium intake,
- checking the composition of the milk formula and replacing it with one richer in Na^+ or supplementing with Na^+ orally.

C. PHARMACOLOGICAL

- fluid restriction in hypervolemic (dilutional) forms and SIADH,
- fluid restriction may be combined with furosemide administration in hypervolemic forms, when hyponatremia is severe and associated with neurological signs,
- adequate sodium intake: 2–4 mmol/kg/day; for premature infants, a higher intake of 3–5 mmol/kg/day is required,
- oral NaCl intake in cases of hyponatremia associated with medication use,
- IV rehydration in moderate or severe cases with:
  - isotonic saline solution (0.9% NaCl) for hypovolemia,
  - hypertonic saline solution (3% NaCl) for seizures or when Na^+<120 mmol/L,

- sodium deficit is calculated using the following formula: $(Na^+_{ideal} – Na^+_{actual}) \times G(kg) \times 0.6$
- Associated therapies:
    - Hydrocortisone (glucocorticoid) is useful in adrenal insufficiency; it restores cortisol secretion and inhibits excessive ADH secretion, thereby correcting hyponatremia;
    - Fludrocortisone (mineralocorticoid), useful in forms of hyponatremia with salt loss (congenital adrenal hyperplasia with 21-hydroxylase deficiency);
    - Levothyroxine in congenital hypothyroidism. Hyponatremia resolves after normalization of thyroid status.

D. FOLLOW-UP

- monitoring of serum sodium levels until stabilization;
- neurological follow-up in the event of seizures or severe forms.

VII.4.1.9. PROGNOSIS

- mild or moderate forms – good prognosis
- severe, untreated cases may lead to: cerebral edema, persistent seizures, long-term neurological complications
- preterm infants are at higher risk of neurological impairment

Complications:

- neurological: cerebral edema, seizures, irritability, lethargy, coma;
- respiratory: apnea, respiratory depression secondary to CNS involvement;
- cardiovascular: hypotension, hemodynamic instability;
- metabolic: metabolic acidosis, worsening of other electrolyte imbalances (K^+, Ca^{2+}, Mg^{2+});
- related to hyponatremia correction: seizures due to too rapid correction, acute osmotic imbalances.

VII.4.2. HYPERNATREMIA

VII.4.2.1. DEFINITION

Hypernatremia is defined as a serum Na^+ level >145 mmol/L and reflects a deficit of free water relative to sodium, with plasma hyperosmolarity.

VII.4.2.2. EPIDEMIOLOGY. INCIDENCE

It is present in 1–5% of the general newborn population, rising to **10–15%** in certain high-risk subgroups:

- insufficient fluid intake,
- excessive water loss (fever, phototherapy, inappropriate thermal environment),
- exclusive breastfeeding with insufficient milk transfer,
- preterm infants (immaturity of fluid and electrolyte regulation mechanisms).

The causes of hypernatremia include:

1. **Hypovolemic hypernatremia** – water loss > Na^+loss:

- Extrarenal losses (most common):
- dehydration due to insufficient breast milk intake:
    - inefficient suckling,
    - delayed lactation,
    - incorrect breastfeeding technique.
- increased losses through the skin:
    - fever,
    - prematurity (thin skin, high insensible losses),
- gastrointestinal fluid loss:
    - acute diarrhea,
    - vomiting.
- renal fluid loss:
    - diuretics (Furosemide),
    - central or nephrogenic diabetes insipidus (rare in newborns),
    - salt-wasting nephropathies (rare).

2. **Isovolemic (euvolemic*)* hypernatremia** – the loss is predominantly of free water, without major changes in extracellular volume:

- congenital central diabetes insipidus (ADH deficiency),
- congenital nephrogenic diabetes insipidus (ADH resistance in the collecting ducts),
- Increased insensible fluid loss without hypovolemia:
    - fever,
    - tachypnea,
    - mechanical ventilation.

3. **Hypervolemic hypernatremia** – usually iatrogenic:

- excessive Na^+administration:
    - hypertonic saline solutions,
    - rapid correction of hyponatremia,
    - dilution errors in infusions,
    - administration of infant formula with high Na^+concentration
- administration of sodium bicarbonate,
- TPN with increased Na^+content

VII.4.2.3. PATHOPHYSIOLOGY

Hypernatremia causes an increase in plasma osmolarity with the shift of water into the extracellular space, which can lead to cellular dehydration, particularly cerebral dehydration.

VII.4.2.4. RISK FACTORS

- prematurity,
- exclusive breastfeeding with latching problems, insufficient transfer,
- fever, sepsis, increased insensible losses,
- diuretic medication,
- inappropriate rehydration,
- renal or endocrine disorders.

VII.4.2.5. CLINICAL DIAGNOSIS

Clinical manifestations depend on the severity and rate of onset of hypernatremia.

- Mild hypernatremia (146–150 mmol/L): irritability, high-pitched crying, thirst (difficult to assess in newborns);
- Moderate hypernatremia (151–160 mmol/L): lethargy, hypertonia, fever, signs of dehydration, weight loss >10%, hypotension, bulging anterior fontanelle, though blood pressure may be normal;
- Severe hypernatremia (>160 mmol/L): seizures, cerebral hemorrhage, coma, venous thrombosis, death.

Neonatal **diabetes insipidus** (DI) is a rare condition characterized by **the inability to concentrate urine**, leading to **polyuria, excessive loss of free water, and hypernatremia**.

Depending on the etiopathogenic mechanism, neonatal diabetes insipidus is classified as:

- **Central (neurogenic) DI** – ADH secretion deficiency,
- **Nephrogenic DI** – renal resistance to ADH action.

The clinical presentation is usually nonspecific and may include polyuria, weight loss, irritability, and lethargy.

VII.4.2.6. LABORATORY DIAGNOSIS

- Serum Na^+>145 mmol/L,
- increased plasma osmolarity,
- low urine specific gravity,
- Variable urinary Na^+,
- elevated hematocrit and urea in dehydration,
- measurement of plasma ADH if diabetes insipidus is suspected

VII.4.2.7. DIFFERENTIAL DIAGNOSIS

The differential diagnosis of neonatal hypernatremia is based on the etiopathogenic mechanism, by distinguishing it from neonatal conditions in which increased serum sodium levels appear as a secondary biochemical manifestation.

- conditions with free water deficit: reduced fluid intake, increased insensible losses, dehydration,
- renal water loss: central or nephrogenic DI, polyuric phase of ARF, tubulopathies,
- asphyxia, sepsis, shock,
- Endocrine disorders: congenital DI, hypothalamic-pituitary disorders,
- iatrogenic: inappropriate PN
- pseudohypernatremia: severe hypoproteinemia, hypolipidemia, laboratory errors.

VII.4.2.8. MANAGEMENT

A. GENERAL PRINCIPLES

- Hypernatremia should be corrected slowly to avoid cerebral edema: decrease $Na^+$by no more than 0.5 mmol/L/h and a maximum of 10 mmol/L/24h.

B. NONPHARMACOLOGICAL

- Optimization of nutrition with correction of breastfeeding technique,
- administering enteral fluids in small, frequent doses if possible,
- careful monitoring of weight, urine output, and temperature,
- adequate humidification in neonatal incubators.

C. PHARMACOLOGICAL

- restoration of circulating volume in cases of hypovolemia:
  - administration of 0.9% NaCl solution, 10–20 mL/kg
- correction of free water deficit can be performed with:
  - 5% glucose solution
  - 0.45% NaCl solution
- in central DI – specific hormonal treatment with Vasopressin (desmopressin) administered intranasally or IV;
- in nephrogenic DI – thiazide diuretics (Chlorothiazide).

D. FOLLOW-UP

- assessment of dietary intake and weight gain,
- frequent monitoring of urine output and electrolytes in severe cases,
- monitoring of electrolytes until normalization,
- neurological and developmental assessment in severe cases,
- in diabetes insipidus – long-term endocrinological follow-up.

VII.4.2.9. PROGNOSIS

- good if treatment is started early;
- poor in severe forms where seizures, intracranial hemorrhages, hyperosmolar encephalopathy, and neurological sequelae may occur;
- increased mortality in severe, uncontrolled hypernatremic dehydration.

Complications:

- *neurological*: cerebral hemorrhages, cerebral edema, cerebral venous thrombosis, seizures, lethargy, coma, permanent neurological damage;
- *cardiovascular and hemodynamic*: severe hypovolemia, hypotension, shock;
- *renal*: acute kidney injury (AKI), oliguria/anuria;
- *metabolic*: metabolic acidosis, hyperglycemia;
- *related to correction of hypernatremia*: acute cerebral edema, worsening of neurological status.

VII.5. HYPOKALEMIA AND HYPERKALEMIA

Potassium (Kalium=K^+) is the primary **intracellular** cation, essential for:

- maintaining cell membrane potential,
- neuromuscular and cardiac excitability,
- renal and acid-base function,
- protein synthesis and active transmembrane transport (Na^+ /K^+ -ATPase).

Normal values:

- full-term newborn: 3.5–5 mmol/L (mEq/L),
- preterm: 3.5–5.5 mmol/L (mEq/L),
- after 3–5 days of life: 3.5–5.5 mmol/L (mEq/L).

VII.5.1. HYPOPOTASEMIA

VII.5.1.1. DEFINITION

Hypokalemia is a decrease in serum potassium concentration below **3.5 mmol/L**, leading to **hyperpolarization of the cell membrane** and a decrease in neuromuscular and myocardial excitability.

VII.5.1.2. EPIDEMIOLOGY. INCIDENCE

Hypokalemia is more commonly encountered in neonatal intensive care units (NICUs), among preterm infants, and among newborns with low birth weight.

Estimated incidence: 5–10% of hospitalized newborns, and the incidence increases in critically ill infants.

Hypokalemia can have several underlying causes:

1. **Excessive potassium loss:**

- renal losses: diuretics (Furosemide), hyperaldosteronism, renal tubular acidosis, osmotic polyuria (hyperglycemia, mannitol);
- gastrointestinal losses: vomiting, gastric aspiration, diarrhea;
- cutaneous losses: premature infants with increased insensible losses;
- Bartter syndrome (a rare genetic disorder of the kidneys that causes electrolyte imbalance due to excessive loss of K^+, $Na^{(+)}$ and Cl^- in the urine);
- drugs that cause K^+ loss: Gentamicin (through destruction of the renal tubules).

2. **Intracellular potassium shift:**

- metabolic or respiratory alkalosis;
- treatment with insulin and glucose;
- rapid correction of acidosis;
- hypothermia, sepsis;
- drugs that cause K^+ to enter the cell: Terbutaline, Albuterol, Isoproterenol, catecholamines.

3. **Insufficient intake:**

- K^+ -deficient parenteral or enteral nutrition;
- delayed initiation of enteral feeding;
- severe prenatal malnutrition.

VII.5.1.3. PATHOPHYSIOLOGY

Hypokalemia in the newborn results from the interaction between the physiological characteristics of the postnatal transition and external factors specific to neonatal intensive care, especially in preterm infants.

In the first days of life, renal K^+ losses may be exacerbated by:

- incomplete maturation of the distal renal tubules with impaired tubular reabsorption mechanisms;
- postnatal fluid and electrolyte fluctuations;
- reduced intracellular reserves;
- frequent metabolic or respiratory impairment during the neonatal period.

VII.5.1.4. RISK FACTORS

- prematurity, SGA;
- administration of: diuretics, beta-agonists, insulin;
- metabolic or respiratory alkalosis;
- vomiting, diarrhea, gastric aspiration;
- reduced intake via IV fluids or TPN;
- polycythemia, hypothermia, peritoneal dialysis.

VII.5.1.5. CLINICAL DIAGNOSIS

Hypokalemia can be classified based on serum potassium levels as:

- mild: 3.5–3.0 mmol/L
- moderate: 3.0–2.5 mmol/L
- severe: <2.5 mmol/L

Hypokalemia may be **asymptomatic**, especially when mild (3.0–3.5 mmol/L). Clinical manifestations, when present, reflect impaired neuromuscular and cardiac function:

1. **Neuromuscular manifestations:**

- hypotonia, lethargy, muscle weakness;
- diminished deep tendon reflexes;
- respiratory muscle hypotonia with respiratory depression (severe cases);
- paralytic ileus and food intolerance;
- constipation.

2. **Cardiac manifestations:**

- arrhythmias: tachycardia, extrasystoles, risk of torsades de pointes.

VII.5.1.6. LABORATORY AND IMAGING STUDIES

1. **Laboratory:**

- Low serum K^+ ;
- Na^+, Cl^-, Mg^{2+}(hypomagnesemia may exacerbate hypokalemia);
- Blood glucose (hyperglycemia may mask intracellular shift);
- Blood gases: metabolic alkalosis → intracellular shift;
- Urinary ionogram: Elevated urinary$^{K^+}$ → renal loss.

2. **ECG:**

- large U waves;
- ST-segment depression;
- Flattened or inverted T waves;
- prolonged QT interval;
- supraventricular arrhythmias.

3. **Imaging:**

- Abdominal X-ray when ileus is suspected.

VII.5.1.7. DIFFERENTIAL DIAGNOSIS

The differential diagnosis of neonatal hypokalemia is based on the etiological mechanism, distinguishing it from neonatal conditions involving digestive or renal potassium loss, endocrine disorders (primary or secondary hyperaldosteronism), acid-base imbalances, iatrogenic conditions, and pseudohypokalemia (hemolyzed sample).

VII.5.1.8. MANAGEMENT

A. GENERAL PRINCIPLES

- restore serum K^+ levels with **caution** and **continuous ECG monitoring;** complete correction should be achieved slowly, over 24 hours;
- prevention of hypokalemia by **ensuring an** adequate potassium **intake** of **1–2 mmol/kg/day**, starting on days 2–3 of life;

B. NONPHARMACOLOGICAL

- Identify and correct the underlying cause (adjust diuretics, treat alkalosis);

- optimization of nutritional intake;
- strict monitoring of urine output and fluid balance;
- Continuous ECG monitoring at levels < 3.0 mmol/L.

C. PHARMACOLOGICAL

- ***Mild hypokalemia (3.0–3.5 mmol/L), asymptomatic:***
  - increase enteral K^+ intake via a potassium-rich formula or fortification of breast milk;
  - increase K^+ supplementation in PN;
  - monitor serum K^+ every 12–24 hours until stabilization.
- ***Moderate hypokalemia (2.5–3.0 mmol/L) and severe (<2.5 mmol/L) or symptomatic:***
  - The K^+ deficit will be calculated using the formula: $(^{K^+}_{ideal} - K^+_{actual}) \times G\ (kg) \times 0.3$.
  - Parenteral potassium administration: 0.5–1.0 mmol/kg/dose, infused over 1–2 hours, followed by continuous maintenance infusion. Correction of the entire deficit should be achieved within 24 hours, under continuous ECG monitoring.
  - Correction of hypomagnesemia if present;
  - treatment of the underlying cause of hypokalemia.

D. FOLLOW-UP

- Reassessment of serum potassium 2–4 hours after IV supplementation;
- Continuous ECG monitoring until normalization;
- TPN adjustment for prevention;
- monitoring of serum potassium levels in newborns treated with diuretics.

VII.5.1.9. PROGNOSIS

- favorable when the diagnosis is established quickly and appropriate correction is performed;
- Delayed treatment may lead to complications.

Complications:

- ventricular arrhythmias,
- apnea,
- cardiopulmonary arrest,
- paralytic ileus,
- slow weight gain.

VII.5.2. HYPERKALEMIA

VII.5.2.1. DEFINITION

Hyperkalemia is defined as a **serum K^+** level **> 5.5 mmol/L** (mEq/L); some newborns exhibit symptoms at levels of 7–8 mEq/L. It is a medical emergency due to **the risk of lethal cardiac arrhythmias**.

VII.5.2.2. EPIDEMIOLOGY. INCIDENCE

Hyperkalemia is encountered in neonatal intensive care units (NICUs), being more common in preterm infants, particularly those born at < 28 weeks' gestation. Estimated incidence: 4–6% in NICUs.

Hyperkalemia can have several underlying causes:

1. **Excessive K^+intake:**

- blood transfusions (especially old blood rich in K^+), exchange transfusion;
- K^+-rich parenteral nutrition;
- incorrect administration of infusion solutions.

2. **Insufficient renal excretion of K^+ :**

- renal tubular immaturity in premature infants;
- oliguria/anuria;
- acute renal failure (perinatal asphyxia, sepsis, hypoperfusion);
- acute tubular necrosis;
- congenital renal disorders: renal dysplasia, renal hypoplasia, hereditary tubular syndromes;

- adrenal insufficiency (congenital adrenal hyperplasia associated with salt loss → ↓serum Na^+, ↓serum Cl^-, ↑serum K^+);
- disruption of the renin-angiotensin-aldosterone system: inhibitory medications (ACE inhibitors, spironolactone, NSAIDs).

3. Increased release of K^+ from cells:

- massive hemolysis: cephalhematoma, other hematomas, hemorrhages, Rh/ABO isoimmunization, birth trauma;
- hemolysis of the blood sample (pseudohyperkalemia);
- hypothermia;
- tissue hypoxia/ischemia;
- tissue damage: destruction, necrosis, NEC;
- metabolic acidosis;
- administration of beta-blockers: propranolol.

VII.5.2.3. PATHOPHYSIOLOGY

Hyperkalemia in newborns is based on the physiological characteristics that distinguish this age group.

- the intracellular K^+content is higher, so that even a low degree of cell lysis can significantly increase potassium levels;
- Na^+ /K^+ -ATPase pump activity is immature, particularly in preterm infants, which limits potassium transfer into cells and prolongs extracellular exposure to K^+ ;
- The neonatal kidney has a reduced capacity for potassium excretion in the first days of life, due to low glomerular filtration, diminished sensitivity to aldosterone, and limited tubular secretion;
- neonatal metabolic transition is often associated with acidosis, which promotes the shift of K^+ from the intracellular to the extracellular space.

All these mechanisms, to which factors such as transfusions, excessive parenteral intake, or hemolysis may be added, explain the tendency of the newborn, especially the preterm infant, toward transient hyperkalemia.

VII.5.2.4. RISK FACTORS

- prematurity,
- perinatal asphyxia,
- severe metabolic acidosis,
- oliguria/anuria, renal failure,
- transfusions: old blood rich in K^+ ,
- hemolysis (large hematoma, Rh/ABO incompatibility),
- use of spironolactone, ACE inhibitors, beta-blockers.

VII.5.2.5. CLINICAL DIAGNOSIS

Like mild hypokalemia, *mild* hyperkalemia (5.5–6.5 mmol/L) may be **asymptomatic**. Clinical manifestations primarily affect the cardiac and neuromuscular systems:

- lethargy or irritability, hypotonia;
- apnea;
- bradycardia, arrhythmias;
- oliguria or anuria;
- in severe cases: seizures, apnea, cyanosis, circulatory collapse, cardiac arrest.

VII.5.2.6. LABORATORY AND IMAGING STUDIES

1. Laboratory:

- Serum K^+ > 6.0 mmol/L (confirmed from non-hemolyzed venous blood);
- Renal function: elevated urea, creatinine;
- blood gases: metabolic acidosis;
- Na^+ , Ca^{2+} ;

- blood glucose.

2. **ECG** – characteristic progressive changes:

- high, pointed T waves;
- prolonged PR interval, decreased P wave amplitude;
- Wide QRS complex;
- ventricular fibrillation or asystole.

3. **Imaging:**

- An abdominal X-ray is performed when NEC is suspected.

VII.5.2.7. DIFFERENTIAL DIAGNOSIS

The differential diagnosis of neonatal hyperkalemia is based on the underlying etiological mechanism, in relation to neonatal clinical-pathological conditions in which hyperkalemia appears as a secondary biochemical manifestation rather than as a standalone disease:

- renal disorders: ARF, obstructive urinary tract syndromes, congenital renal dysplasias,
- endocrine disorders: adrenal insufficiency, congenital disorders of steroid hormone synthesis,
- severe metabolic acidosis occurring in: asphyxia, sepsis, shock,
- pseudohyperkalemia (hemolysis on collection, extreme leukocytosis, thrombocytosis),
- cell lysis syndrome (hemolysis, trauma),
- laboratory errors,
- drugs that increase K^+ .

VII.5.2.8. MANAGEMENT

A. NONPHARMACOLOGICAL

- discontinuation of exogenous K^+administration;
- assessment and optimization of renal function;
- correcting the underlying cause and acidosis, if present;
- verify the sample (rule out hemolysis);
- continuous ECG monitoring if severe or symptomatic;
- frequent monitoring of serum potassium.

B. PHARMACOLOGICAL

Treatment is initiated promptly if $K^+ \geq 6.5$ mmol/L or if ECG changes occur.

- **Myocardial membrane stabilization:**
  - **Calcium gluconate 10%:** 1–2 mL/kg IV slowly (30–60 minutes). ! Does not lower K^+ , but protects the heart.
- **Intracellular displacement of potassium:**
  - **Sodium bicarbonate 4.2%** IV for correction of acidosis: 1–2 mEq/kg/h
  - **Insulin + Glucose:**
    - may be started with an IV bolus – Insulin 0.05 U/kg + 2 ml/kg 10% glucose, then continued with 10% glucose 2–4 ml/kg/h + Insulin 10 U/100 ml, at a rate of 1 ml/kg/h.
  - **Beta-2 adrenergics**: limited use in neonatology (when cardiac dysfunction or hypotension is present).
- **Elimination of potassium from the body:**
  - **Loop diuretics**: Furosemide 1 mg/kg IV (if diuresis is present).
  - **Cation exchange resins** (rarely used in newborns, risk of intestinal necrosis):
  - Sodium polystyrene sulfonate (Kalyxalat) 1 g/kg per dose every 6 hours orally or every 2–6 hours intrarectally; 1 g of resin binds approximately 1 mmol K^+ .
  - **Peritoneal dialysis /** hemofiltration in refractory, severe, or oliguric cases.

C. FOLLOW-UP

- measure serum potassium 1–2 hours after treatment;
- Continuous ECG monitoring if severe or symptomatic;
- adjustment of TPN and protein/electrolyte intake.

VII.5.2.9. PROGNOSIS

The prognosis depends on the underlying condition (asphyxia, renal failure):

- good if treatment is prompt and appropriate;
- delayed treatment may lead to complications.

Complications:

- ventricular arrhythmias,
- cardiac arrest,
- persistent acid-base and electrolyte imbalances,
- hypoxic neurological damage,
- secondary renal impairment.

VII.6. HYPOCALCEMIA AND HYPERCALCEMIA

Calcium is an essential electrolyte involved in:

- neuromuscular excitability,
- coagulation,
- myocardial contraction and enzymatic function,
- bone mineralization.

Calcemia disorders are common in the neonatal period and can significantly affect extrauterine adaptation. During the neonatal period, the regulation of calcium homeostasis undergoes a difficult physiological transition from the intrauterine to the extrauterine environment. After birth, the decrease in placental Ca^{2+}supply is compensated by PTH secretion and the activation of vitamin D metabolism.

Any delay or dysfunction in these mechanisms can lead to **hypocalcemia**, while certain endocrine, genetic, or iatrogenic conditions can cause **hypercalcemia.**

Normal values:

- Total calcium:
  - full-term newborn: 8–10 mg/dL (2–2.6 mmol/L),
  - preterm: 7–9 mg/dL (1.75–2.25 mmol/L).
- Ionized calcium (physiologically active form):
  - full-term and preterm newborns: 4–5.2 mg/dL (1–1.3 mmol/L).

VII.6.1. HYPOCALCEMIA

VII.6.1.1. DEFINITION

Hypocalcemia is a decrease in plasma calcium levels, as follows:

- total calcium <7 mg/dL
- ionized calcium <4 mg/dl

It is classified as:

- **Early hypocalcemia:** < 72 hours of life;
- **Late hypocalcemia:** >72 hours – first weeks.

VII.6.1.2. EPIDEMIOLOGY. INCIDENCE

- *Early hypocalcemia:* 1–3% of full-term newborns, up to 30–50% of preterm infants.
- *Late hypocalcemia:* much rarer, but occurs mainly in newborns and infants fed with phosphorus-rich formulas.

The etiology differs depending on whether the hypocalcemia is early- or late-onset.

1. **Early hypocalcemia:**

- prematurity / SGA – reduced mineral stores, parathyroid immaturity;
- newborns of mothers with diabetes – in addition to hyperinsulinemia causing neonatal hypoglycemia, these newborns may also present with hypercalcitoninemia (which inhibits calcium mobilization from bones), hypoparathyroidism, abnormal vitamin D metabolism, and hyperphosphatemia;
- perinatal asphyxia, sepsis, shock – transient adrenal insufficiency, acidosis;

- hypomagnesemia – inhibits PTH secretion;
- alkalosis or bicarbonate therapy;
- rapid infusion of citrate-buffered blood (exsanguinotransfusion) – chelates ionic calcium;
- phototherapy – by decreasing melatonin secretion and increasing calcium absorption into bone.

2. Late-onset hypocalcemia:

- excessive phosphorus intake (inappropriate infant formula);
- congenital hypoparathyroidism (DiGeorge syndrome, total or partial parathyroid agenesis);
- pseudohypoparathyroidism due to maternal hyperparathyroidism – suppresses fetal parathyroid glands;
- vitamin D deficiency (maternal or neonatal).

VII.6.1.3. PATHOPHYSIOLOGY

At birth, the serum calcium level in the umbilical cord is 10–11 mg/dL. When placental calcium transfer ceases, a transient physiological decrease in neonatal serum calcium occurs within the first 24–48 hours (7.5–8.5 mg/dL), after which serum calcium levels rise. Normally, the newborn responds by increasing **PTH**, the primary hormone regulating calcium.

The mechanisms by which PTH acts to regulate serum calcium are:

- mobilizing calcium from the bones,
- it increases calcium reabsorption in the renal tubules,
- stimulates renal production of 1,25(OH)□D.

Calcitriol, the active form of vitamin D, is a steroid hormone that plays a role in maintaining calcium and phosphorus homeostasis through the following mechanisms:

- it increases intestinal absorption of calcium and phosphate,
- mobilizes calcium and phosphate from bone.

High **phosphorus** levels reduce calcium by forming Ca–P salts, and low **magnesium** inhibits PTH secretion, leading to refractory hypocalcemia.

VII.6.1.4. RISK FACTORS

The following categories of newborns present risk factors for hypocalcemia:

- preterm infants, IUGR;
- newborns with insufficient enteral intake;
- newborns of mothers with diabetes;
- newborns with TPN and insufficient calcium intake;
- newborns who have received massive transfusions of citrated blood;
- newborns with sepsis or respiratory distress;
- newborns with increased oral phosphate intake and low magnesium intake;
- newborns of mothers with hyperparathyroidism or vitamin D deficiency.

VII.6.1.5. CLINICAL DIAGNOSIS

Many newborns with hypocalcemia are ***asymptomatic***, particularly those with *mild* or slowly developing hypocalcemia, which is why screening is recommended for all at-risk newborns. However, *symptomatic hypocalcemia* may present with various neuromuscular and cardiac manifestations due to increased neuronal excitability and impaired cardiac function.

- *neuromuscular:* hypertonia, hyperreflexia, tremor of the extremities, tetany, laryngospasm, seizures (focal or generalized);
- *Cardiac:* arrhythmias, heart failure, or cardiomyopathy in severe cases;
- *respiratory:* apnea, stridor secondary to laryngospasm;
- *gastrointestinal:* feeding difficulties, vomiting, abdominal distension.

VII.6.1.6. LABORATORY AND IMAGING STUDIES

Diagnosis requires laboratory confirmation combined with clinical evaluation. Total serum calcium is found in the body in the form of:

- ionic (free) calcium, which is the biologically active form (~50%),

- serum protein-bound calcium, particularly albumin (~40%),
- the calcium complex bound to serum anions, mainly phosphates, citrates, and sulfates (~10%).

Measuring *ionic calcium* is preferred because it reflects the physiologically active fraction and is not affected by albumin levels or acid-base status.

1. Laboratory tests:

- serum ionic and total calcium,
- serum phosphates (↑ in late-stage hypocalcemia),
- serum magnesium (<1.6 mg/dL indicates hypomagnesemia accompanying hypocalcemia),
- PTH level – in persistent cases
- 25(OH)D level – in persistent cases
- 1,25(OH)□D level – in persistent cases
- blood gases (acidosis may affect ionic calcium),
- albumin,
- serum creatinine and blood urea,
- blood glucose (maternal diabetes),
- FAL,
- urinary calcium (urinary loss).

2. Other tests:

- ECG to assess the QT interval (prolonged);
- renal ultrasound;
- radiological examination may reveal bone demineralization (late-onset);
- genetic testing for suspected syndromes (DiGeorge);
- maternal levels of vitamin D and PTH.

VII.6.1.7. DIFFERENTIAL DIAGNOSIS

The differential diagnosis of neonatal hypocalcemia is based on etiology, age at onset (early or late), maternal and neonatal history, as well as the biological profile of calcium, phosphorus, magnesium, and PTH. In practice, the primary cause is identified. Other conditions that share common manifestations with hypocalcemia include:

- hypoglycemia,
- hypomagnesemia,
- hyponatremia,
- hypo/hyperkalemia,
- sepsis,
- cerebral hemorrhages,
- metabolic disorders (acidosis),
- laboratory errors (hemolysis).

VII.6.1.8. MANAGEMENT

The management of hypocalcemia depends on its severity, the presence of symptoms, and the underlying etiology. The goal is to restore normal calcium levels while identifying and treating the cause.

A. GENERAL PRINCIPLES

- Correction of hypocalcemia is performed only if it is symptomatic or if ionized $Ca^{(2+)}$ is<1 mmol/L;
- Treat the underlying cause (hyperphosphatemia, hypomagnesemia);
- rapid calcium infusion may induce severe bradycardia followed by cardiac arrest;
- ECG monitoring during IV correction.

B. NONPHARMACOLOGICAL

- Optimization of diet (avoidance of milk formulas with excess phosphorus);
- correction of hypoxia, acidosis, and hypothermia,
- ensuring adequate vitamin D intake for the pregnant woman.

C. PHARMACOLOGICAL

- *In mild, asymptomatic cases*—administer oral calcium 50–75 mg/kg/day, in 3–4 doses (calcium gluconate or calcium carbonate);
- *In symptomatic cases* or when Ca^{2+}*< 1 mmol/L* – **EMERGENCY** – administer 10% calcium gluconate, 2 mL/kg, by slow IV infusion (1–2 mg/kg/min), under ECG monitoring. The dose may be repeated every 15 minutes.
- *Maintenance therapy* should be administered with:
    - 10% calcium gluconate, 1–3 mL/kg/day, IV or orally, until serum calcium levels normalize;
    - Vitamin D, 400–800 IU/day, for maintenance (or Calcitriol in hypoparathyroidism).
- *In cases associated with hypomagnesemia*—initially administer magnesium sulfate 25%, 0.2 ml/kg, IV slowly, followed by calcium.
- *In cases associated with hyperphosphatemia* (occurring after 3 days of life)—breastfeeding or a low-phosphorus formula is recommended, combined with oral calcium administration.

D. FOLLOW-UP

- Initial monitoring of ionic and total calcium every 4–6 hours, then every 12–24 hours;
- Reassess Mg, P, and vitamin D if the disorder persists;
- clinical follow-up for recurrence of seizures;
- Long-term monitoring in cases of chronic forms (hypoparathyroidism).

VII.6.1.9. PROGNOSIS

- early transient hypocalcemia resolves within 48–72 hours—favorable prognosis;
- late hypocalcemia secondary to diet – favorable prognosis after adjustment;
- Congenital hypoparathyroidism – chronic course, requires lifelong treatment.

Complications:

- Acute:
    - refractory seizures,
    - ventricular arrhythmias,
    - tetany, laryngospasm,
    - chronic neurological impairment.
- Chronic:
    - rickets and impaired bone mineralization,
    - dental enamel hypoplasia.

VII.6.2. HYPERCALCEMIA

VII.6.2.1. DEFINITION

Hypercalcemia is an increase in plasma calcium levels, defined as:

- total calcium >11 mg/dl (2.75 mmol/l),
- ionized calcium >5.6 mg/dl (1.4 mmol/l).

VII.6.2.2. EPIDEMIOLOGY. INCIDENCE

Neonatal hypercalcemia is much rarer than hypocalcemia, but it is a serious metabolic disorder that requires prompt investigation and treatment. It occurs in 0.5–2% of cases in neonatal intensive care units ( ). Mild, transient hypercalcemia may occur in the first week of life, but it usually resolves spontaneously.

Major causes of neonatal hypercalcemia include:

1. **Iatrogenic causes:**

- excessive administration of calcium or vitamin D to the mother or newborn, hypercalcemic infant formula;
- inadequate phosphate intake in the newborn, especially in preterm infants;
- thiazide medications.

2. **Endocrine disorders:**

- primary neonatal hyperparathyroidism (rare);

- compensatory neonatal hyperparathyroidism secondary to maternal hypoparathyroidism;
- self-limiting secondary hyperparathyroidism associated with renal tubular acidosis;
- congenital hyperthyroidism.

3. Genetic syndromes:

- Williams syndrome (hypercalcemia, supravalvular aortic stenosis, and characteristic facial features);
- idiopathic infantile hypercalcemia;
- familial hypocalciuric hypercalcemia.

4. Other causes:

- extreme prematurity (inability to utilize calcium);
- hypophosphatasia (autosomal recessive bone dysplasia);
- increased intestinal absorption of calcium;
- decreased renal clearance of calcium;
- acute renal failure;
- subcutaneous fat necrosis associated with birth trauma;
- congenital lactase deficiency (rare) – severe hypercalcemia via unknown mechanisms;
- prolonged immobilization (increases bone resorption);
- malignancies (extremely rare) may include congenital leukemia or neuroblastoma.

VII.6.2.3. PATHOPHYSIOLOGY

Neonatal hypercalcemia occurs when the balance between intake, mobilization from bone, and renal excretion is disrupted, leading to excessive accumulation of calcium in the blood. Mechanisms leading to hypercalcemia:

- increased intestinal calcium absorption: excess vitamin D, increased sensitivity to vitamin D;
- increased bone resorption: neonatal primary hyperparathyroidism, immobilization;
- decreased renal excretion or excessive parenteral calcium intake.

Elevated serum calcium suppresses PTH, leading to persistent hypercalcemia with a risk of nephrocalcinosis.

VII.6.2.4. RISK FACTORS

- excessive vitamin D intake;
- high-calcium infant formula;
- PN;
- family history of hyperparathyroidism;
- genetic disorders (Williams syndrome).

VII.6.2.5. CLINICAL DIAGNOSIS

Clinical manifestations vary depending on the severity and rate of rise in blood calcium levels. *Mild* hypercalcemia may be ***asymptomatic*** and discovered incidentally during routine laboratory screening. *Moderate* to *severe* hypercalcemia may involve multiple organ systems:

- *gastrointestinal:* difficulty eating, vomiting, constipation, abdominal pain, and weight stagnation;
- *neurological:* lethargy, hypotonia, irritability, seizures;
- *renal:* polyuria, dehydration, nephrocalcinosis, and renal failure;
- *cardiac:* bradycardia and hypertension;
- *cutaneous:* subcutaneous nodules in fat necrosis.

VII.6.2.6. LABORATORY AND IMAGING STUDIES

1. Initial laboratory evaluation:

- ionized and total serum calcium (↑)
- serum phosphorus (↓) – indicates decreased phosphate, primary hyperparathyroidism, familial hypocalciuric hypercalcemia;
- magnesium, albumin;
- ALP (very ↓) – suggests hypophosphatasia

- PTH
- 25(OH)D and 1,25(OH)□D;
- urinary calcium/creatinine ratio (↓);
- creatinine, blood urea.

2. Other additional tests based on clinical suspicion:

- ECG to assess the QT interval (shortened),
- renal ultrasound to detect nephrocalcinosis,
- skeletal X-ray for bone abnormalities,
- parathyroid imaging if hyperparathyroidism is suspected,
- genetic testing,
- maternal levels of calcium, PTH, and vitamin D.

VII.6.2.7. DIFFERENTIAL DIAGNOSIS

The differential diagnosis of neonatal hypercalcemia is based on etiology, age at onset, and maternal and neonatal history. Other conditions included in the differential diagnosis are:

- severe dehydration,
- primary hyperparathyroidism,
- hypervitaminosis D,
- bone disorders with increased resorption,
- tubular renal disorders.

VII.6.2.8. MANAGEMENT

A. NONPHARMACOLOGICAL—applies *to mild,* **asymptomatic** *forms (total Ca^{2+}<12 mg/dL):*

- discontinuation of calcium and vitamin D intake,
- adequate hydration with isotonic solutions and forced diuresis,
- use of a low-calcium formula if breastfeeding is not possible,
- close monitoring of serum calcium levels every 24–48 hours.

B. PHARMACOLOGICAL

- *Moderate to severe forms (total Ca^{2+}>12 mg/dL or symptomatic)*
  - infusion of 0.9% NaCl, 20 ml/kg over 15–30 minutes + Furosemide 1 mg/kg, IV every 6–12 hours.
- *Other therapies:*
  - inorganic phosphate lowers serum calcium in patients with hypophosphatemia by inhibiting bone resorption;
  - glucocorticoids are indicated for hypervitaminosis A and D, subcutaneous fat necrosis; ineffective in hyperparathyroidism;
  - a diet low in calcium and vitamin D – adjunctive therapy in subcutaneous fat necrosis and Williams syndrome;
  - calcitonin 4–8 IU/kg, SC or IM – inhibits bone resorption;
  - dialysis for severe, refractory hypercalcemia or renal failure;
  - parathyroidectomy with autologous reimplantation – in cases of persistent severe neonatal hyperparathyroidism.

C. FOLLOW-UP

- initial calcium monitoring every 6–12 hours during acute treatment, then every 24–48 hours;
- daily monitoring of electrolytes (sodium, potassium, phosphate) during forced hydration;
- Reassessment of urinary Ca^{2+}/creatinine;
- adjustment of nutritional intake;
- ECG monitoring;
- periodic renal ultrasound for nephrocalcinosis;
- genetic counseling for hereditary disorders;
- growth and development monitoring.

VII.6.2.9. PROGNOSIS

- iatrogenic forms – good prognosis after correction of the cause;
- severe hyperparathyroidism – risk of nephrocalcinosis, renal impairment;
- Williams syndrome – may require long-term monitoring and treatment;
- Untreated – risk of cardiac arrhythmias, renal failure, growth retardation.

Complications:

- *Acute:*
  - dehydration and acute kidney injury,
  - cardiac arrhythmias,
  - hypercalcemic crisis with altered consciousness,
  - pancreatitis (rare).
- *Chronic conditions:*
  - nephrocalcinosis and chronic kidney disease,
  - nephrolithiasis,
  - developmental delay (in severe, prolonged cases).

VII.7. PREMATURE OSTEOPENIA

VII.7.1. DEFINITION

Osteopenia of prematurity, also known as metabolic bone disease of the preterm infant, is a condition characterized by **decreased bone mineral content (calcium and phosphorus)** and **disruption of the bone matrix mineralization process**, occurring predominantly in preterm and newborns, especially those with **a gestational age <32 weeks** and/or **birth weight <1500 g**.

VII.7.2. EPIDEMIOLOGY. INCIDENCE

- Incidence is associated with disease severity and gestational age and ranges from 20–40% in preterm infants <1500 g and may exceed 50% in those weighing <1000 g;
- Severe cases are rarer due to improvements in parenteral and enteral nutrition and the fortification of breast milk,
- the disease usually manifests between 4 and 12 weeks postnatal.

Etiology of OP:

1. **Phosphorus and calcium deficiency**

- low mineral intake through diet and PN,
- unfortified breast milk,
- excessive fluid restriction,
- long-term use of formula,
- use of milk formulas not indicated for feeding premature infants (formulas for full-term newborns, soy-based formulas, lactose-free formulas),
- long-term use of medications: Furosemide, steroids.

2. **Vitamin D deficiency**

- mothers who do not receive adequate vitamin D supplementation during breastfeeding,
- decreased or insufficient absorption of vitamin D,
- malabsorption or inadequate conversion of vitamin D to 25(OH)D (in cholestatic liver disease),
- chronic kidney disease (renal osteodystrophy),
- long-term use of phenobarbital, phenytoin,
- hereditary pseudovitamin D deficiency types I and II.

VII.7.3. PATHOPHYSIOLOGY

The development of OP is multifactorial, involving disruption of normal fetal mineral accumulation, inadequate postnatal mineral intake, and various medical conditions affecting mineral metabolism. In the third trimester of pregnancy, there is an accelerated increase in fetal bone

mineralization through **transplacental transfer of minerals** from the mother (Calcium ~ 120–150 mg/kg/day, Phosphorus ~ 60–70 mg/kg/day). Premature interruption of transplacental mineral transfer will lead to disruption of the bone mineralization process.

Postnatal factors further compromise mineral accumulation. **Immature renal function** leads to increased urinary losses of calcium and phosphorus. Limited **enteral intake** due to feeding intolerance, prolonged NEC, or PN restricts mineral supply. In addition, **the rapid growth rate** of preterm infants requires substantial amounts of minerals that often exceed nutritional intake, leading to progressive bone demineralization.

VII.7.4. RISK FACTORS

Risk factors implicated in OP may include:

- Neonatal factors:
  - preterm birth <32 weeks and <1500 g,
  - TPN prolonged beyond 4 weeks,
  - insufficient intake of calcium and phosphorus,
  - unfortified breast milk used as the sole source of nutrition,
  - bronchopulmonary dysplasia,
  - NEC,
  - short bowel syndrome (malabsorption of vitamin D and calcium),
  - liver disease,
  - kidney disease,
  - chronic medication use (loop diuretics, methylxanthines, glucocorticoids, sodium bicarbonate),
  - immobility—lack of movement and mechanical stimulation, common in premature infants, reduces bone development.
- Maternal factors:
  - vitamin D deficiency,
  - smoking,
  - preeclampsia,
  - chorioamnionitis,
  - placental insufficiency.

VII.7.5. CLINICAL DIAGNOSIS

OP manifests between 4 and 12 weeks of life, but may remain **asymptomatic** for weeks until signs of rickets or even fractures appear. There are no specific diagnostic methods for OP. Diagnosis is based on criteria that include history, clinical signs, biochemical markers, and radiological findings (late sign).

Clinical manifestations appear late, and sometimes the diagnosis is not made in time; therefore, biological screening of premature infants at risk for the disease is recommended.

The following clinical signs may be observed:

- respiratory failure with increased respiratory effort or the inability to wean the preterm infant from respiratory support,
- hypotonia,
- reduced linear growth with head growth,
- frontal bulging,
- wide cranial sutures, wide anterior fontanelle,
- craniotabes,
- "rickets rosary" (inflammation of the costochondral junction),
- Harrison's grooves (visible or palpable bilateral transverse depression located at the level of the diaphragm's insertion on the chest wall),
- enlargement of the wrist, ankle, and knee joints,
- pain on manipulation due to pathological fractures

VII.7.6. LABORATORY AND IMAGING STUDIES

1. **Laboratory:**

The earliest changes in OP are represented by:

- ↓ serum phosphorus < 3.5–4 mg/dL
- ↑ alkaline phosphatase (ALP) activity > 800 IU/L

Table 11. Laboratory tests in osteopenia of prematurity

PARAMETER	SUGGESTIVE VALUES
Phosphatemia	< 4 mg/dL
ALP	> 800 IU/L (values >1000 IU/L—increased risk)
Calcemia	Normal, low, slightly elevated
PTH	Elevated secondary to hypophosphatemia
25(OH)D	Variable, useful for monitoring

2. **Imaging:**

- **Bone radiography:**

X-rays show no changes in the early stages of bone disease due to the absence of significant demineralization or fractures. When bone mineralization is reduced by 20–40%, demineralization can be identified radiologically, which occurs late. The following changes may be observed:

  - decreased metaphyseal bone density,
  - an irregular "spongy" appearance,
  - subperiosteal fracture lines,
  - osteopenia of the skull, spine, scapula, and ribs,
  - formation of new bone,
  - pathological bone fractures or osteoporosis – occasionally

X-rays of the wrist or knee are helpful, repeated after 4–6 weeks if pathological changes were observed.

- **DEXA densitometry** or **quantitative ultrasound** – more sensitive methods, but rarely available in neonatology.

VII.7.7. DIFFERENTIAL DIAGNOSIS

- congenital rickets (hypophosphatemic, vitamin D-dependent),
- osteogenesis imperfecta,
- rare metabolic bone diseases,
- sequelae of severe immobilization,
- severe congenital hypothyroidism.

VII.7.8. MANAGEMENT

A. NONPHARMACOLOGICAL

- **Optimization of enteral nutrition**:
  - fortification of breast milk (required for all preterm infants <1500 g),
  - use of special formulas for preterm infants,
  - early initiation of enteral nutrition in low-birth-weight preterm infants,
  - continuation of preterm infant formula until adequate weight gain is achieved.
- **Physical therapy / early mobilization**:
  - daily passive movements for 5–10 minutes → stimulates mineralization.
- **Minimally invasive care** (avoiding prolonged immobilization)
- **Exposure to natural light** (moderate, for vitamin D)
- **Close monitoring of growth**

B. PHARMACOLOGICAL

In preterm infants with radiological and biochemical signs of osteopenia who do not respond to feeding with breast milk plus formula or special preterm formula, calcium and phosphorus may be administered.

Phosphorus supplementation effectively treats hypophosphatemia and reduces alkaline phosphatase levels.

Calcium supplementation may be added when serum calcium is low or if additional calcium is needed to balance phosphorus supplementation. Close monitoring during supplementation is essential to avoid hyperphosphatemia, hypercalcemia, or an unfavorable calcium-to-phosphorus ratio that could lead to tissue calcification.

Vitamin D: 400–800 IU/day (sometimes up to 1000 IU/day in severe cases). Continued administration of Vitamin D throughout childhood is recommended. In cases of vitamin D metabolism disorders (rare), **calcitriol** administration is indicated**.**

It is necessary to avoid medications that increase the loss of $Ca^{2+}$and P (replacing furosemide with a thiazide diuretic or alternating between them).

C. FOLLOW-UP

- **Weekly monitoring:**
  - FAL,
  - serum P and Ca,
  - Weight / linear growth,
- **X-ray** at 4–6 weeks or if clinical signs appear,
- **Orthopedic evaluation** in case of fractures or deformities,
- **Pediatrician/pediatric nutritionist** after discharge to continue supplementation.

VII.7.9. PROGNOSIS

With early diagnosis and appropriate nutritional intervention, OP is reversible. Most preterm infants with mild-to-moderate OP recover completely by a corrected age of 6–12 months. Severe forms, especially those with fractures, may result in orthopedic sequelae or growth delays, requiring long-term monitoring.

Complications:

- spontaneous fractures (ribs, femur, humerus),
- permanent bone deformities,
- growth disorders,
- hypercalciuria, nephrocalcinosis (due to excessive supplementation).

VII.8. SEXUAL DEVELOPMENT DISORDERS

VII.8.1. DEFINITION

Sexual development disorders (SDDs) are a heterogeneous group of congenital conditions characterized by a mismatch between chromosomal, gonadal, and phenotypic sex.

The neonatal period is critical for identifying these conditions, as some DSDs may represent **medical emergencies** (e.g., congenital adrenal hyperplasia with salt-wasting), and early diagnosis has major implications for prognosis, therapeutic management, and family counseling.

The term DSD has replaced previous terms such as sexual ambiguity, hermaphroditism, pseudohermaphroditism, and intersexuality, as it is considered more precise from an etiopathogenic standpoint and more appropriate from an ethical perspective.

VII.8.2. EPIDEMIOLOGY. INCIDENCE

- The global incidence of DSD is estimated at 1 in 4,500–5,000 newborns, though subtle forms may be much more common;
- cases of DSD evident at birth occur at a rate of 1:10,000;
- The most common neonatal forms are:

- congenital adrenal hyperplasia (CAH)—the most common cause of genital ambiguity in newborns, 46, XX;
- gonadal dysgenesis – most common in 46, XY

The etiology of disorders of sex development is **multifactorial**, including:

1. DSDs caused by chromosomal sex anomalies:

These are caused by numerical or structural changes in the sex chromosomes, affecting gonadal and hormonal development.

- *Sex chromosome aneuploidies:*
  - 45,X (Turner syndrome)
  - 47,XXY (Klinefelter syndrome)
  - 47,XXX
  - 47,XYY
- *Chromosomal mosaicism:*
  - 45,X/46,XX
  - 45,X/46,XY
- *Structural rearrangements of sex chromosomes:*
  - translocations, deletions (e.g., deletion of the SRY region), isochromosomes

2. DSDs caused by gonadal development disorders:

These are characterized by absent or abnormal gonadal differentiation, with insufficient or inappropriate hormonal secretion.

- *Complete gonadal dysgenesis:*
  - 46,XX gonadal dysgenesis
  - 46,XY gonadal dysgenesis
- *Partial gonadal dysgenesis***:**
  - incomplete gonadal development
  - variable hormonal secretion
- *Ovotesticular DSD*—simultaneous presence of ovarian and testicular tissue

3. DSD caused by disorders of sex hormone synthesis:

These are caused by enzymatic defects affecting gonadal or adrenal steroidogenesis.

- *Congenital adrenal hyperplasia (46,XX DSD)*
  - 21-hydroxylase deficiency (90–95% of cases)
  - 11β-hydroxylase deficiency
  - 3β-hydroxysteroid dehydrogenase deficiency
- *Defects in testosterone synthesis (DSD 46,XY)*
  - 17β-hydroxysteroid dehydrogenase deficiency
  - 17α-hydroxylase deficiency

4. DSD caused by disorders of sex hormone action:

These are characterized by normal or increased hormone secretion, but with a deficient tissue response.

- *Androgen receptor defects*
  - complete androgen insensitivity syndrome
  - partial androgen insensitivity syndrome
- *Hormone conversion defects*
  - 5α-reductase deficiency

5. DSD caused by exogenous and maternal factors:

These arise from fetal exposure to substances that interfere with sexual differentiation.

- *Prenatal exposure to androgens*
  - Androgen-secreting maternal tumors
  - maternal treatment with androgens or androgenic progestins

6. DS associated with complex genetic syndromes:

Sexual development disorders may be part of the clinical picture of certain multisystemic genetic diseases.

- Denys–Drash syndrome, Frasier syndrome, Smith–Lemli–Opitz syndrome, campomelic syndrome

VII.8.3. PATHOPHYSIOLOGY

Normal sexual development involves 3 stages:

1. **Sex determination (chromosomal)**

- 46, XX → ovary
- 46, XY → testis via activation of the SRY gene

2. **Gonadal differentiation**

- The testis produces:
    - AMH (regression of the Müllerian ducts)
    - Testosterone (development of Wolffian ducts)
- The ovary requires the absence of androgenic signals for female development.

3. **Phenotypic differentiation**

- Testosterone → formation of Wolffian ducts → epididymis, vas deferens
- DHT via 5α-reductase → development of male external genitalia
- Absence of androgens → female phenotype

Genetic sex is determined at the moment of fertilization and is established by the X and Y sex chromosomes (XX, XY). Gonadal differentiation occurs during weeks 6–7 of gestation; the presence of the SRY gene on the Y chromosome helps transform the gonads into testes, while its absence leads to the formation of an ovary. The formation of the genital ducts occurs during weeks 8–12 of gestation. The testis secretes testosterone and AMH, which determine the development of male genitalia and the regression of female genitalia. The differentiation of the external genitalia occurs between weeks 9–14 of gestation and is stimulated by DHT derived from testosterone.

VII.8.4. RISK FACTORS

- family history of CAH, hypospadias, cryptorchidism, infertility, delayed puberty,
- known genetic disorders (e.g., CYP21A2 mutations, AR mutations),
- pregnancy achieved through in vitro fertilization,
- twin pregnancy with feto-fetal transfusion,
- prenatal exposure to androgens or progestins with androgenic effects, antiandrogenic medications, maternal ovarian or placental tumors secreting androgens,
- prenatal exposure to maternal treatments with spironolactone, anticonvulsants,
- extreme prematurity or fetal stress (rarely may cause transient symptoms).

VII.8.5. CLINICAL DIAGNOSIS

The initial clinical evaluation must be performed promptly and in a multidisciplinary manner, as the choice of social sex depends on a correct diagnosis.

The initial clinical evaluation involves:

- a medical history review for family and maternal history (consanguinity, hormonal treatments),
- careful genital examination (degree of virilization),
- identification of palpable testes.

1. **Signs at birth:**

- Genital ambiguity:
    - micropenis,
    - penoscrotal hypospadias,
    - hypertrophied clitoris,
    - bifid scrotum/fused labia,
    - absence of palpable testes,
    - single urogenital opening.
- Genital asymmetry (one palpable testicle on one side, abnormal gonadal mass on the other side).

2. **Other systemic signs:**
- hypoglycemia, vomiting, dehydration (in congenital adrenal hyperplasia with salt-wasting),
- craniofacial dysplasias or associated malformations (in chromosomal syndromes)—pterygium colli, low hairline in Turner syndrome,
- absence of typical internal organs (uterus, vagina, vas deferens)—evidenced by imaging.

VII.8.6. LABORATORY AND IMAGING STUDIES

The evaluation of DSD is complex and multidisciplinary (neonatologist, endocrinologist, geneticist, urologist, psychologist).

1. **Genetic testing**:
- karyotype (46,XX/46,XY/mosaicism),
- specific tests: FISH for SRY, genetic panels for DSD.

2. **Hormone measurements:**
- 17-OH-progesterone (elevated in 21-hydroxylase deficiency) → screening for CAH,
- testosterone, DHT, T/DHT ratio → 5α-reductase deficiency,
- AMH → presence of testicular tissue,
- LH, FSH → indication of gonadal dysgenesis,
- cortisol, aldosterone, renin → forms associated with adrenal insufficiency,
- Serum electrolytes (Na^+, K^+) → to rule out CAH with salt loss.

3. **Imaging**:
- Pelvic ultrasound:
  - identification of the uterus, vagina, ovaries, and testes
- MRI if ultrasound is inconclusive
- Cystourethrography

4. **Additional tests:**
- ACTH test (for CAH)
- HCG test (assessment of Leydig cell function)

VII.8.7. DIFFERENTIAL DIAGNOSIS

The diagnosis of DSD is usually suspected following external examination of the genital region, and the differential diagnosis is initially based on etiological criteria, followed by:

- cloaca,
- urogenital sinus,
- rectovaginal fistula.

Certain conditions may mimic DSD:

- cryptorchidism,
- penile hypospadias,
- micropenis.

VII.8.8. MANAGEMENT

1. NONPHARMACOLOGICAL
- DSD is a **diagnostic emergency**, not a surgical one.
- Mandatory multidisciplinary approach: neonatologist, endocrinologist, geneticist, pediatric urologist, psychologist
- Family counseling regarding:
  - the diagnostic process,
  - initial uncertainty regarding gender,
  - long-term implications,
- delaying the declaration of the newborn's sex (and, implicitly, the choice of first name) until the results of genetic testing (karyotyping) are available and a diagnosis is established,
- ongoing emotional and psychological support for the family.

2. PHARMACOLOGICAL
- correction of hormonal deficiencies:
    - glucocorticoid replacement in CAH
    - mineralocorticoid replacement when necessary
- targeted hormone therapy:
    - androgens or estrogens depending on the established sex of development
- treatment of complications:
    - correction of electrolyte imbalances
    - Hemodynamic stabilization in cases of adrenal crisis
- staged surgical correction

3. FOLLOW-UP
- periodic endocrinological monitoring:
    - growth, development, puberty
- gonadal reassessment:
    - risk of tumors in certain DSD (e.g., 46,XY gonadal dysgenesis)
- long-term psychological monitoring and emotional support
- review of gender identity throughout development, with appropriate counseling.

VII.8.9. PROGNOSIS

The prognosis is variable and depends on the etiology, the timeliness of diagnosis, and the quality of management.

- CAH – good prognosis with proper replacement therapy: forms with salt-wasting can be life-threatening if not diagnosed early.
- XY gonadal dysgenesis – increased cancer risk if the dysgenetic gonads are not removed.
- Complete androgen insensitivity syndrome – stable female identity, excellent prognosis.
- 5α-reductase deficiency – delayed virilization; requires gender identity counseling.
- Quality of life is influenced by:
    - multidisciplinary support
    - communication with the family
    - psychological assessment and intervention

Complications

- *urological and gynecological*: urinary retention or urinary reflux secondary to genital anomalies, increased risk of urinary tract infections, malformations of the internal or external genital tract
- *long-term*: infertility, possible reconstructive surgeries, continuous monitoring of neoplastic and endocrinological risk
- disorders associated with mineral and energy metabolism (in cases of congenital adrenal hyperplasia).

VII.9. ADRENAL INSUFFICIENCY

VII.9.1. DEFINITION

Adrenal insufficiency (AI) is the inability of the adrenal glands to produce adequate amounts of the adrenal hormones cortisol and aldosterone, which are essential for metabolic, hydroelectrolytic, and cardiovascular homeostasis. In newborns, ACS is a major endocrinological emergency with the potential to be fatal if not promptly recognized and treated.

VII.9.2. EPIDEMIOLOGY. INCIDENCE

AI in newborns is rare but also underdiagnosed, as the manifestations are nonspecific.

- congenital adrenal hyperplasia (CAH): 1 in 15,000–20,000 births,
- adrenal hemorrhage: <2% of newborns with obstetric trauma or asphyxia.

AI can be primary, secondary, tertiary, and transient (due to prematurity), and its etiology is multifactorial.

1. **Primary** – intrinsic involvement of *the adrenal cortex*:
- CAH – the main cause,
- adrenal hemorrhage,
- infections,
- adrenal dysgenesis.
2. **Secondary** (*pituitary*) – adrenocorticotropic hormone (ACTH) deficiency:
- congenital ACTH deficiency,
- pituitary lesions,
- abrupt discontinuation of maternal or neonatal corticosteroid therapy.
3. **Tertiary** *(hypothalamic)* – corticotropin-releasing hormone (CRH) deficiency:
- hypothalamic dysfunction.
4. **Transient** – functional immaturity of *the hypothalamic-pituitary-adrenal* (HPA) *axis*
- extreme prematurity,
- perinatal stress.

VII.9.3. PATHOPHYSIOLOGY

1. *The HPA axis*

CRH, produced by the hypothalamus, stimulates the pituitary to produce ACTH, which in turn stimulates the adrenal glands to produce cortisol and release aldosterone. Cortisol exerts negative feedback on the hypothalamus and pituitary. The HPA axis is functional as early as fetal life, but cortisol reserves may be reduced, especially in preterm infants.

2. *Effects of hormone deficiency:*
- cortisol deficiency → hypoglycemia, hypotension, lethargy,
- aldosterone deficiency → loss of Na^+, retention of K^+, dehydration, circulatory collapse,
- compensatory excess of ACTH (in primary forms) → skin hyperpigmentation.

VII.9.4. RISK FACTORS

1. For primary AI:
- *CAH* - genetic defect in enzymes involved in cortisol synthesis (21-hydroxylase, 17-hydroxyprogesterone),
- *adrenal hemorrhage*—perinatal trauma, asphyxia, sepsis, DIC,
- *infections*—congenital cytomegalovirus infection, congenital tuberculosis,
- *genetic syndromes*: neonatal adrenoleukodystrophy.
2. For secondary/tertiary AI:
- congenital hypopituitarism (ACTH deficiency, panhypopituitarism),
- malformations of the hypothalamic-pituitary region,
- ischemic or hemorrhagic lesions of the CNS.
3. Premature infants:
- functional immaturity of the HPA axis,
- prolonged antenatal corticosteroid therapy,
- sepsis/severe illness with increased cortisol consumption.

VII.9.5. CLINICAL DIAGNOSIS

Clinical signs are **nonspecific**, often similar to sepsis or shock.

1. Common manifestations:
- volume- and vasopressor-refractory hypotension,
- persistent hypoglycemia,
- lethargy, apnea, hypotonia,
- refusal to feed, vomiting.

2. **Specific forms**:

- *Primary AI*:
  - vomiting, weight loss,
  - dehydration,
  - hyponatremia, hyperkalemia.
- *CAH*:
  - virilizing form in girls (clitoromegaly, labial fusion),
  - salt-wasting form – manifests between days 5–15 of life.
- *Secondary AI*:
  - hypoglycemia,
  - no significant electrolyte disturbances,
  - possibly signs of hypopituitarism: recurrent hypoglycemia, prolonged jaundice, micropenis.
- *Acute adrenal crisis:*
  - circulatory collapse,
  - hypovolemic or destructive shock,
  - severe hypoglycemia,
  - major electrolyte disturbances.

VII.9.6. LABORATORY AND IMAGING STUDIES

1. Laboratory tests:

- blood glucose ↓,
- electrolytes: hyponatremia, hyperkalemia (primary forms),
- metabolic acidosis,
- plasma cortisol ↓ or inadequate for the clinical status,
- ACTH:
  - ↑ in primary Cushing's syndrome,
  - ↓ / normal in secondary AI,
- 17-hydroxyprogesterone ↑ in CAH,
- aldosterone ↓ and renin ↑ in primary Cushing's syndrome with mineralocorticoid excess.
- ***ACTH stimulation test*** – performed to confirm the diagnosis.

2. Imaging

- Abdominal ultrasound may reveal adrenal hemorrhage,
- hypothalamic-pituitary MRI – suspected secondary/tertiary Cushing's syndrome.

VII.9.7. DIFFERENTIAL DIAGNOSIS

- neonatal sepsis,
- hypovolemic shock,
- low-output congenital heart disease,
- metabolic disorders,
- acute respiratory distress syndrome (ARDS) in electrolyte disorders.

VII.9.8. MANAGEMENT

CS is a **medical emergency**, and treatment should be initiated as soon as the diagnosis is suspected.

A. NONPHARMACOLOGICAL

- stabilization of vital functions,
- continuous monitoring: oxygen saturation, blood pressure, urine output, blood glucose, serum Na^+, serum K^+,
- restoration of blood volume,
- correction of blood glucose.

B. PHARMACOLOGICAL

- *electrolyte and fluid balance restoration:*
  - 0.9% saline solution, 10–20 mL/kg slow IV bolus, followed by continuous infusion,
  - correction of hypoglycemia: 10% glucose solution, 2 ml/kg bolus, followed by continuous infusion (6–8 mg/kg/min)
- *Glucocorticoid replacement therapy:*
  - IV hydrocortisone hemisuccinate
    - in acute adrenal crisis: 50–75 mg/m²/day
    - maintenance: 7.5–15 mg/m²/day
- *mineralocorticoid therapy:*
  - Oral fludrocortisone, 0.1–0.2 mg/day – in primary AI
- *correction of electrolyte disturbances:*
  - hyponatremia – gradual correction,
  - hyperkalemia – glucose + insulin, 10% calcium gluconate, ion exchange resins.
- *salt supplement*: 1 g/day (in cases with sodium loss).

C. FOLLOW-UP

- serum electrolyte panel (Na^+, K^+) 2–3 days after treatment initiation, then monthly,
- blood glucose, blood pressure, weight,
- periodic endocrinological evaluation,
- adjustment of glucocorticoid doses based on weight and age,
- increase hydrocortisone doses (double or triple) during periods of stress (fever, infections, surgeries),
- educating parents to recognize the signs of an adrenal crisis.

VII.9.9. PROGNOSIS

- AI treated appropriately has a good prognosis, with normal development in most patients,
- Untreated AI is associated with a major risk of shock, arrhythmias, permanent neurological impairment, and increased mortality,
- In CAH, the long-term prognosis is favorable with proper treatment, but requires continuous monitoring and adherence to therapy,
- In secondary AI, the prognosis depends on the etiology of hypopituitarism, but appropriate treatment allows for a satisfactory outcome.

Complications arise as a result of metabolic, hydroelectrolytic, and hemodynamic imbalances, as well as the body's inability to respond to stress:

- *neurological*: seizures, coma, permanent neurological sequelae,
- *cardiovascular*: arrhythmias, severe hypotension, treatment-resistant shock, cardiac arrest,
- *developmental and growth disorders*: stunted growth, delayed bone development, delayed puberty.

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VIII. INFECTIOUS DISEASES

VIII.1. NEONATAL SEPSIS

VIII.1.1. DEFINITION

Neonatal sepsis is a systemic infection occurring within the first 28 days of life, caused by bacterial, fungal, or viral invasion of the bloodstream, accompanied by a systemic inflammatory response and, frequently, organ dysfunction.
It is classified into two main forms:

- Early-Onset Sepsis (EOS), occurring within the first 72 hours of life, most often through vertical transmission from the mother;
- Late-Onset Sepsis (LOS), occurring after 72 hours of life, usually through nosocomial or community transmission.

Important note: this classification is epidemiologically and etiologically relevant, not strictly chronological.

VIII.1.2. EPIDEMIOLOGY AND INCIDENCE

Neonatal sepsis remains one of the leading causes of neonatal mortality worldwide, accounting for 15–20% of deaths occurring within the first 28 days. In developed countries, the incidence is estimated at 0.5–1 case per 1,000 live births, while in preterm infants, particularly those with very low birth weight (VLBW, <1,500 g), it can be 10–15 times higher.
Mortality varies depending on the clinical presentation:

- EOS: 3–5% in term newborns and up to 20% in preterm infants;
- LOS: 10–30%, especially in infections caused by Gram-negative bacteria or fungi.

The main causative agents are:

- for early-onset forms: Streptococcus agalactiae (Group B Streptococcus – GBS), Escherichia coli, Listeria monocytogenes;
- for late-onset forms: Staphylococcus aureus, Staphylococcus epidermidis, Klebsiella spp., Enterobacter spp., Pseudomonas aeruginosa, Candida spp.

Important clinical aspect: over the past decade, there has been a decrease in the incidence of Listeria monocytogenes infections due to dietary measures for pregnant women, but an increase in infections with multidrug-resistant E. coli, particularly in preterm infants.

VIII.1.3. PATHOPHYSIOLOGY

The newborn's immune system is not fully mature, which explains the increased susceptibility to severe infections.
Major immunological features:

- low levels of transplacental maternal IgG antibodies (especially in preterm infants);
- impaired function of neutrophils and monocytes;
- insufficient production of proinflammatory cytokines (IL-1, IL-6, TNF-α);
- reduced complement system activity.

The stages of infection include:

1. Colonization – usually with maternal microorganisms;
2. Invasion – crossing of mucosal or skin barriers;
3. Bacteremia – hematogenous spread;
4. Systemic inflammatory response – release of inflammatory mediators;
5. Organ dysfunction – impaired tissue perfusion, metabolic acidosis, respiratory failure, hypotension.

Important note: In newborns, fever may be absent; hypothermia is often the first sign of systemic infection.

VIII.1.4. RISK FACTORS

Maternal factors:

- Vaginal colonization with Group B Streptococcus (GBS);
- Prolonged rupture of membranes (ROM) >18 hours;
- Intrapartum fever ≥38°C;
- Chorioamnionitis;
- Preterm birth;
- Lack of intrapartum prophylaxis for GBS.

Neonatal factors:

- Prematurity and low birth weight (VLBW, ELBW);
- Prolonged hospitalization in the neonatal intensive care unit (NICU);
- Vascular catheters, mechanical ventilation, total parenteral nutrition;
- Exposure to broad-spectrum antibiotics;
- Neonatal surgical procedures.

VIII.1.5. CLINICAL DIAGNOSIS

The clinical signs of neonatal sepsis are often nonspecific and may be subtle.

General manifestations:

- temperature instability (hypothermia or hyperthermia);
- lethargy, irritability, feeding difficulties;
- apnea, bradycardia, cyanosis;
- hypoglycemia, metabolic acidosis;
- marked or persistent jaundice;
- pallor, petechiae, hypotension

Organ-specific manifestations:

- Respiratory: respiratory distress, increased oxygen requirement;
- Cardiovascular: tachycardia followed by bradycardia, hypotension;
- Gastrointestinal: abdominal distension, vomiting, food intolerance;
- Neurological: hypotonia, seizures, bulging fontanelle.

Key point: A newborn with recurrent apnea or unexplained instability of vital functions should always be evaluated for sepsis.

VIII.1.6. LABORATORY DIAGNOSIS

The diagnosis is based on correlating clinical data with paraclinical findings.

Recommended investigations include:

- Blood culture – represents the gold standard; collection is recommended prior to antibiotic therapy.
- Complete blood count – leukocytosis or leukopenia, thrombocytopenia, immature/total (I/T) ratio >0.2.
- C-reactive protein (CRP) and procalcitonin (PCT)—useful markers for monitoring progression.
- Arterial blood gas analysis, liver, and kidney function tests – to assess organ dysfunction.
- Lumbar puncture – if meningitis is suspected.
- Molecular panels (PCR) – can expedite diagnosis, but do not replace conventional culture.

Important note: negative blood culture results do not rule out sepsis, especially if antibiotic treatment was administered prior to sampling.

VIII.1.7. DIFFERENTIAL DIAGNOSIS

The differential diagnosis should be made with:

- transient tachypnea, aspiration pneumonia;
- congenital heart disease;
- severe hypoglycemia;
- intracranial hemorrhages;
- inborn errors of metabolism.

VIII.1.8. MANAGEMENT

Treatment should be initiated promptly, sometimes before laboratory confirmation.

A. NONPHARMACOLOGICAL

- Stabilization of vital functions (respiration, circulation, thermoregulation);
- Correction of hypoglycemia and metabolic acidosis;
- Ensuring fluid and electrolyte balance;
- Preventing hypothermia through appropriate temperature control;
- Implementation of strict hygiene and antisepsis measures;
- Careful monitoring of vital signs.

B. PHARMACOLOGICAL

- Early-onset sepsis (EOS): ampicillin + gentamicin; alternatively, ampicillin + cefotaxime.
- Late-onset sepsis (LOS): vancomycin + cefotaxime or piperacillin-tazobactam, depending on the local flora.
- Duration of treatment: 7–10 days for uncomplicated bacteremia; 14–21 days for meningitis or complicated infections.
- Antifungal treatment (fluconazole or amphotericin B) is indicated for confirmed fungal infections.

C. FOLLOW-UP

- Clinical reevaluation at 24–48 hours;
- Monitoring of CRP and PCT to guide the duration of therapy;
- Monitoring of neurological and auditory development in severe cases.

VIII.1.9. PROGNOSIS

The prognosis depends on gestational age, the causative agent, the timing of treatment initiation, and the severity of organ dysfunction. Premature infants and infections with Gram-negative bacilli have a more guarded prognosis. Late complications may include delayed neuropsychomotor development, hearing disorders, or motor deficits.

VIII.1.10. CONCLUSIONS. KEY POINTS

- Neonatal sepsis is a medical emergency; treatment should not be delayed pending laboratory confirmation.
- Distinguishing between EOS and LOS has epidemiological value and provides guidance on etiology.
- Hypothermia is often an early sign of sepsis.
- CRP and PCT are useful for monitoring progression, not for definitive diagnosis.
- Prevention through GBS screening and hospital hygiene significantly reduces mortality.

VIII.2. MENINGITIS

VIII.2.1. DEFINITION

Neonatal meningitis is inflammation of the meninges caused by a bacterial, fungal, or viral infection occurring within the first 28 days of life. Most often, meningitis occurs as a complication of neonatal sepsis, but it can also occur as an isolated infection, through hematogenous spread or direct inoculation.

Depending on the time of onset, the following are described:

- Early-Onset Meningitis (EOM), occurring within the first 72 hours of life, through vertical transmission;
- Late-onset meningitis (LOM), occurring after 72 hours, usually through nosocomial or community transmission.

Important note: Approximately 10–15% of cases of neonatal meningitis may present with negative blood cultures.

VIII.2.2. EPIDEMIOLOGY AND INCIDENCE

The incidence of neonatal meningitis ranges from 0.25 to 0.5 cases per 1,000 live births, being significantly higher in preterm infants (2–4 cases/1,000). Overall mortality ranges from 15% to 25%, and approximately half of the survivors develop neurological sequelae (deafness, developmental delay, epilepsy).

Common causative agents:

- Streptococcus agalactiae (GBS);
- Escherichia coli (especially K1 strains);
- Listeria monocytogenes;
- In late-onset forms: Staphylococcus aureus, Klebsiella spp., Pseudomonas aeruginosa, Enterobacter spp., Candida spp.

Important clinical feature: E. coli K1 strains possess a polysaccharide capsule similar to the blood-brain barrier antigen, which allows them to cross the blood-brain barrier and explains their meningeal tropism.

VIII.2.3. PATHOPHYSIOLOGY

Neonatal meningitis usually results from bacterial invasion of the meninges through successive mechanisms:

1. Colonization: microorganisms colonize the skin, mucous membranes, or respiratory tract;
2. Bacteremia: entry of the pathogen into the bloodstream;
3. Crossing the blood-brain barrier: bacterial adhesion to the cerebral endothelium and entry into the subarachnoid space;
4. Meningeal inflammation: activation of proinflammatory cytokines leads to cerebral edema, increased intracranial pressure, and decreased cerebral perfusion.

Key point: the newborn's blood-brain barrier is not fully mature, which facilitates the spread of pathogens and explains the increased vulnerability.

VIII.2.4. RISK FACTORS

Maternal factors

- Vaginal colonization with Group B Streptococcus (GBS);
- Intrapartum fever ≥38°C;
- Premature rupture of membranes (>18 hours);
- Chorioamnionitis;
- Maternal bacteriuria with GBS;
- Lack of intrapartum prophylaxis.

Neonatal factors

- Prematurity;
- Associated neonatal sepsis;
- Invasive catheters (umbilical line, central venous catheter);
- Prolonged mechanical ventilation;
- Congenital immunodeficiency;
- Prolonged exposure to antibiotics;
- Neonatal surgical procedures.

VIII.2.5. CLINICAL DIAGNOSIS

The clinical signs of neonatal meningitis are often nonspecific, and the onset can be insidious.
General manifestations:

- Fever or hypothermia;
- Lethargy, irritability, refusal to feed;
- Apnea, bradycardia, cyanosis;
- Thermal and circulatory instability;
- Seizures.

Specific neurological signs:

- Bulging anterior fontanelle;
- Hypotonia or hypertonia;
- Fixed gaze, opisthotonos, sensitivity to handling;
- Abnormal primitive and sucking reflexes;
- High-pitched crying, signs of intracranial hypertension.

Important clinical feature: approximately 50% of cases present with seizures within the first 24 hours of disease onset.

VIII.2.6. LABORATORY AND IMAGING STUDIES

A positive diagnosis is based on demonstrating meningeal inflammation and identifying the causative agent.
Essential investigations:

- Blood culture: positive in 50–90% of cases; sampling must be performed before antibiotic therapy.
- Lumbar puncture: the primary test for confirmation.
- Cerebrospinal fluid (CSF) with a cloudy appearance, leukocytosis (>100/mm³, predominance of PMNs), elevated protein levels (>150 mg/dL), and hypoglycorrhachia (CSF/blood ratio <0.4).
- The presence of bacteria on Gram stain is an early diagnostic sign.
- Inflammatory markers: elevated CRP and procalcitonin.
- Neuroimaging: transfontanellar ultrasound, CT, or MRI—useful for evaluating complications (abscesses, ventriculitis, hydrocephalus).
- Molecular tests (PCR): rapidly identify bacterial DNA, especially in cases with negative cultures.

Important note: a normal CSF result does not rule out meningitis if the puncture was performed at an early stage; repeat testing in 24–48 hours is indicated if clinical suspicion persists.

VIII.2.7. DIFFERENTIAL DIAGNOSIS

Neonatal meningitis must be differentiated from:

- intraventricular hemorrhage;
- hypoxic-ischemic encephalopathy;
- hypoglycemia and hypocalcemia;
- brain abscesses;
- viral infections (CMV, HSV, enteroviruses).

Important clinical finding: seizures or a bulging fontanelle without an obvious cause require the exclusion of meningitis via lumbar puncture.

VIII.2.8. MANAGEMENT

The treatment of neonatal meningitis is a medical emergency and must be initiated immediately after the collection of biological samples.

A. General measures

- Stabilization of vital functions (respiration, circulation, thermoregulation);
- Correction of metabolic and electrolyte imbalances;

- Maintaining blood glucose within normal limits;
- Monitoring blood pressure and urine output;
- Adherence to hygiene and isolation measures to prevent secondary infections.

B. Antibiotic treatment

Treatment is empirical at onset, subsequently adjusted based on the antibiotic susceptibility test.

- Early-onset meningitis (EOM): ampicillin + cefotaxime; alternatively, ampicillin + gentamicin.
- Duration of treatment: at least 14 days for infections with GBS and Listeria monocytogenes; 21 days for Gram-negative bacilli.
- Late-onset meningitis (LOM): vancomycin + cefotaxime or vancomycin + meropenem, depending on local susceptibility.
- For fungal infections: intravenous amphotericin B or fluconazole.
- Anticonvulsants (phenobarbital) for seizure control.
- Adjuvant corticosteroid therapy (e.g., dexamethasone) is used selectively, prior to the first dose of antibiotic, to reduce hearing sequelae in GBS infections.

Important note: Meropenem effectively crosses the blood-brain barrier and is used in severe Gram-negative infections.

C. Follow-up

- Clinical and laboratory reevaluation after 24–48 hours;
- Repeat lumbar puncture at 48–72 hours if the course is unfavorable;
- Transfontanellar ultrasound at the end of treatment;
- Mandatory audiological testing;
- Monitoring of neurological development during the first year of life.

VIII.2.9. PROGNOSIS

The prognosis depends on the causative agent, the timing of treatment initiation, and gestational age. Premature infants and infections caused by Gram-negative bacilli or fungi have a more severe course. Mortality ranges from 15–25%. Up to half of survivors may have neurological sequelae: developmental delay, epilepsy, hearing loss, or cerebral palsy.

VIII.2.10. CONCLUSIONS. KEY POINTS

- Neonatal meningitis is usually a complication of sepsis.
- The diagnosis is confirmed by CSF analysis and positive cultures.
- Clinical manifestations are often nonspecific; seizures and a bulging fontanelle are warning signs.
- Empirical treatment should be initiated immediately after specimen collection.
- Monitoring of neurodevelopment and hearing is essential at discharge.

VIII.3. OTHER BACTERIAL OR FUNGAL INFECTIONS

VIII.3.1. DEFINITION

"Other bacterial or fungal infections" in the newborn include a heterogeneous group of infectious conditions distinct from neonatal sepsis or meningitis, but which can have a significant impact on morbidity and mortality in the first weeks of life.

These include:

- skin and soft tissue infections (impetigo, cellulitis, abscess, omphalitis);
- neonatal urinary tract infections;
- gastrointestinal infections (infectious necrotizing enterocolitis);
- eye infections (gonococcal ophthalmia, Chlamydia conjunctivitis);
- bone and joint infections;
- systemic fungal infections (invasive candidiasis, aspergillosis).

VIII.3.2. EPIDEMIOLOGY AND INCIDENCE

Localized bacterial infections occur in 2–5% of newborns, and invasive fungal infections in 5–10% of preterm infants weighing <1000 g.

- In neonatal intensive care units (NICUs), Candida spp. is the third leading cause of late-onset sepsis.
- Staphylococcus aureus, Streptococcus agalactiae (group B), Enterobacteriaceae, and Pseudomonas aeruginosa are the main bacterial agents involved.
- The risk increases significantly in the presence of vascular catheters, mechanical ventilation, prolonged antibiotic therapy, and parenteral nutrition.

VIII.3.3. PATHOPHYSIOLOGY

Localized neonatal infections occur through:

- skin and mucosal colonization of the newborn immediately after birth;
- vertical transmission (from the mother, through the birth canal);
- horizontal transmission (nosocomial, via medical equipment or staff hands)

In preterm infants with immature immunity, the skin and mucosal barrier is fragile, and the inflammatory response is weak. In fungal infections, intestinal colonization with Candida can progress to systemic invasion, especially in the context of a microbiota altered by antibiotics.

VIII.3.4. RISK FACTORS

- Prematurity (<32 weeks) and low birth weight (<1500 g);
- Central venous catheters;
- Mechanical ventilation;
- Total parenteral nutrition (lipids and glucose—ideal culture media for fungi);
- Broad-spectrum antibiotic therapy (carbapenems, cephalosporins);
- Congenital or transient immunodeficiencies;
- Poor skin and umbilical hygiene.

VIII.3.5. CLINICAL MANIFESTATIONS

Symptoms vary depending on the location:

1. **Cutaneous and mucosal infections**

- Neonatal impetigo: fragile vesicles that rupture easily, leaving yellowish-honey-colored crusts (S. aureus, Streptococcus pyogenes).
- Disseminated staphylococcal pustulosis: multiple lesions on the trunk and limbs.
- Omphalitis: redness, swelling, and purulent discharge at the umbilical stump, with a risk of sepsis.

2. **Urinary tract infections**

- Fever, lethargy, feeding difficulties, prolonged jaundice;
- May be the first signs of a urinary tract malformation;
- Common pathogens: E. coli, Klebsiella, Proteus.

3. **Gastrointestinal infections**

- Abdominal distension, bilious vomiting, blood in the stool;
- May precede necrotizing enterocolitis (NEC).

4. **Eye infections**

- Gonococcal ophthalmia: severe purulent conjunctivitis within the first 48 hours;
- Chlamydia trachomatis conjunctivitis: onset between days 5–14, mucopurulent discharge.

5. **Bone and joint infections**

- Limited movement of a limb, localized erythema, tenderness on palpation;
- Pathogens: S. aureus, Kingella kingae, Streptococcus agalactiae.

6. Systemic fungal infections

- Invasive candidiasis: persistent fever, apnea, papulomacular rash, abdominal distension, hepatosplenomegaly;
- May involve the central nervous system, liver, and kidneys.
- Aspergillosis: rare but severe in immunocompromised patients.

VIII.3.6. LABORATORY DIAGNOSIS

- Blood culture (for bacteria and fungi) – gold standard test;
- Local exudates (umbilicus, skin, urine, ocular secretions);
- Urine culture (for urinary tract infections, with proper collection via catheterization);
- Complete blood count: leukocytosis or leukopenia, thrombocytopenia;
- CRP, procalcitonin – markers of inflammation;
- PCR and fungal cultures (Candida albicans, parapsilosis, tropicalis);
- Abdominal and brain ultrasound – for fungal dissemination.

VIII.3.7. DIFFERENTIAL DIAGNOSIS

- Sterile inflammatory reactions (e.g., diaper rash);
- Seborrheic or atopic dermatitis;
- Viral infections (HSV, enterovirus);
- False-negative blood cultures following empirical antibiotic therapy.

VIII.3.8. MANAGEMENT

A. General principles

- Rapid identification of the source of infection;
- Removal of any non-essential invasive devices;
- Correction of metabolic disorders;
- Maintaining body temperature and fluid and electrolyte balance.

B. Antibiotic treatment

- Minor skin infections: topical mupirocin, antiseptics (chlorhexidine);
- Omphalitis: oxacillin or cefazolin ± gentamicin (10–14 days);
- Urinary tract infections: ampicillin + gentamicin or cefotaxime (10–14 days);
- Gonococcal ophthalmia: ceftriaxone 25–50 mg/kg/day IV (3–5 days);
- Chlamydia: oral erythromycin 50 mg/kg/day (14 days);
- Osteomyelitis/Arthritis: oxacillin or cefazolin (3–4 weeks), adjusted based on antibiotic susceptibility testing.

C. Antifungal treatment

- Invasive candidiasis: amphotericin B (1 mg/kg/day) or fluconazole (6–12 mg/kg/day);
- Duration: at least 14 days after cultures turn negative;
- In disseminated forms: voriconazole or echinocandins (caspofungin) in resistant cases.

D. Adjuvant measures

- Close monitoring (blood glucose, renal and hepatic function);
- Transfusions if anemia or thrombocytopenia is present;
- In cases of severe fungal sepsis, consider removing central catheters.

E. Prevention

- Strict hand hygiene and sterilization of medical equipment;
- Avoidance of unnecessary antibiotic therapy;
- Antifungal prophylaxis in preterm infants <1000 g (fluconazole 3–6 mg/kg every 72 hours);
- Proper care of the umbilical stump with mild antiseptics;
- Maternal screening for infections (gonorrhea, chlamydia, group B streptococcus).

VIII.3.9. PROGNOSIS

The prognosis is generally good for localized infections, but systemic forms, particularly fungal ones, can be severe. Disseminated candidiasis has a mortality rate of 20–30%, and neurological sequelae may occur in cases of fungal meningitis. Complete recovery is possible with early diagnosis and appropriate treatment.

11. Conclusions. Key Points

- Localized bacterial and fungal infections are common in hospitalized preterm infants and newborns;
- The most common include omphalitis, skin, urinary tract, ocular, and fungal infections;
- Diagnosis is based on cultures and careful clinical evaluation;
- Treatment is etiologically specific, tailored to the antibiogram;
- Prevention through hygiene and antibiotic stewardship is essential.

VIII.4. CONGENITAL SYPHILIS

VIII.4.1. DEFINITION

Congenital syphilis is an infection caused by Treponema pallidum transmitted from the mother to the fetus through the placenta during pregnancy, or more rarely during childbirth. Vertical transmission can occur at any stage of the maternal disease, but the risk is highest in the primary and secondary stages.

VIII.4.2. EPIDEMIOLOGY AND INCIDENCE

Congenital syphilis remains a major cause of neonatal morbidity and mortality, although it is entirely preventable. The global incidence is estimated at approximately 500 cases per 100,000 live births, with significant regional variations.

The risk of fetal transmission is:

- 60–80% in primary and secondary syphilis;
- 40% in early latent syphilis;
- <10% in late latent syphilis.

Untreated maternal infection can lead to: spontaneous abortion, intrauterine death, preterm birth, or a newborn with early congenital syphilis

VIII.4.3. PATHOPHYSIOLOGY

Treponema pallidum crosses the placenta starting in the 14th week of gestation, but severe fetal involvement usually occurs after the 20th week. The fetal body reacts with chronic inflammation and tissue destruction, leading to involvement of multiple organs: liver, spleen, bones, central nervous system, kidneys, and skin.

Important note: Maternal treatment with penicillin before the 20th week of pregnancy prevents congenital infection in most cases.

VIII.4.4. RISK FACTORS

- Untreated or inadequately treated maternal infection;
- Lack of serological screening during pregnancy;
- Reinfection during pregnancy;
- Coinfection with HIV;
- Poor socioeconomic status and limited access to medical care.

VIII.4.5. CLINICAL MANIFESTATIONS

Congenital syphilis is divided into two clinical forms:

A. Early congenital syphilis: occurs from birth up to 2 years of age.

Common manifestations:

- Hepatosplenomegaly;
- Cholestatic jaundice;
- Serous-bloody rhinorrhea ("snuffles");
- Maculopapular rash on the palms and soles;
- Bullous skin lesions, syphilitic pemphigus;
- Generalized lymphadenopathy;
- Anemia, thrombocytopenia;
- Osteochondritis and periostitis (Parrot's pseudoparalysis);
- Meningitis, hydrocephalus, or seizures.

B. Late congenital syphilis: occurs after the age of 2 years, as a result of untreated chronic infection.

Hutchinson's classic triad:

- Abnormal dentition (barrel-shaped teeth – "Hutchinson teeth");
- Sensorineural hearing loss;
- Interstitial keratitis.

Other manifestations:

- Bone deformities (sword-shaped tibias, saddle nose);
- Perioral scars (radiating fissures, "rhagades");
- Ocular lesions (optic nerve atrophy);
- Mental retardation or behavioral disorders.

Important clinical note: the absence of signs at birth does not rule out congenital syphilis—symptoms may appear after several weeks.

VIII.4.6. DIAGNOSIS

Diagnosis is based on a combination of clinical, serological, and, when possible, microbiological data.

1. Maternal serological tests

- Nontreponemal: VDRL (Venereal Disease Research Laboratory), RPR (Rapid Plasma Reagin);
- Treponemal: FTA-ABS (Fluorescent Treponemal Antibody Absorption), TPHA (Treponema Pallidum Hemagglutination Assay).

Screening is performed at the first prenatal visit and repeated in the third trimester or at the time of delivery, depending on the epidemiological risk.

2. Neonatal diagnosis

- VDRL or RPR titer in the newborn ≥4 times higher than the maternal titer;
- Positive treponemal tests;
- Direct identification of T. pallidum in lesions or amniotic fluid (dark-field microscopy, PCR);
- Cerebrospinal fluid: pleocytosis, elevated protein levels, positive VDRL;
- Bone radiography: metaphyseal and periosteal changes.

VIII.4.7. DIFFERENTIAL DIAGNOSIS

- Other congenital infections (toxoplasmosis, rubella, CMV, herpes);
- Neonatal hepatitis of other etiologies;
- Bacterial osteomyelitis;
- Congenital hematologic disorders;
- Neonatal lupus.

VIII.4.8. MANAGEMENT

A. Treatment of the mother

- Benzathine penicillin G is the treatment of choice, depending on the stage of the infection;

- Women allergic to penicillin must be desensitized—there is no effective alternative for preventing fetal transmission.

B. Treatment of the newborn

- Crystalline penicillin G: 50,000 IU/kg/dose IV every 12 hours (for the first 7 days) or every 8 hours (after 7 days), for 10–14 days;
- Alternatively, penicillin G procaine 50,000 IU/kg/day IM for 10 days, if there is no CNS involvement.
- Treatment should be initiated immediately after clinical or serological confirmation, without waiting for complete results.

C. Follow-up

- Clinical and serological reevaluation at 1, 3, 6, and 12 months;
- A ≥4-fold decrease in the VDRL titer by 6 months indicates an adequate therapeutic response;
- If the titer remains unchanged or increases, retreatment is recommended;
- Periodic audiological and ophthalmological examination;
- Neurodevelopmental assessment up to 2 years of age.

VIII.4.9. PROGNOSIS

The prognosis is favorable if treatment is administered promptly. Without treatment, perinatal mortality may exceed 40%. Untreated survivors may develop severe neurological, skeletal, ocular, or auditory sequelae.

Important point: Proper treatment of the mother during pregnancy almost completely prevents congenital infection.

VIII.4.10. CONCLUSIONS. KEY POINTS

- Congenital syphilis is preventable through prenatal screening and appropriate treatment of the mother;
- Vertical transmission is possible at all stages of maternal disease;
- Penicillin remains the only effective treatment;
- Post-treatment monitoring is essential to confirm cure;
- Prenatal education and monitoring of pregnant women are key components of prevention.

VIII.5. CONGENITAL TOXOPLASMOSIS

VIII.5.1. DEFINITION

Congenital toxoplasmosis is an infection caused by the protozoan *Toxoplasma gondii*, transmitted from mother to fetus via the placenta during pregnancy. Fetal infection occurs exclusively as a result of primary maternal infection acquired during pregnancy; chronic maternal forms do not pose a risk of transmission.

VIII.5.2. EPIDEMIOLOGY AND INCIDENCE

The incidence ranges from 1 to 10 cases per 10,000 live births, depending on the prevalence of maternal infection and the effectiveness of prenatal screening. Vertical transmission occurs in approximately 30–40% of cases of untreated acute maternal infection, and the risk of fetal involvement depends on the gestational stage:

- Infection in the first trimester → less frequent transmission, but severe lesions;
- Infection in the third trimester → frequent transmission, but milder effects.

VIII.5.3. PATHOPHYSIOLOGY

Toxoplasma gondii is an obligate intracellular parasite with three life stages:

- oocyst (the form shed by cats, the definitive hosts);
- trophozoite (the active, invasive form);

- tissue cyst (the latent form).

Maternal infection occurs through ingestion of oocysts from soil, water, fruit, or undercooked meat. Trophozoites cross the placenta and reach the fetus, causing inflammation and tissue necrosis, particularly in the central nervous system and the retina.

Important note: vertical transmission does not occur if the maternal infection occurred before pregnancy and the woman has protective immunity (positive IgG antibodies).

VII.5.4. RISK FACTORS

- Consumption of undercooked meat (pork, lamb, game);
- Handling raw food without proper hygiene;
- Contact with contaminated soil (gardening without gloves);
- Contact with feces from an infected cat;
- Lack of pre-existing maternal immunity.

VIII.5.5. CLINICAL MANIFESTATIONS

Manifestations depend on the timing of fetal infection and the degree of involvement. Approximately 70–90% of newborns are asymptomatic at birth but may develop late sequelae.

A. Symptomatic forms at birth

The classic *Sabin-Pinkerton* triad:

- Hydrocephalus;
- Intracranial calcifications;
- Chorioretinitis.

Other manifestations: hepatosplenomegaly, jaundice, petechial rash, microcephaly, seizures, anemia, intrauterine growth restriction.

B. Late-onset forms

- Appear in the following months or years;
- Recurrent chorioretinitis, visual disturbances, psychomotor retardation, epilepsy.

Important clinical finding: the presence of intracranial calcifications and chorioretinitis in a newborn always requires the exclusion of congenital toxoplasmosis.

VIII.5.6. DIAGNOSIS

Diagnosis is based on serological testing and demonstration of active infection in the mother and/or child.

- Maternal diagnosis

Serology:

- Positive IgM → recent infection (within the last 6 months);
- IgG positive → previous infection (immunity);
- IgG negative + IgM negative → susceptibility;
- The IgG avidity test helps distinguish between recent infection (<12 weeks) and past infection.
- Amniotic fluid PCR test (after week 18) to detect Toxoplasma gondii DNA.
- Neonatal diagnosis

Serology:

- The presence of specific IgM or IgA antibodies in the newborn confirms congenital infection (IgG antibodies may come from the mother).
- PCR from blood or CSF;
- Imaging studies: transfontanellar ultrasound, brain CT (periventricular calcifications, hydrocephalus);
- Ophthalmological examination: chorioretinitis;
- Complete neurological examination.

VIII.5.7. DIFFERENTIAL DIAGNOSIS

- Other congenital infections (CMV, rubella, herpes, syphilis);
- Congenital metabolic disorders;
- Malformations of the central nervous system;
- Hypoxic-ischemic encephalopathies.

VIII.5.8. MANAGEMENT

A. Treatment of the mother
- The goal is to prevent fetal transmission.
- Spiramycin: 1 g every 8 hours *by mouth*, until delivery – reduces the risk of transplacental transmission;
- If fetal infection is confirmed (positive PCR in amniotic fluid):
- Pyrimethamine + sulfadiazine + folinic acid (avoid during the first trimester).

B. Treatment of the newborn
- Pyrimethamine + sulfadiazine + folinic acid:
- Pyrimethamine 1 mg/kg/day,
- Sulfadiazine 50 mg/kg/dose every 12 hours,
- Folinic acid 10 mg every 3 days.
- Duration of treatment: 12 months.
- Monthly hematologic monitoring (risk of megaloblastic anemia or leukopenia).

C. Follow-up
- Periodic ophthalmological and neurological examinations (at least every 3–6 months);
- Serological monitoring until specific antibodies (IgM/IgA) become negative;
- Repeated brain ultrasounds to monitor the progression of hydrocephalus.

VIII.5.9. PROGNOSIS

- The prognosis depends on the timing of fetal infection and the promptness of treatment.
- First-trimester infections cause severe lesions but are less likely to be transmitted;
- Early maternal treatment and postnatal therapy significantly reduce the risk of sequelae.
- Without treatment, approximately 85% of symptomatic cases develop permanent visual or neurological impairment.

VIII.5.10. CONCLUSIONS. KEY POINTS

- Congenital toxoplasmosis results exclusively from primary maternal infection during pregnancy.
- The classic triad: hydrocephalus, intracranial calcifications, and chorioretinitis.
- Spiramycin prevents transplacental transmission, and the pyrimethamine-sulfadiazine combination treats confirmed infection.
- Neurological and ophthalmological monitoring is essential.
- Nutrition education and hygiene remain the primary preventive measures.

VIII.6. CYTOMEGALOVIRUS INFECTION

VIII.6.1. DEFINITION

Congenital cytomegalovirus (CMV) infection is caused by transplacental transmission of the virus from mother to fetus during pregnancy. CMV belongs to the Herpesviridae family and is the most common congenital viral infection worldwide.

Two forms are distinguished:

- Congenital infection: transmitted intrauterinely, through the placenta;
- Perinatal/postnatal infection: acquired during birth (through cervical-vaginal secretions) or later (through breast milk or transfusions).

VIII.6.2. EPIDEMIOLOGY AND INCIDENCE

- Congenital CMV infection affects approximately 0.5–2% of newborns, representing the leading infectious cause of sensorineural hearing loss.
- Of the infected newborns, ~10–15% are symptomatic at birth;
- Of those who are asymptomatic, 10–15% may develop late neurological or hearing sequelae.
- The rate of fetal transmission depends on the type of maternal infection:
- Primary infection during pregnancy → 30–40% risk of transmission;
- Reinfection or reactivation of a previous infection → 1–2% risk of transmission.

VIII.6.3. PATHOPHYSIOLOGY

Cytomegalovirus infects endothelial, epithelial, and hematopoietic cells, causing inflammation, necrosis, and tissue calcifications. Vertical transmission occurs transplacentally, with the virus crossing the trophoblastic barrier.
In the fetus, CMV causes:

- brain damage (microcephaly, periventricular calcifications);
- liver and spleen damage (hepatosplenomegaly, jaundice);
- impaired organogenesis and neuronal development disorders.

Important note: the risk of severe fetal damage is higher when the primary infection occurs during the first trimester of pregnancy.

VIII.6.4. RISK FACTORS

- Primary maternal infection during pregnancy;
- Maternal immunosuppression;
- Frequent contact with young children (salivary or urinary transmission);
- Reinfection with a different CMV strain;
- Transfusions with blood not tested for CMV.

VIII.6.5. CLINICAL MANIFESTATIONS

A. Symptomatic congenital infection occurs in 10–15% of newborns infected in utero.
Typical manifestations:

- Jaundice, hepatosplenomegaly;
- Microcephaly;
- Periventricular calcifications;
- Petechiae, purpura (“blueberry muffin rash”);
- Thrombocytopenia, anemia;
- Sensorineural hearing loss;
- Chorioretinitis;
- Intrauterine growth restriction;
- Seizures, hypotonia, lethargy.

The characteristic triad of congenital CMV:

- Microcephaly;
- Periventricular calcifications;
- Chorioretinitis.

B. Asymptomatic congenital infection

Most newborns appear clinically normal at birth but may subsequently develop hearing loss, psychomotor delay, or learning disabilities.

VIII.6.6. DIAGNOSIS

A. Maternal diagnosis

- CMV serology (IgM and IgG):
- IgM positive → recent infection;

- Positive IgG + low-avidity test → acute infection;
- Positive IgG with high avidity → past infection, no risk of transmission.
- PCR test from maternal blood or urine.
- Amniocentesis (after week 20) with CMV DNA detection by PCR → confirms fetal infection.

B. Neonatal diagnosis

- PCR for CMV DNA in urine, saliva, or blood (within the first 21 days of life);
- Serology: CMV-specific IgM;
- Complete blood count: anemia, thrombocytopenia;
- Elevated transaminases;
- Neuroimaging: transfontanellar ultrasound / CT – periventricular calcifications, ventriculomegaly;
- Ophthalmological examination – chorioretinitis;
- Audiological test – hearing loss.

Important note: the diagnosis of congenital infection is established only if the virus is detected within the first 21 days of life. After this period, it is considered a perinatal infection.

VIII.6.7. DIFFERENTIAL DIAGNOSIS

- Other congenital infections (toxoplasmosis, rubella, herpes, syphilis);
- Hypoxic-ischemic encephalopathy;
- Metabolic disorders (glutaric aciduria, propionic acidemia).

VIII.6.8. MANAGEMENT

A. Treatment of the mother

There is no standard antiviral therapy recommended during pregnancy. Treatment with antivirals (e.g., valganciclovir) is reserved for clinical trials and selected cases. Prenatal counseling and careful fetal ultrasound monitoring are recommended

B. Treatment of the newborn

- Indication: symptomatic newborns with CNS or auditory involvement.
- Drug of choice: ganciclovir 6 mg/kg/dose IV every 12 hours or oral valganciclovir 16 mg/kg/dose every 12 hours.
- Duration of treatment: 6 months (may be extended to 12 months in severe cases).
- Monitoring: weekly blood count—risk of neutropenia and thrombocytopenia.
- In cases without CNS involvement, antiviral treatment is not mandatory.

C. Follow-up

- Periodic neurological, ophthalmological, and audiological evaluation (at 1, 3, 6, 12 months, and annually until age 6);
- Monitoring of psychomotor and language development;
- Repeated hearing evaluation, even in children who are asymptomatic at birth.

VIII.6.9. PROGNOSIS

- The prognosis depends on the severity of the congenital infection.
- Symptomatic newborns have a 5–10% risk of mortality and a 40–60% risk of permanent neurological sequelae (hearing loss, microcephaly, psychomotor retardation).
- Asymptomatic infants have a good prognosis but require long-term auditory and neurodevelopmental follow-up.

Key point: sensorineural hearing loss can develop gradually, even in children who appear healthy at birth.

VIII.6.10. CONCLUSIONS. KEY POINTS

- CMV is the most common congenital viral infection.
- The diagnosis is established only if the virus is identified within the first 21 days of life.

- Characteristic triad: microcephaly, periventricular calcifications, chorioretinitis.
- Antiviral treatment (ganciclovir/valganciclovir) is indicated in symptomatic cases.
- Long-term auditory and neurological follow-up is essential.

VIII.7. TUBERCULOSIS

VIII.7.1. DEFINITION

Neonatal tuberculosis is a rare form of *Mycobacterium tuberculosis* infection that occurs in newborns, transmitted from the mother during the intrauterine, perinatal, or postnatal period. Congenital transmission occurs through intrauterine infection of the fetus, while postnatal transmission occurs through inhalation of bacilli from the family or hospital environment.

VIII.7.2. EPIDEMIOLOGY AND INCIDENCE

Neonatal tuberculosis is rare but has a high mortality rate (up to 40%) if not diagnosed and treated early. Incidence is closely linked to the prevalence of tuberculosis among women of childbearing age, particularly in endemic regions (Asia, Africa, Latin America).
Modes of transmission:

- transplacental (via infected umbilical cord blood);
- through ingestion of contaminated amniotic fluid (lung or digestive tract lesions);
- during labor (aspiration of infected secretions);
- postnatal (exposure to a person with active tuberculosis, most commonly the mother).

VIII.7.3. PATHOPHYSIOLOGY

Mycobacterium tuberculosis enters the fetal body via the placental circulation or through inhalation/ingestion of contaminated amniotic fluid. Primary granulomatous lesions form in the liver, lungs, or lymph nodes. In cases of intrauterine transmission, a primary liver lesion may be identified, accompanied by dissemination to the lungs, meninges, and other organs.
Important note: if the source of infection is maternal, the child should always be evaluated for congenital tuberculosis, even in the absence of symptoms.

VIII.7.4. RISK FACTORS

- Mother with untreated or late-diagnosed active tuberculosis;
- Maternal immunosuppression (HIV-positive);
- Premature birth;
- Lack of appropriate tuberculosis prophylaxis or treatment during pregnancy;
- Postnatal exposure to individuals with active pulmonary tuberculosis.

VIII.7.5. CLINICAL MANIFESTATIONS

Symptoms usually appear within the first 2–4 weeks of life. The clinical presentation is nonspecific and may mimic neonatal sepsis.
Common manifestations:

- Persistent fever, lethargy, lack of suckling reflex;
- Hepatosplenomegaly;
- Cough, respiratory distress, tachypnea;
- Generalized lymphadenopathy;
- Abdominal distension, vomiting, diarrhea;
- Cholestatic jaundice;
- Miliary skin lesions (rare).

In severe cases: tuberculous meningitis, disseminated pneumonia, respiratory failure.
Key point: neonatal tuberculosis should be suspected in any newborn with unexplained sepsis and a mother with a history of active tuberculosis.

VIII.7.6. DIAGNOSIS

Diagnosis is difficult and relies on a combination of clinical, imaging, and microbiological data.
Diagnostic criteria for congenital tuberculosis (Beitzke/Cantwell)
The presence of one of the following:

- Tuberculous lesion demonstrated in the first days of life;
- Hepatic or pulmonary granuloma with histological confirmation;
- Exclusion of postnatal exposure;
- Mother with confirmed genital or placental tuberculosis.

Laboratory tests

- Chest X-ray: miliary infiltrates, hilar lymphadenopathy;
- Tuberculin skin test (PPD): often negative in the first few weeks;
- PCR for M. tuberculosis in gastric aspirate, CSF, blood, urine, or pleural fluid;
- Culture for Mycobacterium tuberculosis (gold standard, but slow);
- Liver or lung biopsy – caseous granulomatous lesions;
- Blood culture and complete blood count – often nonspecific.

Differential diagnosis

- Bacterial or fungal sepsis;
- Congenital pneumonia;
- Toxoplasmosis, syphilis, CMV;
- Hemophagocytic disease;
- Rare congenital neoplasms.

VIII.7.7. MANAGEMENT

Treatment should be initiated immediately upon clinical suspicion, without waiting for complete microbiological confirmation.

A. First-line treatment (intensive phase)

- Isoniazid (H): 10 mg/kg/day;
- Rifampicin (R): 15 mg/kg/day;
- Pyrazinamide (Z): 30–35 mg/kg/day;
- Ethambutol (E): 20 mg/kg/day (optional, in severe cases).
- Duration of the intensive phase: 2 months.
- Maintenance phase
- Isoniazid + Rifampicin for an additional 4–10 months, depending on severity and location.
- In tuberculous meningitis: treatment is extended to 12 months and adjunctive corticosteroid therapy is added (prednisone 1–2 mg/kg/day, 4–6 weeks).

B. Treatment of the mother and prophylaxis for the newborn

- Mothers with active tuberculosis: complete treatment according to WHO guidelines;
- Exposed newborns without signs of disease: prophylactic isoniazid for 6 months + BCG vaccination postponed until completion of prophylaxis.

Important note: breastfeeding is not contraindicated if the mother has no active breast lesions and is following appropriate antituberculosis therapy.

C. Follow-up

- Monthly clinical monitoring during the first 6 months;
- Chest X-ray at 2, 6, and 12 months;
- Hepatic and ophthalmological evaluation (drug side effects);
- Monitoring of growth and neuropsychomotor development;
- Microbiological monitoring until cure is confirmed.

VIII.7.8. PROGNOSIS

- The prognosis depends on the timing of diagnosis and the initiation of treatment.
- Early diagnosis and complete treatment result in cure in over 90% of cases;
- Delayed diagnosis or disseminated forms can be fatal;
- Neurological sequelae occur particularly in tuberculous meningitis.

VIII.7.9. CONCLUSIONS. KEY POINTS

- Neonatal tuberculosis is a rare but severe and potentially fatal condition.
- It should be suspected in any newborn with prolonged sepsis and a mother with tuberculosis.
- Diagnosis is based on PCR and cultures for M. tuberculosis;
- Combination therapy with 3–4 antituberculosis drugs should be initiated immediately;
- Isoniazid prophylaxis prevents active disease in exposed newborns.

VIII.8. LYME DISEASE

VIII.8.1. DEFINITION

Lyme disease (borreliosis) is a zoonosis caused by Borrelia burgdorferi sensu lato, transmitted through the bite of an infected tick (Ixodes ricinus). The congenital form involves transplacental transmission of the infection from mother to fetus during pregnancy. Although rare, congenital borreliosis can lead to spontaneous abortion, intrauterine death, premature birth, or neonatal infection with neurological, cardiac, or cutaneous involvement.

VIII.8.2. EPIDEMIOLOGY AND INCIDENCE

Lyme disease is the most common vector-borne disease in the Northern Hemisphere. The incidence of maternal infection varies depending on the endemic region: Central Europe, North America, and Northeast Asia. Vertical transmission is rare but has been documented through the isolation of Borrelia burgdorferi from the placenta, amniotic fluid, and fetal tissue.
Without treatment, maternal infection during pregnancy is associated with:

- spontaneous abortion (≈15–20%);
- intrauterine fetal death;
- preterm birth;
- congenital neonatal infection (≈2–5% of untreated maternal cases).

VIII.8.3. PATHOPHYSIOLOGY

Following the bite of an infected tick, Borrelia burgdorferi multiplies locally and spreads via the bloodstream. In pregnant women, the spirochete can cross the placenta and infect the fetus.
Fetal infection leads to:

- placental inflammation and uteroplacental insufficiency;
- lesions of fetal organs (heart, liver, brain);
- systemic inflammatory response.

Important note: prompt treatment of the maternal infection (with pregnancy-safe antibiotics) prevents vertical transmission.

VIII.8.4. RISK FACTORS

Residence or activities in endemic areas (forests, tall grass, rural areas);
Occupational exposure (foresters, farmers, veterinarians);
Untreated or late-treated maternal infection;
Lack of regular prenatal care;
Pregnancy during the tick season (April–October).

VIII.8.5. CLINICAL MANIFESTATIONS

The clinical presentation of congenital borreliosis varies depending on the timing of maternal infection.

A. In the newborn

- Premature birth or low birth weight;
- Rash resembling erythema migrans (rare);
- Hepatosplenomegaly;
- Cholestatic jaundice;
- Anemia, thrombocytopenia;
- Hypotonia, lethargy;
- Cardiac lesions (congenital atrioventricular block, myocarditis);
- Aseptic meningitis or encephalitis;
- Hydrocephalus, cerebral calcifications.

B. Late-onset forms (appearing after several months)

- Delayed psychomotor development;
- Hearing or vision problems;
- Recurrent episodes of fever;
- Chronic skin or joint lesions (arthritis).

Important clinical note: symptoms may be subtle and nonspecific—diagnosis requires careful correlation between the maternal history and neonatal signs.

VIII.8.6. DIAGNOSIS

The diagnosis of congenital borreliosis requires documentation of maternal infection and confirmation of fetal or neonatal infection.

A. Maternal diagnosis

- History of a tick bite or erythema migrans;
- Positive serology (ELISA, confirmed by Western blot);
- PCR for Borrelia DNA in blood or amniotic fluid;
- Fetal ultrasound evaluation – may show signs of hydrops or growth restriction.

B. Neonatal diagnosis

- Serology: Borrelia-specific IgM antibodies (do not cross the placental barrier, thus confirming congenital infection);
- PCR in blood or CSF;
- CSF: lymphocytic pleocytosis, elevated protein levels;
- Transfontanellar ultrasound – hydrocephalus or brain lesions;
- ECG and echocardiography – atrioventricular conduction disturbances.

Important note: a positive maternal serological diagnosis does not automatically confirm fetal infection—it is necessary to demonstrate IgM antibodies in the newborn or detect bacterial DNA.

VIII.8.7. DIFFERENTIAL DIAGNOSIS

- Other congenital infections (toxoplasmosis, CMV, rubella, syphilis);
- Hypoxic-ischemic encephalopathies;
- Metabolic disorders;
- Bacterial or viral meningitis.

VIII.8.8. MANAGEMENT

A. Treatment of the mother

- The antibiotic of choice during pregnancy: amoxicillin 500 mg every 8 hours orally, for 14–21 days;
- Alternatively: cefuroxime axetil 500 mg every 12 hours;

- Doxycycline is contraindicated during pregnancy (risk of fetal dental and bone damage).
- Early treatment prevents vertical transmission and fetal complications.

B. Treatment of the newborn

- Crystalline penicillin G: 50,000 IU/kg/dose IV every 12 hours (for the first 7 days) or every 8 hours (after 7 days), for 14 days;
- Alternatively: Ceftriaxone 50–75 mg/kg/day IV for 14–21 days;
- In neurological forms: extend treatment to 21–28 days.
- Avoid doxycycline in the first years of life.

C. Adjuvant measures and follow-up

- Periodic neurological, cardiological, and ophthalmological evaluations;
- Serological monitoring at 3, 6, and 12 months;
- Monitoring of psychomotor development;
- Symptomatic treatment (antiepileptic drugs, diuretics, if indicated).

VIII.8.9. PROGNOSIS

- The prognosis is generally favorable if the maternal infection is treated appropriately and early.
- Without treatment, the following may occur: spontaneous abortion, fetal death, or neurological or cardiac sequelae.
- Neonatal infection treated early has a good outcome, without sequelae.

VIII.8.10. CONCLUSIONS. KEY POINTS

- Lyme disease is a tick-borne infection, rarely transmitted vertically.
- Congenital diagnosis is based on IgM antibodies in the newborn or a positive PCR test.
- Early treatment of maternal infection prevents fetal involvement.
- Penicillin G and ceftriaxone are the drugs of choice for the newborn.
- Prevention consists of avoiding tick bites and prompt treatment of maternal infection.

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IX. NEONATAL SURGICAL EMERGENCIES

IX.1. DEFINITION

Neonatal surgical emergencies are acute conditions, whether congenital or acquired, that threaten the newborn's life and require rapid evaluation and surgical intervention. They constitute a critical component of neonatal practice, as early diagnosis and proper stabilization can mean the difference between survival and death, or between full recovery and severe sequelae. Essentially, any newborn with bilious vomiting, a distended abdomen, unexplained respiratory distress, or an inability to feed should be considered, until proven otherwise, a potential surgical case.

IX.2. EPIDEMIOLOGY AND INCIDENCE

Surgical emergencies occur in approximately 1–2% of newborns, but the frequency is significantly higher in preterm infants and those with congenital malformations. The most common are digestive obstructions (duodenal atresia, jejunoileal atresia, intestinal malrotation with volvulus), abdominal wall malformations (gastroschisis, omphalocele), and congenital respiratory emergencies, such as diaphragmatic hernia. Necrotizing enterocolitis, which can also occur in apparently healthy newborns, is currently considered the most common acquired surgical emergency in the neonatal period. Furthermore, a significant number of emergencies present as nonspecific syndromes: neonatal sepsis, respiratory distress, or feeding intolerance. Therefore, clinical suspicion must always be at the forefront of the neonatologist's mind.

IX.3. PATHOPHYSIOLOGY AND ETIOLOGY

Most neonatal surgical emergencies stem from a congenital malformation that arises during the first weeks of embryonic development, when the digestive tract, diaphragm, and abdominal wall form. Failure of the primitive structures to canalize or separate leads to atresias, fistulas, or intestinal malformations. Other emergencies, such as necrotizing enterocolitis, occur later through acquired mechanisms—intestinal ischemia, infection, or abnormal bacterial colonization. In turn, thoracic emergencies (diaphragmatic hernia, pneumothorax) cause acute respiratory failure, while abdominal wall pathologies expose the viscera to heat loss, evaporation, and infection. Thus, underlying each case is a fundamental disruption of the neonatal physiological balance—whether of structural or functional origin.

IX.4. RISK FACTORS

Certain conditions increase the likelihood of a surgical emergency: prematurity, low birth weight, a family history of malformations, intrauterine infections (rubella, CMV, toxoplasmosis), or exposure to teratogenic substances during pregnancy. Polyhydramnios, frequently observed on ultrasound, is a prenatal warning sign for upper gastrointestinal obstructions, while oligohydramnios may suggest associated renal malformations.

IX.5. CLINICAL, LABORATORY, AND IMAGING DIAGNOSIS

The evaluation of a newborn suspected of requiring surgical emergency care is based on careful clinical observation, combined with simple but well-chosen imaging studies. Warning signs include bilious vomiting (an early indicator of distal obstruction), progressive abdominal distension, absence of meconium passage, early respiratory distress, inability to perform gastric intubation, or herniation of viscera through the abdominal wall. In other situations, the signs may be insidious: feeding difficulties, digestive intolerance, pallor, apnea.

Abdominal radiography remains the first diagnostic step. The classic *"double* bubble" image is suggestive of duodenal atresia, and the presence of multiple air-fluid levels suggests jejunoileal obstruction. Abdominal ultrasound plays an essential role in detecting malrotation, volvulus, necrotizing enterocolitis, and diaphragmatic hernia. Laboratory tests may reveal metabolic acidosis, leukocytosis, elevated CRP, or electrolyte imbalances. Diagnosis is often a team effort—the neonatologist, pediatric surgeon, and radiologist work closely together to rapidly determine the course of action.

IX.6. MANAGEMENT

A. General Principles

Any newborn with suspected surgical pathology must be stabilized prior to surgery. This includes withholding oral feeding (NPO), placing a nasogastric tube for continuous suction, correcting dehydration and electrolyte imbalances, and initiating broad-spectrum antibiotic therapy. Assisted ventilation and temperature control are vital, especially in preterm infants. The goal is to create a stable physiological "zero moment" in which the surgeon can operate under optimal conditions.

B. Management of Major Emergencies

Esophageal atresia with tracheoesophageal fistula presents with frothy saliva, coughing, and cyanosis during the first attempts at feeding. The diagnosis is confirmed by the inability to pass a gastric tube through the fistula. Treatment consists of ligating the fistula and reconstructing the esophagus, ideally within the first 24–48 hours.

Congenital intestinal obstructions (duodenal, jejunoileal, colonic) cause bilious vomiting and abdominal distension. Surgical intervention aims to resect the affected segment and restore intestinal continuity. The prognosis is excellent if there are no associated malformations. Intestinal malrotation with volvulus is an absolute emergency, as intestinal ischemia sets in rapidly. Clinical suspicion (green vomiting, distended abdomen, pain, acidosis) warrants immediate laparotomy. *The Ladd procedure*, which corrects the rotation and releases the obstructive bands, is the standard treatment.

Necrotizing enterocolitis represents the most serious acquired surgical emergency. Initially, treatment is medical—intestinal rest, antibiotic therapy, gastric drainage—but the presence of pneumoperitoneum or signs of intestinal necrosis requires surgical intervention with resection and a temporary stoma.

Congenital diaphragmatic hernia presents immediately after birth with severe respiratory distress. Surgery is not performed immediately; the priority is respiratory stabilization, gentle ventilation, and, in some cases, ECMO support. Once the patient is stabilized, the abdominal organs are reduced into the peritoneal cavity and the diaphragmatic defect is repaired.

Gastroschisis and omphalocele are visible at birth. Exposed intestinal loops must be protected with sterile moist dressings and covered to prevent dehydration and infection. Reduction of the abdominal contents is performed gradually (using a *silo*) or, if possible, during the same procedure. Parenteral nutritional support is mandatory until bowel transit resumes.

Anorectal malformations require immediate identification of the level of obstruction. Temporary colostomy followed by definitive correction via *the PSARP procedure* is the current standard of care. Spontaneous or iatrogenic pneumothorax must be promptly recognized and treated by needle decompression or placement of a pleural drain. Neonatal testicular torsion, although rare, requires emergency surgical exploration to save the contralateral gonad.

C. Postoperative Care

The postoperative period is often critical. The infant requires care in a neonatal intensive care unit, with continuous monitoring of vital signs, maintenance of fluid and electrolyte balance, adequate analgesia, and gradual resumption of enteral feeding. Total parenteral nutrition is frequently indispensable in the first few days, especially after extensive intestinal procedures. Surgical wound care and infection prevention remain essential for a favorable outcome.

IX.8. PROGNOSIS

The prognosis for neonatal surgical emergencies varies depending on the type of condition, the timing of diagnosis, birth weight, and the presence of other malformations. In modern neonatal care centers, the survival rate exceeds 90% for most isolated conditions, but drops to less than 50% in complicated cases involving severe respiratory failure, sepsis, or multiple anomalies. The factor that most influences the outcome is time—every hour lost between the onset of symptoms and proper stabilization can radically alter the prognosis.

IX.9. CONCLUSIONS. KEY POINTS

Key points:

- Neonatal surgical emergencies require close collaboration between the neonatologist, pediatric surgeon, and anesthesiologist.
- Warning signs must be recognized early: bilious vomiting, abdominal distension, and absence of bowel movements.
- Preoperative stabilization is essential for survival.
- Most cases have a favorable prognosis if treated in a timely manner.
- Prenatal education, morphological ultrasounds, and specialized neonatal transport can prevent severe complications.

Self-assessment questions

- What are the clinical signs that rule out a surgical emergency in a newborn?
- Why is preoperative stabilization essential before any intervention?
- What are the differences in clinical presentation between gastroschisis and omphalocele?
- When is necrotizing enterocolitis considered an indication for surgery?
- What role does the multidisciplinary team play in the prognosis of these conditions?

X. VASCULAR AND DERMATOLOGICAL CONDITIONS

X.1. HEMANGIOMAS

X.1.1. DEFINITION

Hemangiomas are benign vascular tumors that arise from the proliferation of endothelial cells, leading to the formation of new capillaries or blood vessels. They are the most common vascular tumors of childhood and may be present at birth or appear in the first weeks of life. They are characterized by a dynamic course:

- a rapid proliferative phase in the first few months,
- followed by a phase of slow regression in the following years.

X.1.2. EPIDEMIOLOGY. INCIDENCE

The incidence of hemangiomas is approximately 5–10% of full-term newborns.

- They are three times more common in girls than in boys.
- Premature infants and newborns with low birth weight (<1500 g) are at increased risk (up to 25%).
- In over 80% of cases, hemangiomas are isolated, and the rest are part of complex syndromes (*PHACE, LUMBAR, Kasabach-Merritt*).

Classification:

The modern classification (ISSVA – International Society for the Study of Vascular Anomalies, 2023) divides vascular lesions into:

1. Vascular tumors – characterized by active endothelial proliferation (e.g., infantile hemangioma, congenital hemangioma).
2. Vascular malformations – dysplastic vascular structures without active proliferation (discussed later).

Hemangiomas themselves can be:

- Infantile hemangioma (IH) – appears postnatally, grows rapidly, then slowly regresses.
- Congenital hemangioma (CH): present at birth; may be:
- Rapidly involuting congenital hemangioma (RICH) – completely resolves within 12–18 months;
- Non-involuting congenital hemangioma (NICH) – does not resolve.

X.1.3. PATHOPHYSIOLOGY

The exact mechanisms are not fully understood, but involve:

- Abnormal proliferation of endothelial cells, mediated by angiogenic factors such as VEGF (Vascular Endothelial Growth Factor) and bFGF (basic Fibroblast Growth Factor).
- Placental origin: some endothelial cells in the hemangioma express antigens specific to the placental endothelium (GLUT-1).
- Predisposing factors: perinatal hypoxia, maternal estrogens, prematurity, multiple pregnancies, chorioamnionitis.

1. Proliferative phase

Begins 1–3 weeks after birth and lasts up to 6–12 months. The lesion grows rapidly, becomes raised, bright red in color, with irregular borders.

2. Involution phase

Starting around 1 year of age, the hemangioma fades, flattens, and shrinks in size. By 5–7 years of age, over 90% of hemangiomas have completely regressed, leaving a small area of atrophy or telangiectasia.

Location:

- The most common locations: face, scalp, trunk, and cervical region.
- They may also occur on internal organs: liver, upper respiratory tract, gastrointestinal tract.
- Periorbital, labial, nasal, or auricular locations can cause significant cosmetic and functional complications.

X.1.4. CLINICAL DIAGNOSIS

The diagnosis is usually clinical and visual, based on:

- postnatal onset;
- rapid growth in the first few months;
- intense red color (superficial) or bluish-purple color (deep);
- soft, compressible consistency;
- absence of pulsations and murmur.

X.1.5. LABORATORY AND IMAGING STUDIES

1. **Imaging**

Indicated in atypical cases or when deep involvement is suspected:

- Doppler ultrasound: shows intense blood flow and a lobulated structure;
- MRI: useful for determining the extent of the lesion;
- CT: rarely used, reserved for complex cases.

2. **Additional tests**

In multiple or segmental forms, the following are recommended:

- Liver ultrasound (possible multiple hepatic hemangiomas);
- Cardiological evaluation (for PHACE syndrome);
- Coagulation tests (to rule out Kasabach-Merritt syndrome).

X.1.6. MANAGEMENT

A. General Approach

Most hemangiomas do not require active treatment, but rather periodic clinical monitoring (every 4–6 weeks), as they regress spontaneously.

B. Drug therapy

- Oral propranolol (beta-blocker): is the treatment of choice.
- Dose: 2–3 mg/kg/day in 2–3 divided doses, under cardiac monitoring.
- Effect: reduction of blood flow and endothelial proliferation.
- Topical timolol (gel or solution) – for superficial, small lesions.
- Systemic corticosteroids (prednisone): indicated only if propranolol is contraindicated or ineffective.
- Alpha interferon or vincristine – in refractory cases or Kasabach-Merritt syndrome.

C. Surgical/laser treatment

- Surgical excision: rarely, only for residual, disfiguring hemangiomas.
- Laser therapy (PDL – Pulsed Dye Laser): effective for residual ulcerations and telangiectasias.

X.1.7. PROGNOSIS

The prognosis is excellent in most cases. Over 90% of infantile hemangiomas resolve completely by age 7. Residual scars are rare and can be cosmetically corrected later. The prognosis is guarded only in complicated forms (ulcerated, with ocular or respiratory involvement).

Complications:

- Ulceration (the most common, painful, and prone to infection);
- Local hemorrhage;
- Compression of adjacent structures (eyes, nose, airways);
- Feeding difficulties (oral hemangiomas);

- Significant aesthetic and psychological impact;
- *Kasabach-Merritt syndrome*—rare but serious: thrombocytopenia and coagulopathy.

X.1.8. CONCLUSIONS. KEY POINTS

Key points

- Hemangiomas are the most common benign tumors in childhood.
- They are characterized by a proliferative phase followed by spontaneous regression.
- Diagnosis is clinical; ultrasound is used for deep forms.
- Propranolol is the first-line treatment; most cases do not require intervention.
- The prognosis is very good, with a self-limiting course.

Self-assessment questions

- What are the key differences between infantile and congenital hemangiomas?
- What is the role of propranolol in the treatment of hemangiomas?
- What are the common complications of infantile hemangiomas?
- What imaging methods are used for deep forms?
- How is the appropriate timing for surgical or laser intervention determined?

X.2. VASCULAR TUMORS

X.2.1. DEFINITION

Vascular tumors are abnormal proliferations of endothelial cells, characterized by the formation of tissue masses composed of blood vessels. They differ from vascular malformations in that they exhibit active endothelial proliferation, with a dynamic course—rapid growth, stabilization, followed by partial or complete regression. In the neonatal period, the most important types are:

- infantile hemangioma (discussed earlier),
- congenital hemangioma,
- kaposiform hemangioendothelioma,
- angiosarcoma (rare, malignant).

X.2.2. EPIDEMIOLOGY. INCIDENCE

Vascular tumors account for approximately 4–10% of all neonatal tumors.

- Infantile hemangioma is by far the most common, followed by Kaposi-like hemangioendothelioma (KHE), which is rare but can be life-threatening.
- Most vascular tumors are isolated; more rarely, they occur in the context of syndromic anomalies (PHACE, Kasabach-Merritt, LUMBAR).

Classification (ISSVA, 2023)

According to the updated classification of the International Society for the Study of Vascular Anomalies (ISSVA), vascular tumors are divided into:

1. **Benign vascular tumors**
- Infantile hemangioma
- Congenital hemangioma (RICH / NICH)
- Epithelioid hemangioma
- Pyogenic granuloma

2. **Intermediate vascular tumors (locally aggressive)**
- Kaposiform hemangioendothelioma (KHE)
- Bacillary angiomatosis (extremely rare in newborns)

3. **Malignant vascular tumors**
- Angiosarcoma (very rare in the neonatal period)

X.2.3. PATHOPHYSIOLOGY

The mechanisms involve:

- Abnormal activation of proangiogenic genes (VEGF, PDGF, angiopoietins);
- Hormonal and hypoxic influences on fetal endothelial cells;
- In congenital cases, a disruption of embryonic vascular development during weeks 6–10 of gestation.

In Kaposiform hemangioendothelioma, cell proliferation is uncontrolled, with the formation of dysplastic vascular networks that can consume massive amounts of platelets (Kasabach-Merritt syndrome).

X.2.4. CLINICAL DIAGNOSIS

Based on:

- Age of onset and progression of the lesion;
- Appearance (color, texture, consistency);
- Presence of complications (ulceration, bleeding, pain, signs of coagulopathy).

Types:

1. **Congenital hemangioma (CH)**

Unlike infantile hemangioma, it is fully formed at birth. It can be:

- RICH (Rapidly Involuting Congenital Hemangioma) – completely involutes within 12–18 months;
- NICH (Non-Involuting Congenital Hemangioma) – does not regress; sometimes requires surgical treatment.

Lesions are firm, well-defined, sometimes pulsatile, with a visible superficial venous network.

2. **Kaposiform hemangioendothelioma (KHE)**

A rare but potentially serious vascular tumor that appears during the neonatal period or in the first months of life. It is an aggressive endothelial proliferation, without metastatic potential, but with a high risk of consumption coagulopathy (Kasabach-Merritt syndrome).

Clinical features:

- A purplish, firm, warm-to-the-touch, infiltrative plaque, usually on the trunk, arm, or lower limb;
- May be painful and grow progressively in size;
- May extend deeply, involving muscle or fascia.

Kasabach-Merritt syndrome

- Represents a severe hematologic complication of KHE:
- Marked thrombocytopenia (<50,000/mm³);
- Consumption coagulopathy (low fibrinogen, elevated D-dimer);
- Risk of severe bleeding and multi-organ dysfunction.

It is a neonatal medical emergency requiring complex therapy.

3. **Pyogenic granuloma** (capillary lobular hemangioma)

A benign, rapidly proliferating lesion appearing as a bright red, friable nodule that bleeds easily. It may occur on the oral mucosa, scalp, or trunk, often following minor trauma. Treatment is surgical (complete excision) or laser.

X.2.5. LABORATORY AND IMAGING STUDIES

1. **Imaging**

- Doppler ultrasound: first step – shows intense vascularization, lobular pattern;
- MRI: to assess the extent of tissue involvement;
- Angiography: rarely, for cases requiring embolization.

2. **Laboratory tests**

- Complete blood count, fibrinogen, D-dimer (to screen for Kasabach-Merritt syndrome);

- Liver function and coagulation tests in cases of multiple hemangiomas (suspected liver involvement).

X.2.6. MANAGEMENT

A. General Approach

Treatment depends on the tumor type, size, location, and presence of complications. Some lesions (RICH) require only monitoring, while others (KHE, NICH) require immediate intervention.

B. Medical treatment

- Propranolol – remains the first-line treatment for proliferative hemangiomas and some benign tumors. It reduces blood flow and endothelial proliferation.
- Systemic corticosteroids – useful in the acute phase of Kasabach-Merritt syndrome to reduce vascular inflammation.
- Vincristine / Sirolimus – are second-line therapies, effective in refractory Kaposi-like hemangioendothelioma. Sirolimus (an mTOR inhibitor) yields excellent results, with tumor shrinkage and normalization of platelet counts.
- Transfusions and supportive care – in complicated cases, platelets and cryoprecipitate are administered; adequate oxygenation, maintenance of fluid and electrolyte balance, and intensive monitoring.

C. Surgical and laser treatment

- Surgical excision: indicated for well-defined tumors resistant to drug therapy.
- Laser therapy (PDL, Nd:YAG): effective for superficial lesions and controlling recurrent bleeding.
- Selective embolization: used in cases of extensive KHE with a high risk of hemorrhage.

X.2.7. PROGNOSIS

Depends on the histological type:

- Congenital hemangioma (RICH) has an excellent prognosis, with complete regression.
- NICH persists but remains stable and can be surgically excised with good results.
- KHE has a guarded prognosis without prompt treatment, but the prognosis has improved significantly with the introduction of sirolimus therapy.

Recurrences are rare but possible in cases of incomplete excision.

X.2.8. CONCLUSIONS. KEY POINTS

Key points

- Vascular tumors are distinguished from vascular malformations by active endothelial proliferation.
- Kaposiform hemangioendothelioma is the most severe form, often associated with Kasabach-Merritt syndrome.
- The diagnosis is clinical, supplemented by Doppler ultrasound and coagulation studies.
- Propranolol, corticosteroids, and sirolimus are the mainstays of modern therapy.
- The prognosis is good in most cases if the diagnosis is made early.

Self-assessment questions

- What is the fundamental difference between vascular tumors and vascular malformations?
- What are the clinical features of Kaposiform hemangioendothelioma?
- What is the clinical significance of Kasabach-Merritt syndrome?
- What role does sirolimus play in the treatment of vascular tumors?
- What imaging methods are essential for assessing the extent of a vascular tumor?

X.3. CAPILLARY MALFORMATIONS / CAPILLARY SPOTS

X.3.1. DEFINITION

Capillary malformations are congenital structural anomalies of the dermal capillary network, characterized by permanent dilation of superficial capillaries without endothelial proliferation. Unlike hemangiomas, they do not progress through phases of growth and involution, but persist throughout life and may intensify with age.
The common names vary:

- port-wine stains (nevus flammeus),
- pink macules (salmon spots, stork bite, angel's kiss).

X.3.2. EPIDEMIOLOGY. INCIDENCE

- Capillary malformations occur in 0.3–0.5% of newborns, with no gender predominance.
- Transient forms (pink-salmon spots) are much more common, observed in 30–40% of newborns.
- Most are isolated and benign, but some may be associated with neurocutaneous syndromes (e.g., Sturge-Weber, Klippel-Trénaunay).

Classification:
According to the International Society for the Study of Vascular Anomalies (ISSVA, 2023), capillary malformations are classified as simple vascular malformations and include:

- Nevus flammeus (port-wine stain)
- Transient salmon patches
- Congenital capillary telangiectasias
- Complex capillary malformations associated with other vascular anomalies (Sturge-Weber, Klippel-Trénaunay).

X.3.3. PATHOPHYSIOLOGY

Capillary malformations are caused by incomplete or abnormal development of the dermal capillary plexus during the embryonic period (weeks 6–10 of gestation). There is a persist e dilation of the capillaries and an increase in local blood flow, without active cellular proliferation. In the case of port-wine stains, there is an alteration in local vasomotor innervation, which leads to a loss of capillary tone and its permanent dilation.

X.3.4. CLINICAL DIAGNOSIS

The diagnosis is based on the typical appearance and progression over time. The lesions are flat, non-proliferative, with no changes in temperature or consistency.

1. Salmon patches (nevus simplex)

- These are the most common vascular lesions in newborns;
- They are typically located on the eyelids, glabella (root of the nose), and nape of the neck (stork bite);
- Pale pink or salmon-colored, flat, and become more pronounced when the baby cries;
- Benign and transient, they disappear spontaneously by the age of 1–2 years (except for cervical lesions, which may persist).

2. **Nevus flammeus** (port-wine stain)

- A flat, well-defined, reddish-purple lesion;
- Usually unilateral, located on the face, trunk, or limbs;
- Does not fade when pressed and does not resolve spontaneously;
- Becomes darker in color and slightly raised with age.

3. **Congenital capillary telangiectasias**

- Fine, linear, red vessels, rarer in newborns;
- May be isolated or associated with genetic syndromes (e.g., hereditary hemorrhagic telangiectasia).

Associated syndromes:

1. ***Sturge-Weber syndrome***

- A neurocutaneous malformation characterized by:
- facial port-wine stain (in the territory of the ophthalmic trigeminal nerve);
- leptomeningeal angioma (visible on brain MRI);
- congenital glaucoma;
- seizures and neuropsychological delay.

2. ***Klippel-Trénaunay syndrome***

- Complex malformation with:
- an extensive port-wine stain on a limb;
- local tissue hypertrophy;
- associated venous and lymphatic malformations.

3. ***Parkes-Weber Syndrome***

- Similar to the previous condition, but with arteriovenous fistulas that increase local blood flow and may lead to heart failure.

X.3.5. LABORATORY AND IMAGING STUDIES

Generally, these are not necessary. However, in cases of extensive facial lesions, especially in the trigeminal territory (V1), neurological and ophthalmological evaluation is mandatory to rule out Sturge-Weber syndrome (associated leptomeningeal malformation).

X.3.6. DIFFERENTIAL DIAGNOSIS

- Infantile hemangioma: has a postnatal onset and a proliferative course;
- Transient erythema of the newborn: a fleeting rash without capillary dilation;
- Secondary cutaneous telangiectasias (in neonatal lupus, genetic syndromes).

X.3.7. MANAGEMENT

A. General Approach

Most capillary malformations do not require medical treatment, but only monitoring and parental counseling. Minor lesions are benign, without complications.

B. Laser therapy

The treatment of choice for persistent port-wine stains is the pulsed dye laser (PDL).

- Treatment ideally begins after 6–12 months of age;
- It is most effective for superficial, red lesions;
- Requires 4–6 sessions at intervals of several months;
- Minimal side effects (transient erythema, temporary hyperpigmentation).

C. General care and psychological support

For facial lesions, counseling parents is essential—the focus is on the benign nature of the condition and the availability of effective cosmetic treatments. In older children, psychological support may be necessary in cases of visible stigmatization.

X.3.8. PROGNOSIS

- Salmon-pink spots disappear spontaneously within the first 2 years of life.
- Port-wine stains persist throughout life, but can be significantly faded with laser treatment.
- Association with neurocutaneous syndromes requires multidisciplinary follow-up (neurology, ophthalmology, dermatology, pediatric surgery).

X.3.9. CONCLUSIONS. KEY POINTS

Key points

- Capillary malformations are structural lesions, not proliferative tumors.
- Salmon-pink spots are transient; port-wine stains are permanent.

- Facial localization, especially in the V1 territory, requires exclusion of Sturge-Weber syndrome.
- Laser therapy is the standard treatment for persistent lesions.
- Parent education and counseling are essential components of management.

Self-assessment questions

- What is the key difference between capillary malformations and hemangiomas?
- What is the clinical significance of a port-wine stain on the forehead and eyelid?
- What is the treatment of choice for nevus flammeus?
- What syndromes may be associated with extensive capillary malformations?
- Which vascular lesions resolve spontaneously in the first years of life?

X.4. ANOMALIES OF LYMPHATIC CIRCULATION

X.4.1. DEFINITION

Lymphatic circulation anomalies represent a heterogeneous group of congenital conditions caused by abnormal development of the lymphatic system, with the formation of dilations, cysts, or dysplastic lymphatic networks. These may occur in isolation or in association with other vascular malformations and may involve the skin, subcutaneous tissues, viscera, or deep spaces (mediastinum, retroperitoneum).

The most common forms encountered in the neonatal period are:

- Lymphangiomas (simple, cavernous, cystic);
- Cervical lymphatic cyst (cystic hygroma);
- Congenital lymphedema.

X.4.2. EPIDEMIOLOGY. INCIDENCE

- Estimated incidence: approximately 1 in 4,000 to 1 in 6,000 births;
- It can be detected prenatally (via prenatal ultrasound) or diagnosed postnatally;
- There is no gender predominance;
- Most common locations: cervical, axillary, mediastinal, retroperitoneal, and inguinal regions.

Cystic hygroma is diagnosed prenatally by ultrasound in 70–80% of cases and may be associated with chromosomal abnormalities (Turner syndrome, trisomy 21, trisomy 18, trisomy 13).

Classification:

According to the International Society for the Study of Vascular Anomalies (ISSVA, 2023), lymphatic anomalies are classified as complex vascular malformations and are subdivided into:

- Simple lymphatic malformations – affect only the lymphatic vessels;
- Combined lymphatic malformations – coexist with venous or capillary anomalies (e.g., Klippel-Trénaunay syndrome);
- Primary congenital lymphedema – caused by hypoplasia or aplasia of the lymphatic vessels.

X.4.3. PATHOPHYSIOLOGY

The lymphatic system develops between the 6th and 9th weeks of gestation. Normally, lymphatic vessels form from endothelial buds that fuse with the venous system. Any disruption at this stage can lead to:

- lymphatic hypoplasia – insufficient development of lymphatic channels;
- aplasia – absence of vessels in a given area;
- lymphatic dilation and stasis – the formation of multilocular cysts (lymphangiomas).

At the molecular level, mutations have been described in the PIK3CA, VEGFR3 (FLT4), and CCBE1 genes, which are involved in the regulation of lymphatic endothelial growth.

X.4.4. CLINICAL DIAGNOSIS

The diagnosis is based on the typical appearance: a soft, compressible, translucent mass with no signs of inflammation. In cystic hygroma, the lesion may be visible as early as the neonatal period or detected prenatally.

Main types and clinical features:

1. **Lymphangiomas (cystic lymphatic malformations)**

Benign, soft, compressible tumors consisting of dilated lymphatic networks filled with clear or milky-yellow fluid. They can be superficial or deep, frequently located in the cervical, axillary, mediastinal, or retroperitoneal regions. Lymphangiomas are classified as:

- microcystic – fine, disseminated networks at the skin level;
- macrocystic – cysts >1 cm, well-defined;
- mixed – a combination of the two types.

Clinical manifestations:

- Soft, painless, translucent mass;
- Pinkish-bluish color;
- Grows slowly but progressively;
- May suddenly increase in size in the event of infection or intracystic hemorrhage;
- Sometimes causes compression of vital structures (trachea, esophagus).

2. **Cystic hygroma** (cervical lymphatic cyst)

A specific form of macrocystic lymphangioma, usually located in the posterior triangle of the neck, unilateral or bilateral. It often appears as a soft, fluctuant mass that enlarges during crying or Valsalva maneuvers. In large newborns, it may cause respiratory or feeding difficulties. Possible associations:

- Turner syndrome (45,XO);
- Trisomies 21, 18, 13;
- Noonan, Roberts, Fryns syndromes;
- Non-immune fetal hydrops (when the hygroma is massive).

3. **Congenital lymphedema**

It is an accumulation of lymphatic fluid in the interstitial spaces due to impaired lymphatic drainage. It can be:

- primary (idiopathic, genetic—e.g., Milroy syndrome, Turner syndrome);
- secondary (associated with other malformations or trauma).

Manifestations:

- firm edema that does not spread when pressed, frequently in the legs;
- the skin is thick, sometimes with lymphatic papules;
- bilateral in genetic forms, unilateral in secondary forms.

X.4.5. LABORATORY AND IMAGING STUDIES

- **Doppler ultrasound**

First-line investigation:

- reveals a multilocular cystic structure;
- absence of internal blood flow;
- relationships with neighboring vessels and organs.

- **MRI**

Provides detailed information on extent, relationships, and planes of dissection—essential prior to surgery.

- **Genetic testing and fetal ultrasound**

Indicated in the presence of associated anomalies or when a genetic syndrome is suspected.

X.4.6. MANAGEMENT

A. General Approach

Treatment is tailored to the size and location of the lesion. Small, asymptomatic malformations may be monitored, but large or compressive ones require intervention.

B. Interventional treatment

- Sclerotherapy (first-line treatment in most cases)
    - Under ultrasound guidance, sclerosing agents (OK-432 – Picibanil, bleomycin, doxycycline, ethanol, topical sirolimus) are injected.
    - This causes controlled local inflammation, followed by fibrosis of the cystic walls.
    - 2–4 sessions may be repeated.
    - Success rate: 80–90% in macrocystic forms.
- Surgery

Indications:

- failure of sclerosing therapy;
- severe vital compression;
- suspected malignancy.

Complete excision is ideal but difficult in infiltrative forms due to the risk of damaging nerves and large blood vessels.

C. Adjuvant drug therapy

- Sirolimus (mTOR inhibitor): effective in diffuse, recurrent forms;
- Antibiotics – for secondary infections;
- Systemic corticosteroids – to reduce transient inflammation.

X.4.7. PROGNOSIS

- The prognosis is generally favorable in cases that are treated appropriately.
- Macrocystic malformations respond excellently to sclerotherapy, while microcystic ones may recur.
- Cystic hygroma associated with chromosomal abnormalities has a guarded prognosis.
- Long-term postoperative follow-up is important for preventing recurrence.

Complications:

- Tracheal compression → respiratory distress;
- Infection → fever, local erythema, increased mass volume;
- Intracystic hemorrhage;
- Recurrence after partial drainage;
- Significant aesthetic and functional impairments (in the cervico-facial region).

X.4.8. CONCLUSIONS. KEY POINTS

Key points

- Lymphatic anomalies are structural malformations, not tumors;
- Lymphangiomas and cystic hygromas are the most common neonatal forms;
- Diagnosis is based on ultrasound and MRI;
- The treatment of choice is ultrasound-guided sclerotherapy;
- The main complications are compression, infection, and recurrence.

Self-assessment questions

- What is the difference between a lymphangioma and a cystic hygroma?
- What role does Doppler ultrasound play in the diagnosis of lymphatic malformations?
- What is the first-line treatment for macrocystic lymphangiomas?
- What genetic syndromes may be associated with cystic hygroma?
- What major complications can arise in the course of these lesions?

X.5. PIGMENTARY ABNORMALITIES

X.5.1. DEFINITION

Pigmentary abnormalities represent qualitative or quantitative variations in skin pigmentation, caused by changes in the synthesis, distribution, or number of melanocytes in the epidermis. They can be hyperpigmentation (excess melanin) or hypopigmentation/depigmentation (melanin deficiency) and can be congenital or acquired early in life. In newborns, most pigmentary abnormalities are benign and transient, but some may signal genetic syndromes, metabolic, or neurocutaneous disorders.

X.5.2. EPIDEMIOLOGY. INCIDENCE

- Pigmentary abnormalities are observed in over 50% of newborns.
- The frequency varies depending on skin phototype and ethnic origin.
- Some forms (large congenital nevi, Ito's hypomelanosis) are rare, with an incidence of less than 1 in 10,000 births.

General classification:

1. **Congenital hyperpigmentation**

- Congenital melanocytic nevi
- Café-au-lait spots
- Dermal melanosis (Mongolian spot)
- Lentigines, congenital freckles

2. **Congenital hypopigmentation / depigmentation**

- Albinism
- Piebaldism
- Ito's hypomelanosis
- Depigmented nevus

3. **Transient pigmentation of the newborn**

- Toxic erythema, neonatal melanotic pustulosis, postnatal physiological pigmentation

X.5.3. PATHOPHYSIOLOGY

Skin pigmentation depends on the number of melanocytes and their activity. Melanocytes produce melanin in melanosomes, which are transferred to keratinocytes. Pigmentary abnormalities may occur due to:

- changes in the number of melanocytes (hyperplasia or hypoplasia);
- alterations in their function (reduced or excessive melanin synthesis);
- abnormal distribution of melanosomes in the epidermis;
- genetic skin mosaicism (in Ito's hypomelanosis).

X.5.4. CLINICAL DIAGNOSIS

The diagnosis is based on appearance, location, age of onset, and course. The number, shape, and distribution of the lesions are evaluated.

1. **Congenital hyperpigmentation**

- **Congenital melanocytic nevus**

Definition: A pigmented skin lesion present at birth, consisting of clusters of melanocytes.
Clinical appearance:

- Brown color, varying from beige to black;
- Smooth or slightly raised surface;
- May be covered with hair (hairy nevus).

Classification:

- Small: <1.5 cm;
- medium: 1.5–20 cm;
- large/giant: >20 cm (may cover the trunk or limbs).

Risk: Large congenital nevi carry an increased risk of malignant melanoma (1–10%), especially if there is deep dermal proliferation or leptomeningeal extension. Treatment:

- Periodic clinical and dermatoscopic monitoring;
- Prophylactic surgical excision in large cases or those with atypical changes.

- **Café-au-lait spots**

Definition: Flat, light brown ("café-au-lait") hyperpigmented lesions with well-defined borders.
Significance:

- They may be isolated (without pathological significance);
- ≥6 spots >5 mm in young children raise suspicion of neurofibromatosis type 1 (NF1);
- They may also occur in other genetic syndromes (McCune-Albright, Noonan).

5.3. Congenital dermal melanosis (Mongolian spot)
Appearance:

- A flat, blue-gray lesion, frequently located in the sacral or gluteal region;
- Results from the presence of persistent dermal melanocytes;
- Disappears spontaneously in the first years of life.

Increased frequency in Asian, African, and Latin American newborns. Benign, with no pathological significance.

2. Congenital hypopigmentation

- **Congenital albinism**

Definition: A genetic disorder characterized by the total or partial absence of melanin synthesis.
It can be:

- oculocutaneous (skin + hair + eyes);
- ocular (affecting only the eyes).

Clinical presentation:

- Very fair skin, whitish hair, translucent iris;
- Photophobia, nystagmus, low visual acuity.

Cause: mutations in the TYR, OCA2, TYRP1, and SLC45A2 genes.
Complications: increased risk of sunburn and skin cancer.

- **Piebaldism**

Definition: An autosomal dominant genetic disorder characterized by localized absence of melanocytes.
Appearance:

- Symmetrical depigmented areas, especially on the forehead, chest, and limbs;
- Often accompanied by a white tuft (a frontal strand of white hair);
- Present at birth, stable over time.

Cause: mutations in the KIT gene (stem cell factor receptor).

- **Ito's hypomelanosis**

Definition: A mosaic condition characterized by hypopigmented bands or stripes arranged in a spiral pattern on the trunk and limbs, following Blaschko's lines.
Significance: May be associated with neurological (developmental delay, seizures), skeletal, and ocular abnormalities.
Diagnosis: clinical; genetic confirmation may reveal chromosomal mosaicism.

- **Nevus depigmentos**

A solitary, well-defined hypopigmented lesion present at birth; stable over time. Unlike vitiligo, it does not progress and has no hyperemic margins. Benign, with no systemic significance.

3. **Transient pigmentation in the newborn**

- **Postnatal physiological pigmentation**

Newborns may exhibit subtle pigmentation in the first few days, especially in the genital, areolar, or axillary regions, due to stimulation of melanocytes by maternal hormones.

- **Neonatal melanotic pustulosis**

Superficial pustular lesions at birth, which heal leaving transient hyperpigmented spots. Benign, self-limiting, no specific treatment.

X.5.5. LABORATORY AND IMAGING STUDIES

- **Dermatoscopy**

Useful for differentiating atypical nevi, monitoring progression, or detecting malignant transformation.

- **Additional investigations**
  - Ophthalmological examination in albinism;
  - Genetic testing in syndromic cases;
  - Brain MRI if neurological signs are present (Ito's hypomelanosis).

X.5.6. MANAGEMENT

- Most lesions do not require treatment, only monitoring;
- Sun protection is essential in patients with hypopigmentation (albinism, piebaldism);
- Surgical or laser excision for large pigmented nevi or those with suspicious changes;
- Genetic counseling for hereditary forms;
- Psychological support in visible or stigmatizing cases.

X.5.7. PROGNOSIS

- Benign lesions (Mongolian spot, isolated café-au-lait spots) have a favorable prognosis;
- Albinism and piebaldism persist throughout life;
- Large congenital nevi require long-term dermatologic follow-up;
- Ito's hypomelanosis may have a variable prognosis depending on systemic associations.

X.5.8. CONCLUSIONS. KEY POINTS

Key points

- Pigmentary abnormalities are common, and most are benign;
- Distinguishing between hyperpigmentation and hypopigmentation is essential for diagnosis;
- Large congenital nevi carry a risk of malignancy;
- Multiple café-au-lait spots may indicate neurofibromatosis;
- Ito's hypomelanosis requires neurological and genetic evaluation.

Self-assessment questions

- What is the difference between a small congenital nevus and a giant congenital nevus?
- What is the clinical significance of multiple café-au-lait spots?
- How does piebaldism differ from vitiligo?
- What systemic conditions may be associated with Ito's hypomelanosis?
- What care measures are essential for children with albinism?