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NEONATOLOGY (Differential diagnosis of hemorrhagic disorders and anemia in newborns)

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LIST OF MAIN ABBREVIATIONS

ADP	—	adenosine diphosphate
INH	—	indirect anticoagulants
APS	—	activated protein C
APTT	—	activated partial thromboplastin time (synonym for APTT)
AT	—	antithrombin III
VW	—	von Willebrand disease
HDN	—	hemorrhagic disease of the newborn
DIC	—	disseminated intravascular coagulation
PCC	—	prothrombin complex concentrate
INR	—	international normalized ratio
UFH	—	unfractionated heparin
NR	—	normalized ratio
PAI-1	—	plasminogen activator inhibitor type 1
PAI-2	—	plasminogen activator inhibitor type 2
PT	—	prothrombin time
PGG2	—	prostaglandin G2
PGN2	—	prostaglandin H2
FDP	—	fibrin degradation products
PT	—	prothrombin test
PR	—	prothrombin ratio
PTI	—	prothrombin index
FFP	—	fresh frozen plasma
TPA	—	tissue plasminogen activator
TT	—	thrombin time
PAF	—	platelet activating factor
WF	—	von Willebrand factor
IUGR	—	intrauterine growth restriction
NSG	—	neurosonography
LPI	—	lipoprotein-associated coagulation inhibitor

RASK — regulation of blood aggregate state
SFMC — soluble fibrin monomer complexes
TXA2 — thromboxane A2
FN — fibronectin
BP — blood pressure
BLD — bronchopulmonary dysplasia
IVH — Intraventricular hemorrhage
ZPK — eplacement blood transfusion
CBV — circulating blood volume
CEC — circulating erythrocyte volume
EAR — early anemia of prematurity
rEP — recombinant erythropoietin
CNS — central nervous system
HR — heart rate
ES — erythrocyte suspension
EPO — erythropoietin
RBC — red blood cell count
HGB — hemoglobin level
HCT — hematocrit
MCV — mean corpuscular volume
MCH — mean corpuscular hemoglobin
MCHC — mean corpuscular hemoglobin concentration
RDW — red blood cell distribution width
WBC — white blood cell count

INTRODUCTION

The hemostasis system occupies a special place among the body's physiological systems. First and foremost, it is a connecting link, "uniting" the body into a single whole. Pathological changes in any of the body's systems are always accompanied by hemostasis disorders. The hemostasis system is particularly important in the neonatal period, when it undergoes serious daily changes. Most hemostasis indicators only reach adult values at the age of one year.

Blood clotting disorders play an important role in the pathogenesis of most serious conditions in the neonatal period. They can act as complications of the underlying disease, as well as trigger the development of a number of pathological conditions. The danger of these disorders is often associated with the development of cerebral hemorrhages, which are potentially disabling factors.

Hemostasis disorders should be considered a general pathological pattern of severe conditions in newborns and a factor of increased risk of mortality and disability. Ignorance of these features by practicing physicians leads to misinterpretation of hemostasis indicators in newborns and, accordingly, to incorrect therapy. Knowledge of the physiology and pathology of the hemostasis system in newborns allows practising physicians to more effectively treat a wide variety of pathological conditions that develop during the neonatal period.

HEMOSTASIS SYSTEM

The hemostasis system is a set of functional, morphological and biochemical mechanisms that stop bleeding and at the same time keep the blood in a liquid state, mainly inside the vessels. In the human body, all this is controlled by the RAS system, which regulates the aggregate state of the blood.

This regulation is carried out by complex mechanisms involving involve factors of the coagulation, anticoagulation and fibrinolytic systems of the blood. Disruption of functional interactions can lead to serious pathological conditions in the body, consisting of either increased bleeding or intravascular thrombus formation. Factors that keep blood in a liquid state include:

1) the inactive state of the blood coagulation system factors found
in the vascular bed;

2) high blood flow velocity in newborns;

3) the special properties of the vascular endothelium.

The hemostasis system includes subsystems

1. Coagulation
2. Anticoagulation
3. Fibrinolytic

Types of hemostasis

1. Vascular - contraction of the vessel at the site of injury and shunting of blood above the damaged area
2. Platelet (cellular)
3. Plasma coagulation

Cellular hemostasis refers to the sticking together of blood cells (aggregation), their attachment to the vessel wall or a foreign surface (adhesion), and the release of substances from blood cells that activate plasma hemostasis.

The main functions of platelets are:

- angiotropic;
- adhesive-aggregative;
- release reaction.

The angiotrophic function is associated with the participation of platelets in the trophism of the vascular wall;

The adhesive-aggregation function is the ability of platelets, under the influence of a number of factors (adrenaline, ADP, collagen) that appear in the bloodstream as a result of damage to the vascular wall, to enter a state of adhesion and aggregation, forming a platelet thrombus. In this case, damage to the vascular wall can be not only mechanical, but also hypoxic, infectious or toxic in nature.

Table 1. Blood coagulation factors

Factor	Name of factor	Properties and functions
I	Fibrinogen	A protein glycoprotein produced by parenchymal cells in the liver, which is converted into fibrin under the influence of thrombin.
II	Prothrombin	A glycoprotein, the inactive form of the enzyme thrombin, synthesised in the liver with the participation of vitamin K.
III	Thromboplastin	A lipoprotein (proteolytic enzyme) involved in local haemostasis, capable of activating factor X (the external pathway of prothrombinase formation) upon contact with plasma factors (VII and Ca). Converts prothrombin to thrombin.
IV	Calcium	Potentiates most blood coagulation factors — participates in the activation of prothrombinase and the formation of thrombin, is not consumed during the coagulation process.
V	Proaccelerin	As-globulin, produced in the liver, necessary for the formation of prothrombinase.
VI	Accelerin	Potentiates the conversion of prothrombin to thrombin.
VII	Proconvertin	Synthesised in the liver with the participation of vitamin K, in its active form together with factors III and IV, it activates factor X.
VIII	Antihemophilic globulin A	A complex glycoprotein, the site of synthesis is not precisely established, activates the formation of thromboplastin.
IX	Antihemophilic globulin B (Christmas factor)	Beta globulin, produced in the liver, participates in the formation of thrombin

X	Thrombotropin (Stuart-Prower factor)	Glycoprotein, produced in the liver, involved in thrombin formation.
XI	Precursor of plasma thromboplastin (Rosenthal factor)	A glycoprotein that activates factor X.
XII	Contact activation factor (Hageman factor)	Activator of the initial reaction of blood coagulation and the kinin system (initiates and localises thrombus formation)
XIII	Fibrin stabilising factor	Fibrinase, stabilises fibrin in the presence of calcium, catalyses fibrin transamination (converts unstable fibrin into stable fibrin)
	Fletcher factor	Plasma prekallikrein, activates factors VII and IX, converts kininogen to kinin
	Fitzgerald factor	Kininogen, in its active form (kinin), activates factor XI
	von Willebrand factor	A component of factor VIII, released from the endothelium into the bloodstream, where it binds to the coagulation part to form complete factor VIII (antihemophilic globulin A)

The release reaction is a process in which factors involved in the plasma coagulation pathway are released from platelets that have entered a state of aggregation. Blood coagulation is a proteolytic cascade. Each enzyme (coagulation factor) is present in plasma in an inactive state. Upon activation, the coagulation factor undergoes proteolytic cleavage with the release of the active factor from the precursor molecule. (Table 1).

Factors synthesized in the liver:

— vitamin K-dependent factors: II, VII, IX, X;

— thrombin-sensitive factors: I, V, VIII, XIII;

— contact factors: XII, XI, BM kininogen, prekallikrein;
— serine protease factors: XII, XI, X, IX, VII, II, plasmin.

Plasma hemostasis can be imagined as a finely tuned biochemical relay race, where one activated enzyme passes the signal to the next, ultimately leading to blood clot formation. In this process, inactive precursors (proenzymes) are sequentially converted into active coagulation factors, each step amplifying the response. For clarity, this complex system is traditionally described as a cascade of enzymatic reactions operating through two interconnected pathways: the extrinsic and intrinsic mechanisms. Despite their different starting points, both pathways converge on a single goal—the formation of fibrin, the structural backbone of a blood clot.

The extrinsic pathway is triggered when blood comes into contact with damaged tissue and tissue factor (factor III) is released. This initiates coagulation by activating factor VII. Activated factor VII rapidly converts factor X into its active form, Xa, and to a lesser extent activates factor IX, although this reaction plays a minor role in overall clot formation. Factor Xa then catalyzes the conversion of prothrombin (factor II) into thrombin, a reaction that is dramatically accelerated in the presence of factor Va and phospholipid surfaces. Through this pathway, fibrin formation begins within seconds, producing the first bursts of thrombin. These early thrombin molecules act as powerful amplifiers, activating additional coagulation factors such as V, VIII, and XIII, thereby intensifying the clotting response.

The intrinsic pathway, in contrast, is initiated directly within the bloodstream and begins with the activation of Hageman factor (factor XII). This activation occurs on the phospholipid membranes of platelets and is stimulated by substances such as exposed endothelial collagen and adrenaline. Once activated, factor XII triggers the conversion of factor XI, with kallikrein contributing to this reaction. Activated factor XI subsequently activates factor IX. On the platelet surface, factor IXa works together with factor VIIIa and calcium ions to convert factor X into Xa through proteolytic cleavage. As in the extrinsic pathway, factor Xa then transforms prothrombin into thrombin, a step greatly enhanced by factor Va and phospholipids.

The final stage of plasma coagulation centers on the transformation of fibrinogen into fibrin. Thrombin cleaves fibrinogen molecules by removing two fibrinopeptides A and two fibrinopeptides B, producing fibrin monomers. These monomers spontaneously assemble into dimers, trimers, and larger oligomers, eventually forming soluble fibrin fibrils. Under the influence of calcium ions, activated fibrin-stabilizing factor (factor XIIIa) converts this fragile, soluble fibrin into a stable, insoluble network. This stabilization renders the clot resistant to fibrinolytic enzymes and other proteolytic agents.

As the final touch, platelets infiltrate the fibrin mesh in large numbers, compacting and strengthening the clot. Clot retraction follows, tightening the fibrin network and reducing its volume. The resulting structure—composed of platelets, erythrocytes, and dense fibrin fibers—is strong enough to effectively seal even large blood vessels and bring bleeding to a halt.

Anticoagulant mechanisms. Pathological anticoagulants

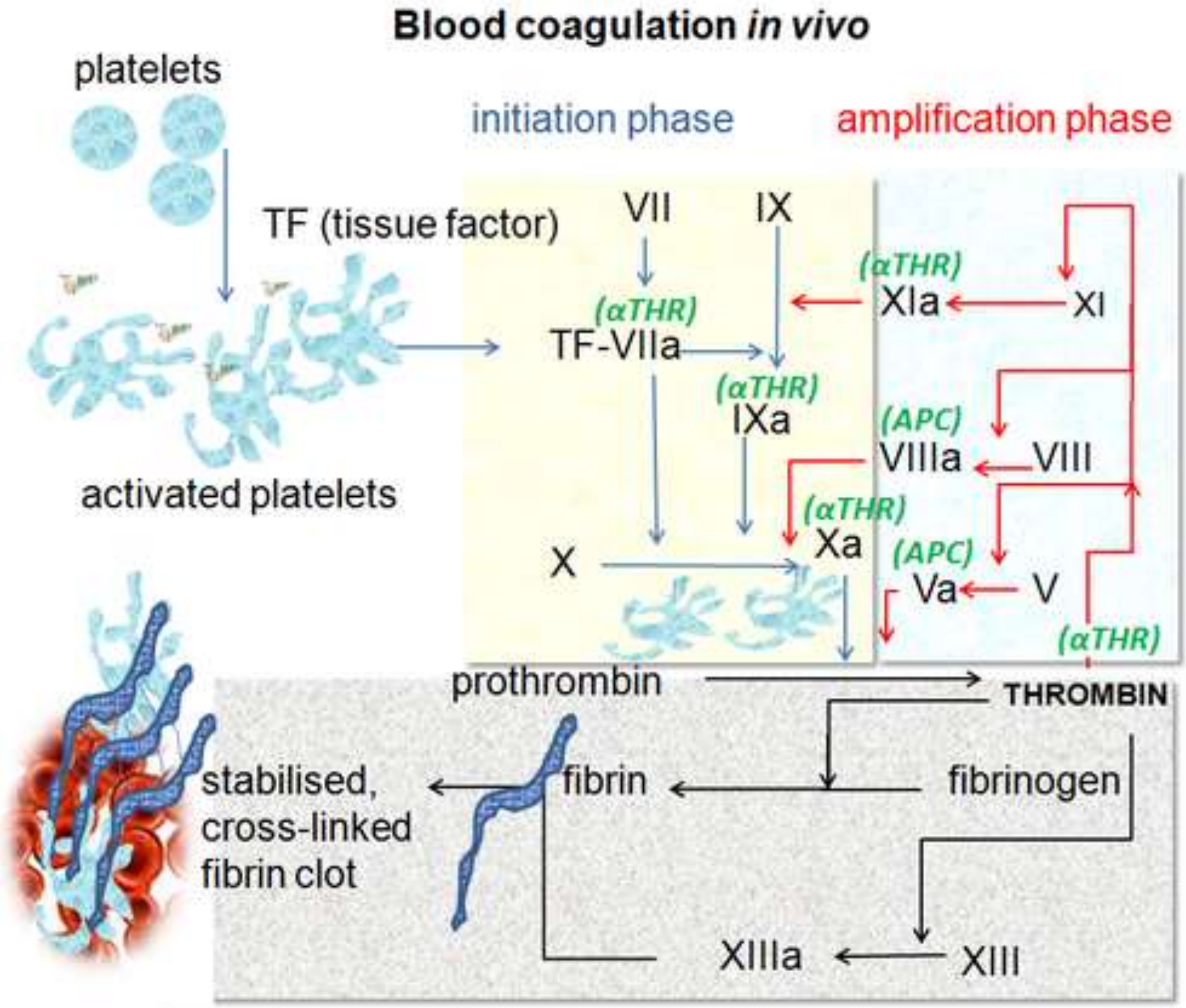
Physiological anticoagulants keep the blood in a liquid state and limit the process of thrombus formation. These include antithrombin III, heparin, proteins C and S, alpha2macroglobulin, and fibrin strands.

Antithrombin III is an alpha2globulin that accounts for 75% of all anticoagulant activity in plasma. It is the main plasma cofactor of heparin and inhibits the activity of thrombin, factors Xa, IXa, VIIa, and XPa.

Heparin is a sulphated polysaccharide found in mast cells that transforms antithrombin III into an immediate-acting anticoagulant, enhancing its effects 1,000-fold by activating non-enzymatic fibrinolysis.

Proteins C and S are synthesised in the liver with the participation of vitamin K. Protein C inactivates activated factors VIII and V. Protein S reduces the ability of thrombin to activate factors VIII and V. Fibrin strands have an antithrombotic effect, as they adsorb up to 80-85% of blood thrombin. Thrombin concentrates in the forming clot and does not spread through the bloodstream.

Picture 2. Blood coagulation



The Fibrinolytic System

Once a fibrin clot has fulfilled its lifesaving role in stopping bleeding, the body activates an equally important counterprocess—fibrinolysis. This system carefully dissolves the clot, restoring normal blood flow through the vessel and preventing unnecessary obstruction. Beyond reopening vessels, the fibrinolytic system plays a key role in wound healing, tissue remodeling, and the regulation of many physiological processes that maintain vascular balance.

At the heart of fibrinolysis lies a coordinated enzymatic network composed of four essential elements: plasmin, the principal enzyme responsible for fibrin degradation; plasminogen, its inactive circulating precursor; plasminogen activators, which initiate enzyme activation; and plasminogen inhibitors, which restrain the process and prevent excessive clot breakdown.

Activation of plasminogen can proceed through both external and internal pathways, ensuring that fibrinolysis is precisely matched to the body's needs. This flexibility allows clot dissolution to occur locally and at the appropriate time.

Several factors are capable of triggering plasminogen activation. These include tissue-derived activators located within the vascular wall, which respond to endothelial signals; blood-borne activators, which circulate in plasma; and thrombin, a central coagulation enzyme that paradoxically also promotes clot resolution. In addition, specific enzymes such as urokinase, produced primarily in the kidneys and accounting for approximately 15% of plasminogen activation, and streptokinase, a powerful external activator, contribute to the conversion of plasminogen into active plasmin.

Once formed, plasmin efficiently cleaves fibrin fibers into soluble degradation products, gradually dismantling the clot. Throughout this process, plasminogen inhibitors tightly regulate enzyme activity, ensuring that fibrinolysis remains controlled and does not compromise vascular integrity.

- In this way, the fibrinolytic system acts as the natural counterpart to coagulation—quietly removing what is no longer needed and restoring normal circulation once healing is underway.
- alkaline and acid phosphokinases;
- lysosomal enzymes of damaged tissues (lysozymes);
- kallikrein-kinin system together with factors XII, XIV, XV.

Fibrin is destroyed by the enzyme plasmin or fibrinolysin, which is converted into its active form from plasminogen or profibrinolysin (210 mg/l) contained in the blood.

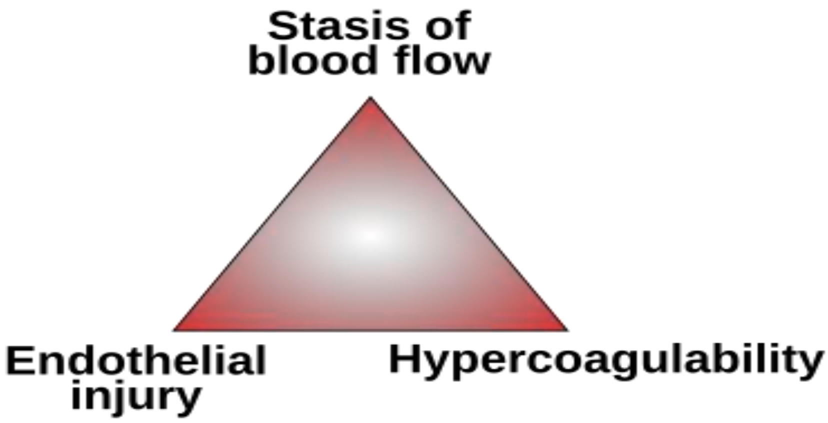
In addition to fibrinolysis, fibrin autolysis may occur (due to erythrocyte and leukocyte enzymes) – aseptic autolysis, or – dissolution of fibrin by staphylococcal and streptococcal enzymes – septic autolysis.

If conditions for fibrinolysis are not present, either organisation (replacement with connective tissue) or recanalisation (formation of a channel within the thrombus) occurs. In some cases, the thrombus may detach from the site of its formation and cause blockage of the vascular bed (embolism), which can lead to death.

Rudolf Virchow (1821-1902)

The classical concepts of the mechanisms of blood coagulation were developed by Rudolf Virchow and are presented in the form of a triad, shown in.

Picture 3. Virchow's triad



In this triad, vascular wall pathology can be represented by a wide range of pathological processes leading to damage to vascular wall structures associated with hypoxia, infection, trauma, and metabolic disorders.

Blood flow pathology is characterised by hemodynamic disorders accompanied by microcirculation disorders (arterial hypotension, shock, stasis).

Blood composition pathology is associated with bacteraemia, viraemia, intravascular hemolysis, and polycythaemia.

PHYSIOLOGICAL FEATURES OF HEMOSTASIS AT BIRTH.

1. Low levels (40-60% of healthy adults) of vitamin K-dependent blood coagulation factors: II, VII, IX, X, with a subsequent decrease in the first 2-3 days after birth, as well as contact factors (prekallikrein; kininogen; factors XII, XI, XIII and plasminogen), but normal levels of other blood clotting factors.
2. Normal values of platelet adhesive activity and low values of platelet aggregation activity.
3. Increased permeability and fragility of the vascular wall.
4. Hypercoagulation of whole blood in the first hours and days of life, although prothrombin time is prolonged.

In healthy, full-term newborns who experience an uncomplicated perinatal period, reduced levels of vitamin K–dependent coagulation factors are most often linked not to an actual deficiency of vitamin K, but to the temporary immaturity of liver function after birth. During this early neonatal phase, the liver has not yet reached full enzymatic efficiency, which naturally limits the synthesis of several clotting proteins.

In a small proportion of newborns—approximately 2–5%—the concentration of these vitamin K–dependent clotting factors is noticeably lower than in the majority of infants. This physiological variability creates a vulnerable window in which the balance between coagulation and bleeding may be disturbed. As a result, these infants are at an increased risk of developing hemorrhagic manifestations, despite appearing otherwise healthy.

Distinctive Features of Hemostasis in Premature Newborns

Hemostasis in infants born prematurely—particularly those with very low birth weight—differs markedly from that of full-term newborns. These differences are further pronounced in infants who developed in utero under conditions of chronic hypoxia, where prolonged oxygen deprivation disrupts normal vascular and hematologic maturation.

First, the vascular wall in these infants is structurally immature, characterized by increased permeability and heightened fragility. As a result, blood vessels are more susceptible to damage and rupture, predisposing premature newborns to bleeding complications.

Second, plasma thrombomodulin levels, a sensitive marker of endothelial injury, are significantly elevated in premature infants compared with healthy full-term newborns. This finding reflects ongoing endothelial dysfunction and impaired regulation of coagulation processes.

Finally, platelet functional capacity is reduced. Premature infants exhibit diminished spontaneous platelet aggregation as well as a weaker aggregation response to thrombin stimulation. This functional platelet insufficiency represents a critical risk factor for the development of intraventricular hemorrhages, one of the most serious complications of prematurity.

Together, these features illustrate the fragile balance of hemostasis in premature newborns and explain their heightened vulnerability to hemorrhagic events during the early neonatal period.

Table 2.

Hemocoagulation factors in newborns compared to adults

Factor	I (g/l)	II %	VIII %	XI %	XII %	XIII %	AT III %
Adults	3.0	100	100	100	100	100	100
24-31 weeks	2.8	31	87	20	20	-	27
32-35 weeks	2.6	33	90	-	33	-	44
36-37 weeks	2.3	52	125	-	-	-	51
38-40 weeks	2.2	54	97	31	47	50	60

In addition to vascular and platelet immaturity, plasma coagulation in premature infants is also significantly altered. When compared with full-term newborns, premature infants exhibit reduced levels of nearly all procoagulant factors, with the notable exception of factor XIII, whose concentration remains relatively preserved. At the same time, fibrinogen levels are lower, further weakening the formation and stabilization of the fibrin clot.

The imbalance of the coagulation system is most pronounced during the first day of life in premature infants, when hypocoagulation reaches its maximum expression. In contrast, full-term newborns typically experience their greatest shift toward hypocoagulation later, between the third and sixth days of life, reflecting differences in the timing of postnatal adaptation and hepatic maturation.

These temporal and quantitative distinctions help explain why premature infants are particularly vulnerable to bleeding complications immediately after birth and underscore the need for careful hemostatic monitoring in this population.Early hypocoagulation in premature infants is explained by a pronounced deficiency in the synthesis of coagulation factors in the liver.

They also have a more pronounced decrease in contact factors (XII, prekallikrein, high-molecular-weight kininogen). Transient fibrinolysis is observed in the first hour of life, even more actively than in full-term infants, followed by its more profound suppression at very low levels of plasminogen and anticoagulants (antithrombin III, protein C). Together, these shifts result in a less stable hemostatic system and a significantly higher incidence of both bleeding and intravascular coagulation in this group of newborns. Virtually any pathology observed in premature newborns can be complicated by bleeding or DIC syndrome.

CLASSIFICATION OF HEMORRHAGIC DISORDERS IN NEWBORNS.

Diseases accompanied by hemorrhagic syndrome in newborns are a group of diseases of various origins, the main clinical manifestation of which is increased bleeding.

Table 3. Classification of hemorrhagic disorders in newborns

Area Disorders Haemostasis	Nature Disorders Haemostasis	Diseases
Coagulopathies	Primary	Haemorrhagic disease of the newborn Hereditary coagulopathies von Willebrand disease Haemophilia Afibrinogenemia, hypofibrinogenemia, dysfibrinogenemia Factor XIII deficiency
	Secondary	Secondary vitamin K-dependent coagulopathy in cases of prolonged PP and severe liver disease with cholestasis Coagulopathy in liver diseases Liver
Thrombocytopenia	Primary	Isoimmune thrombocytopenia

		• Transimmune thrombocytopenia • Hypomegakaryocytosis, amegakaryocytosis
	Secondary	Wiskott-Aldrich syndrome Thrombocytopenia in systemic inflammatory response syndrome systemic inflammatory response syndrome
Thrombocytopathies	Primary Secondary	Drug-induced Thrombocytopenia Hereditary Predominantly Drug-induced
Combined hypo-coagulation and thrombocytopenia	Secondary	• DIC syndrome in acidosis, hypoxia, infectious diseases, acute haemolysis, leukocytosis, trauma, burns

Hemorrhagic disorders in newborns are classified as primary and secondary (symptomatic).

Hemorrhagic Disorders in Newborns and Children

Hemorrhagic disorders in early life may arise from primary defects of the hemostatic system or develop secondarily as a consequence of underlying pathological conditions. These disorders differ in origin but share a common clinical manifestation—an increased tendency to bleeding.

Primary hemorrhagic disorders are directly linked to congenital or inherited abnormalities of coagulation, platelets, or vascular regulation. They include hemorrhagic disease of the newborn, as well as hereditary coagulopathies such as hemophilia, afibrinogenemia, and other rare factor deficiencies. Disorders of platelet number and function are also prominent in this group. These include thrombocytopenic purpura, which may be congenital or immune-mediated—such as alloimmune and transimmune (autoimmune) forms—as well as inherited conditions like Wiskott–Aldrich syndrome and developmental defects of the megakaryocytic lineage, including hypoplasia or aplasia. In addition, thrombocytopathies may occur, either as inherited disorders or as acquired conditions, particularly following exposure to platelet-inhibiting drugs. Notably, platelet dysfunction may develop in newborns whose mothers received salicylates or other antiplatelet agents during the final days of pregnancy.

In contrast, secondary hemorrhagic disorders arise as complications of systemic disease or severe physiological stress. These include decompensated disseminated intravascular coagulation (DIC) syndrome, secondary thrombocytopenic hemorrhagic syndrome, and coagulopathic bleeding associated with infections or viral hepatitis. Another important entity is vitamin K–deficient hemorrhagic syndrome, which may occur in conditions such as mechanical (obstructive) jaundice that impair vitamin K absorption. Drug-induced thrombocytopathic syndromes also belong to this group and reflect the adverse effects of medications on platelet function.

Together, these disorders illustrate the complexity of hemorrhagic conditions in neonates and children, emphasizing the need for careful differentiation between primary hemostatic defects and secondary, disease-related disturbances. The causes of bleeding in the neonatal period are varied and are due to the influence of the following factors:

— predominant damage to the coagulation link of hemostasis;
— predominant damage to the platelet-vascular link
of hemostasis;
— mixed hemostasis disorders.

HEMORRHAGIC DISEASE OF THE NEWBORN (HDN).

Develops in 0.25–1.5% of newborns in the absence of vitamin K prophylaxis. There are three forms of NHD: early (first 24 hours of life), classic (1–5 days of life) and late (2–8 weeks of life, less commonly up to 6 months).

Hemorrhagic disease of the newborn is a preventable bleeding disorder that develops in approximately 0.25–1.5% of infants when vitamin K prophylaxis is not administered at birth. The condition reflects the critical role of vitamin K in the synthesis of key coagulation factors during the early neonatal period.

Clinically, HDN presents in three distinct forms, differentiated by the time of onset. The early form appears within the first 24 hours of life, the classic form develops between days 1 and 5, and the late form manifests between 2 and 8 weeks of age, with rare cases reported up to 6 months. Despite differences in timing and clinical presentation, all three forms share a common underlying mechanism—vitamin K deficiency.

In contemporary international medical guidelines, this condition is increasingly referred to as “vitamin K–dependent hemorrhagic syndrome,” a term that more accurately reflects its pathophysiological basis rather than age alone.

Newborns are naturally predisposed to vitamin K deficiency, and in nearly half of all infants, this deficiency is particularly pronounced. This vulnerability arises from a combination of prenatal and postnatal factors, including limited placental transfer of vitamin K, immature hepatic synthesis of clotting factors, low vitamin K content in breast milk, and delayed colonization of the gut with vitamin K–producing bacteria.

Together, these factors create a critical window during which newborns are at increased risk of bleeding, underscoring the importance of timely vitamin K prophylaxis immediately after birth. (Table 4).

Table 4. Factors leading to vitamin K deficiency in newborns

Period of child development	Factors leading to vitamin K deficiency
Intrauterine period	Mother's intake during pregnancy: indirect anticoagulants (from the neodicoumarin group); anticonvulsants (phenobarbital, diphenin, phenytoin, etc.); • broad-spectrum antibiotics; • acetylsalicylic acid and indomethacin preparations Gestosis against a background of low oestrogen synthesis (daily oestrogen excretion in urine – less than 10 mg)

	Hepatopathy and enteropathy in the mother Intestinal dysbiosis and dysbacteriosis in the mother
Intranatal period	Chronic hypoxia and foetal asphyxia during labour Caesarean section delivery Birth trauma
Postnatal period	Prematurity Late breastfeeding Absence or insufficient breastfeeding Prolonged parenteral nutrition Broad-spectrum antibiotics Malabsorption syndrome Mechanical jaundice of various origins (biliary atresia, cholestasis, etc.) Hepatitis Coeliac disease Mucoviscidosis Cystic fibrosis of the pancreas α_1-antitrypsin deficiency Abetalipoproteinemia

Vitamin K crosses the placenta only in minimal amounts, which explains why its concentration in umbilical cord blood is consistently lower than in maternal circulation. As a result, every newborn enters postnatal life with limited vitamin K reserves.

After birth, this deficit is not immediately corrected. Breast milk provides only small quantities of vitamin K, containing approximately 15 μg/L, which is substantially less than the amount found in cow's milk or infant formulas. In addition, the neonatal intestine is initially sterile, and the intestinal microflora capable of synthesizing vitamin K becomes fully active only after 3–5 days of life. Together, these factors create a temporary but clinically important period of vitamin K insufficiency.

Vitamin K plays a pivotal biochemical role in the coagulation system. Several key clotting factors—prothrombin (factor II), proconvertin (factor VII), antihemophilic globulin B (factor IX), and the Stuart–Prower factor (factor X)—are synthesized in the liver as inactive precursor proteins. Their conversion into functional coagulation factors requires vitamin K–dependent γ-carboxylation of glutamic acid residues, a reaction catalyzed by the enzyme γ-glutamyl carboxylase.

This post-translational modification increases the negative charge of the coagulation factor molecules, enabling them to bind calcium ions. Calcium binding is essential for the attachment of these factors to platelet phosphatidylcholine membranes, where they assemble into highly efficient enzyme complexes. These complexes are indispensable for the rapid generation of thrombin and, ultimately, for the formation of a stable fibrin clot.In the absence/deficiency of vitamin K, there is a decrease in the content of functionally active coagulation factors in the blood and an increase in the concentration of inactive precursors of vitamin K-dependent factors, referred to by the abbreviation ***PIVKA (Protein Induced by Vitamin K Absence*****)**.

Vitamin K enters the human body primarily in the form of phylloquinone (vitamin K_1)—chemically known as 2-methyl-1,3-phytyl-14-naphthoquinone—which is found in plant-based foods. The minimum daily requirement for vitamin K_1 is approximately 2 μg per kilogram of body weight. In addition to dietary intake, the intestinal microflora synthesizes menaquinone (vitamin K_2). In adults, vitamin K_2 is absorbed from the intestine only minimally, if at all. In contrast, infants are able to absorb vitamin K_2, making it an important endogenous source of vitamin K during early life.

Because of this dependence on intestinal synthesis, newborns and young infants are particularly vulnerable to conditions that disrupt gut microflora. Diarrhea and the use of broad-spectrum antibiotics, especially third-generation cephalosporins, suppress vitamin K–producing bacteria in the intestine. As a result, vitamin K deficiency may develop, significantly increasing the risk of hemorrhagic complications.

The vitamin K content of neonatal nutrition further contributes to this vulnerability. Colostrum and breast milk contain an average of only about 2 μg/L of vitamin K_1, whereas cow's milk contains approximately 5 μg/L. These values clearly demonstrate that breast milk alone cannot fully satisfy a newborn's vitamin K requirement, making intestinal synthesis essential. However, the establishment of normal intestinal microflora occurs gradually during the first week of life, and in the initial days after birth, the synthesis of vitamin K_2 is insufficient to compensate for this deficit.

As early as the 1950s, clinical observations revealed that hemorrhagic disease of the newborn occurred more frequently in breastfed infants than in those who were bottle-fed. This observation later gained further significance with the recognition of the late form of vitamin K–dependent hemorrhagic disease, first described in the 1970s. It was noted that breastfed infants—most commonly during the first three months of life—were more likely to develop severe bleeding complications, including intracranial hemorrhages, often in association with intercurrent illnesses.

Subsequent studies showed that the vast majority of infants who developed late hemorrhagic disease had either not received vitamin K prophylaxis at birth or had been given vitamin K only orally, which is less reliable than parenteral administration. These findings provided strong evidence for the critical role of early vitamin K supplementation in preventing life-threatening bleeding in infancy.It is customary to distinguish between three types of hemorrhagic disease of the newborn:

- Early;
- Classic;
- Late.

Early HCN occurs within the first 24 hours after birth. It is usually associated with the mother's medication (anticonvulsants, oral anticoagulants, broad-spectrum antibiotics, especially hepatotoxic ones).

Clinical picture. The early form of hemorrhagic disease of the newborn (HDN) may begin before birth, during the intrauterine period. In such cases, signs of bleeding are already present at the time of delivery. Intracranial hemorrhages can be detected immediately after birth through neurosonographic (ultrasound) examination of the brain. Other early manifestations include cephalohematomas, cutaneous hemorrhages, and bleeding from the umbilical stump.

The prenatal onset of bleeding has been convincingly documented by numerous pediatric studies, confirming that vitamin K deficiency–related hemorrhagic processes may develop even before postnatal adaptation begins.

However, vitamin K deficiency alone is not always sufficient to trigger overt hemorrhagic syndrome. Severe perinatal asphyxia and birth trauma act as powerful provoking factors, tipping the fragile hemostatic balance toward clinically significant bleeding. Under these stressful conditions, the transition from a latent deficiency state to a full-blown hemorrhagic syndrome becomes much more likely.

Picture 4. Petechiae

Cutaneous hemorrhagic manifestations in early hemorrhagic disease of the newborn may be especially prominent in areas exposed to pressure or minor trauma. Bleeding often appears in dependent regions, such as the buttocks, as well as in deeper tissues, including subaponeurotic hemorrhages. Hemorrhages may also develop at sites of even minimal mechanical impact, for example, under monitoring electrodes, reflecting the extreme fragility of the hemostatic balance in affected infants.

Among the earliest and most severe clinical signs, bleeding may occur in vital organs. These include pulmonary hemorrhage, hemorrhages within the abdominal organs—most commonly involving the liver, spleen, and adrenal glands—as well as melena, indicating gastrointestinal bleeding. Such manifestations signal a rapid progression of the hemorrhagic process and require immediate clinical attention.Profuse bleeding manifests itself in pallor of the skin and mucous membranes, tachycardia, and laboratory signs of post-hemorrhagic anemia. If assistance is not provided in a timely manner, the child may die from hemorrhagic shock due to acute blood loss. Skin and subcutaneous hemorrhages (purpura) in the form of petechiae and widespread ecchymoses are less common.

Picture 5. Cephalohematoma

The classic form of HRH. It occurs both in children whose mothers received drugs during pregnancy that increase the risk of developing HRH, and in newborns who are exclusively breastfed. The frequency of the classic form of HBD is 400 to 1,700 cases per 100,000 births. A typical manifestation of the disease is bleeding that occurs between the 2nd and 5th days of life. A breastfed baby may experience melena (intestinal bleeding) and bloody vomiting (hematemesis); there may be skin hemorrhages, ecchymosis, petechiae), bleeding when the umbilical cord stump falls off or, in boys, after circumcision, nosebleeds, cephalohematomas, and subaponeurotic hemorrhages.

Picture 6. Nosebleed

In children with severe hypoxia and birth injuries, vitamin K deficiency can also manifest as intracranial haemorrhages, as well as internal, pulmonary, and other types of bleeding.

Picture 6. Bleeding from the umbilical wound

Melena refers to intestinal bleeding in the newborn and is most often recognized by the appearance of a pink or reddish ring around the stool on the diaper. This subtle but characteristic sign allows early suspicion of gastrointestinal bleeding in infants.

In children with melena, hyperbilirubinemia may develop as a consequence of increased breakdown of red blood cells within the intestinal lumen. In some cases, melena is accompanied by bloody vomiting, indicating involvement of the upper gastrointestinal tract.

The development of melena is commonly associated with the formation of small erosions or ulcers on the mucous membrane of the stomach and duodenum. Their origin is believed to be largely related to elevated glucocorticoid levels in newborns, which arise as part of the physiological stress response to birth. Additional contributing factors include increased gastric acidity, gastroesophageal reflux, and peptic esophagitis, all of which may facilitate mucosal injury and lead to bloody vomiting.

The role of constitutional factors, including hereditary predisposition, in the development of melena remains uncertain and has not yet been clearly defined.

Picture 6. Melena in newborns

Melena observed on the first day of life requires careful differentiation from the so-called “swallowed maternal blood syndrome.” This benign condition occurs in approximately one out of three newborns who pass blood-stained stools shortly after birth and results from ingestion of maternal blood during delivery or breastfeeding.

To distinguish true neonatal intestinal bleeding from swallowed maternal blood, the Apt test is used. In this test, a sample of bloody vomitus or stool is diluted with water to produce a pink solution containing hemoglobin. After centrifugation, 4 ml of the supernatant is mixed with 1 ml of a 1% sodium hydroxide solution. The color of the mixture is evaluated after two minutes.

A change in color from pink to brown indicates the presence of hemoglobin A, confirming that the blood is of maternal origin. In contrast, persistence of the pink color signifies alkali-resistant fetal hemoglobin (HbF), confirming true neonatal bleeding (meconium-related).

In cases of profuse, persistent, or recurrent melena, or when bleeding is noted directly from the anus, additional causes must be excluded. These include anorectal trauma, papillomas, intestinal angiomatosis, vascular malformations, and other forms of surgical gastrointestinal pathology. Prompt evaluation is essential to ensure timely and appropriate management.

Late HBD. The first report of HBD with late onset dates back to 1977. Late VHD is unpredictable bleeding caused by severe vitamin K deficiency in children aged 2-12 weeks, with the highest incidence between the 2nd and 6th weeks of life. In about half of cases, the late form of VHD manifests itself as intracerebral hemorrhages. Late VHD is predominant in children who are exclusively breastfed, have diarrhea with fat malabsorption lasting more than 1week, coeliac disease, biliary atresia, cystic fibrosis of the pancreas, or massive use of broad-spectrum antibiotics. Moreover, three-quarters of these children have liver dysfunction. This means that the newborn's liver cannot adequately synthesise blood clotting factors or create sufficient reserves of vitamin K. There is always an unpredictable risk of hemorrhagic complications at birth. Newborns with prolonged jaundice should probably be examined more thoroughly to identify liver pathology.

If a child has conjugated hyperbilirubinemia, the administration of vitamin K should be considered.

Clinical manifestations of late HBHD may include intracranial hemorrhages (in more than 60% of cases), extensive skin ecchymoses, melena, hematemesis, and bleeding from injection sites. Polypharmacy, especially with the simultaneous use of three or more platelet inhibitors, increases the risk of hemorrhage in vitamin K deficiency.

Diagnosis of Hemostasis Disorders

The diagnosis of hemostasis disorders is established through an integrated assessment that combines anamnestic data, clinical presentation, and laboratory findings. Particular attention is paid to the presence of risk factors for hemorrhagic disease of the newborn (HDN), which provide important diagnostic clues even before laboratory confirmation.

Clinical manifestations of bleeding, when correlated with a suggestive history, are then substantiated by laboratory investigations (see Table 5). In cases of HDN, laboratory testing typically reveals a marked reduction in prothrombin levels, often reaching approximately 10% of adult values or even lower. The degree of reduction in other vitamin K–dependent coagulation factors may vary, reflecting individual differences in the severity of vitamin K deficiency.

Importantly, fibrinogen concentrations, levels of other non–vitamin K–dependent clotting factors, and platelet counts are usually within normal ranges. This characteristic laboratory profile helps distinguish HDN from other hemorrhagic conditions associated with thrombocytopenia or global coagulation factor deficiencies.

Bleeding is caused by damage to the vascular-platelet or coagulation links of the hemostasis system. *The vascular-platelet type of bleeding* is characterised by the appearance of ecchymoses and petechiae, as well as nasal, gastrointestinal and intracranial hemorrhages. *The coagulation type of bleeding* is characterised *by* soft tissue hematomas (subcutaneous, intermuscular), prolonged bleeding from postoperative incisions, gastrointestinal and intracranial hemorrhages.

Laboratory methods:

measurement of platelet count and function (adhesion, aggregation) by microscopy or using hematological analysers (in screening tests) and aggregometers; functional coagulation, or so-called clotting tests (based on the assessment of clotting time manually or using coagulometers of various designs);

determination of fibrinolysis parameters;

amidolytic (tests using chromogenic substrates for thrombin, plasmin, factor Xa, Xa, etc., and photometers with a fixed measurement wavelength);

immunological methods that allow the level of the desired antigen or antibodies to be detected in APS, etc. Detection of genetic abnormalities by PCR (Leiden resistance mutations of factor Va to activated protein C, prothrombin gene G20210, methylene tetrahydrofolate reductase gene, etc.)

Tests for assessing the vascular-platelet link of hemostasis

Bleeding time is the time from the moment a standard skin wound is made to the moment the blood stops flowing. It characterises the functional activity of platelets and the interaction of platelets with vascular wall. Bleeding time does not reveal all platelet disorders (no such method exists), but this screening test allows for the suspicion of thrombocytopathies of various origins, von Willebrand disease, and disorders of the proaggregant properties of the vascular wall. It is prolonged in thrombocytopenia, severe thrombocytopathies, and von Willebrand factor deficiency.

The average *platelet count* in newborns ranges from 150,000 to 500,000**.** In the first three days of life, the lower limit of normal may be 125 for full-term babies and 100 for premature babies. then at 2-3 weeks and 6-7 weeks, their number rises to an upper limit of 750 and returns to the range of 150-500 by the 9th week (Wiedmeier SE et al., 2009).

Tests for assessing the plasma link of hemostasis:

Activated partial thromboplastin time (APTT). APTT is used as a screening test to assess the internal plasma coagulation cascade, screen for lupus anticoagulant, and monitor the anticoagulant effect of heparins. APTT is a more significant test for the primary detection of pathology than prothrombin time, as it detects relatively common hemophilia A and B.

Prothrombin time (PT) is a widely used screening test for assessing the extrinsic cascade of plasma coagulation. PT is commonly used to determine factor VII activity, monitor treatment with indirect anticoagulants, and screen the hemostasis system.

Prothrombin index (PTI), % = PT of normal control plasma (or average PT of the normal range) / PT of patient plasma) x 100

INR (International Normalised Ratio), Latin abbreviation INR (International Normalised Ratio) - an additional method of presenting prothrombin test results, recommended for monitoring therapy with indirect anticoagulants by the WHO Expert Committee, the International Committee for the Study of Thrombosis and Hemostasis, and the International Committee for Standardisation in Hematology.

Thrombin time (TT) - determination of thrombin time. The test characterises the final stage of the coagulation process - the conversion of fibrinogen to fibrin under the action of thrombin. It is influenced by the concentration of fibrinogen in plasma and the presence of fibrin degradation products.

The INR and PTI indicators are derived from the prothrombin time indicator. INR is defined as the prothrombin ratio (PR) to the degree of the international sensitivity index (ISI):

$$\text{ПО} = \frac{\text{ПТВбольного}}{\text{ПТВнорма}}; \ \text{INR} = \text{PR}^{\text{ISI}}$$

$$\text{ПТИ} = \frac{\text{ПТВнорма}}{\text{ПТВбольного}} 100\%.$$

Quantitative determination of fibrinogen is the basic test for hemostasis. Fibrin formation and stabilisation are the final stage of thrombus formation, in which soluble fibrinogen is converted into insoluble fibrin under the action of thrombin and factor XIII.

Fibrinogen degradation products (FDP). In a number of pathologies characterised by blood coagulation activation (DIC, thrombosis, thrombophilia), the fibrinogen pool expands, resulting in an increase in the amount of soluble, including fibrin monomer complexes (FMC). All newborns with clinical manifestations of hemorrhagic syndrome undergo monitoring of vital functions with constant assessment of the degree of blood loss. Intensive monitoring is carried out in the intensive care unit and includes: assessment

Table 5.

Laboratory data for the most common haemorrhagic syndromes (Volodin N.N. et al., 2007)

Indicators	Normal values in full-term infants	Haemorrhagic disease of the newborn (vitamin K deficiency	Haemophilia	Thrombocytopenia Penia	DIC syndrome (phase 2
Time Clotting	2-4 min	Prolonged	prolonged	Normal	extended
Bleeding time	3-4 min	Normal	normal	Prolonged	prolonged
Number platelets	150-400x10/L	Normal	normal	Decreased	decreased
Prothrombin time	13-16 sec	Prolonged	normal	Normal	prolonged
Thrombin time	10-16 sec	Normal	normal	Normal	prolonged
APTV	45-60 sec	Extended	extended	Normal	prolonged
Fibrinogen	1.5-3 g/l	Normal	normal	Normal	decreased
Products degradation fibrinogen	0-7 mg/ml	Normal	normal	Normal	elevated

Perfusion disorders, monitoring of blood pressure, heart rate, respiratory rate, Sat02, blood count indicators (Ht, Hb).

Treatment

Management of hemorrhagic disease of the newborn focuses on correcting vitamin K deficiency and restoring effective coagulation. Feeding with expressed breast milk is continued up to seven times a day, in accordance with the infant's age-related nutritional requirements, ensuring adequate energy intake while minimizing additional stress.

The cornerstone of therapy is vitamin K administration, preferably intravenously, although intramuscular injection is also acceptable. Following intravenous vitamin K administration, prothrombin time and activated partial thromboplastin time typically normalize within approximately four hours, reflecting rapid restoration of vitamin K–dependent coagulation factor activity.

The standard therapeutic dose of vitamin K_1 (phylloquinone) is 1 mg. However, in current clinical practice in our country, vikasol (vitamin K_3)—a water-soluble menadione derivative—is most commonly used, despite being less effective than phylloquinone (vitamin K_1, Konakion). Vikasol does not exert a direct effect; instead, its activity depends on hepatic conversion into phylloquinone and menadione. Because only a small fraction of administered vikasol undergoes this conversion, treatment of hemorrhagic disease of the newborn often requires repeated dosing.

In cases of HDN, vikasol is typically administered twice at 12-hour intervals. Full-term newborns receive 5 mg (intravenously or intramuscularly), while premature infants are given 2–3 mg. In some cases, to raise the level of vitamin K–dependent coagulation factors to above 30% of adult values, vikasol may be administered three times.

Caution is essential when using vikasol. High doses (exceeding 10 mg) or prolonged administration increase the risk of adverse effects, including the formation of Heinz bodies in erythrocytes and the development of hyperbilirubinemia. For this reason, dosing must be carefully monitored and limited to the minimum effective course.

Local Therapy and Prevention

Local treatment of melena is aimed at reducing gastrointestinal bleeding and stabilizing the mucosal surface. For this purpose, a 0.5% sodium bicarbonate solution is administered orally at a dose of one teaspoon three times daily, helping to neutralize gastric acidity and reduce mucosal irritation. In addition, a thrombin solution prepared in ε-aminocaproic acid is given orally at the same dosage—one teaspoon three times a day. To prepare this mixture, ampoules of dry thrombin are dissolved in 50 ml of a 5% ε-aminocaproic acid solution, followed by the addition of 1 ml of a 0.025% adroxon solution, enhancing the local hemostatic effect.

When bleeding is profuse or recurrent and accompanied by signs of post-hemorrhagic anemia, systemic replacement therapy becomes necessary. In such cases, fresh frozen plasma or fresh whole blood (stored for no longer than two days) is administered intravenously by drip infusion at a dose of 10–15 ml/kg, restoring coagulation factors and circulating volume.

Effective prevention of hemorrhagic disease of the newborn is achieved through the intramuscular administration of vitamin K_1 immediately after birth. This simple and well-established measure reliably prevents vitamin K deficiency–related bleeding and remains the cornerstone of neonatal hemorrhage prevention.

Picture 7. Vitamin K

Vitamin K_1 is administered intramuscularly at birth in a dose of 0.5–1.0 mg for full-term newborns. Premature infants receive lower doses adjusted to body weight: 0.5 mg for those weighing more than 1000 g, and 0.3 mg for infants with a birth weight below 1000 g.

Vikasol is administered at a dose of 1 mg per kilogram of body weight. Prophylactic vitamin K supplementation is particularly important for high-risk groups, including children with obstructive jaundice accompanied by malabsorption, premature infants receiving broad-spectrum antibiotics, and children maintained on total parenteral nutrition. In these cases, vitamin K should be given intramuscularly once every 5–7 days at a dose of 1–2 mg, ensuring adequate support of vitamin K–dependent coagulation.

According to a number of Russian pediatric hematologists, early initiation of breastfeeding—ideally within the first 30 minutes after birth—may have a modest preventive effect. Early feeding appears to reduce the severity of the physiological decline in vitamin K–dependent clotting factors typically observed between the third and fifth days of life, thereby contributing to a more stable hemostatic balance during the early neonatal period.

Picture 8. Prevention with vitamin K3

Maternal Prophylaxis and the Need for Neonatal Vitamin K

Women with epilepsy who receive anticonvulsant therapy are at increased risk of giving birth to infants with vitamin K deficiency, as these drugs accelerate vitamin K metabolism. For this reason, such mothers are advised to receive oral vitamin K at a dose of 20 mg per day for two weeks prior to delivery, or alternatively 10 mg of vikasol intramuscularly during labor. However, maternal supplementation alone is not sufficient and does not replace the need for parenteral vitamin K administration to the newborn immediately after birth, which remains mandatory.

HEREDITARY COAGULOPATHIES

Hereditary coagulopathies represent a group of genetically determined disorders of the coagulation system that may manifest with bleeding as early as the neonatal period. According to data published by V. Kunzer (1968), the frequency of neonatal bleeding varies significantly depending on the specific coagulation factor deficiency:

Hemophilia A and B, prothrombin deficiency — approximately 10%

Factor V and factor XI deficiencies (hemophilia C, parahemophilia) — less than 5%

Afibrinogenemia — about 67%

Factor X deficiency (Stuart–Prower disease) — approximately 39%

Factor VII deficiency — around 18%

Factor XIII deficiency — 80–100%

Clinical Presentation

The appearance of bleeding manifestations in an outwardly healthy newborn is highly suggestive of an underlying hereditary defect of the hemostatic system. Of particular concern is the detection of massive intracranial hemorrhages within the first hours or days of life in infants without hypoxia or other perinatal complications, which necessitates immediate and thorough evaluation of coagulation function.

Across all types of hereditary coagulopathies, neonatal bleeding tends to present with similar features. Common manifestations include prolonged bleeding after circumcision, persistent bleeding from the umbilical stump, oozing or bloody discharge from injection sites, formation of large cephalohematomas, and deep hematomas, especially in the gluteal region following intramuscular injections.

Deficiencies involving the prothrombin complex factors are often associated with ecchymoses, epistaxis, and hematemesis. A hereditary coagulation disorder should also be suspected when fresh blood repeatedly appears during lumbar punctures, or when recurrent melena or bloody vomiting occurs, particularly in combination with other signs of bleeding tendency.

Certain features are especially characteristic of afibrinogenemia, including delayed healing of the umbilical wound and other injuries, often accompanied by the formation of keloid scars.

Importantly, hereditary coagulopathies are not limited to postnatal diagnosis—they may be identified during the neonatal period or even antenatally, allowing for early planning of management and prevention of severe bleeding complications.

Hemophilia. Among all hereditary coagulopathies, hemophilia A and B account for approximately 94–96% of cases, making them the most common inherited bleeding disorders. Hemophilia is a genetic disease transmitted in an X-linked recessive pattern and therefore predominantly affects males, while females are usually asymptomatic carriers. Hemophilia B is historically known as Christmas disease.

The disorder is characterized by severely impaired blood coagulation and a pronounced tendency to bleeding, resulting from insufficient activity of key coagulation factors—primarily factor VIII (hemophilia A) or factor IX (hemophilia B) (and, less commonly, factor XI).

Pathogenesis. Under normal conditions, factors VIII and IX are present in plasma in extremely small concentrations—approximately 1–2 mg/100 ml for factor VIII and 0.3–0.4 mg/100 ml for factor IX, corresponding to roughly one molecule of factor VIII per one million molecules of albumin. Despite these low levels, they play a crucial amplifying role in the coagulation cascade.

When either factor VIII or IX is absent or severely deficient, the first phase of coagulation, particularly through the intrinsic activation pathway, is dramatically slowed or may fail entirely. As a result, clot formation becomes ineffective, and bleeding persists.

Clinical Presentation. The clinical picture of hemophilia is dominated by prolonged bleeding following even minimal trauma to the skin or mucous membranes. Patients show a marked tendency toward deep, localized hemorrhages (hematomas) involving the subcutaneous tissue, muscles, joints, and internal organs.

These hemorrhages may occur after minor injuries, trivial blows, or even spontaneously.

Hemophilia most commonly becomes apparent in the second half of the first year of life or during the early second year, when children become more physically active. However, in some cases, symptoms may appear later—or, more rarely, during the neonatal period.

A distinctive feature of hemophilic bleeding is its delayed onset. Bleeding often begins 30 minutes to 4 hours after injury, rather than immediately, and is typically prolonged and resistant to local hemostatic measures. Even routine procedures such as venipuncture, subcutaneous, or intramuscular injections may provoke bleeding that persists for hours or days.

Following intramuscular injections, large and deep hematomas are particularly characteristic. These may compress adjacent nerves, leading to paresis or paralysis. Among all bleeding manifestations, hemarthroses (joint hemorrhages) are the most typical and represent the leading cause of chronic disability in patients with hemophilia due to progressive joint destruction.

Diagnosis and Differential Diagnosis. Diagnosis is based on a combination of family history, clinical findings, and laboratory investigations. A strong diagnostic clue is the presence of male relatives on the maternal side with a history of abnormal bleeding.

Laboratory evaluation reveals a marked prolongation of venous blood clotting time as measured by the Lee–White method (normal ≈ 8 minutes, significantly prolonged in hemophilia). A characteristic finding is a disturbance in the first phase of coagulation, manifested by reduced prothrombin consumption (normally 80–100%), since not all prothrombin is incorporated into the clot.

Additional key diagnostic markers include a prolonged activated partial thromboplastin time (APTT) and reduced plasma levels of factor VIII or IX, which confirm the specific type of hemophilia.

Treatment. In hemophilia, it has the following features: intramuscular injections are prohibited (all drugs can be administered intravenously or prescribed orally); bleeding of any location and severity, swelling and pain in the joint, suspected hemorrhage into internal organs — indications for immediate (even at night!) administration of concentrated antihemophilic drugs; the same should be done in case of trauma with damage to the skin; any surgical interventions are possible only after administration of antihemophilic globulin preparations. Only superficial veins are used for infusions. Currently, the emergence of antihemophilic factor (Hemoktin STD) in treatment, which contains the active substances coagulation factor VIII and FV, has brought significant prospects for improving the prognosis in the treatment of hemophilia. The drug is used for the prevention and treatment of bleeding in hemophilia A.

Local therapy: application of tampons with hemostatic sponge, thrombin, breast milk to the site of bleeding, skin and mucous membrane defects. In cases of hemarthrosis, the joint is immobilised for 3–4 days and an elastic bandage is applied (but not longer). In cases of very severe, painful hemarthrosis, joint puncture and blood removal (by a surgeon!) is indicated after cryoprecipitate transfusion. The effectiveness of local application of cold (ice) is disputed by many.

Von Willebrand disease. Von Willebrand disease (angiohemophilia) is a hereditary disorder, usually transmitted in an autosomal dominant pattern, characterised by increased bleeding tendency combined with prolonged bleeding time, low levels of factor VIII in the blood, and very low (or absent) platelet adhesion to glass and platelet aggregation with ristocetin.

Clinical picture. In severe cases (factor VIII level below 5% of normal), it is virtually indistinguishable from the manifestations of hemophilia. At higher levels of factor VIII, the vascular-platelet type of bleeding comes to the fore: periodic profuse skin hemorrhages, nasal, uterine, and gastrointestinal bleeding (hematomas are also possible, in particular at the site of intramuscular injections and hemarthrosis).

Diagnosis. The disease can only be diagnosed through simultaneous and dynamic study of factor VIII levels and platelet properties, because even the most typical defects for this disease can periodically disappear.

Characteristic defects include: a very sharp increase in bleeding time; low platelet adhesion to glass fibres or glass beads; low blood factor VIII levels; low platelet aggregation with ristocetin. The latter defect is the most persistent. The platelet count is always normal. Endothelial tests can be either positive or negative.

Treatment. For all forms of BV, infusions of FFP (15 ml/kg) as a hemostatic agent or cryoprecipitate, factor VIII concentrate (20 IU/kg of patient body weight) 14 14 15 14 32 19 30 containing both factor VIII and factor V are highly effective. As with hemophilia A, aminocaproic acid (0.05 g/kg 4 times a day orally) and dicynone are indicated. Acquired coagulopathies include bleeding caused by liver disease. Hepatic hemorrhagic syndrome occurs in severe hepatitis, congenital fetal edema, cirrhosis of the liver as a result of galactosemia, α1-antitrypsin deficiency, and tyrosinemia. Usually, the liver is sharply enlarged, dense, jaundiced, ascites, often skin hemorrhagic manifestations, melena, hematemesis. A deficiency of blood clotting factors synthesized by the liver, as well as antithrombin III, is typical. Due to necrosis of liver cells and damage to the vascular endothelium, decompensated DIC syndrome and thrombocytopenia are possible.

Treatment consists of replacement transfusion of fresh frozen plasma at a dose of 10-15 ml/kg intravenously by drip.

THROMBOCYTOPENIA IN NEWBORNS

Thrombocytopenia is the most frequently encountered disorder of hemostasis in the neonatal period. Despite its high prevalence, it is often underrecognized and does not always have clinical significance. By definition, thrombocytopenia is a reduction in the platelet count of peripheral blood to below 150,000/μL.

Classification. From a pathogenetic standpoint, neonatal thrombocytopenia develops as a result of:

Increased platelet consumption or destruction

Impaired platelet production

A mixed (combined) mechanism

I. Thrombocytopenia Due to Increased Platelet Destruction

1. Immunopathological forms

Transimmune (autoimmune)

Isoimmune (alloimmune)

2. Vasopathies

Large hemangiomas (Kasabach–Merritt syndrome)

Shock (infectious-toxic, hypoxic, etc.)

Systemic inflammatory response syndrome (septic, hypoxic)

Pulmonary pathology:

Respiratory distress syndrome of any origin

Aspiration syndrome

Pneumonia

Pulmonary hypertension

Infections without systemic inflammatory response

3. Disseminated intravascular coagulation (DIC) syndrome

4. Thrombocytopathies

Primary hereditary: Wiskott–Aldrich syndrome, May–Hegglin anomaly, Shwachman–Diamond syndrome, etc.

Secondary acquired: Drug exposure, hyperbilirubinemia, immune complex disorders, severe metabolic acidosis, generalized viral infections, phototherapy, prolonged total parenteral nutrition, and certain inherited metabolic diseases

5. Thrombotic conditions

Isolated or generalized thrombosis due to trauma

Congenital anticoagulant deficiencies (antithrombin III, protein C, etc.)

Maternal antiphospholipid syndrome

6. After extracorporeal or replacement procedures

Exchange transfusions

Plasmapheresis

Hemadsorption

7. Drug-related platelet consumption

Heparin

Talazoline

Intralipid

II. Thrombocytopenia Due to Impaired Platelet Production

1. Megakaryocytic hypoplasia

Isolated forms

TAR syndrome

Aplastic anemia

Congenital leukemia

Neuroblastoma

Chromosomal disorders (trisomies 9, 13, 18, 21)

2. Reduced thrombopoiesis associated with

Polycythemia

Severe asphyxia following intrauterine hypoxia

Severe infections and sepsis

Maternal drug therapy (e.g., tolbutamide, thiazides)

Preeclampsia and eclampsia

Extremely low birth weight

Severe antenatal hypoxia

Cold stress

Hemolytic disease of the newborn

Deficiency of thrombopoietin synthesis

Downregulation syndrome

III. Thrombocytopenia of Mixed Etiology

Thyrotoxicosis

Histiocytosis

Primary and Secondary Thrombocytopenia

Clinically, neonatal thrombocytopenia is divided into primary and secondary forms.

Primary thrombocytopenic purpura occurs in otherwise healthy newborns, where thrombocytopenia and bleeding are the only abnormalities present. In the vast majority of cases, this form is immune-mediated, either transimmune (autoimmune) or alloimmune, and represents a distinct group requiring targeted diagnostic and therapeutic approaches.

Transimmune (Autoimmune) Thrombocytopenic Purpura. Transimmune thrombocytopenic purpura develops as a result of transplacental transfer of maternal antiplatelet autoantibodies or sensitized lymphocytes directed against platelets. This condition is observed when the mother suffers from idiopathic thrombocytopenic purpura (ITP), systemic lupus erythematosus, or Evans syndrome.

Importantly, even if a woman had ITP only in childhood or achieved complete remission after splenectomy or conservative therapy—with normal platelet counts during pregnancy—the risk of neonatal thrombocytopenia remains significant. In such cases, the probability of thrombocytopenia in the newborn is approximately 50%, and a similar proportion of affected infants develop clinically evident bleeding.

There is no direct correlation between the severity of maternal thrombocytopenia during pregnancy or delivery and the degree of thrombocytopenia in the child. Clinically significant bleeding usually appears when the platelet count falls below 25,000–30,000/μL (Frank's threshold).

Typical clinical manifestations include cutaneous hemorrhagic syndrome (petechiae and ecchymoses), bleeding from mucous membranes, melena, and epistaxis. Apart from hemorrhagic signs, newborns are generally otherwise healthy. Intracranial hemorrhages are possible but rare, and when they occur, they are often accompanied by scleral hemorrhages.

A characteristic feature of the disease course is that the later bleeding appears after birth, the milder the clinical manifestations tend to be. Thrombocytopenia usually persists for 1.5–2 months, although the intensity of bleeding decreases sharply after the first two weeks, provided no additional provoking factors are present. Progression of transimmune thrombocytopenia to chronic ITP is uncommon, occurring in less than 5% of cases.

Diagnosis. Diagnosis is based on a careful maternal history and the laboratory detection of high levels of IgG or antiplatelet antibodies on the surface of maternal platelets.

Treatment. For mothers with ITP or systemic lupus erythematosus, delivery by cesarean section is recommended due to the increased risk of intracranial hemorrhage in thrombocytopenic newborns.

After birth, infants are fed with formula for the first two weeks, followed by the introduction of breastfeeding under strict monitoring of platelet counts.

The most effective treatment approach includes:

Intravenous immunoglobulin (IVIG) at a dose of 0.4–1 g/kg daily for 5 days

Prednisolone at 2 mg/kg/day

Glucocorticoid therapy is reserved for severe thrombocytopenia and should not exceed one week, as prolonged treatment may suppress platelet production. In cases of critically low platelet counts or confirmed intracranial hemorrhage, platelet transfusions are indicated.

If bleeding is limited to the skin, symptomatic therapy may be sufficient and includes: ε-aminocaproic acid (0.05 g/kg orally, four times daily; only after excluding DIC). Calcium pantothenate (0.01 g orally, three times daily). Etamsylate sodium (dicynone) (0.05 g orally, three times daily)

Alloimmune Thrombocytopenic Purpura (ATP). According to various authors, alloimmune thrombocytopenic purpura develops in approximately 1 out of 350–1000 newborns and is responsible for 3–10 cases of intracranial hemorrhage per 100,000 births, making it one of the most dangerous immune-mediated bleeding disorders in the neonatal period.

The pathogenesis of ATP is conceptually similar to that of hemolytic disease of the newborn; however, the immunological conflict in this case is caused exclusively by platelet-specific antigens. Most commonly, ATP develops when the mother lacks, but the fetus inherits from the father, the PLA1 platelet antigen.

Maternal sensitization leads to the production of antibodies that cross the placenta and destroy fetal platelets.

Clinically, alloimmune thrombocytopenic purpura is more severe than transimmune (autoimmune) thrombocytopenia. The disease is characterized by a pronounced skin hemorrhagic syndrome, frequently accompanied by gastrointestinal bleeding. Intracranial hemorrhages occur in 10–15% of affected infants, and mucosal bleeding is typically more intense and extensive. A notable clinical feature is that the later bleeding begins after birth, the more severe the disease course tends to be.

Diagnosis. Diagnosis is based on a combination of immunological and clinical findings, including:

Elevated levels of IgG on the newborn's platelets

Detection of antiplatelet antibodies in the mother's serum

Normal levels of platelet-bound IgG in the mother

Agglutination of the newborn's platelets when exposed to maternal serum

It is important to emphasize that, aside from bleeding manifestations, affected newborns are otherwise clinically normal. Hepatomegaly and splenomegaly are absent, and there are no signs of systemic inflammation. The presence of inflammatory foci, additional hematologic abnormalities (other than thrombocytopenia), or organ enlargement should prompt evaluation for alternative causes of thrombocytopenia.

Treatment and Care. Initial management includes feeding with milk formula for 1–2 weeks to reduce the intake of maternal antibodies.

In cases of severe bleeding with a confirmed diagnosis, treatment includes:

Transfusion of platelet concentrate prepared from 250–300 ml of maternal blood. Intravenous immunoglobulin (IVIG) at a dose of 1.0 g/kg body weight daily for 3–5 days. Prednisolone at 2 mg/kg/day for 3–5 days, with discontinuation within one week. Mild bleeding is managed with symptomatic therapy alone.

The risk of recurrence of ATP in subsequent pregnancies is high—approximately 75%. Moreover, bleeding severity in subsequent affected infants is usually equal to or greater than that observed in the first child. Therefore, when a fetus is considered to be at high risk for ATP, prenatal intervention may be required. Under ultrasound guidance, the fetal umbilical vein is catheterized, and if ATP is confirmed, the fetus receives: Intravenous immunoglobulin at 1 g/kg of fetal body weight once weekly, combined with Dexamethasone (3–5 mg) or washed maternal platelets

Hypoplastic Thrombocytopenic Purpura. Hypoplastic thrombocytopenic purpura in newborns is a rare condition caused by impaired platelet production due to developmental defects of the bone marrow. It may result from isolated hypoplasia of the megakaryocytic lineage, often associated with skeletal anomalies such as absence of the radial bones (Landolt syndrome) or phocomelia. In more severe cases, hypoplasia involves all hematopoietic cell lines, as seen in aplastic anemia, Fanconi pancytopenia, congenital leukemia, osteopetrosis, and congenital histiocytosis. The mode of inheritance is typically autosomal recessive.

Clinically, the disorder manifests with thrombocytopenia and bleeding, including purpura, epistaxis, intestinal bleeding, and other hemorrhagic signs. In most cases, symptoms become apparent within the first days of life, although later onset is occasionally observed. Diagnosis is based on the combination of early-onset bleeding and persistently low platelet counts, supported by bone marrow findings and associated congenital anomalies.

Kasabach–Merritt Syndrome. Kasabach–Merritt syndrome is characterized by severe thrombocytopenia associated with large cavernous hemangiomas. The underlying mechanism is excessive platelet sequestration and consumption within the abnormal vascular structures. In addition to platelets, coagulation factors—reflected by low plasma fibrinogen levels—and erythrocytes may also be consumed.

This consumptive process can lead to microangiopathic hemolytic anemia, with characteristic fragmented erythrocytes (schistocytes) detectable in the peripheral blood smear.

Treatment. Treatment depends on the underlying mechanism and severity of consumption. In cases where consumption of plasma coagulation factors is confirmed, transfusion of fresh frozen plasma is indicated to restore hemostatic balance. In addition, the use of platelet aggregation inhibitors—dipyridamole (Curantil) and acetylsalicylic acid—each administered at a total daily dose of 5 mg/kg divided into three oral doses, has been shown to reduce platelet trapping within hemangiomas. This approach often leads to normalization of platelet counts and coagulation parameters.

Wiskott-Aldrich syndrome is a hereditary disease (familial thrombocytopenia with eczema and low immunological reactivity). This disease is inherited recessively, is associated with the X chromosome, and occurs in boys. It is characterised by a triad of symptoms: hemorrhagic phenomena (on the skin and intestinal bleeding), eczema, and infectious pathology (otitis, sepsis, etc.). Hematologically, thrombocytopenia with pronounced eosinophilia and a normal number of megakaryocytes in the bone marrow are detected. The course is chronic.

The prognosis is unfavourable. Wiskott-Aldrich syndrome differs from Verelhof disease in its typical clinical picture and hereditary nature of transmission characterised by a combination of X syndromes with recurrent purulent infections due to immunodeficiency states.

Table 6.

Principles of treatment of hemorrhagic syndrome in newborns

Causes	Treatment
Coagulopathies: Primary GrBN	Vikasol + SZP
Secondary Gr BN	Same
Hereditary deficiency of blood coagulation factors (VII, VIII, II, IX, XI)	SZP, with factor VIII deficiency - cryoprecipitate (0.5 doses)
Hereditary factor XIII deficiency	SZP

Thrombocytopenia, thrombocytopathy Isoimmune TP	Standard Ig for intravenous administration, dicynone, in severe cases ZPK
Transimmune TP	Standard Ig for intravenous administration, dicynone, prednisolone, in severe cases ZPK
Thrombocytopathy (most often drug-induced)	Discontinuation of relevant drugs
TAR syndrome	Thromboconcentrate
Kazabakh-Merritt syndrome	Thromboconcentrate, surgical treatment of haemangioma, erythromass anaemia
Kazabakh-Merritt syndrome	Thromboconcentrate, surgical treatment of haemangioma, erythromass anaemia
Wiskott-Aldrich syndrome	Pentaglobin, dicynone
Haemorrhagic syndrome of mixed origin: DIC	Treatment of the underlying disease, SZP, heparin

DISSEMINATED INTRAVASCULAR BLOOD CLOTTING (DIC)

This is a non-specific hemostasis pathology based on disseminated blood clotting in the vessels with the formation of multiple microclots and blood cell aggregates that block blood circulation in organs and tissues, causing profound dystrophic changes with subsequent development of hypocoagulation, thrombocytopenia and hemorrhages due to consumption coagulopathy.

Synonyms for *DIC* are consumption coagulopathy, defibrination syndrome, intravascular coagulation with secondary fibrinolysis, thrombohemorrhagic consumption disorder. DIC is not an independent disease; it does not occur without some kind of impact that activates the coagulation system.

The most common *causes* of DIC syndrome in newborns (Hathaway W.E., 1987). Infections leading to massive damage to the vascular endothelium and shock:

• bacterial sepsis;

• candidiasis;

• generalised herpes infection;

• congenital rubella and cytomegaly.

Hypoxia - acidosis - ischamia:

• severe asphyxia during labour;

• post-hemorrhagic shock;

• dehydration shock;

• respiratory distress syndrome (hyaline membrane disease);

• meconium aspiration syndrome;

• apneic episodes;

• atelectasis, pneumonia;

• pulmonary hemorrhages. Cold injury. Polycythemia.

Tissue damage and release of tissue thromboplastin:

• obstetric disorders, placental diseases;

• premature placental abruption;

• ZVUR;

• Maternal hypertension;

• death of one fetus in twins;

• placental chorioangioma;

• widespread thrombosis;

• fulminant purpura;

• necrotising enterocolitis;

• tumours and leukemia;

• brain damage (necrosis and hemorrhages). Other causes:

. GBN;

• liver disease;

• giant hemangioma.

The leading causes of DIC syndrome are generalised infections (bacterial and viral), septicemia, immune complex processes, and pregnancy complications. Frequent causes of this syndrome are iatrogenic effects: treatment with drugs that cause platelet aggregation, increase blood clotting, drugs with defibrinating and fibrinolytic action, drugs that reduce the anticoagulant and fibrinolytic potential of blood, as well as prolonged artificial lung ventilation.

In newborns who are born healthy and full-term, DIC syndrome is extremely rare.

Predisposing factors for the development of DIC syndrome in newborns:

— underdevelopment of the reticuloendothelial system, which ensures removal of intermediate coagulation products;

— inadequate vascularisation at the microcirculatory level;

— insufficient capacity for compensatory synthesis by the liver of blood coagulation factors fibrinogen, vitamin K-dependent factors, AT-III and plasminogen.

In premature infants, babies with intrauterine growth restriction (IUGR), and those who developed under conditions of chronic intrauterine hypoxia, the hemostatic system is profoundly immature and imbalanced. In these infants, the activity of both procoagulant and anticoagulant factors, as well as contact activation factors, is significantly reduced. At the same time, fibrinolytic activity is relatively increased, despite low plasminogen levels, and platelet aggregation capacity is diminished. These abnormalities are further compounded by increased permeability and fragility of the vascular wall.

As a result, these newborns exist in a precarious hemostatic state. They are simultaneously predisposed to bleeding and thrombotic events, as the initially heightened fibrinolytic response and limited anticoagulant reserves are rapidly exhausted during the first hours and days of life.

Hypoxia, which is commonly accompanied by metabolic acidosis and reduced peripheral perfusion, plays a central role in triggering disseminated intravascular coagulation (DIC). In this context, DIC develops primarily through tissue injury and mediator release, rather than through platelet dysfunction or activation of the intrinsic coagulation pathway. This mechanism predominates in hypoxic newborns.

In addition, hypoxia causes direct hepatic injury, leading to a marked reduction in the synthesis of coagulation factors by the liver. This hepatic component further aggravates coagulation instability and significantly contributes to the overall hemostatic failure observed in these vulnerable infants.

Classification of DIC syndrome

By pathogenesis:

1. Infectious-septic.
2. Primarily aseptic (often transformed into infectious-septic

septic):

• associated with the destruction of organs, tissues and cells (burns, compression syndrome, acute intravascular hemolysis, amniotic fluid embolism, intrauterine fetal death, etc.);

• neoplastic (tumours, leukemia, etc.).

Based on clinical course, the following are distinguished:

1. Acute DIC syndrome, developing suddenly within 24 hours (including the fulminant (catastrophic) form).
2. Subacute DIC syndrome, lasting 1–3 weeks.
3. Chronic DIC syndrome, lasting more than 1 month (with a prolonged period of hypercoagulation and/or platelet hyperaggregation), including in chronic inflammatory and immunoinflammatory processes and chronic hemolysis.
4. Latent DIC syndrome, occurring without clinical manifestations, diagnosed by laboratory tests.

Stages of DIC syndrome:

1. Stage I — hypercoagulation (possible decrease in platelet aggregation function and activation of fibrinolysis).
2. Stage II — transitional with increasing coagulopathy and thrombocytopenia, multidirectional shifts in general coagulation tests.
3. Stage III — profound hypocoagulation (up to complete blood coagulation failure) with pathological fibrinolysis.

4. Stage IV — recovery (or, in unfavourable cases, the phase of outcomes and complications).

Pathogenesis of DIC syndrome. The pathogenesis of disseminated intravascular coagulation syndrome is based on profound dysfunction of all components of the hemostasis system, characterised by their sequential activation and depletion. For this reason, there is a change in the phases of DIC syndrome from hypercoagulation and high spontaneous platelet aggregation at the beginning to a transitional period and subsequent profound hypocoagulation, up to complete blood coagulopathy and thrombocytopenia at the end.

The first stage is *hypercoagulation.* The nature of the syndrome or the rate of its development is determined by the duration of the first stage. In acute DIC, its duration is 15–20 minutes. In rapid DIC, it can be sharply reduced. Intravascular blood clotting is accompanied by the consumption of coagulants, anticoagulants, and platelets in the process of their irreversible aggregation. There is pronounced generalized hyperplastinemia. Blood sampling from a vein is not possible at this stage due to needle thrombosis.

The concentration of thrombin in plasma increases rapidly, leading to the formation of a large number of fibrin monomers from fibrinogen, which do not have time to polymerise due to a relative deficiency of factor XIII and bind to fibrinogen molecules, further hindering the fibrin polymerisation process.

Loose thrombi are formed. They consist of fibrin, which has a gel-like consistency, aggregates of platelets and erythrocytes, and, in the case of sepsis, leukocytes. These thrombi differ significantly in structure from classic wall-adherent thrombi that form in large vessels. These loose blood clots, which are not attached to the vessel wall and contain unstable (soluble) fibrin, can be called prethrombi.

In some cases of DIC syndrome, initiated by primary damage to the endothelial lining, microthrombi are formed that are attached to the vascular wall and usually contain insoluble stable fibrin. Circulating microthrombi are emboli and block small vessels, thereby disrupting microcirculation in organs and tissues. Severe tissue hypoxia, metabolic acidosis, and uncorrectable hemodynamic disturbances develop.

The second stage is *consumption coagulopathy* with sub-stages 2a and 2b.

Stage 2a is characterised by depletion of coagulation factors due to their consumption without excessive activation of fibrinolysis. Blood clotting time is usually within normal limits. Under conditions of tissue hypoxia, the release of tissue thromboplastin from the vascular wall increases, further activation of blood coagulation occurs, and procoagulants are consumed again. Thus, a "vicious circle" develops, leading to complete depletion of the blood coagulation system.

In stage 2b, progressive activation of fibrinolysis occurs against a background of increasing hypocoagulation. Activation of fibrinolysis has an adaptive significance, as it contributes to the partial release of microthrombi from the microcirculatory bed and the elimination of tissue ischemia. The number of platelets in the plasma decreases and the fibrinogen content gradually decreases. In addition, the concentration of PDFs increases, which bind to fibrinogen to form soluble fibrin monomer complexes (SFMCs), which increases the existing fibrinogen deficiency.

Picture 9. DIC in a newborn

The third stage is *hypocoagulation* (pathological fibrinolysis). This stage is characterised by the depletion of all coagulation factors and anticoagulants, severe hypofibrinogenemia and thrombocytopenia, as well as pathological enhancement of fibrinolytic activity (secondary hyperfibrinolysis caused by high thrombinaemia). Fibrinolysis and fibrinogenolysis occur in parallel, leading to a ten- to hundredfold increase in the level of PDF in the blood. As a result of the interaction of PDF with fibrinogen molecules and fibrin monomers, a huge amount of RFMC, resistant to the action of thrombin, is formed. Activation of the plasma kallikrein-kinin system, closely associated with the activation of Hageman factor, leads to an increase in the permeability of the vascular wall and a decrease in its tone. The accumulation of activated proteases, including late components of the C5-C9 complement system, causes the appearance of poikilocytes and schizocytes in the peripheral bloodstream.

The fourth stage is *the outcome stage* or the stage of residual manifestations of microthrombus vascular blockage.

Disseminated intravascular coagulation (DIC) syndrome may act as a key trigger for the development of multiple organ failure syndrome (Fig. 3). This severe systemic condition is characterized by the simultaneous or sequential failure of several vital organs, including the development of acute renal failure, hemolytic–uremic syndrome, respiratory distress syndrome, and acute adrenal insufficiency known as Waterhouse–Friderichsen syndrome.

The clinical presentation of DIC is nonspecific, which often complicates early diagnosis. One of the earliest and most consistent signs is prolonged bleeding from injection sites, venipuncture wounds, and surgical incisions. A cutaneous hemorrhagic syndrome of varying intensity is commonly observed, ranging from petechiae to extensive ecchymoses. In addition, spontaneous bleeding may occur, including nasal, pulmonary, and gastrointestinal hemorrhages, often presenting as melena.

Bleeding may also involve internal organs, particularly the lungs, kidneys, gastrointestinal tract, and brain. At the same time, paradoxical thrombotic manifestations develop as a result of widespread microvascular clot formation. These include skin necrosis, acute renal failure due to renal vascular thrombosis, and acute adrenal insufficiency, which results from hemorrhage and necrosis of the adrenal glands. Other signs of vascular thrombosis include swelling of the limbs, acrocyanosis, and generalized cyanosis.

Neurological involvement is frequent and manifests as varying degrees of central nervous system depression, focal neurological symptoms, and progressive deterioration of consciousness. Respiratory failure, including an adult-type respiratory distress syndrome, further contributes to the severity of the condition.

Thus, newborns with decompensated DIC syndrome typically develop multiple organ failure, which may occur with or without prominent hemorrhagic manifestations. In the majority of infants who progress to stage III DIC, microangiopathic hemolytic anemia develops, reflecting extensive intravascular red blood cell destruction within the microcirculation.

Damage to the nervous system, up to and including coma and convulsions, is both a sign of changes in the brain and a reflection of the degree of peripheral blood flow decompensation, i.e. shock. Chronic DIC syndrome manifests itself as mild trauma and bleeding from the mucous membranes, impaired kidney function, and transient neurological syndromes. Thrombophlebitis is common.

Diagnosis of DIC Syndrome. The diagnosis of disseminated intravascular coagulation (DIC) syndrome is based on a combination of the clinical picture and urgent laboratory evaluation. Because DIC is a rapidly evolving and potentially life-threatening condition, laboratory diagnostics must be performed without delay and follow a clearly structured, stepwise approach using simple, rapidly available tests.

Importantly, laboratory investigations should not only confirm the presence of DIC, but also reflect the stage (phase) and clinical form of the syndrome, while simultaneously allowing for dynamic monitoring of ongoing therapy (Table 5).

Two diagnostic levels are distinguished:

“Express diagnostics”, which provides essential information on the state of hemostasis within 20–30 minutes

The “working program”, which enables a more detailed and comprehensive evaluation of coagulation abnormalities.

Express Diagnostics of DIC Syndrome. Rapid ("express") diagnostics form the cornerstone of early DIC detection and include the following key tests:

Platelet count

A decrease in platelet number is one of the earliest and most sensitive indicators of DIC. If the platelet count remains within normal limits, the presence of acute or subacute DIC syndrome is unlikely, particularly in the neonatal period.

Whole blood clotting time (Lee–White method).

This test reflects a deficiency of most plasma coagulation factors, with the exception of factors VII and XIII. Prolongation of clotting time indicates significant impairment of the coagulation system and supports the diagnosis of DIC.

This rapid diagnostic framework allows clinicians to quickly assess the severity and direction of hemostatic disturbances and initiate timely, targeted therapy while awaiting more detailed laboratory results.

Table 7.

Laboratory indicators in the dynamics of DIC syndrome (E. T. Zubovskaya, 2009)

Indicator	**Stage of DIC syndrome**				
	Normal	**I**	**II**	**III**	**IV**
Platelet count	150 400× 109/L	300	150	100 and below	200
Blood clotting time Blood, min	5	less than 4	10–20	12–20	7–10
ACTV,	45–55	less than 40	50	more than 60	45
Fibrinogen, g/l	3.0	2–3	2 and less	1.5 and less	1.5–2
Thrombin time, s	18–20	18 and less	25–28	30–35	18–22
Thrombin time, s	18–20	18 and below	25–28	30–35	18–22
PDF, mcg/ml	0–10	20 and above	15 and above	20–25	30–40

Laboratory Diagnosis and Staging of DIC Syndrome. Further laboratory evaluation of disseminated intravascular coagulation (DIC) syndrome relies on tests that assess both coagulation factor depletion and activation of fibrinolysis. These indicators not only confirm the diagnosis, but also help determine the stage of DIC and guide ongoing treatment.

Activated partial thromboplastin time (APTT). Measurement of APTT allows detection of deficiency of all plasma coagulation factors except factors VII and XIII. Prolongation of APTT reflects progressive consumption of coagulation factors.

Thrombin time (TT). Thrombin time is prolonged to varying degrees depending on the phase of DIC and the concentration of fibrinogen. Its prolongation reflects both hypofibrinogenemia and the inhibitory effects of fibrin degradation products (FDPs).

Fibrinogen concentration. A fibrinogen level below 1.5 g/L indicates hypofibrinogenemia. A level below 0.5 g/L is diagnostic of afibrinogenemia

D-dimer test. The D-dimer reflects the concentration of fibrin degradation products, which are generated when plasmin breaks down fibrin clots. Elevated D-dimer levels indicate active fibrinolysis and are seen in DIC, venous thrombosis, pulmonary embolism, and liver damage.

According to Walters D.V., normal D-dimer values range from 0.5–1.0 μg/mL (500–1000 ng/mL).

Laboratory Changes Across the Stages of DIC. The most pronounced disturbances in hemostasis occur during the second and third stages of DIC syndrome.

Stage II (Consumption–Hypercoagulation Phase). This stage is characterized by mixed laboratory findings, reflecting simultaneous hypercoagulation and emerging hypocoagulation:

Blood clotting time and APTT may be shortened or remain normal;

Prothrombin index decreases to 50% or lower;

Fibrinogen concentration falls to 0.9–1.1 g/L or less;

Thrombin time is prolonged, due to hypofibrinogenemia and the antithrombin and antipolymerase effects of FDPs;

Plasma FDP levels rise significantly, often exceeding 10 μg/mL and reaching 40–120 μg/mL, reflecting secondary activation of fibrinolysis;

Platelet count decreases to 100–50 × 10^9/L, and platelet function deteriorates;

Platelets exhibit hypoaggregation in response to ADP, collagen, and adrenaline. Clinically, DIC becomes apparent when:

Fibrinogen falls below 1 g/L

Prothrombin index drops below 45%

Platelet count decreases below 90 × 10^9/L

Stage III (Hypocoagulation–Depletion Phase)

As DIC progresses and multiple platelet–fibrin microthrombi form within the microcirculation, a profound depletion of all hemostatic components develops:

Fibrinogen decreases to 0.5 g/L or less

Prothrombin index falls below 40%

FDP levels rise sharply

Plasminogen concentration decreases

Thrombin time becomes markedly prolonged

Blood clotting time is either undetectable or extremely prolonged

Severe thrombocytopenia and thrombocytopathy develop

Platelets lose their ability to aggregate entirely

Clinically, this stage manifests as a severe hemorrhagic syndrome, often life-threatening.

Stage IV (Recovery or Residual Phase)

If treatment is successful, DIC enters stage IV, in which acute coagulation disturbances subside. However, the clinical picture is dominated by the consequences of prior intravascular coagulation, including:

Thrombosis and thromboembolism

Residual hemorrhages

Ischemic and dystrophic changes in organs and tissues

Table 8.

Laboratory diagnosis of the main causes of hemorrhagic syndrome in newborns

Тест		АПТВ	ПТВ	ПТИ	МНО	ТВ	фI	Тромбо-циты	d D
Геморрагическая болезнь		↑	↑	↓	↑	N	N	N	N
ДВС	1 фаза	↓	↑	↓		↓	↑	N	↑
	2 фаза	↑	↑	↓	↑	↑	↓	N ↓	↑
	3фаза	↑↑	↑	↓	↑	↑	↓↓	↓ ↓	↑
Поражение печени		↑	↑	↓	↑	↓	↓	N	
Тромбоцитопения		N	N	N	N	N	N	↓↓ ↓	N

Legend: N – normal level of the indicator;

↑↑ significant increase (elongation) of the indicator;

↑ increase (elongation) of the indicator;

↓ decrease (shortening) of the indicator;

↓↓ significant decrease (shortening) of the indicator

Coagulogram indicators are gradually normalising. At this stage, the hemostasiogram indicators are also divergent.

According to ICD-X, the disease is registered under the heading: P60 Disseminated intravascular coagulation in the foetus and newborn.

The treatment of patients with DIC syndrome is an art based on a combination of knowledge, the ability to observe and notice, analyse and synthesise, make quick decisions and evaluate "feedback" — the patient's response to therapy. In most cases, active therapy is carried out.

Stages of therapy

- Correction *of hypoxemia* (oxygen therapy, including mechanical ventilation)

- Administration of SZP to replenish the deficiency of procoagulants and anticoagulants (since a deficiency is typical for newborns antithrombin III) and restoration of blood anti-protease activity.

Picture 10. Fresh frozen plasma

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- Correction of *hypovolemia* and *anemic syndrome* (colloids, FFP transfusion, 0.9% NaCl, and hemotransfusion in severe anemia)
- Correction of *hemodynamic* disorders (cardiotonics - dopamine+\-dobutamine, vasopressors (adrenaline) or, in cases of adrenal insufficiency, GCS)
- Correction of acidosis (ventilator, in cases of decompensated metabolic acidosis – 4% p-pNaHC03)
- Correction of *hemostasis* disorders (proteolysis inhibitors = fibrinolysis inhibitors: gordox/contrycal)
- Treatment of infectious syndrome (antibiotic therapy, immunotherapy)
- *Detoxification* (maintaining adequate diuresis, efferent detoxification methods - plasmapheresis, etc.)

Heparin Therapy: When Clotting Turns Against the Newborn. In newborns, heparin therapy is never routine—it is a deliberate response to clear signs that coagulation has crossed the line from protection to destruction. Anticoagulation becomes necessary only when thrombosis declares itself clinically: gangrenous or necrotic skin lesions, acute renal failure, or unmistakable syndromes of large-vessel thrombosis. These signs signal that microcirculatory and macrovascular clotting is actively threatening organ survival.

Before heparin can be allowed to act, the body must be prepared to respond to it. Heparin is ineffective without antithrombin III, its essential cofactor. Therefore, therapy begins not with heparin, but with fresh frozen plasma transfusion, restoring depleted antithrombin reserves. Only once this physiological foundation is rebuilt can anticoagulation safely proceed.

In newborns with confirmed thrombosis or unequivocal decompensated DIC, treatment starts decisively. A loading dose of heparin (75–100 IU/kg) is administered intravenously over 10 minutes, followed by a continuous infusion of 25 IU/kg per hour. This regimen aims to halt further clot propagation while preserving what remains of the fragile hemostatic balance.

When thrombosis is suspected rather than proven, and ultrasound findings are inconclusive, caution prevails. In these cases, a gentler approach is chosen: a loading dose of 25–40 IU/kg and a maintenance infusion of 10–15 IU/kg per hour. This strategy acknowledges a fundamental neonatal paradox—the same child can bleed and clot simultaneously.

Modern neonatology increasingly favors low-molecular-weight heparins such as fraxiparin and enoxaparin. These agents act with greater specificity against factor Xa, persist longer in circulation, and—critically—do not grossly distort standard coagulation tests when used in low to moderate doses. Their pharmacologic predictability makes them especially suited to the unstable hemostatic terrain of the newborn.

Stopping heparin is as important as starting it. Abrupt withdrawal is avoided, as it may provoke rebound thrombosis. Instead, doses are tapered gradually, and platelet antiaggregants, most commonly dipyridamole (Curantil), are introduced to support microcirculatory flow during recovery.

Prevention: Stopping DIC Before It Begins

True prevention of DIC does not start in the coagulation cascade—it begins earlier, with the prevention of critical systemic insults. Hypoxia, infection, shock, metabolic derangements, and endothelial injury are the real architects of DIC; controlling them is the most effective prophylaxis.

Technology also plays a quiet but powerful role. Advances in vascular catheter design have reduced their thrombogenic potential, lowering the risk of catheter-induced endothelial damage. When total parenteral nutrition is delivered through vascular access, it is common practice to add heparin directly to infusion solutions. A concentration of 1.0 IU per 1 ml of infused fluid provides a continuous intake of 3–5 IU of heparin per hour, helping to prevent catheter-associated thrombosis.

Yet even prevention must respect neonatal vulnerability. In premature infants, whose cerebral vasculature is exceptionally fragile, this approach carries a risk. To reduce the likelihood of intraventricular hemorrhage, lower concentrations—0.5 IU per 1 ml of infused fluid—are used, striking a careful balance between thrombosis prevention and bleeding risk.

THROMBOSIS AND EMBOLISM IN NEWBORNS

The true frequency of thrombotic and embolic events in newborns remains difficult to define, largely because many episodes develop silently and escape clinical detection. However, targeted studies reveal a striking reality: thrombi are identified in 9–10% of deceased newborns, and among infants who require prolonged vascular catheterization, thrombotic lesions are detected in as many as 20–60% of cases. These findings suggest that neonatal thrombosis is far more common than traditionally assumed.

At the core of thrombus formation lie three interdependent mechanisms, classically described as a neonatal adaptation of Virchow’s triad:

Damage or dysfunction of the vascular wall

In newborns, the endothelium is particularly vulnerable. Mechanical injury from vascular catheters, inflammatory mediators, hypoxia, or ischemia disrupts endothelial integrity, transforming the vessel wall from an anticoagulant surface into a powerful trigger of coagulation.

Disturbances of blood flow

Slowed or turbulent circulation promotes platelet adhesion and fibrin deposition. This is especially relevant in conditions such as hypotension, shock, cardiac dysfunction, venous stasis around catheters, or impaired microcirculation in critically ill infants.

Altered rheological properties of blood.

The fluidity of neonatal blood is easily compromised. Polycythemia, severe dehydration, and hypoxia increase blood viscosity, slowing flow and enhancing cellular aggregation. In addition, congenital deficiencies of natural anticoagulants further shift the balance toward thrombosis, even in the absence of overt vessel injury.

Together, these factors create a fragile equilibrium in which the neonatal circulation can rapidly tip from physiological adaptation to pathological clot formation. In this context, thrombosis is not an isolated event, but the end result of overlapping vascular, hemodynamic, and hematological vulnerabilities.

Pathogenesis

In newborns, abnormalities and damage of the vascular wall are most commonly associated with invasive interventions, particularly the use of vascular catheters. Arterial catheters pose the greatest risk, as they can directly injure the vessel wall and initiate thrombus formation. Additional contributing factors include delayed closure of the ductus arteriosus and the development of thrombi within the duct, which may later serve as a source of embolization.

The state of the hemostatic system at birth can be broadly described as a tendency toward “hyperhemostasis” and thrombosis. This reflects the physiological hypercoagulable state of the mother, which is transferred to the newborn during the perinatal period. Immediately after delivery and placental separation, maternal hemostasis is programmed to prevent excessive blood loss from the large placental detachment site—effectively a major wound—resulting in a strong procoagulant bias.

This physiological orientation is mirrored in the newborn. Neonatal blood clots more rapidly in vitro than the blood of older children. One of the key mechanisms underlying this phenomenon is the reduced concentration of natural anticoagulants, including antithrombin III and proteins C and S, in neonatal plasma. At the same time, the levels of factor VIII and von Willebrand factor are significantly higher in newborns than in adults, further enhancing coagulation potential.

In contrast, the fibrinolytic system in newborns—particularly in premature infants—is functionally fragile. Due to low plasminogen levels, fibrinolysis is easily exhausted, limiting the ability to dissolve formed clots. This imbalance between enhanced coagulation and insufficient fibrinolysis creates a delicate hemostatic equilibrium, predisposing newborns to thrombotic complications, especially in the presence of additional risk factors.

Important factors contributing to the development of thrombosis:

- vascular catheters;
- polycythemia;
- hyperthrombocytosis (e.g., in neonatal candidiasis);
- shock and severe bacterial and viral infections with vasculitis;
- antiphospholipid syndrome in the mother;
- hyperuricemia.

Role of Hereditary Factors in Neonatal Thrombosis

Hereditary predisposition plays a significant role in the development of thrombosis in newborns. To date, multiple genetically determined thrombophilic conditions have been identified, each affecting different components of the hemostatic system. These conditions may act independently or in combination, markedly increasing the risk of thrombus formation during the neonatal period.

1. Thrombophilia Associated with Deficiency or Dysfunction of Physiological Anticoagulants.

This group includes inherited abnormalities that weaken the natural anticoagulant defense mechanisms of blood coagulation:

Antithrombin III deficiency or dysfunction

Protein C deficiency

Protein S deficiency

Thrombomodulin abnormalities

Tissue factor pathway inhibitor deficiency

Excess activity of protein C inhibitor

Heparin cofactor II deficiency

Plasminogen activator inhibitor abnormalities

Excess histidine-rich glycoprotein

Heparin–antithrombin III complex inhibitor abnormalities

These defects reduce the capacity to limit clot formation and promote uncontrolled coagulation.

2. Thrombophilia Associated with Deficiency or Abnormality of Procoagulant Factors.

In these conditions, structural or functional changes in coagulation factors directly enhance thrombogenesis:

Factor V Leiden mutation, resulting in resistance to activated protein C (present in approximately 2–6% of the Caucasian population).

Prothrombin gene mutation (G20210→A)

Thrombogenic dysfibrinogenemias

Plasminogen deficiency or structural abnormalities

Deficiencies of factor XII, prekallikrein, or high-molecular-weight kininogen

These abnormalities increase thrombin generation or impair fibrinolysis.

3. Thrombophilia Associated with Platelet Hyperaggregability.

This group includes genetic conditions that enhance platelet activation and aggregation:

Polymorphisms of the platelet glycoprotein IIIa gene

Polymorphism of the methylenetetrahydrofolate reductase (MTHFR) gene, leading to hyperhomocysteinemia, a recognized prothrombotic factor.

Clinical Manifestations. The clinical spectrum of neonatal thrombotic disease was elegantly systematized by A. Zipursky and B. Schmidt (1987), whose observations remain highly relevant today. Their work highlights an essential principle: thrombosis in the newborn is rarely an isolated event. Instead, it emerges at the intersection of several vulnerable systems acting simultaneously.

In the neonatal period, thrombosis most often develops against a background of physiological immaturity of hemostatic regulation, where the delicate balance between coagulation, anticoagulation, and fibrinolysis is easily disrupted. This inherent instability is frequently compounded by inherited thrombophilic traits, which silently predispose the infant to excessive clot formation long before clinical signs appear.

Superimposed on this fragile baseline are perinatal stressors—hypoxia, infection, shock, dehydration, invasive procedures, and vascular catheterization—which act as triggering events. Together, these factors convert a latent prothrombotic tendency into overt disease.

Thus, the clinical manifestations of neonatal thrombosis should be viewed not as isolated symptoms, but as the final expression of cumulative hemostatic vulnerability, where genetic predisposition, developmental immaturity, and environmental stress converge to produce thrombotic pathology.

Table 9.

Site of vascular obstruction	Clinical picture
Veins Inferior vena cava	Oedema and cyanosis of the legs; often associated with renal vein thrombosis
Superior vena cava	Oedema of the soft tissues of the head, neck, and upper chest; chylothorax may develop
Renal veins	Enlarged kidney(s), haematuria

Adrenal veins	Often haemorrhagic necrosis of the adrenal glands and Clinical picture of adrenal insufficiency
Portal and hepatic veins	Usually, in the acute phase, clinical symptoms are absent
Arteries Aorta	Congestive (overload) heart failure: difference in systolic pressure in the upper and lower extremities, decreased femoral pulse
Peripheral	Absence of pulse on palpation, skin discolouration, decreased skin temperature
Cerebral	Apnoea, generalised or localised seizures.
Pulmonary	Respiratory disorders, pulmonary hypertension
Coronary	Congestive heart failure, cardiogenic shock, typical ECG changes, hypertension, haemodynamic heart failure,
Renal	Anuria
Mesenteric	Clinical signs of necrotising enterocolitis

Diagnosis and Therapeutic Approach

The detection of thrombosis in newborns begins with visualization. To confirm the presence—or confidently exclude the absence—of a thrombus, clinicians rely primarily on ultrasound-based techniques, including Doppler studies, which allow real-time assessment of blood flow. In selected cases, particularly when large vessels are involved or diagnostic uncertainty persists, contrast angiography is employed to precisely delineate the location and extent of vascular occlusion.

Unlike many neonatal conditions, the treatment of thrombosis lacks a unified, evidence-based strategy. Recommendations proposed by different authors often diverge, reflecting the absence of large-scale, controlled studies and the ethical and practical limitations of conducting such trials in newborns. As a result, management is frequently individualized and guided by pathophysiological reasoning rather than strict protocols.

The cornerstone of therapy lies not in aggressive anticoagulation, but in the correction of modifiable risk factors. When polycythemia is present, therapeutic bloodletting combined with fresh frozen plasma transfusion is performed to improve blood rheology and restore hemostatic balance. If vascular catheters are contributing to endothelial injury or flow disturbance, their removal is prioritized whenever feasible.

In newborns with hereditary deficiencies of natural anticoagulants, such as protein C or antithrombin III, the potential role of systemic anticoagulants—including neodicumarine—may be considered, although such decisions require extreme caution and careful risk–benefit evaluation.

For superficial thromboses, treatment is often conservative. Local therapy with heparin-containing ointments applied to the overlying skin may be sufficient to limit thrombus extension and promote resolution. In most neonatal cases, however, specific antithrombotic therapy is used sparingly, reserved only for situations where the benefits clearly outweigh the substantial risk of hemorrhage.

Thus, the management of neonatal thrombosis is best understood not as a standardized algorithm, but as a carefully balanced clinical judgment, aiming to reduce thrombotic risk while respecting the extraordinary fragility of neonatal hemostasis.

ANEMIA

Anemia in Newborns and Infants. Anemia is a hematological syndrome defined by a reduction in red blood cell mass and/or hemoglobin concentration, resulting in impaired oxygen delivery to tissues. In the neonatal period, anemia reflects not a single disease, but a final common pathway of multiple prenatal, perinatal, and postnatal processes.

Diagnostic Criteria. During the **first and second weeks of life**, anemia is diagnosed when:

Hemoglobin is <150 g/L in capillary blood

Venous hemoglobin is <130 g/L

Red blood cell count is <4.5 × 10^{12}/L

Hematocrit is <40%

These thresholds apply **only in the absence** of acute blood loss.

By **3–4 weeks of life**, physiological adaptation lowers normal limits:

Hemoglobin <120 g/L (capillary blood)

Red blood cell count <4.0×10^{12}/L

A defining feature of neonatal hematology is the dominance of fetal hemoglobin (HbF):

90–95% at 34–36 weeks of gestation

50–70% at birth

1–2% by 1 year of age

The gradual replacement of HbF by adult hemoglobin is a key determinant of neonatal oxygen transport and anemia dynamics.

Classification of Anemia in Newborns and Infants. Although the causes of anemia in early life are numerous, the mechanisms of development are limited, allowing anemia to be grouped into three major pathogenetic categories.

I. ANEMIA DUE TO BLOOD LOSS (POST-HEMORRHAGIC)

1. Antenatal Blood Loss

- Placental integrity disruption
- Abnormalities of the umbilical cord and its vessels
- Feto–fetal transfusion
- Feto–maternal transfusion

2. Intranatal Blood Loss

- Feto–maternal transfusion during delivery
- Obstetric complications:
    - Cesarean section
    - Premature placental abruption
    - Umbilical cord rupture
    - Placenta previa
    - Traumatic amniocentesis
- Structural abnormalities of the placenta and umbilical cord
- Umbilical cord compression
- Birth trauma

- Excessive placental transfusion

3. Postnatal Blood Loss

- Internal hemorrhage:
    - Intraventricular hemorrhage
    - Massive cephalohematoma
    - Rupture of parenchymal organs
- Gastrointestinal bleeding
- Coagulation disorders
- Bleeding from umbilical vessels
- **Iatrogenic blood loss (frequent blood sampling)**

II. ANEMIA DUE TO INCREASED RED BLOOD CELL DESTRUCTION (HEMOLYTIC)

1. Congenital (Intraerythrocytic Defects)

- **Membrane defects**

(e.g., hereditary spherocytosis with hyperbilirubinemia and reticulocytosis)

- Enzyme deficiencies (enzymopathies)
- Glucose-6-phosphate dehydrogenase (G-6-PDH) deficiency
- Heinz body formation
- Hemoglobinuria
- Hemoglobinopathies

2. Acquired (Extra-erythrocytic Factors)

- General hematopoietic disorders:
- Fanconi anemia (pancytopenia)
- **Immune hemolysis:**
- Rh and ABO incompatibility
- Minor blood group incompatibility (Kell, Duffy)
- Maternal autoimmune diseases
- Mechanical, chemical, or thermal injury
- Vitamin E (tocopherol) deficiency (reticulocytosis, pyknocytosis)

- Congenital infections:
- Syphilis
- Toxoplasmosis
- Hepatitis B and C
- Cytomegalovirus
- Sepsis

III. ANEMIA DUE TO SUPPRESSED ERYTHROPOIESIS (HYPOREGENERATIVE)

1. Congenital Forms

- Hypoplastic and aplastic anemias
- Selective erythroid failure:
- **Diamond–Blackfan anemia**
- Associated congenital anomalies (heart defects, skeletal abnormalities, growth retardation)

2. Acquired Forms

- Secondary bone marrow suppression due to:
    - Renal, hepatic, or thyroid disease
    - Severe bacterial or viral infections
- Nutritional deficiencies:
- Vitamin B_{12} (cyanocobalamin)
- Folic acid
- Iron
- Protein and amino acids
- Trace elements and micronutrients
- **Erythropoietin deficiency**

Morphological Classification. Based on red blood cell size, anemia is further classified as:

- Macrocytic

- Normocytic
- Microcytic

This morphological approach helps narrow the diagnostic pathway and identify the dominant pathogenetic mechanism.

Post-Hemorrhagic Anemia in Newborns

Etiology: When Blood Is Lost Before Life Begins. Post-hemorrhagic anemia in the newborn is, at its core, the consequence of blood leaving the fetal circulation—sometimes quietly, sometimes catastrophically—long before clinical signs become obvious.

One of the most frequent hidden mechanisms is feto-maternal transfusion, in which fetal blood crosses into the maternal circulation. This transfer may occur spontaneously or be provoked by invasive or mechanical interventions such as amniocentesis, external version of the fetus, or obstetric manipulation. Epidemiological data suggest that one in 400 pregnancies is associated with a fetal blood loss of 30 ml or more, while one in 2,000 pregnancies involves massive transplacental hemorrhage exceeding 100 ml.

In monozygotic twins with a monochorionic placenta, inter-twin transfusion syndrome represents one of the most dramatic causes of fetal anemia. Due to venous placental anastomoses, blood is shunted from one twin to the other. In 13–33% of such pregnancies, the hemoglobin difference between twins exceeds 50 g/L, and severe anemia in the donor twin is associated with a perinatal mortality of 70–100%.

The placenta itself may become a source of blood loss. Placental hemorrhages occur in cases of placenta previa, placental abruption (3–6 per 1,000 live births), surgical incision of the placenta during cesarean section, chorioangiomas, placental hematomas, or abnormal placental architecture.

The umbilical cord is another vulnerable structure. Hemorrhage may result from umbilical cord hemangiomas (1:5,000–6,000 births), rupture of a short or normal cord, or the presence of aberrant vessels.

After birth, blood loss may continue or newly develop. Postnatal hemorrhages include:

- massive cephalohematomas
- subaponeurotic hemorrhages
- intraventricular hemorrhages, especially in infants with extremely or very low birth weight
- ruptures of the liver or spleen
- pulmonary hemorrhage
- bleeding into the adrenal glands, retroperitoneal space, or other internal organs

A frequently underestimated contributor is iatrogenic blood loss. Repeated phlebotomy for laboratory testing may account for a substantial proportion of circulating blood volume in newborns and significantly aggravate anemia.

Clinical Picture. Acute Post-Hemorrhagic Anemia.

Acute post-hemorrhagic anemia typically manifests within the first 24 hours of life. The classic presentation includes:

- pallor of the skin and mucous membranes
- tachycardia and tachypnea
- muffled heart sounds with a soft systolic murmur
- hypotension and reduced venous pressure
- weak peripheral pulse
- muscle hypotonia, lethargy
- a weak, rapidly exhausted cry
- a characteristic “agonized, adult-like” facial expression
- moaning respiration and apnea episodes

Importantly, clinical severity does not always mirror the degree of anemia. When blood loss exceeds 15–20% of circulating blood volume (CBV), signs of hypovolemic (post-hemorrhagic) shock may develop: persistent pallor despite oxygen therapy, threadlike pulse, arterial hypotension (below 50 mmHg in full-term infants and 45 mmHg in preterm infants), oliguria or anuria, lethargy, and a prolonged white spot test (>3 seconds).

Pallor may appear hours later, and a key diagnostic clue is its lack of response to oxygen therapy.

Laboratory findings may initially be misleading**. Hemoglobin and erythrocyte counts in capillary blood can be normal immediately after bleeding, falling only hours later due to hemodilution.** Because the hydremic response develops rapidly in full-term infants, hematocrit measurement is often the earliest and most reliable indicator of acute anemia.

The anemia is typically normochromic.Reactive changes such as thrombocytosis, leukocytosis with a left shift, and nucleated erythrocytes may be present.

In contrast to hemolytic anemia:

- hepatosplenomegaly is absent
- jaundice does not occur
- the direct Coombs test is negative

A striking neonatal feature is the low threshold for shock. In older children, shock develops after loss of ~35% of blood volume; in newborns, it may occur with losses of only 15%. Yet paradoxically, some newborns tolerate 25% or even greater losses without shock.

The fetus itself is even more resilient. There are documented cases of intrauterine blood loss exceeding 50% of CBV (up to 200 ml) without signs of shock at birth. For this reason, when risk factors are present, hemoglobin and hematocrit should be assessed at birth and repeated every 6–12 hours during the first day of life.

Chronic Post-Hemorrhagic Anemia.

Chronic blood loss produces a more subtle picture:

- persistent pallor
- moderate tachycardia with a soft systolic murmur
- tachypnea

The liver and spleen may be moderately enlarged, reflecting extramedullary hematopoiesis.

In cases of hemorrhage into abdominal organs (adrenal glands, liver, spleen), the disease may evolve in two stages:

initial mild anemia followed on days 3–5 of life by sudden hematoma expansion, organ rupture, and the abrupt development of post-hemorrhagic shock, intestinal obstruction, or acute adrenal insufficiency.

Despite sometimes profound anemia at birth (Hb <90–100 g/L; erythrocytes <2.0×10^{12}/L), shock or severe heart failure may be absent initially.

With chronic blood loss, anemia becomes hypochromic and microcytic, reflecting iron depletion. In fact, post-hemorrhagic anemia is virtually the only true cause of iron-deficiency anemia in the neonatal period.

The most common cause of chronic post-hemorrhagic anemia in the first week of life is feto-maternal transfusion.

Diagnosis of Feto-Maternal Transfusion. Diagnosis is based on detecting fetal erythrocytes in the maternal circulation and elevated fetal hemoglobin levels. The most widely used method is the Kleihauer–Betke test, which exploits the resistance of HbF to acid elution.

After treatment with citrate-phosphate buffer:

- fetal erythrocytes (HbF) appear bright red
- maternal erythrocytes (HbA) appear as pale, ghost-like cell shadows

Physiological Anemia of Infancy. What is known today as physiological anemia of infancy was poetically described by A. F. Tur (1957) as “benign constitutional anemia.” This term captures its essence: a predictable, self-limited state that reflects normal postnatal adaptation rather than disease.

From Fetal Abundance to Postnatal Pause. During intrauterine life, erythropoiesis is remarkably active. The fetal organism exists in a relatively hypoxic environment, which stimulates high levels of erythropoietin production. As a result, the fetus has:

- Elevated hemoglobin and erythrocyte counts
- Pronounced reticulocytosis
- Frequent presence of nucleated erythrocytes in peripheral blood

It is important to note that erythropoietin does not cross the placenta. Therefore, maternal stimulation of erythropoiesis has no effect on fetal red blood cell production—the fetus regulates its hematopoiesis independently.

The Moment of Birth: Oxygen as a Signal to Stop.

Birth dramatically changes the rules. Within hours, the proportion of oxygenated hemoglobin rises from approximately 50% to 95%. This sudden abundance of oxygen acts not as a stimulus, but as a powerful inhibitory signal to erythropoiesis.

The consequences are rapid and measurable:

- Nucleated erythrocytes disappear from peripheral blood within the first days
- Erythropoietin levels become virtually undetectable by the middle of the first week of life
- Reticulocyte counts fall sharply, reflecting suppression of red blood cell production

In essence, the bone marrow enters a temporary postnatal pause, no longer driven by hypoxic demand.

The Physiological Nadir. A few days after birth, as erythropoiesis remains suppressed, both the red blood cell count and hemoglobin concentration begin to decline. This decrease is physiological, not pathological.

The nadir of erythropoietic activity occurs at 6–8 weeks of life, after which erythropoietin synthesis gradually resumes, followed by renewed hemoglobin production.

In healthy full-term infants, the lowest hemoglobin values are typically observed at 2–3 months of age, averaging around 120 g/L. The lower limit of normal (5th percentile) during this period is approximately 95–100 g/L.

Why Does Hemoglobin Fall So Low?

The explanation lies in a mismatch between growth and production.

On one side of the equation:

- Infants experience rapid weight gain and linear growth

- Blood volume expands quickly

On the other side:

- Erythropoiesis and hemoglobin synthesis are temporarily reduced

As a result, although the total amount of hemoglobin in the body continues to increase, its concentration per unit of blood volume decreases. The faster the infant grows, the more pronounced this dilutional effect becomes.

Thus, physiological anemia is not a failure of hematopoiesis, but a reflection of successful growth outpacing red blood cell production.

Clinical Meaning

Physiological anemia of infancy:

- Is self-limited
- Requires no treatment
- Resolves as erythropoietin production and erythropoiesis resume

Recognizing this condition is crucial to avoid unnecessary investigations and interventions, distinguishing normal developmental physiology from true pathological anemia.

Anemia in Premature Infants. Anemia in premature infants follows a different biological script than in full-term newborns. It reflects not only postnatal adaptation, but also the unfinished work of intrauterine development. Clinically and pathogenetically, two distinct forms are recognized:

- Early anemia of prematurity — developing within the first 2 months of life
- Late anemia of prematurity — appearing after 3 months of age

Late Anemia of Prematurity: The Iron Story.

When late anemia develops in a premature infant, researchers are remarkably unanimous in their conclusions: iron deficiency is the leading cause. Once obvious confounders such as infection, chronic inflammation, or occult blood loss are excluded, iron depletion remains the dominant mechanism.

This is hardly surprising. Premature infants:

- Miss the critical third-trimester period of iron accumulation
- Grow rapidly

- Expand blood volume faster than iron stores can support

Thus, late anemia is best understood as a nutritional–metabolic consequence of prematurity.

Early Anemia of Prematurity: A Multifactorial Failure of Adaptation.

Early anemia in premature infants is far more complex. It is polyetiological, reflecting the convergence of developmental immaturity, altered physiology, and iatrogenic factors.

At its core lies a fundamental paradox: the premature infant enters an oxygen-rich world with a hematopoietic system that is not yet ready to respond appropriately.

Key contributing mechanisms include:

- Abrupt rise in oxygen tension when placental respiration is replaced by pulmonary respiration→ suppresses erythropoietin production
- Physiological delay in the shift of erythropoietin synthesis from the liver (fetal site) to the kidneys (postnatal site)
- Insufficient endogenous erythropoietin production, compounded by reduced stimulation from other hematopoietic growth factors
- Larger postnatal distribution volume and faster clearance of erythropoietin, reducing its biological effect
- Lower initial hematocrit compared to full-term infants
- Accelerated destruction of fetal erythrocytes

Premature infants continue to synthesize fetal hemoglobin (HbF) until reaching a postconceptional age equivalent to 40 weeks. This delays the switch to adult hemoglobin (HbA) and increases the HbF/HbA ratio.

While HbF has a high affinity for oxygen, this very property makes erythrocytes more vulnerable to oxidative damage, especially in an environment rich in oxygen and poor in antioxidant defenses.

Additional factors deepen the anemia:

- Rapid depletion of hematopoietic substrates
- Immaturity of antioxidant protection systems

- Hemodilution due to accelerated growth
- Adverse antenatal and postnatal conditions
- Blood loss during laboratory testing

The latter is particularly significant:

In a premature infant weighing <1000 g, the loss of just 1 ml of blood is equivalent to a 70 ml blood loss in an adult.

Epidemiology. The reported incidence of early anemia of prematurity varies widely—from 16.5% to 91.3%—and shows a clear inverse relationship with:

- Gestational age
- Birth weight

The more premature the infant, the higher the risk and severity of anemia.

Severity of Early Anemia (A. I. Khazanov, 1986)

Grade I:

Hb 100–85 g/L, RBC up to 2.5×10^{12}/L

Grade II:

Hb 84–70 g/L, RBC up to 2.0×10^{12}/L

Grade III:

Hb <70 g/L, RBC <2.0×10^{12}/L

A Key Insight

Today it is believed that early anemia of prematurity results not only from low erythropoietin production, but also from reduced or absent bone marrow sensitivity to erythropoietin. In other words, even when erythropoietin is present, the immature marrow may simply be unable to respond.

The Role of Nutrient Deficiencies. Depending on maternal health, pregnancy course, and nutrition, premature infants may also develop deficiency-related anemias:

- **Iron deficiency**

→ hypochromic, microcytic anemia with clinical symptoms

- Folic acid deficiency

→ macrocytosis, neutrophil hypersegmentation, leukopenia, thrombocytopenia, megaloblastic marrow changes, delayed growth and psychomotor development

- Vitamin E deficiency

→ anisocytosis, poikilocytosis, “target-like” erythrocytes, reticulocytosis, shortened erythrocyte lifespan, hemolytic episodes, edema, thrombocytosis

- Vitamin B_{12} deficiency

→ macrocytic megaloblastic anemia, glossitis (“lacquered tongue”), poor appetite and weight gain, hepatosplenomegaly, and neurological manifestations (peripheral myelopathy)

Fortunately, vitamin deficiency anemias have become far less common in recent decades due to the routine enrichment of formulas designed for premature infants.

In Summary. Anemia of prematurity is not a single disease, but a reflection of developmental incompleteness—a state where growth outpaces hematopoiesis, oxygen suppresses erythropoietin, and medical care itself contributes to blood loss.

Understanding this helps clinicians treat anemia without mistaking physiology for pathology—and intervene only when adaptation fails.

Late Anemia of Prematurity: When Growth Outruns Iron. Late anemia of prematurity is not an accident—it is the price of rapid growth paid with insufficient iron. While early anemia reflects immaturity of regulation, late anemia reflects exhaustion of reserves.

Why Late Anemia Develops. The development of late anemia of prematurity is driven by a convergence of factors, all pointing toward iron deficiency as the final common pathway:

- Prematurity itself, with incomplete third-trimester iron accumulation
- Exposure to adverse perinatal factors
- Perinatal blood loss
- Immediate clamping of the umbilical cord, reducing neonatal iron stores by ≈20%

- High postnatal metabolic rate, rapidly consuming fetal iron reserves
- Failure to meet physiological iron requirements (≥0.5 mg/kg/day) through nutrition
- Erythropoietin therapy, accelerating erythropoiesis without parallel iron supply
- Low efficiency of endogenous iron reutilization
- Infectious diseases, which redirect iron into the reticuloendothelial system as a protective mechanism

At birth, premature infants have the same amount of iron per kilogram as full-term infants and are not deficient in vitamins or other hematopoietic factors. The problem lies elsewhere:

They grow faster than their iron stores can support.

By 3 months of age, tissue iron stores are depleted, and iron-deficiency anemia (IDA) emerges.

Clinical Manifestations. Anemia in premature infants announces itself gradually.

General Signs

- Pallor of skin and mucous membranes
- With Hb <80 g/L:
  - Decreased motor activity
  - Hypotonia
  - Tachycardia with a soft systolic murmur
  - Tachypnea, apnea episodes
  - Poor appetite and inadequate weight gain

Severity Spectrum

Mild Late Anemia

- Lethargy, decreased appetite
- Moderate pallor
- Irritability
- Liver enlargement 2–4 cm

- Hb 90–80 g/L
- RBC 3.5–3.0 × 10^{12}/L
- Hypochromia

Moderate Late Anemia

- Pronounced lethargy, apathy, hypodynamia
- Tearfulness
- Marked anorexia
- Dry, pale skin
- Tachycardia, functional systolic murmur
- Hb ≈66 g/L
- RBC ≤2.8 × 10^{12}/L

Severe Late Anemia (now rare)

- Extreme lethargy and sluggishness
- Anorexia, constipation
- Pale, wax-like skin
- Brittle nails and hair
- Angular cheilitis
- Tachycardia, systolic murmur
- Lower-limb pastosity
- Hepatosplenomegaly
- Hb <66 g/L
- RBC <2.5 × 10^{12}/L

Treatment Philosophy

Early Anemia: What Not to Do

Early anemia of prematurity should not be treated empirically with iron. Multiple studies show that blanket administration of iron or high-dose vitamins (B_6, B_{12}, E) is ineffective unless deficiency is proven.

Management begins with:

- Identification and elimination of non-iron causes
- Adequate protein intake

- Use of formulas adapted specifically for premature infants

If deficiencies are confirmed, targeted therapy (iron, folate, vitamin E) is justified.

Modern Pathogenetic Approach

The most physiologically sound strategy is:

Recombinant human erythropoietin (rhEPO) + iron

Erythrocyte Transfusion: A Powerful but Dangerous Tool

Erythrocyte transfusion is one of the most common neonatal interventions. Its goal is simple:

Restore adequate tissue oxygen delivery.

It rapidly improves oxygenation and reduces compensatory cardiac overload. But this power comes with cost.

Risks of Transfusion

- Infection (CMV, HBV, HCV, syphilis, HIV)
- Immune hemolysis
- Immunosuppression
- Volume overload → persistent ductus arteriosus
- Iron overload (hemosiderosis, cirrhosis)
- Electrolyte and acid–base disturbances
- Hypoglycemia
- Suppression of endogenous erythropoietin
- Reduced oxygen affinity of HbA → contributes to retinopathy of prematurity

How to Reduce Transfusions (Ohls R.K., 2013)

- Delayed cord clamping

Infant held 30–45 s below placenta level

- Erythropoietin from day 1

400 IU/kg SC

or Epokrin 200 IU/kg IV with amino acids

- Iron supplementation

Parenteral: 3 mg/kg weekly

or 0.5 mg/kg/day IV, then oral 6 mg/kg/day

- Blood-sparing diagnostics
    - Micro-sampling (I-Stat, VIA)
    - Remove central lines early
    - Avoid routine frequent tests
    - Daily phlebotomy loss accounting
- Define minimal acceptable Hb/Ht

Based on oxygen needs, ventilation, age:

- <2 weeks
- 2–4 weeks
- 4 weeks

Prevention and Treatment of Late Anemia

Universal Iron Prophylaxis (28 days–12 months)

Weight	**Dose (elemental iron)**
<1000 g	4 mg/kg/day
1000–1500 g	3 mg/kg/day
1500–3000 g	2 mg/kg/day

Therapeutic Iron (IDA)

- 5–8 mg/kg/day
- Strict monitoring to prevent hemosiderosis

Vitamin Support

- Vitamin E (≤2000 g): 5–10 mg/day for 3 months
- Folic acid: 1 mg/day in 14-day courses

Methemoglobinemia: "Hidden Anemia"

Here anemia exists without anemia.

Hereditary Forms

- Methemoglobin reductase deficiency (enzymeopathy)
- M-hemoglobinopathy (abnormal globin chains)

Autosomal recessive; carrier rate ≈1% worldwide

Among Yakuts: 7%

Clinical Hallmark

- Cyanosis from birth
- Grey-earthy → dark-purple skin tone
- Lips, nails, mucosa most affected

When MtHb >30%:

- Agitation
- Tachycardia, tachypnea
- Apnea

Despite high Hb and RBC, tissues are hypoxic → functional anemia

Diagnosis

Simple bedside test:

- Normal blood → red on filter paper
- MetHb → stays brown

Confirm with:

- MtHb level
- NADH-MtHb-R activity
- Hb electrophoresis

Treatment

- Ascorbic acid 0.1–0.15 g ×3/day
- Riboflavin 0.01 g ×2–3/day
- Methylene blue 1–2 mg/kg IV→ then oral ×3/day

If ineffective → evaluate for:

- M-hemoglobinopathy
- G-6-PD deficiency

Final Thought

Late anemia of prematurity is not failure — it is growth demanding more than biology can yet supply. Understanding this allows clinicians to support adaptation, not fight physiology.

QUESTIONS FOR INDEPENDENT STUDY:

1). Physiological features of the haemostasis system in newborns.

2). The state of haemostasis in premature infants.

3). General analysis of the coagulation status of newborns.

4). Features of clinical manifestations, diagnosis and treatment of hereditary coagulopathies in the neonatal period.

5). Features of the clinic, diagnosis, and treatment of thrombocytopenia in newborns.

7). Etiology, pathogenesis, clinical presentation, course, outcomes, and treatment of DIC syndrome in newborns.

8). Thrombosis in newborns (diagnosis, treatment).

9). Differential diagnosis of haemorrhagic disorders in newborns.

10). Etiology of GrBN.

12). Predisposing factors for GHD.

13). "Risk groups" for GRBN among newborns.

14). Pathogenesis of HNB.

15). Clinical manifestations of HBD in newborns:

16). Diagnosis of HBD.

17). Scope of clinical and laboratory examination of haemostasis in HBD.

18). Differential diagnosis of HBD.

19). Treatment of HNB.

20). Complications and prognosis for HBD.

21). Differential diagnosis of false and true melena in newborns

22) Prevention

SITUATIONAL TASKS.

Task No. 1

A 3-day-old male newborn (D.) was admitted to the neonatal pathology unit from the maternity hospital with a preliminary diagnosis of intestinal bleeding. *Perinatal History*. The child was born to an 18-year-old primigravida. Pregnancy was notable for a threatened miscarriage at 32–34 weeks of gestation, which required inpatient treatment. Delivery occurred at 38 weeks. Labor proceeded with a prolonged first stage lasting 15 hours, followed by a second stage of 25 minutes. The amniotic-free interval was 4 hours. No operative interventions were required. At birth, the newborn weighed 2950 g and measured 51 cm in length. Apgar scores were 7 and 8 points at 1 and 5 minutes, respectively. The initial postnatal condition was assessed as moderately severe, primarily due to neurological symptoms. *Early Postnatal Course*. Breastfeeding was initiated on the first day of life; however, the mother suffered from hypogalactia, resulting in insufficient milk intake. On the third day of life, the infant developed a single episode of hematemesis, followed by melena. In response, the newborn received 0.3 ml of a 1% vicasol solution intramuscularly and ε-aminocaproic acid orally. Despite this therapy, melena persisted, prompting transfer to a specialized neonatal unit. *Clinical Examination on Admission* General condition: moderate**.** Skin: slightly icteric**.** Hair: presence of lanugo**.** Umbilical ring: low-lying**.** Respiratory system: puerile breathing, no added sounds**.** Cardiovascular system: heart sounds clear, rhythmic**.** Abdomen: soft, painless on palpation**.** Liver: palpable 1 cm below the costal margin**.** Spleen: not palpable**.** Stool: melena present**.** *Neurological Status***.** The newborn appeared lethargic. Primitive reflexes were depressed, muscle tone was unstable and rapidly exhausted, and tremor of the hands occurred in response to stress or stimulation. *Preliminary Clinical Impression***.** This case represents a full-term newborn with early-onset gastrointestinal bleeding, neurological depression, and insufficient enteral intake in the context of possible vitamin K–dependent hemorrhagic syndrome, requiring urgent evaluation of the hemostasis system, exclusion of melena neonatorum, and assessment for coagulopathy-related bleeding.

Complete blood count: Hb - 180 g/l, RBC - $5.4x10^{12}$ /l, HST - 0.94, PLT - $310.0x10^{9}$ /l, WBS - $5.9x10/^{9}$ l, band neutrophiles - 3%, segmented neutrophiles - 51%, LYM- 38%, monocytes - 8%, ESR -2 mm/hour.

<u>*Duke's bleeding time*</u> - 2 minutes.

Burker's coagulation time: start - 3.5 minutes, end - 7 minutes.

Coagulogram: kaolin time - 100" (normal 40-60"), APTT - 90" (normal range 45-65"), Prothrombin Time (PT) by Quick - 26" (normal range 13-16"), thrombin time - 10" (normal range 10-16"), prothrombin complex - 25%.

Biochemical blood analysis: total protein - 48.4 g/l, bilirubin: indirect - 196 μmol/l, direct - none, urea - 4.2 mmol/l, potassium -4.8 mmol/l, sodium -140 mmol/l, AST - 38 units, ALT - 42 units.

Neurosonography: the pattern of convolutions and sulci is smoothed. The echogenicity of the subcortical ganglia is slightly increased. The depth of the large occipital cistern is8 мм (normal range up to6 mm).

Task for problem No. 1

1. What is your preliminary diagnosis?
2. What factors could have led to the development of this disease in this case?
3. What links in hemostasis do you know?
4. Evaluate the results of the complete blood count.
5. Evaluate the results of the coagulogram. What do the tests show?

Task No. 2

A male newborn, delivered from the third pregnancy, was born at 37 weeks of gestation by caesarean section performed for prolonged gestosis. The mother's medical history was notable for chronic gastritis and dysfunction of the biliary system. The infant was born without signs of asphyxia, with a birth weight of 2900 g, and initially appeared clinically stable. *Postnatal Course.* On the third day of life, alarming symptoms developed. The newborn began to regurgitate fresh blood, and his stools became dark and tar-like. In addition, cherry-red stains were noted on the diaper, consistent with intestinal bleeding. *Physical Examination.* A thorough clinical examination revealed no significant pathological changes in the internal organs. The abdomen was soft, non-tender, and there were no signs of hepatosplenomegaly or congenital anomalies. The overall condition remained relatively stable despite ongoing bleeding. *Laboratory Findings.* Complete blood count: Moderate decrease in erythrocyte count. Reduced hemoglobin. Mild thrombocytopenia. No inflammatory changes detected. Hemostasis assessment: Prothrombin index (PI): 9% (severely reduced). Activated partial thromboplastin time (APTT): 74 seconds (markedly prolonged). Other coagulation parameters within normal limits. *Clinical Interpretation.* The combination of early neonatal gastrointestinal bleeding, severe hypoprothrombinemia, prolonged APTT, and absence of inflammatory or structural pathology strongly suggests a vitamin K–dependent hemorrhagic syndrome of the newborn. The timing (day 3 of life) and laboratory profile are characteristic of the classic form of hemorrhagic disease of the newborn.

Task for problem No. 2

1. Make a preliminary diagnosis and justify it.
2. Provide emergency care.
3. Pathogenesis of the disease.
4. Differential diagnosis of this disease.
5. Does this child need to see a surgeon?

Task No. 3

A male newborn, the product of a third pregnancy, entered the world at 37 weeks of gestation by caesarean section, the delivery necessitated by prolonged gestosis. His mother's medical history included chronic gastritis and functional disorders of the biliary tract, conditions that subtly framed the metabolic background of the pregnancy. Birth itself was uneventful. The infant cried immediately, showed no signs of asphyxia, and weighed 2900 g. The first two days of life passed without incident, creating an impression of normal neonatal adaptation. That calm ended on the third day of life. ***The First Signs.*** The infant began to regurgitate fresh, bright-red blood. Almost simultaneously, his stools darkened, and cherry-red stains appeared on the diaper — a silent but unmistakable signal of gastrointestinal bleeding. Despite these alarming manifestations, the child's general examination remained deceptively reassuring. ***Physical Examination.*** A careful assessment of the internal organs revealed no structural abnormalities. The abdomen was soft, the liver and spleen were not enlarged, and there were no signs of infection, trauma, or congenital malformations. The infant appeared stable, masking the seriousness of the underlying disorder.

Complete blood count: Hb-120 g/l; RBC-2.1· 1012/l; HST-0.85; WBS =12.3· 109/l; eosinophil -0.5%; segmented neutrophils-40%; band neutrophiles-6%; LYM-44%; monocytes -9%; PLT-240·109/l; ESR-3 mm/h.

Coagulogram: Prothrombin test 8%; prothrombin index 50%; maximum clotting activity in microcoagulation test 6%; prothrombin time 26 seconds; partial thromboplastin time 75 seconds; prothrombin consumption 95%; fibrinolysis 100 min.; paracoagulation tests negative.

The child was transferred to the intensive care unit.

1. What is your preliminary diagnosis?
2. What predisposing factors are reflected in the medical history?
3. What is the complication of the underlying disease?
4. Identify the range of diseases for differential diagnosis of the underlying disease.
5. What is the emergency medical care for this patient?

Task No. 4.

A male newborn, weighing 3800 g, was delivered following a premature birth. The immediate postnatal period appeared reassuring: the infant was born without signs of asphyxia, cried promptly, and adapted to extrauterine life. However, the family history raised an early red flag—recurrent episodes of bleeding in male relatives on the maternal line, suggesting a hereditary predisposition to coagulation disorders. Delivery was complicated by a fracture of the left clavicle, indicating mechanical birth trauma. By the end of the first day of life, the infant's clinical course began to deviate from the expected pattern. A tense cephalohematoma formed over the left parietal region, and simultaneously, an extensive subcutaneous hematoma developed above the left clavicle, far exceeding what would normally be anticipated from birth injury alone. The most alarming sign appeared shortly thereafter. Following excision of the umbilical cord remnant, persistent bleeding from the umbilical wound was observed—bleeding that failed to stop spontaneously and required attention.

Clinical blood analysis showed Hb -140 g/l; RBC 3.1 1012/l; CI-0.95; Ht - 0.45; PLT – 280x109/l; WBS-9.3 109/l; eosinophiles-1%; band neutrophils-6%; segmented neutrophils - 40%; LYM- 44%; monocytes - 9%; ESR 3 mm/h.

Duke's bleeding time– 3 minutes.

Burker's coagulation time: start - 3 minutes, end - 15 minutes.

Coagulogram: APTT - 120", Quick prothrombin time - 16". PCR detects the presence of an abnormal factor VIII gene.

1. Make a diagnosis and justify it.
2. Indicate the classification of the disease.
3. Determine the aetiology.
4. Prescribe treatment
5. Determine the prognosis.

Task No. 5.

A 2-day-old male newborn is being treated in the neonatal intensive care unit. He was born to a mother with a long-standing bleeding tendency, manifested by heavy and prolonged menstrual bleeding and recurrent epistaxis—a detail that would later acquire diagnostic significance.This was the mother’s first pregnancy, complicated by maternal anemia, gestosis, and hemodynamic disturbances of uteroplacental blood flow, suggesting chronic intrauterine stress. Delivery occurred at 34 weeks of gestation and was rapid, leaving little time for physiological adaptation. *Condition at Birth.* The newborn’s condition at birth was severe. His Apgar score was 5, and he required mask ventilation for 5 minutes to establish adequate respiration. From the first hours of life, he was transferred to the intensive care unit. *Current Status* At 48 hours of life, the infant remains in an incubator, receiving: Nasal CPAP respiratory support. Infusion therapy. Enteral nutrition. Despite intensive care, the clinical picture is concerning. Hemorrhagic Manifestations. Examination reveals widespread hemorrhagic skin lesions: Ecchymoses scattered over the trunk and limbs. Multiple confluent ecchymoses on the face, disproportionate to handling or routine procedures. The pattern and extent of bleeding suggest spontaneous hemorrhages, rather than trauma-related lesions.

Complete blood count: Hb 168 g/l; RBC 4.1×1012/l; CI 0.95; Ht 0.5; PLT– 320 x 109/L; WBS 9.7 x 109/L; Eosinophils 1%; band neutrophils 6%; segmented neutrophils - 40%; LYM 44%; monocytes 9%; ESR 3 mm/h.

Duke's bleeding time– 12 minutes.

Burker's coagulation time: start - 3 minutes, end - 7 minutes.

Coagulogram: APTT - 46'', Quick prothrombin time - 16'', PI -88%. Factor VIII and von Willebrand factor levels are reduced – 5%. Platelet aggregation with ristocetin is reduced.

Platelet aggregation activity stimulated by ADP is normal.

1. Make a diagnosis and justify it.
2. Determine the aetiology.
3. Indicate the pathogenesis of the disease.
4. Perform a differential diagnosis.
5. Prescribe treatment.

Task No. 6.

A male newborn was delivered from the first pregnancy, which progressed without complications, to young, healthy parents. The birth was full-term and uncomplicated. At birth, the infant weighed 3400 g, measured 52 cm, and received Apgar scores of 8 and 9 points. From the very first minutes of life, the child appeared active and vigorous. Muscle tone was satisfactory, and physiological reflexes were brisk and symmetrical. The skin was pink, warm, and well perfused. However, even during the initial examination, an unexpected detail stood out: multiple petechiae and small, spot-like hemorrhages scattered across the face, contrasting sharply with the infant’s otherwise excellent condition. *Early Postnatal Course*. By the end of the first day of life, the clinical picture changed. The newborn developed blood-tinged regurgitation, followed shortly by melena. Black, loose stools appeared, and cherry-colored streaks were visible on the diaper, signaling ongoing gastrointestinal bleeding. *Physical Examination*. Respiratory system: Nasal breathing was free. Respiration was puerile, with no rales auscultated. Cardiovascular system: Borders of relative cardiac dullness: Right: 1 cm to the right of the right parasternal line. Left: 1 cm to the left of the left midclavicular line. Upper: upper edge of the 3rd rib. Heart sounds were clear and rhythmic, heart rate 144 beats per minute. Blood pressure measured 78/56 mm Hg. Abdomen: Soft and painless on palpation. Liver: Palpable 2 cm, 1.5 cm, 1/3 (by standard topographic lines). Spleen: Palpable 1 cm below the costal margin, firm and elastic. Stool: Black, loose, with cherry-colored streaks on the diaper. Urine: Light yellow. Genitalia: Male, correctly formed; testes descended into the scrotum.

Complete blood count: Hb -178 g/l; RBS- 4.8×1012/l; CI-1.05; Ht-0.59; PLT -20×109/l; WBS 14.7×109/l; eosinophils 3%; band neutrophils 6%; segmented neutrophils 54%; LYM 30%; monocytes 7%; ESR 1 mm/h.

Duke's bleeding time– 9 minutes.

Burker's coagulation time: start – 3 minutes, end – 7 minutes.

Coagulogram: APTT - 42", Quick prothrombin time - 16", PI 92%, OFT 1 mg/ml.

Positive reaction of platelet thromboagglutination of the child with the mother's blood serum. IgG content on the child's platelets is elevated.

1. Make a diagnosis and justify it.
2. Determine the aetiology.
3. Perform a differential diagnosis.
4. Prescribe treatment.

Task No. 7.

A newborn girl was delivered to a 30-year-old woman with systemic lupus erythematosus, a chronic autoimmune condition that shaped the course of pregnancy from its earliest stages. This was the mother's first pregnancy, marked by a series of complications: a threatened miscarriage, hemodynamic disturbances of uteroplacental blood flow, and mild gestosis, all pointing to chronic intrauterine stress. Given the maternal disease and obstetric risks, delivery was performed by planned caesarean section at 36 weeks of gestation. *Condition at Birth.* The infant was born preterm, with a birth weight of 2000 g and a length of 44 cm. Immediately after birth, her condition was assessed as moderate, primarily due to signs of central nervous system depression. Apgar scores were 8 and 8 at 1 and 5 minutes, respectively. *Early Clinical Findings.* On physical examination, the newborn's most notable feature was the presence of isolated petechial hemorrhages scattered over the skin of the trunk and limbs. These cutaneous findings appeared in the absence of trauma, infection, or invasive procedures, drawing attention to a possible disturbance of the hemostatic system.

Complete blood count on day 1: Hb 188 g/l; RBC 5.0 1012/l; Ht 0.6; PLT 45x109/l; WBS-12.0×109/L; eosinophils 2%; band neutrophils-4%; segmented neutrophils - 56%; LYM-34%; monocytes 4%; ESR 1 mm/h.

<u>Duke's bleeding time</u>– 9 minutes.

Burker's coagulation time: start – 3 minutes, end – 7 minutes.

Coagulogram: APTT - 42", Quick prothrombin time - 16", PI- 92%, OFT 2 mg/ml.

1. Make a diagnosis and justify it.
2. Describe the pathogenesis.
3. Prescribe tests.
4. Prescribe a diet.
5. Prescribe treatment.

Task No. 8.

A girl was born to a mother with a history of multiple miscarriages. This was her fifth pregnancy, which was complicated by acute respiratory viral infection in the first trimester. The birth was her first, at 40 weeks. Her condition at birth was satisfactory, with an Apgar score of 8/9. Weight 3600 g, length 53 sm. There is a giant haemangioma on the right thigh, protruding above the surface of the skin. No pathologies were found in the internal organs or neurological status.

Clinical blood test immediately after birth: Hb 188 g/l; RBS.5.0×1012/l; CI 1.0; Ht-0.6; PLT – 300x109/l; WBS 14.7 × 109/L; eosinophils 3%; band neutrophils 6%; segmented neutrophils 54%; LYM 33%; monocytes 4%; ESR 1 mm/h.

On the third day, the child's condition worsened due to central nervous system depression syndrome. Pronounced jaundice appeared. Petechiae were noted on the face, trunk, and limbs.

Clinical blood test on day 3 – Hb 130 g/l; RBC 3.2 1012/l; CI -1.05; Ht-0.45; PLT – 44x109/l; WBS -9.0 109/l; eosinophils 4%; band neutrophils - 6%; segmented neutrophils- 44%; LYM - 40%; monocytes 6%; ESR 3 mm/h.

Biochemical blood analysis – total bilirubin 280 μg/L; indirect 270 μg/l, direct 10 μg/l.

Coagulogram – APTT 49"; PT 16"; PI 90%.

1. Make a diagnosis and justify it.
2. Describe the pathogenesis.
3. Prescribe treatment.
4. Determine the prognosis.
5. Conduct further observation.

Task No. 9.

A male newborn was delivered to a 43-year-old mother, an X-ray technician, whose occupational exposure and obstetric history immediately placed the pregnancy in a high-risk category. This was her second pregnancy, complicated from early gestation by recurrent acute respiratory viral infections beginning in the first trimester, maternal anemia, and gestosis. The family history was already burdened: the mother’s first child, a daughter, has Down syndrome, underscoring a background of chromosomal and developmental risk. At 20 weeks of gestation, prenatal ultrasound revealed a severe skeletal anomaly — atresia of the radial bone, indicating a major defect of limb development. *Birth and Physical Characteristics.* Delivery occurred at 39 weeks of gestation. The infant was born with: Birth weight: 1900 g. Length: 40 cm. From the moment of birth, the child demonstrated multiple congenital abnormalities, including: Microcephaly. Radial bone atresia. Numerous stigmata of dysembryogenesis. These findings were consistent with a severe congenital developmental disorder, rather than isolated malformations. *Postnatal Condition.* The newborn's condition was assessed as serious from birth, due to the combination of congenital pathology and a pronounced hemorrhagic syndrome. *Clinical examination revealed:* Multiple ecchymoses scattered across the face, trunk, and limbs. Hemorrhagic regurgitation, indicating upper gastrointestinal bleeding. Red-colored urine, consistent with hematuria. Bleeding was spontaneous, widespread, and disproportionate to handling or procedures, suggesting a profound defect in primary hemostasis or platelet production, rather than trauma-related hemorrhage.

1. Make a diagnosis and justify it.
2. Describe the pathogenesis.
3. Prescribe tests. Expected results.
4. Prescribe treatment.
5. Determine the prognosis.

Task No. 10.

A newborn girl was born to a mother suffering from chronic pyelonephritis. This pregnancy carried an exceptionally heavy obstetric burden. It was the fifth pregnancy in a 35-year-old woman with secondary infertility, a history of multiple miscarriages, and conception achieved through IVF with ICSI. The pregnancy was complicated by severe gestosis, and its course ended abruptly at 33 weeks of gestation. Delivery was performed by emergency caesarean section due to premature detachment of a normally located placenta accompanied by massive bleeding. During labor, the mother developed a high-grade fever of 39°C, and chorioamnionitis was diagnosed. *Birth and Immediate Condition.* The infant was born in a state of profound asphyxia, with an Apgar score of 2 points. Anthropometric parameters reflected extreme prematurity: Birth weight: 1200 g Length: 42 cm. From the first moments of life, the newborn's condition was assessed as extremely severe, dominated by: Acute respiratory failure Severe cerebral depression. Cardiovascular insufficiency. *Early Neonatal Course.* The infant demonstrated a pronounced tendency to hypothermia. The skin was pale, with a marbled pattern and acrocyanosis, indicating profound circulatory instability. Hemorrhagic manifestations appeared almost immediately: Multiple ecchymoses on the face and trunk. Persistent bleeding from injection sites. The child was placed on artificial invasive ventilation of the lungs (AIWL) from the first minute of life. Physical Examination. Cardiovascular system: Heart sounds slightly muffled. Pulse: 110 beats per minute. Blood pressure: 47/23 mm Hg. Abdomen: Moderately distended. Liver: Palpable 3 cm below the costal margin. Spleen: Palpable 2 cm below the costal margin. These findings reflected systemic hypoperfusion and venous congestion. Clinical Deterioration. On the second day of life, the hemorrhagic process escalated dramatically. The infant developed: Pulmonary hemorrhage. Gastrointestinal bleeding. Bleeding became multifocal, involving the skin, lungs, gastrointestinal tract, and injection sites, consistent with severe systemic coagulopathy.

Complete blood count: Hb-124 g/l, RBC – 2.2×1012/l; CI – 0.9; PLT– 68.0·109/l; WBS – 4.1·109/l, myelocytes – 9%, band neutrophils – 10%, segmented neutrophils – 61%, eosinophils – 1%, LYM – 10%, monocytes – 9%, toxic granularity of neutrophils. ESR – 6 mm/hour.

Coagulogram: APTT 86"; PT 16"; fibrinogen 0.2, OFT 44 mg/ml, ethanol test – strongly positive. Procalcitonin test 0.75 ng/L. C-reactive protein 10 mg/l.

NSG – Grade 2 VJK on both sides.

1. Make a diagnosis based on the hemorrhagic syndrome.
2. Indicate the aetiology of the disease.
3. Perform a differential diagnosis.

4. Determine the principles of therapy.

5. Determine the prognosis.

SAMPLE ANSWERS TO SITUATIONAL TASKS

Reference answers for task No. 1.

1. Your preliminary diagnosis.

Main: Hemorrhagic disease of the newborn, classic, moderate form. Gastrointestinal bleeding.

Symptoms: Grade II cerebral ischemia, CNS depression syndrome. Transient hyperbilirubinemia (conjugated jaundice).

Background: ZVUR 1st degree, hypotrophic variant.

2. What factors could have led to the development of this disease?

Hemorrhagic disease of the newborn is characterised by a deficiency of vitamin K, which does not readily pass from the mother through the placenta to the fetus. A deficiency develops of activated vitamin K-dependent blood clotting factors synthesised in the liver: factor II (prothrombin), factor VII (proconvertin), factor IX (antihemophilic globulin B), factor X (Stuart-Prower factor), which are un able to bind calcium ions (Ca2+) and fully participate in the process of hemostasis.

3. *What links in hemostasis do you know?*

There are three links in the hemostasis system:

1) vascular;

2) plasma (12 main factors and 3 additional factors);

3) platelet.

4. *Evaluate the blood test results.*

The clinical blood test is within the age norms.

5. *Evaluate the results of the coagulogram*.

A coagulogram is important for diagnosing GrBN. In a coagulogram, the following indicate a deficiency of activated vitamin K-dependent factors in a patient:

1) an increase in kaolin time to 100 seconds (normal range is 40-60 seconds)

indicates a violation of phase I of blood coagulation – prothrombinase formation, involving XII, XI, IX, VIII factors, von Willebrand factor, platelet factor 3 and calcium ions;

2) an increase in activated partial thromboplastin time (APTT) to 90 minutes (normal range is 45-65 minutes);

3) increase in prothrombin time according to Quick to 26 s (normal range 12-14s) indicates a deficiency of 4 factors of the prothrombin complex – II (prothrombin), V (proaccelerin), VII (proconvertin) and X (Stuart-Prower factor Stewart-Prower);

4) a decrease in the prothrombin complex to 25%.

The Duke bleeding time in the patient is normal and is 2 minutes (the time from the moment of puncturing the skin of the finger with a Frank needle to the absence of a blood spot on the filter paper is normally 2-4 minutes). This test is prolonged in thrombocytopenia, thrombocytopathies and vasopathies, but does not change in GrBN.

The Burkner blood clotting time in this case is 3.5 minutes (normally 2.5-5.5 minutes); prolongation of this test is observed in coagulopathy (deficiency of coagulation factors XII, XI, IX, and VIII involved in the formation of active plasma thromboplastin – prothrombinase) and with the administration of heparin; a shortening of the test indicates a tendency toward hypercoagulation.

Reference answer to question No. 2.

1. *Make a preliminary diagnosis.*

Basis: Hemorrhagic disease of the newborn, classic, gastrointestinal bleeding.

Background: Grade 1 ZVUR, hypotrophic variant.

2. Provide emergency care

1). Incubator mode with a temperature of 33ºC.

2). Moisturised, heated 40% oxygen through a funnel or in an oxygen tent.

3). Feed expressed breast milk at room temperature (unpasteurised) at 25 ml 7 times a day.

4). Solution of thrombin and adroxon in a 5% solution of ε-aminocaproic acid, administered orally (dissolve an ampoule of dry thrombin in 50 ml of a 5% solution of ε-aminocaproic acid and add 1 ml of a 0.025% solution of adroxon and give 3-4 times a day, one teaspoon at a time, orally).

5). Vicassol solution 1% - 0.3 ml intramuscularly - 2 times a day.

6). If there is no effect, continued gastrointestinal bleeding, or a threat of post-hemorrhagic shock, administer 30 ml of single-group plasma intravenously over 30 minutes.

3. Pathogenesis of the disease.

Hemorrhagic disease of the newborn is characterised by a deficiency of vitamin K, which does not readily pass from the mother through the placenta to the fetus. A deficiency develops of activated vitamin K-dependent blood clotting factors synthesised in the liver: factor II (prothrombin), factor VII (proconvertin), factor IX (anthemophilic globulin B), factor X (Stewart-Prower factor), which are unable to bind calcium ions (Ca2+) and fully participate in the hemostasis process.

4. *Differential diagnosis of this disease.*

1). With "swallowed maternal blood" syndrome (perform the Apt test).

2). With "background" diseases associated with hypoproduction of vitamin K-dependent factors and hemorrhagic syndrome (congenital TORCH infections, sepsis).

3). With hemophilia B (although it rarely manifests in newborns).

4). With hereditary deficiency of proconvertin (factor VII), Stuart-Prower factor (factor X), proaccelerin (factor V), prothrombin (factor II) – tests with snake venoms from the gyurza and efra are used.

5. Does this child need to consult a surgeon?

There is no need to consult a pediatric surgeon.

Reference answer to question No. 3.

1. What is your preliminary diagnosis?

Primary: Classic hemorrhagic disease of the newborn, early stage. Gastrointestinal bleeding (melena). Bloody vomiting (hematemesis). Background: Prematurity at 35 weeks. Intrauterine growth restriction (IUGR) of the hypotrophic type, grade I severity.

2. What predisposing factors are reflected in the medical history?

Prematurity;

gestosis at 30 weeks of pregnancy with low estrogen levels;

SARS in a pregnant woman 2 weeks before delivery;

prescription of ampicillin to the woman in the last weeks of pregnancy for acute bronchitis.

3*. What is the complication of the underlying disease?*

Acute post-hemorrhagic anemia, severe. Hypovolemic (post-hemorrhagic) shock, stage of decentralisation of blood circulation.

4*. Identify the range of diseases for differential diagnosis of the underlying disease.*

Hemorrhagic disease of the newborn must be differentiated from:

1) maternal blood swallowing syndrome (perform the Apt test);

2) thrombocytopenia;

3) acquired thrombocytopathies;

4) DIC syndrome;

5) hemophilia A, B (rarely occurs in newborns);

6) intussusception;

7) hiatal hernia.

5*. What is the emergency medical care for this patient?*

Emergency care for hemorrhagic disease of the newborn complicated by hypovolemic (post-hemorrhagic) shock will consist of the following:

1) Administer 30 ml of freshly frozen plasma intravenously.

2) Administer 0.3 ml (3 mg) of Sol. Vikasoli 1% intramuscularly.

3) In case of melena:

a) administer 1 teaspoon of the following solution orally: 1 ampoule of Thrombini (125 ED) + Sol. Acidi aminocapronici 0.5% 50 ml + Sol. Adroxoni 0.025% 1 ml.

4) In case of hypovolemic shock after replenishment of BCC by plasma transfusion, it is necessary to monitor blood pressure, heart rate and diuresis every hour. Diuresis

less than 0.5 ml/kg/h indicates the preservation of centralised blood circulation. In this case, it is necessary to:

a) continue infusion therapy with crystalloid solutions (Sol.Natrii chloridi 0.9% 120 ml intravenously by drip);

b) Sol. Dopamini 10 mcg/min intravenously and titrate the dose according to blood pressure, heart rate, and diuresis (until normalisation).

5) Oxygen therapy – mechanical ventilation with FiO2 = 0.5.

6) Blood transfusion of 25 ml of erythrocyte mass of the same group to the patient, followed by monitoring of the hematocrit level. Administer the entire volume of erythrocyte mass within 40 minutes. The volume of erythrocyte mass can be calculated using the following formula:

Body weight (kg) BCC (ml/kg) (Hctж-Hctб)

Volume of erythrocyte mass = Hct erythrocyte mass

Hctж is the desired hematocrit;

Hctb is the patient's hematocrit;

Hct erythrocyte mass – erythrocyte mass hematocrit is 0.7 (70%);

CBV – circulating blood volume = 80 ml/kg.

Reference answer to problem No. 4.

1. *Make a diagnosis and justify it.*

Considering the family history (bleeding in males on the female side), male gender, delayed bleeding after injuries (cephalohematoma, extensive subcutaneous hematoma above the left clavicle, bleeding from the umbilical wound), mild anemia, normal platelet count, leukocytes, no changes in the leukocyte formula, normal bleeding time with prolonged clotting time, prolonged APTT, normal prothrombin time, presence of an abnormal factor VIII gene, the following diagnosis can be made:

Primary: Hemophilia A. Umbilical bleeding. Subcutaneous hemorrhage in the left paraclavicular region. Cephalohematoma.

Concomitant: Birth trauma to the skull – cephalohematoma of the left parietal region. Fracture of the left clavicle.

2. *Indicate the classification of the disease.*

Hemophilia A

Hemophilia B

Hemophilia C

3. *Determine the etiology.*

Factor VIII deficiency, X-linked recessive disease (gene in Xq28); only boys are affected.

4. *Prescribe treatment.*

Rest

Pressure bandage on cephalohematoma

Deso bandage

Antihemophilic sponge, thrombin on the umbilical wound

Antihemophilic globulin

Cryoprecipitate 30 IU/kg twice daily, repeat if necessary

repeat

Fresh frozen plasma 25 ml/kg.

5. *Determine the prognosis.*

Overall, the prognosis is favourable if there is no massive hemorrhage in vital organs (adrenal glands, brain).

Reference answer to task No. 5.

1. *Make a diagnosis and justify it.*

Considering that the newborn boy was born to a mother with a history of bleeding (heavy, prolonged menstruation, nosebleeds), the pregnancy was complicated by anemia, gestosis, hemodynamic disorders of uteroplacental blood flow, premature delivery at 34 weeks, rapid delivery, severe condition at birth due to moderate asphyxia, respiratory failure, cutaneous hemorrhagic syndrome of the vascular-platelet and hematoma types, increased bleeding time according to Duke - 3 minutes, reduced content of factor VIII, von Willebrand factor (5%), platelet aggregation with ristocetin is reduced, and platelet aggregation activity stimulated by ADP is normal. The diagnosis can be made:

Primary: Von Willebrand disease, severe form. Multiple ecchymoses, petechiae on the face, trunk, and limbs.

Background: Prematurity at 34 weeks. Moderate asphyxia.

2. *Determine the etiology.*

An autosomal dominant disorder (12p13.3) caused by a quantitative deficiency or qualitative defect of von Willebrand factor, which is synthesised by endothelial cells and megakaryocytes. von Willebrand factor is a carrier of factor VIII, which is necessary for successful platelet adhesion to damaged endothelium.

3. *Indicate the pathogenesis of the disease.*

In addition to impaired platelet adhesion, there is a low level of factor VIII in the patient's blood plasma.

Increased bleeding in this case occurs in two types: vascular-platelet (characteristic of thrombocytopenia and thrombocytopathy) and hemorrhagic (characteristic of defects in the coagulation link of hemostasis – hemophilia).

4. *Perform a differential diagnosis.*

Hemophilia

Hemorrhagic disease of the newborn

Von Willebrand disease is characterised by a sharp increase in bleeding time, a decrease in von Willebrand factor in blood plasma, and reduced platelet aggregation with ristocetin.

5. *Prescribe treatment.*

Transfusion of fresh frozen plasma 15 ml/kg or factor VIII cryoprecipitate 30 IU/kg (50 IU/kg for VCHK) twice a day; if necessary, the administration can be repeated.

For mild forms, prescribe aminocaproic acid, etamzilate intramuscularly or intravenously 0.5-1 ml of a 12.5% solution once a day or orally 0.05 g 3-4 times a day for 7-10 days. The duration of the course depends on the intensity of bleeding, but should be no less than 6-7 days and no more than 14 days.

Reference answer to task No. 6.

1. *Make a diagnosis and justify it.*

Considering that the boy was born full-term from the first, normally proceeding pregnancy, the first full-term birth of young healthy parents, without asphyxia, with multiple petechiae, small-spot hemorrhages, the appearance of gastrointestinal bleeding by the end of the first day, moderate enlargement of the spleen, severe thrombocytopenia, prolonged bleeding time, positive thrombocyte agglutination reaction of the child's thrombocytes with the mother's blood serum, high IgG content in the child's thrombocytes, the following diagnosis can be made:

Primary: Isoimmune thrombocytopenia, severe form. Neonatal melena, gastrointestinal bleeding, skin hemorrhages.

2. *Determine the etiology.*

Antigenic incompatibility occurs when the mother lacks platelet antigens and the child has them. The mother's body produces antibodies to the fetus's platelets, which cross the feto-placental barrier and destroy the fetus's platelets.

3. *Perform a differential diagnosis.*

Transimmune thrombocytopenia (presence of autoantibodies to platelets in the mother)

Heterimmune and haptenic thrombocytopenia (associated with medication use or ARVI or other infectious diseases)

TAR syndrome (absence or low content of megakaryocytes in the myelogram, platelet shedding disorder, radial bone atresia, congenital malformations)

Kazabakh-Merritt syndrome (presence of giant hemangioma)

Wiskott-Aldrich syndrome (low isohemagglutinin titre, small platelet size, recurrent infections)

Heglin anomaly (shortened lifespan of extremely large platelets)

Thrombocytopenia in infections (presence of other symptoms infection)

4. *Prescribe treatment.*

Standard immunoglobulin 800 mg/kg IV slowly through a lineomat daily for 3-5 days or 1000-1500 mg/kg once every 2-3 days.

Transfusion of washed maternal platelets 10-30 ml/kg or washed platelets from an Ag-negative donor, individually selected for antigen compatibility, 10-30 ml/kg intravenously by drip.

Prednisolone 1-2 mg/kg per day orally. 2/3 of the dose in the morning, the remaining third at 16:00 for 3-5 days.

5. *Prescribe nutrition for the child on the first day.*

Feeding with Detolak adapted milk formula is indicated.

V on day 1 = 30 kcal/kg = 30 x 3.4 = 60 kcal = 73 ml on day 1.

Reference answer to task No. 7.

1. *Make a diagnosis and justify it.*

Considering that the newborn girl was born to a mother suffering from lupus erythematosus at 36 weeks with a weight of 2000 g, a length of 44 cm with central nervous system depression syndrome, isolated petechiae on the skin, thrombocytopenia, prolonged bleeding time, normal clotting time, APTT and PI, the following diagnosis can be made:

Primary: Moderate transimmune thrombocytopenia, skin hemorrhages.

Concomitant: Grade 2 cerebral ischemia, CNS depression syndrome.

Background: Prematurity at 36 weeks. Moderate intrauterine growth restriction, hypoplastic variant.

2. *Describe the pathogenesis.*

Transplacental transfer of maternal IgG antiplatelet autoantibodies or a clone of lymphocytes sensitised to autoplatelets in the child's blood causes thrombocytolysis and the development of thrombocytopenia of varying severity.

3. *Prescribe an examination.*

Determination of antiplatelet antibodies in the mother's blood and milk

Determination of IgG on the mother's platelets

4. *Prescribe nutrition.*

Feed the newborn with a mixture

V on day 1 = 30 kcal/kg = 30 x 2 = 60 kcal = 72 ml on day 1.

5. *Prescribe treatment.*

Drug therapy is indicated in the presence of severe hemorrhagic syndrome accompanied by bleeding. Therapy is based on intravenous administration of standard immunoglobulin at 800 mg/kg for 3 days.

Reference answer to task No. 8.

1. Make a diagnosis and justify it.

Considering that the girl was born to a mother with a history of multiple miscarriages since her 5th pregnancy, which was complicated by ARVI in the 1st trimester, with a giant hemangioma on the right thigh protruding above the skin surface, the appearance of pronounced jaundice and bleeding on the 3rd day, normochromic anemia and thrombocytopenia in the absence of changes in the coagulogram, the following diagnosis can be made:

Primary: Hemangioma of the right thigh. Kazabakh-Merritt syndrome.

Complication: Conjugated hyperbilirubinemia. Hemolytic anemia, mild.

2. *Describe the pathogenesis.*

In giant hemangioma, platelet deposition, sequestration and lysis occur, leading to the development of hemorrhagic syndrome.

3. *Prescribe treatment.*

Natural feeding on demand.

Prednisolone 4-8 mg/kg per day for 28 days. Repeat course after 6-8 weeks. Surgical treatment of hemangioma.

4. Determine the prognosis.

During treatment with prednisolone, the tumour regresses and there is a noticeable release of platelets into the blood. The prognosis is favourable.

5. *Conduct further observation.*

Follow-up by a vascular surgeon and pediatrician.

Reference answer to task No. 9.

1. Make a diagnosis and justify it.

Considering that the boy was born to a 43-year-old mother, the laboratory technician's X-ray, the pregnancy was complicated by multiple acute respiratory viral infections from the first trimester, anemia, gestosis, there is a daughter with a hereditary pathology, at 20 weeks of pregnancy, an ultrasound scan revealed radial bone atresia in the fetus, the child was born weighing 1900 g, measuring 40 cm in length, with microcephaly, radial bone atresia, multiple stigmata of dysembryogenesis, in serious condition with hemorrhagic syndrome and thrombocytopenia, the following diagnosis can be made:

Primary: TAR syndrome, multiple ecchymoses on the skin. Melena. Hematuria.

Competing: Pathology in/of development – microcephaly.

Background: ZVUR grade 3, dysplastic variant.

2. *Describe the pathogenesis.*

Embryogenesis disorder at 7-9 weeks of gestation, leading to hypomegakaryocytosis or amegakaryocytosis, atresia of the radial bones and other developmental defects (heart, kidneys, brain).

3. *Prescribe tests. Expected results*.

Complete blood count (thrombocytopenia)

Hemostasis system examination (prolonged bleeding time with normal clotting time, prothrombin time within normal limits, slightly prolonged APTT, normal fibrinogen content)

Myelogram (hypomegakaryocytosis)

4. *Prescribe treatment.*

Platelet count in thrombocytopenia less than 10x109/L 20-30 ml/kg IV drip. Repeat if necessary, after 3-4 days.

Stem cell or bone marrow transplantation for stable thrombocytopenia less than 20×109/L.

5. *Determine the prognosis.*

Unfavourable.

Reference answer to task No. 10.

1. *Make a diagnosis.*

DIC syndrome, ecchymosis on the body, bleeding from injection sites, melena, pulmonary hemorrhage, complicated by moderate post-hemorrhagic anemia, in a child with early congenital sepsis, born in severe asphyxia with prematurity at 33 weeks, severe ZVUR, hypotrophic variant.

2. *Indicate the etiology of the disease*.

DIC – a component of SCD in:

Severe viral and bacterial infections

Hypothermia

Severe hypoxia and asphyxia

Pathological acidosis

Shock

Acute hypotension

Destruction and trauma (severe intravascular hemolysis, leukolysis, massive trauma, burns, destruction of parenchymal organs, necrosis)

2. *Perform differential diagnosis.*

Table 10.

Indicators	Normal	GrBN	Haemophilia	Thrombocytopenia penia	DIC2 f
Time clotting	2-4 min	Extended	Extended	Normal	Extended
Time Bleeding	3-4 min	Normal	Normal	Extended	Extended
Number platelets	150 400x109/L	Normal	Normal	Decreased	Reduced
PV	13-16 s	Extended	Standard	Normal	Extended
TV	10-16 s	Standard	Normal	Normal	Extended
ACTV	45-60 s	Extended	Extended	Normal	Extended
Fibrinogen	1.5-3.0 g/l	Normal	Normal	Normal	Reduced
Products degradation	0-7 mg/ml	Normal	Normal	Normal	Elevated

fibrinogen					

4. *Determine the principles of therapy.*

Adequate treatment of the underlying disease (antibacterial, immunocorrective)

Respiratory support. AIWL.

Correction of acidosis

Replenishment of circulating blood volume, inotropic support

Replacement therapy with fresh frozen plasma 10-20 ml/kg IV drip

Parenteral nutrition and infusion therapy

Syndrome-specific therapy (heparin for thrombosis, glucocorticoids for adrenal insufficiency, transfusion of red blood cell mass in severe anemia, thromboconcentrate – for thrombocytopenia)

5. *Determine the prognosis.*

DIC syndrome is a serious complication of severe diseases, leading to death in 30-50% of cases.

TESTS FOR SELF-PREPARATION

Tests with 1 correct answer:

1. Hemorrhagic disease of the newborn is characterised by:
   A. low levels of vitamin K-dependent blood clotting factors
   B. pathological fibrinolysis
   C. formation of intravascular thrombi
   D. thrombocytopenia
   E. decreased blood fibrinogen levels
2. In the pathogenesis of melena in newborns, the leading role is played as a result of birth stress:
   A. excess glucocorticoids
   B. glucocorticoid deficiency

C. hereditary defects in glucocorticoid biosynthesis

D. hyperproduction of fetal somatotropic hormone

E. excess anticoagulants

3. Vitamin K2 is synthesised in

A. the liver

B. the intestines

C. the stomach

D. the spleen

E. plant-based foods

4. Melena is

A. intestinal bleeding

B. blood in the urine

C. nosebleed

D. bleeding from the umbilical wound

E. there is no correct answer

5. Hematemesis is

A. bloody vomiting

B. blood in the urine

B. Nosebleed

C. bleeding from the umbilical wound

D. All answers are correct

6. Stage I of DIC syndrome is characterised by

A. increased activity of the blood coagulation system (hypercoagulation)

B. a decrease in the level of blood coagulation factors

C. a decrease in platelet count

D. an increase in platelet count

E. a decrease in the amount of coagulation factor VII

7. The minimum daily requirement of vitamin K1 for a newborn is:

A. 2 mcg/kg

B. 8 mcg/kg

C. 20 mcg/kg

D. 10 mcg/kg

E. 5 mcg/kg

8. In thrombocytopenia:

A. bleeding time is significantly prolonged, blood clotting time is reduced

B. Bleeding time is within normal limits, blood clotting time is prolonged

C. Bleeding time is prolonged, blood clotting time is prolonged

D. Bleeding time is shortened, clotting time is prolonged

E. bleeding time is prolonged, blood clotting time is within normal limits

9. Isoimmune thrombocytopenic purpura occurs as a result of:

A. insufficient platelet production

B. incompatibility of the mother's and foetus's blood according to the ABO system

C. incompatibility of the mother's and foetus's blood according to platelet antigens

D. hereditary increased platelet destruction

E. incompatibility between the mother's and foetus's blood according to the Rhesus factor

10. To diagnose false and true melena, the following are used:

A. Apt test

B. Coombs test

C. Wasserman reaction

D. Foam test

E. PCR

11. The clinical picture of stage I DIC syndrome is characterised by:

A. the clinical picture of the underlying disease, symptoms of CNS intoxication (increasing acidosis, hypovolemia)

B. Microcirculatory hemorrhagic syndrome (petechial rash, bleeding from injection sites)

C. microcirculatory or hematoma-type thrombohemorrhagic syndrome (profuse bleeding)

D. picture of septic shock

E. All answers are correct

12. The clinical picture of stage II DIC syndrome is characterised by:

A. the clinical picture of the underlying disease, symptoms of CNS intoxication (increasing acidosis, hypovolemia)

B. Microcirculatory haemorrhagic syndrome (petechial rash, bleeding from injection sites)

C. Microcirculatory or hematoma-type thrombohemorrhagic syndrome (profuse bleeding)

D. picture of septic shock

E. All answers are correct

13. The clinical picture of stage III DIC syndrome is characterised by:

A. the clinical picture of the underlying disease, symptoms of CNS intoxication (increasing acidosis, hypovolemia)

B. Microcirculatory haemorrhagic syndrome (petechial rash, bleeding from injection sites)

C. Microcirculatory or hematoma-type thrombohemorrhagic syndrome (profuse bleeding)

D. Septic shock

E. All answers are correct

14. Clinical signs of classic hemorrhagic disease of the newborn usually appear on:

A. the 1st-2nd day of life;

B. the 2nd-5th day of life;

C. the 7th–10th day of life.

D. the 10th day of life

E. the 20th day of life

15. Transplacental thrombocytopenic purpura occurs in newborns with:

A. insufficient platelet production;

B. incompatibility of the mother's and fetus's blood according to the ABO system;

C. incompatibility of the mother's and fetus's blood according to platelet antigens;

D. Immune thrombocytopenic purpura in the mother.

E. incompatibility of the mother's and fetus's blood according to the Rh system;

16. Healthy newborns at birth have:

A. normal platelet count

B. low platelet count

C. an increased platelet count

D. normal platelet count with lower ability to aggregate with adrenaline

E. a reduced platelet count and reduced ability to aggregate

17. The main cause of late anemia in premature babies is

A. Increased hemolysis of red blood cells

B. Insufficient bone marrow maturity

C. Decreased production of erythropoietin

D. Significant depletion of iron reserves

18. Anemia in newborns is diagnosed in the 3rd-4th week of life if the hemoglobin level is below ____ g/l

A. 120

B. 130

C. 140

D. 150

Tests with several correct answers:

17. The most effective drugs used in stage III DIC syndrome

A. heparin

B. proteolysis inhibitors: trasilol, gordox, contrycal

C. cryoprecipitate

D. dicynone

E. SZP

18. Features of hemostasis in premature newborns at birth:

A. more active fibrinolysis with low levels of plasminogen and anticoagulants

B. increased platelet aggregation properties

C. decreased platelet aggregation properties

D. high levels of plasminogen with active fibrinolysis

D. hypocoagulation of whole blood against a background of high levels of anticoagulants

19. Hemorrhagic disease of the newborn is caused by a deficiency of the following blood clotting factors:

A. II (prothrombin)

B. V (proaccelerin)

C. VII (proconvertin)

D. VIII (antihemophilic globulin)

E. X (prothrombinase)

20. The clinical manifestations of hemorrhagic disease of the newborn are:

A. Hematemesis

B. hepatitis

C. melena

D. hemarthrosis

E. pneumonia

21. A newborn with isoimmune thrombocytopenic purpura needs to undergo the following tests:

A. Complete blood count

B. Biochemical blood test

C. Coagulogram

D. determination of antiplatelet antibodies in the mother

E. determination of antiplatelet antibodies in the child

22. In stage II of DIC syndrome, the following is observed:

A. deficiency of blood coagulation factors, decrease in platelet count

B. activation of fibrinolysis

C. hemolysis of erythrocytes

D. decreased functional activity of platelets

E. a decrease in the number of factorVII in the coagulation system

23. Clinical forms of hemorrhagic disease of the newborn:

A. late

B. classic

C. clinical

D. intrauterine

E. early

24. The hemostasis system includes the following subsystems:

A. coagulating

B. anticoagulant

C. fibrinolytic

D. Plasma

E. Platelet

25. Types of hemostasis:

A. vascular

B. anticoagulant

C. Fibrinolytic

D. Plasma coagulation

E. Platelet (cellular)

26. Primary hemorrhagic disorders include:

A. hemorrhagic disease of the newborn

B. thrombocytopenic purpura

C. hemophilia

D. Wiskott-Aldrich syndrome, thrombocytopenic hemorrhagic syndrome, DIC

E. DIC syndrome, thrombocytopenic purpura, coagulopathy in liver diseases

27. The clinical signs of isoimmune thrombocytopenic purpura are:

A. petechial hemorrhages on the skin

B. small spotted hemorrhages on the skin

C. presence of malformations

D. prematurity

E. presence of dysembryogenesis stigmata

28. Factors contributing to the development of late-onset hemorrhagic disease of the newborn:

A. diarrhea with fat malabsorption

B. Cystic fibrosis of the pancreas

C. Use of anticoagulants by the mother during pregnancy

D. use of anticonvulsants by the mother during pregnancy

E. taking broad-spectrum antibiotics

Answer keys

with 1 correct answer:

1 - A, 2 - A, 3 - B, 4 - A, 5 - A, 6 - A, 7 - A, 8 - D, 9 - B, 10 - A, 11 - A, 12 - B, 13 - B, 14 - B

15-D, 16-B, 17-D, 18-A

with multiple correct answers

17-B, C, D; 18-A, C; 19-A, B, D; 20-A, B; 21-A, D, E; 22-A, B; 23-A, B, D; 24-A, B, C, D; 25-A, D, E; 26-A, B, C; 27-A, B; 28-A, B.

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