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V. N. Karazin Kharkiv National University

HEMORRHAGIC DISEASE OF THE NEWBORN

Methodical recommendations
for students of the 5th year of the medical faculty

Kharkiv – 2020

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CONTENTS

List of abbreviations.....	4
Introduction.....	5
Neonatal Coagulation Disorders. Classification.....	6
Etiology and pathogenesis of hemorrhagic disease of the newborn.....	7
Classification of hemorrhagic disease of the newborns	14
Clinical manifestations of hemorrhagic disease of the newborn.....	15
Additional research methods for diagnosis of hemorrhagic disease.....	16
Differential diagnosis	18
Therapeutic strategy and prevention of hemorrhagic disease of the newborn.....	21
Questions for self-control.....	24
References	28

LIST OF ABBREVIATIONS

VKDB – vitamin K deficiency bleeding
HDN – hemorrhagic disease of the newborn
RDA – Recommended Dietary Allowance
LDL – low density lipoprotein
Gla – γ -carboxyglutamate
Glu – glutamate
PIVKA – protein induced by vitamin K absence or antagonism
MGP – Matrix Gla protein
PCC – prothrombin complex concentrates
1, 25(OH) 2D3 – calcitriol
PT – Prothrombin time
APTT – Activated partial thromboplastin time
INR – International normalized ratio
IM – intramuscularly
FFP – Fresh frozen plasma
PCC – Prothrombin complex concentrates
PPSB – Prothrombin-Proconvertin-Stuart Factor-Antihemophilic Factor B
ITP – Immune thrombocytopenia purpura, also known as idiopathic
SLE – Systemic lupus erythematosus
CMV – Cytomegalovirus
HIV – Human Immunodeficiency Virus
NAIT – Neonatal Alloimmune Thrombocytopenia
DIC – Disseminated Intravascular Coagulation
FDP – Fibrin degradation products
MRI – Magnetic resonance imaging

INTRODUCTION

Hemorrhagic disease of the newborn, also known as vitamin K deficiency bleeding, is a coagulation disturbance in newborn infants due to vitamin K deficiency. It most often develops in the first days and weeks of life.

Hemorrhagic disorders in the neonatal period are caused by a number of features of hemostasis. Hemorrhagic disorders are clinically recorded in about 16 % of newborns. Common hemorrhages are detected in 40–45 % of infants. The most common causes of hemorrhagic conditions in the neonatal period are violations of the coagulation ability of blood and platelet hemostasis.

Hemorrhagic disease of the newborn is a rare disease of the neonatal period. Hemorrhaging is excessive bleeding and it's a potentially life-threatening condition. Newborns are at risk for vitamin K deficiency bleeding caused by inadequate prenatal storage and deficiency of vitamin K in breast milk. Vitamin K is usually the first vitamin given at birth.

Incidence of Vitamin K deficiency unexpected bleeding accounts for 0.25 %–1.7 % during the first week of life in previously healthy-appearing neonates (early VKDB of the newborn, formerly known as classic hemorrhagic disease of the newborn). The rate of late VKDB (often manifesting as sudden central nervous system hemorrhage) ranges from 4.4 to 7.2 per 100 000 births, according to reports for Europe and Asia.

When a single dose of oral vitamin K has been used for neonatal prophylaxis, the rate has decreased from 6.4 to 1.4 per 100 000 births. Parenteral neonatal vitamin K prophylaxis prevents the development of late VKDB in infants, with the rare exception of those with severe malabsorption syndromes.

The disease has an unfavorable prognosis in some cases, including due to complications. Therefore, prevention, timely diagnosis and adequate treatment are important in neonatology and Pediatrics in General.

NEONATAL COAGULATION DISORDERS. CLASSIFICATION

Neonatal bleeding results from disorders of platelets, coagulation proteins, and disorders of vascular integrity. While healthy newborns have low levels of some coagulation proteins, this is normally balanced by the paralleled decrease in fibrinolytic activity.

There is no single classification of hemorrhagic syndrome in newborns. It is proposed to distinguish two groups of children with hemostatic disorders: clinically "healthy" newborns, whose bleeding is the only deviation from the norm, and "sick" newborns, when hemorrhagic syndrome develops against the background of pathology in childbirth or after birth. However, severe forms of congenital factor deficiency can occur in both "healthy" and "sick" newborns.

Table 1. Etiopathogenetic classification

Causes of neonatal bleeding	The types
1. Platelet Disorders	
A. Thrombocytopenia	(Platelet count $<150 \times 10^9/L$, in premature - less $100 \times 10^9/L$) occurs in 1–4 % of term newborns, 40–72 % of sick preterms and 25 % of ICN admissions; of these, 75 % present before age 72h. Causes include: • Decreased platelet production occurs in congenital infections (e.g., CMV, Rubella, HIV), certain syndromes (e.g., Thrombocytopenia Absent Radius, Fanconi), sepsis and Hemolytic Disease of Newborn. • Increased platelet consumption, occurs in: – Maternal auto-immune disease (e.g., ITP, SLE) – Asphyxia/Shock – Neonatal Alloimmune Thrombocytopenia – Maternal thiazide intake – IUGR with toxemia of pregnancy – Necrotizing enterocolitis – Thrombosis (due to catheters, hemangiomas) – Sepsis – Hemolytic disease of the newborn – Exchange transfusion – Heparin-induced thrombocytopenia – Polycythemia/Hyperviscosity
B. Impaired platelet function	It is rare in the newborn except for: • Decreased platelet adhesiveness associated with indomethacin therapy • Von Willebrand's Disease

2. Coagulation Protein Disorders	A. Congenital factor deficiencies: – X-linked recessive: Hemophilia A (Factor VIII) and Hemophilia B (Factor IX) – Autosomal recessive (rare): Factors V, VII, X, XI, XII, XIII, afibrinogenemia B. Acquired deficiencies: Most common is Vitamin K deficiency.
1. Combined Platelet and Coagulation Factor Disorders	A. Disseminated Intravascular Coagulation (DIC) occurs secondary to inappropriate systemic activation of normal clotting mechanisms after endothelial injury. Infants have low platelet counts and fibrinogen levels, prolonged PT and PTT, and elevated Fibrin Degradation Products. B. Hepatic Dysfunction due to several causes (e.g., shock, infection, inherited conditions); most have prolonged PT and decreased factor and fibrinogen levels.
2. Disorders of Vascular Integrity	Hemangiomas or vascular malformations that may rupture and directly bleed, or sequester platelets and secondarily cause bleeding.

ETIOLOGY AND PATHOGENESIS OF HEMORRHAGIC DISEASE OF THE NEWBORN

Grandidier in 1871 and Townsend in 1894 grouped together various forms of neonatal bleeding and associated them with disturbed coagulation. At the same time the term “hemorrhagic disease of the newborns” appeared. When the clotting system became better understood in the last decade of the 19th century, effective symptomatic treatment was developed: gelatin, serum injection, and the transfusion of fresh blood. In 1935, Danish biochemist Henrik Dam has given out a fat-soluble vitamin (coagulations vitamin), for this work he was awarded the Nobel Prize in 1943. Four years later, Waddell introduced vitamin K administration into therapy and prevention of neonatal hemorrhagic disease.

VKDB (vitamin K deficiency bleeding) or HDN (hemorrhagic disease of the newborns) is a form of bleeding that is caused by reduced activity of VK-dependent coagulation factors (II, VII, IX, X), has normal or even increased activity of VK-independent coagulation factors, and responds to VK.

Vitamin K plays a key role in blood clotting. Because vitamin K is not efficiently passed on from mother to baby in utero, most babies are born with low stores of this vitamin in their system. Newborn babies, absorb only approximately 30 % of ingested vitamin K, compared to 50–70 % in adults.

Vitamin K metabolism and biological role

- The fat-soluble vitamin was isolated by a Danish biochemist in 1929. In 1935, the vitamin was named vitamin K. The metabolic pathways have not been fully investigated.

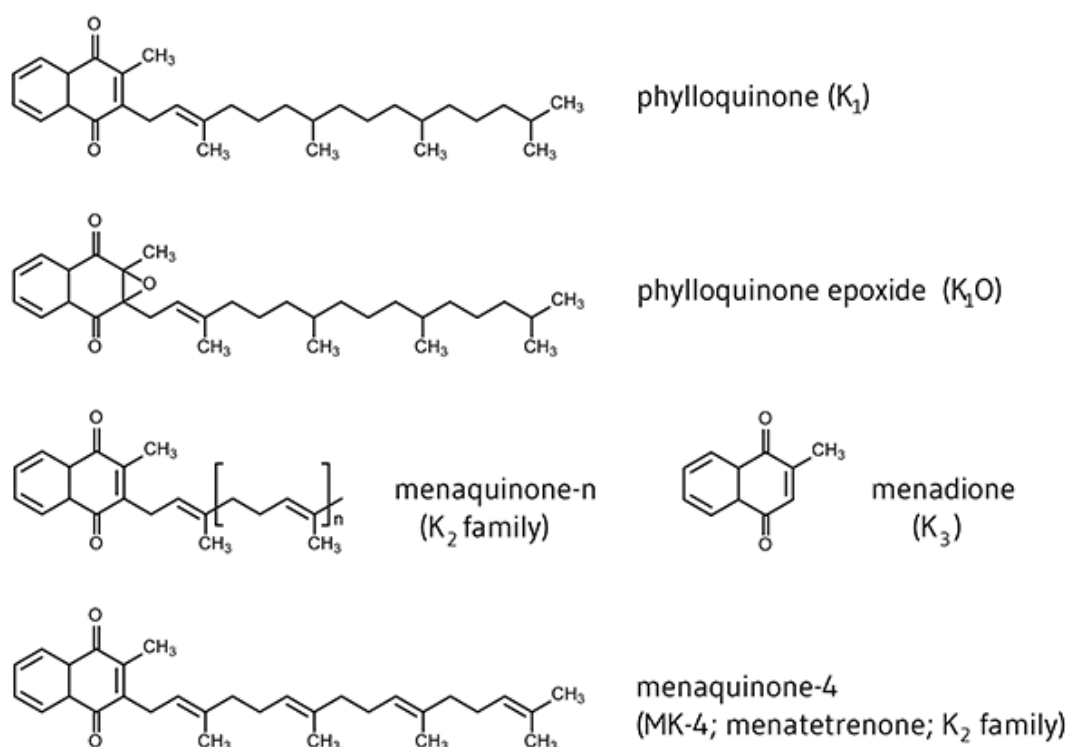
- Vitamin K exists as naturally occurring **vitamin K₁** (phylloquinone) in green leafy vegetables and vegetable oils, and dairy products. Vitamin K

given to neonates as a prophylactic agent is an aqueous, colloidal solution of vitamin K₁. For the first time vitamin was isolated from Lucerne.

- **Vitamin K₂** (menaquinone) as produced in the gut by bacteroides fragilis and E. coli. First isolated from rotting flour.

- Synthetic **vitamin K₃** (menadoine sodium bisulfite) which is water-soluble and capable of producing serious jaundice in newborns, especially those with instability of glutathione and deficiency of G₆PD.

- Phylloquinone have a 20 C side chain, whereas menaquinones have a 30 C side chain. The isoprenoid chain makes these vitamin hydrophobic or lipophilic. The synthetic vitamin K (menadione, menadiol diacetate) have only hydrogen in place of isoprenoid side chain that makes these vitamin water-soluble (Fig.1).



<https://lpi.oregonstate.edu/mic/vitamins/vitamin-K>

Figure 1. Chemical Structures

- **Dietary Sources of Vitamin K:**

- Rich sources of vitamin K₁ are green leafy vegetables such as spinach, cabbage, cauliflower. Milk is a poor source. Appreciable amounts are also present in margarine and liver. Vitamin K is present in vegetable oils and is particularly rich in olive, canola, and soybean oils. Bioavailability of phylloquinone from plant products is 10–20 %.

- A rich source of vitamin K₂ is purified meat in which vitamin K₂ is synthesized by bacteria. Vitamin K₂ is synthesized by the intestinal bacterial flora such as E.coli in humans.

– Recommended average daily allowance (RDA) is **50–100 mg/day**. Approximately equal amounts are provided by the synthesis of vitamin by the intestinal bacterial flora.

- **Absorption** occurs in the upper small intestine.

– The absorption of vitamin K (K_1 and K_2) require bile salts. Vitamins K_1 and K_2 are metabolized in the intestine into an intermediate substance – menadion (vitamin K_3). Vitamin K_3 is readily absorbed without requiring bile salts. Transported from the mucosal cells to the liver by binding to chylomicrons. Subsequently, the deposited form of menaquinone-4 is synthesized from menadione in extrahepatic tissues.

– There is evidence (with the help of radioisotope labeled vitamin K_1) that a complete change of vitamin K_1 in the body occurs within 2.5 hours in adults.

– Fat malabsorption is associated with impaired absorption of vitamin K and other fat soluble vitamins. Vitamin K is important for the coagulation process. In its deficiency coagulation process is grossly affected resulting in tendency for bleeding and hemorrhages. Absorption of vitamin K may also be decreased by mineral oil, bile acid sequestrants (Cholestyramine, Colestipol) and Orlistat (weight loss medication).

– Vitamin K is stored in liver. Also present in significant amount in spleen and skeletal muscle. Vitamin K released to the blood stream and transported in the blood by associating with beta-lipoproteins (LDL).

– The deposit is in the form of menaquinone-4 in the pancreas, brain and salivary glands.

The functions of vitamin K

1. Vitamin K is needed to synthesize coagulation factors II (prothrombin), VII (Stable factor or proconvertin), IX, and X (Stuart-Prower factor), as well as plasma antiproteases C and S, which play an important role in the anti-coagulation system.

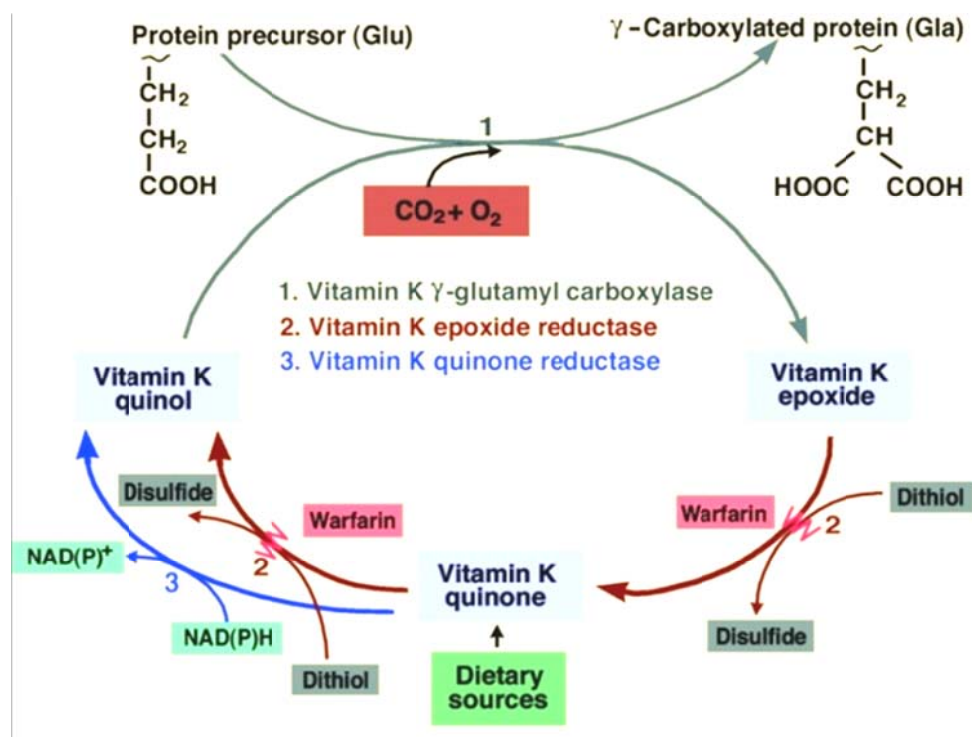
– It brings about post-translational modification of certain blood clotting factors. The clotting factors II, VII, IX and X are synthesized as inactive precursors in the liver. Vitamin K act as a coenzyme for the carboxylation of glutamic acid residues present in **the protein** and this reaction is catalyzed by a carboxylase (microsomal). Vitamin K-dependent proteins are a heterogeneous group, including clotting factor proteins and proteins found in bone, lung, kidney, and placenta. It involves the conversion of glutamate (Glu) to γ -carboxyglutamate (Gla) and requires vitamin K, O_2 and CO_2 . The formation of γ -carboxyglutamate is inhibited by dicumarol, an anticoagulant found in spoiled sweet clover. Warfarin is a synthetic analogue that can inhibit vitamin K action.

– Role of Gla in clotting: γ -Carboxyglutamic acid (Gla) residues of clotting factors are negatively charged (COO^-) and they combine with positively charged

calcium ions (Ca^{2+}) to form a complex. The complex binds to the phospholipids on the membrane surface of the platelets. Leads to increased conversion of prothrombin to thrombin.

– With a lack of Vitamin K in the liver, there is a synthesis of inactive decarboxylated forms of Vitamin K -dependent coagulation factors (II, VII, IX, X), unable to bind calcium ions (PIVKA – protein induced by vitamin K absence or antagonism). In studies, the level of PIVKA – II – decarboxylated form of prothrombin is determined more often.

2. Vitamin K cycle. Vitamin K is a fat-soluble vitamin, the body stores very little of it, and its stores are rapidly depleted without regular dietary intake. Because of its limited ability to store vitamin K, the body recycles it through a process called the vitamin K cycle. The vitamin K cycle allows a small amount of vitamin K to function in the gamma-carboxylation of proteins many times, decreasing the dietary requirement (Fig.2).



<http://www.bloodjournal.org/content/108/6/1795?sso-checked=true>

Figure 2. Vitamin K cycle

3. Synthesis of Bone Calcium-Binding Proteins

– Vitamin K is also important in synthesis of two proteins that contain γ -carboxyglutamate that are present in bone – **osteocalcin** and **bone matrix Gla** protein. Osteocalcin is involved in the regulation of bone mineralization. Osteocalcin is a protein synthesized by osteoblasts, a calcium binding protein present in the bone. The synthesis of osteocalcin by osteoblasts is regulated by the active form of vitamin D, $1,25(\text{OH})_2\text{D}_3$ or calcitriol. The mineral-binding capacity of osteocalcin requires vitamin K-dependent gamma-carboxylation

of three glutamic acid residues. Osteocalcin acts by its ability to bind hydroxyapatite.

- After gamma carboxylation osteocalcin binds tightly to calcium. Osteocalcin also contains hydroxy proline, so its synthesis is dependent on both vitamins K and C; in addition, its synthesis is induced by vitamin D. The release into the circulation of osteocalcin provides an index of vitamin D status.

- Matrix Gla protein- MGP has been found in bone, cartilage, and soft tissue, including blood vessels. MGP prevents the calcification of soft tissues and cartilages, while facilitating normal bone growth and development.

- Protein S. The vitamin K-dependent anticoagulant protein S is also synthesized by osteoblasts, but its role in bone metabolism is unclear. Children with inherited protein S deficiency suffer complications related to increased blood clotting as well as decreased bone density.

Features of vitamin K metabolism in infants

Vitamin K deficiency in newborns is caused by:

- Sterile intestinal flora
- Very little vitamin K crossing the placental barrier from maternal circulation, as a result, the concentration of Vitamin K in the blood of the fetus and reserves at the time of birth are small.
- The level of BB1 in the umbilical cord blood ranges from very low (less than 2 mg/ml) to undetectable.
- Vitamin K₂ begins to accumulate gradually during the first months of life
- Perhaps Vitamin K₂ accumulates more slowly in infants on breastfeeding, as dominated by the primary gut flora (*Bifidumbacterium*, *Lactobacillus*), not synthesizing Vitamin K₂. Bacteria producing Vitamin K₂ (*E. coli*, *Bacteroides fragilis*) are more common in children receiving artificial mixtures
- Impaired absorption caused by biliary obstruction or small intestinal diseases
- Sterile bacterial flora caused by administration of antibiotics results in non-availability of microbial source of vitamin K
- In umbilical cord blood elevated level of PIVKA – II is detected in 10–52 % of newborns, indicating in favor of VK deficiency. 50–60 % of children who are breastfed and do not receive Vitamin K prophylactically have a high level of PIVKA – II to 3–5 days of life.
- The source of Vitamin K for newborns is the exogenous pathway with breast milk (the level of Vitamin K from 1 to 10 µg/L, the average amount is 2-2.5 µg/L), an artificial mixture (about 50 µg/L in mixtures for full-term children, 60–100 µg/L – for premature infants) or in the form of a drug. Human breast milk contains only small amounts of vitamin K. Since it is indigenously produced in the gut by bacterial flora, dietary deficiency of vitamin K in healthy subjects is rare.

Features of hemostasis in newborns

1. Indicators of hemostasis of newborns have a significant difference from the reference values of adults and changing in dynamics after birth.
2. Hypocoagulation orientation of hemostasis on the background of increased intravascular coagulation and fibrinolysis activity is typical for premature and full-term newborns.
3. Low level of blood clotting factors (40–50 % of the level in adults, except factors I, V, VIII, XII, the level of which, as in adults).
4. Increased fibrinolysis.
5. Low Plasminogen level (50-60 % of the level in adults).
6. Elevated levels of heparin in the blood.
7. The platelet count was normal ($180\text{--}350 \times 10^9/\text{L}$), but their low ability to aggregation.

Table 2. Reference Values for Coagulation Tests in Healthy Children*

TEST	28-31 Wk gestation	30-36 Wk gestation	FULL TERM	1-5 Yr	6-10 Yr	11-18 Yr	ADULT
SCREENING TESTS							
Prothrombin time (sec)	15.4 (14.6-16.9)	13.0 (10.6-16.2)	13.0 (10.1-15.9)	11 (10.6-11.4)	11.1 (10.1-12.0)	11.2 (10.2-12.0)	12 (11.0-14.0)
Activated partial thromboplastin time (sec)	108 (80-168)	53.6 (27.5-79.4)	42.9 (31.3-54.3)	30 (24-36)	31 (26-36)	32 (26-37)	33 (27-40)
Bleeding time (min)				6 (2.5-10)	7 (2.5-13)	5 (3-8)	4 (1-7)
PROCOAGULANTS							
Factor I Fibrinogen	256 (160-550)	243 (150-373)	283 (167-399)	276 (170-405)	279 (157-400)	300 (154-448)	278 (156-40)
Factor II Prothrombin	31 (19-54)	45 (20-77)	48 (26-70)	94 (71-116)	88 (67-107)	83 (61-104)	108 (70-146)
Factor V Labile factor, proaccelerin	65 (43-80)	88 (41-144)	72 (34-108)	103 (79-127)	90 (63-116)	77 (55-99)	106 (62-150)
Factor VII Stable factor or proconvertin	37 (24-76)	67 (21-113)	66 (28-104)	82 (55-116)	86 (52-120)	83 (58-115)	105 (67-143)
Factor VIII Antihemophilic factor	79 (37-126)	111 (5-213)	100 (50-178)	90 (59-142)	95 (58-132)	92 (53-131)	99 (50-149)
von Willebrand factor	141 (83-223)	136 (78-210)	153 (50-287)	82 (60-120)	95 (44-144)	100 (46-153)	92 (50-158)

TEST	28-31 Wk gestation	30-36 Wk gestation	FULL TERM	1-5 Yr	6-10 Yr	11-18 Yr	ADULT
Factor IX Christmas factor	18 (17-20)	35 (19-65)	53 (15-91)	73 (47-104)	75 (63-89)	82 (59-122)	109 (55-163)
Factor X Stuart-Prower factor	36 (25-64)	41 (11-71)	40 (12-68)	88 (58-116)	75 (55-101)	79 (50-117)	106 (70-152)
Factor XI Plasma thromboplast in antecedent	23 (11-33)	30 (8-52)	38 (40-66)	30 (8-52)	38 (10-66)	74 (50-97)	97 (56-150)
Factor XII Hageman factor	25 (5-35)	38 (10-66)	53 (13-93)	93 (64-129)	92 (60-140)	81 (34-137)	108 (52-164)
Prekallikrein	26 (15-32)	33 (9-89)	37 (18-69)	95 (65-130)	99 (66-131)	99 (53-145)	112 (62-162)
High- molecular- weight kininogen	32 (19-52)	49 (9-89)	54 (6-102)	98 (64-132)	93 (60-130)	91 (63-119)	92 (50-136)
Factor XIIIa Fibrin-stabili- zing factor		70 (32-108)	79 (27-131)	108 (72-143)	109 (65-151)	99 (57-140)	105 (55-155)
Factor XIIIb		81 (35-127)	76 (30-122)	113 (69-156)	116 (77-154)	102 (60-143)	98 (57-137)
ANTICOAGULANTS							
Antithrom- bin-III	28 (20-38)	38 (14-62)	63 (39-87)	111 (82-139)	111 (90-131)	106 (77-132)	100 (74-126)
Protein C		28 (12-44)	35 (17-53)	66 (40-92)	69 (45-93)	83 (55-111)	96 (64-128)
Protein S:							
Total (units/mL)		26 (14-38)	36 (12-60)	86 (54-118)	78 (41-114)	72 (52-92)	81 (61-113)
Free (units/mL)				45 (21-69)	42 (22-62)	38 (26-55)	45 (27-61)
Plasminogen (units/mL)		170 (112-248)	195 (125-265)	98 (78-118)	92 (75-108)	86 (68-103)	99 (77-122)
Tissue-type plasminogen activator (ng/mL)		8.48 (3.00-16.70)	9.6 (5.0-18.9)	2.15 (1.0-4.5)	2.42 (1.0-5.0)	2.16 (1.0-4.0)	1.02 (0.68- 1.36)
Antiplasmin (units/mL)		78 (40-116)	85 (55-115)	105 (93-117)	99 (89-110)	98 (78-118)	102 (68-136)
Plasminogen activator inhibitor-I		5.4 (0.0-12.2)	6.4 (2.0-15.1)	5.42 (1.0-10.0)	6.79 (2.0-12.0)	6.07 (2.0-10.0)	3.60 (0.0-11.0)

* Data from Andrew M, Paes B, Johnston M: Development of the hemostatic system in the neonate and young infant, *Am J Pediatr Hematol Oncol* 12:95, 1990; and Andrew M, Vegh P, Johnston M, et al: Maturation of the hemostatic system during childhood, *Blood* 80:1998, 1992.

CLASSIFICATION OF HEMORRHAGIC DISEASE OF THE NEWBORN

VKDB is categorized according to the timing of first symptoms:

I. **Early-onset** VKDB manifests within 24 hours of birth due to the low level of vitamin K in the fetus (not more than 50 % of the adult level).

II. **Classic** VKDB occurs within two to seven days due to the low intake of vitamin K with breast milk and the lack of proper intestinal microflora involved in the synthesis of vitamin K.

III. **Late-onset** VKDB occurs within two weeks to six months and due to a secondary violation of the synthesis of polypeptide precursors of blood clotting factors due to liver disease (hepatitis, biliary atresia, prolonged parenteral nutrition or malabsorption syndrome, etc.).

Rare cases of VKDB occur also after week 15; therefore the upper age limit should be 6 months and not 3 months. In idiopathic VKDB the cause (other than breast-feeding) is unknown. In secondary VKDB additional factors can be demonstrated, such as poor intake or absorption of VK and increased consumption of VK. Most often cholestasis is present.

Code ICD X:

P53 Hemorrhagic disease of the fetus and newborn

R54.0 Hematemesis newborn

R54.1 Melena of the newborn

R54.2 Rectal bleeding in the newborn

R54.3 Gastro-intestinal bleeding in the newborn

Risk factors for hemorrhagic disease of the newborn

The risk factors for VKDB vary, depending on the type.

I. Early-onset VKDB:

Risk of developing it is higher if their birth mother takes certain medications while pregnant, including:

- antiseizure drugs that interfere with vitamin K metabolism, such as phenytoin, phenobarbital, carbamazepine, or primidone
- blood thinning medications, such as warfarin (Coumadin) or aspirin
- antibiotics, such as cephalosporins
- antituberculosis medications, such as rifampin and isoniazid

II. Classic VKDB

Classic onset VKDB occurs typically in babies who have not received prophylactic vitamin K at birth. Newborn's risk of developing it is higher if they are exclusively breast-fed.

III. Late-onset VKDB

Late onset VKDB is also more common in babies who did not receive a vitamin K shot. Risk factors include 3 main groups.

1. Children with deficiency of Vitamin K intake:
 - breast-fed babies, low levels of vitamin K in breast milk
2. Children with malabsorption of Vitamin K in the gastrointestinal tract.
 - biliary atresia, which causes slow bile flow
 - cystic fibrosis
 - celiac disease
 - chronic diarrhea
 - hepatitis
 - short bowel syndrome
 - A1-antitrypsin deficiency, which may cause lung and liver disease
 - Chronic exposure to broad spectrum antimicrobials
3. Children receiving long-term parenteral nutrition with inadequate supply of vitamin K.

CLINICAL MANIFESTATIONS OF HEMORRHAGIC DISEASE OF THE NEWBORN

I. Early-onset VKDB

- Early onset occurs within 24 hours of birth.
- The early form of HBN is characterized by the appearance of bleeding in the first hours or day after birth in the form of skin hemorrhages, intracranial hemorrhages, and kephalohematoma.
- This form cannot be prevented by prescribing vitamin K after delivery.

II. Classic VKDB

- The classical form of GRB of newborns is manifested by bleeding on the 2–5 day of life.
- The estimated prevalence of this form of VKDN without prophylactic use of vitamin K is 0.25–1.5 %
- Characterized by the appearance of melena, hematemesis, skin hemorrhages (ecchymosis, petechiae), nosebleeds, bleeding from the umbilical wound and blood clotting disorder at the injection site. Melena is an intestinal bleeding, diagnosed by detection on a diaper around the fecal masses of the pink rim, can be accompanied by bloody vomiting. The cause of melena is the formation of small ulcers on the mucous membrane of the stomach and duodenum, in the genesis of which the excess of newborn glucocorticoids plays a leading role as a result of labor stress, ischemia of the stomach and intestine. A certain role in the occurrence of melena and bloody vomiting is played by increased acidity of gastric juice, gastroesophageal reflux and peptic esophagitis.
- Children with severe birth trauma and hypoxia have a high risk of hemorrhages under aponeurosis, internal hematomas.

III. Late-onset VKDB

- Symptoms appear in the period from 8 days to 6 months

- Late hemorrhagic disease of the newborn (HDN) may occur without an underlying disorder or as a secondary manifestation of an underlying disorder.
- It may be seen in fully breast-fed infants without a routine supplementation of vitamin K. In contrast, idiopathic late HDN is defined as HDN without the presence of any risk factor, such as gastroenteritis or use of antibiotics. Severe hemorrhagic symptoms frequently occur.
- Late HDN results in severe hemorrhage especially hemorrhage in the central nervous system with a frequency of 30 to 75 %. Intracranial hemorrhages are represented by subdural hematomas (40 %), parenchymal (40 %), intraventricular (10 %) and subarachnoid (10 %) hemorrhages.
- Bör O, Akgün N. research (1987–1997) showed that patients with late HDN had convulsions in 47 % of cases, feeding intolerance and poor sucking in 47 % of cases, irritability in 33 % of cases, neonatal reflexes were reduced or absent in 60 %, and ecchymoses in 20 % of cases.
- If there is a strong clinical suspicion of VKDB (eg, clinically apparent bleeding and known refusal of vitamin K prophylaxis), the infant should be treated immediately, even before test results are available. Administration of vitamin K (1 mg, IM) at the birth can reduce these severe complications.
- In 30–50 % of cases intracranial hemorrhages lead to disability or death.
- Deficiency of vitamin K may be accompanied by thrombosis, as a violation of the synthesis of anticoagulants – proteins C and S also occurs with deficiency of vitamin K in the liver.

Diagnostic criteria

I. Complaints and history:

Anamnesis data, allowing even before birth to identify newborns that may have signs of bleeding, are presented in risk factors.

II. Physical examination:

A full examination of the newborn is carried out 2 hours after birth. The survey in the first hours or days may reveal cutaneous hemorrhage, intracranial hemorrhage, and cephalogematoma when adequately carried out childbirth.

III. Laboratory examination (see the initial workup for VKDB)

ADDITIONAL RESEARCH METHODS FOR DIAGNOSIS OF HEMORRHAGIC DISEASE

The initial workup for VKDB in a newborn

1. Prothrombin time (PT), sec.
2. Activated partial thromboplastin time (APTT), sec.
3. International normalized ratio (INR), sec.
4. Fibrinogen levels, g/L

Table 3. Reference Values

Characteristic	Premature	Full-Term
Prothrombin time (sec)	11–22	10–16
Activated partial thromboplastin time (sec)	28–101	31–55
Fibrinogen (g/L)	1,5–3,7	1,7–4,0

1. At signs of DIC syndrome, the following parameters are further investigated: products of fibrinogen degradation (PDF), D-dimer.

2. A platelet count

3. Thrombin clotting time (TCT) is optional

4. Determination of the level of PIVKA can help in diagnosis of Vitamin K deficiency, but it is not related to the main diagnostic markers in practice.

5. A direct blood measurement of vitamin K is not useful, because its levels normally are low in newborns.

6. Instrumental study. Imaging Studies MRI exposes the neonate to no radiation and is becoming the preferred way to study the brain because tissue damage can be better defined.

7. Specialist advice. A full coagulopathy work-up and hematology consultation are required if clinical and laboratory findings are suggestive of non-vitamin K deficiency bleeding. A work-up that includes functional tests and imaging are mandatory if liver disease is suspected. Hereditary defects in the coagulation system must always be considered among the differential diagnoses.

HDN is characterized by:

- In a bleeding infant a prolonged one-stage prothrombin time (a decreased Quick value, which means prothrombin time expressed as percent of normal) due to reduction in Prothrombin, FVII, FIX, and FX levels. Prolongation of prothrombin time, often 4 times or more.

- Reduction of PTI is below 60 %

- An increase in INR

- Lengthening of APTT

- Normal thrombin time

- Normal (or increased) fibrinogen level and platelet count

- The diagnosis is proven, if administration of VK is followed by a shortening of the prothrombin time (after only 30 minutes) or cessation of bleeding.

An example of the diagnosis formulation:

Hemorrhagic disease of the newborn, the classical form, gastrointestinal bleeding (P53, ICD-X)

DIFFERENTIAL DIAGNOSIS

Differential diagnosis is made between the following diseases:

- **Swallowed blood syndrome**

- Apt test for fetal hemoglobin. Purpose: To differentiate fetal blood from swallowed maternal blood in the evaluation of bloody stools. Method: Mix specimen with 3–5 ml of tap water and centrifuge. Supernatant must have a pink color to proceed. To 5 parts of supernatant, add 1 part of 0.25 N (1%) NaOH. Interpretation: A pink color persisting over 2 minutes indicates fetal hemoglobin. Adult hemoglobin gives a pink color that becomes yellowish brown in 2 minutes or less indicating denaturation of the adult hemoglobin.)

- **Congenital coagulopathy**

- Hemophilia is characterized by recessive inheritance linked to X-linked (affects boys), a disease rarely seen in the neonatal period (possible bleeding from the umbilical cord remnant, massive cephalhaematoma). Hemophilia is characterized by hematoma type of bleeding, hemorrhages in the joints. Laboratory findings: a significant lengthening of blood clotting time and partial thromboplastin time, as well as a decrease in the level of VIII clotting factor in hemophilia A or IX – in hemophilia B.

- **Thrombocytopathy/thrombocytopenia**

- Thrombocytopenia is characterized by petechial-purple type of bleeding, normal indicators of coagulation hemostasis with a decrease in the number of platelets, lengthening the bleeding time and reducing the retraction of the blood clot. There may be hemorrhages on the mucous membranes of the oral cavity, melena, very rarely – nasal and pulmonary hemorrhages, intracranial hemorrhages, and hematuria.

- The causes of thrombocytopenia may be infections, immune disorders, bone marrow abnormalities, medical effects, excessive peripheral utilization (with giant hemangioma Kasabach–Merritt, etc.), hereditary thrombocytopenia (Wiskott-Aldrich syndrome, etc.), etc.

- **Transimmune neonatal thrombocytopenia (TNT)** develop as a result of penetration through the placenta of autoantibodies mother, who had ever TP or other autoimmune disease, or suffering from drug allergy. Clinical manifestations of TNT in newborns develop in the first days of life, but can occur later, until the end of the 1st month of life. Antibodies are transmitted passively, the body itself does not produce antibodies, recovery occurs after 5–12 weeks. The prognosis is favorable.

- **Neonatal Alloimmune Thrombocytopenia (NAIT)**

- Sometimes known as isoimmune thrombocytopenia, this is the result of sensitization of the mother to antigens present on fetal platelets during gestation. These antigens are inherited from the father and are thus absent on maternal platelets. The antibodies created then cross the placenta and attack the

fetal platelet. The incidence of NAIT is approximately 1 in 1500 pregnancies and is the platelet equivalent of haemolytic disease of the newborn.

- Suspect NAIT in a thrombocytopenic newborn that is otherwise well, normal maternal platelets, no history of maternal autoimmune disease or ITP. The neonate with NAIT is at risk for intracranial hemorrhage in utero and during delivery.

- NAIT varies in severity from mild/moderate which typically resolves in the first week of life without sequelae, to severe with extensive intracranial hemorrhage (up to 20 % of cases) leading to either death or serious neurological sequelae.

- The most common presentations in severe NAIT are petechiae, purpura, and cephalohematoma at birth.

- The diagnosis depends on demonstrating platelet antigen incompatibility between mom and neonate or mom and father.

- The most commonly detected antibodies are those directed against human platelet antigen (HPA)-1a (80 %) and HPA-5b (10–15 %) – this permits prenatal diagnosis in at risk fetuses

- **Neonatal Autoimmune Thrombocytopenia**

- This form of neonatal thrombocytopenia occurs in neonates whose mothers have Idiopathic Thrombocytopenia Purpura (ITP), Werlhof disease, or Systemic Lupus Erythematosus (SLE). These mothers carry antibodies directed against platelets. The platelet associated IgG antibody can passively cross the placenta and cause thrombocytopenia in the fetus and the newborn in 10 % of cases.

- The clinical manifestations are less severe than in NAIT; the risk of intracranial hemorrhage is less than 1 %, greatest during passage through the birth canal. Most cases usually resolve by 4–6 weeks.

- All neonates of moms with an autoimmune disease should have a cord blood platelet count determined at birth.

- Fetal scalp sampling can also be used to measure to fetal platelet count.

- The platelet count should be repeated for 3–4 days.

- The maternal platelet count is sometimes a useful indicator of the probability that the infant will be affected

- **Disseminated Intravascular Coagulation (DIC)**

- DIC syndrome in newborns ("secondary hemorrhagic disease of newborns") can be caused by various etiological factors. The pathogenesis of DIC in newborns is associated with increased activity of tissue factor (thromboplastin), cytokine secretion (I-1, I-6, I-8, tumor necrosis factor) and excessive thrombin production. Increased vascular expression of E-selectin also develops during DIC.

- DIC develops in newborns with any pathology and especially often in premature infants with serious pathology. Clinical manifestations of DIC syndrome are characterized by a combination of thrombotic and hemorrhagic symptoms in the same patient.

– DIC develops in the form of two successive phases. Phase I – hypercoagulation due to the massive entry of thromboplastin into the bloodstream, thrombin is formed, which turns fibrinogen into fibrin monomer. Phase II – hypocoagulation due to consumption of blood clotting factors and possibly secondary fibrinolysis.

– Typical clinical manifestations of DIC are prolonged bleeding from injection sites, less often - spontaneous bleeding, massive pulmonary, intestinal, nasal bleeding, purpura (petechiae, ecchymosis, hematomas), hemorrhages to the internal organs and brain, clinical signs of vascular thrombosis, including skin necrosis, ulcerative-necrotic enterocolitis, acute renal failure, gangrene of the limbs, edema syndrome, RDS, symptoms of severe peripheral disorders circulation.

– Laboratory diagnostics. The most typical prolongation of PT, APTT, an increase in degradation products of fibrin (FDP), soluble fibrin-monomeric complexes, thrombocytopenia, depletion of fibrinogen, factors V and VIII. In General, the diagnosis is made taking into account the clinical situation.

Table 4. Differential diagnosis of HDN and DIC syndrome

The symptom	HDN	DIC
Clinical:		
Bleeding from places injections'	Not typical	Not typical
Microangiopathic hemolytic anemia	Not typical	Typical
Arterial hypotension	Not typical	Typical
Multiple organ failure	Not typical	Typical
Laboratory:		
Platelet count	Norm	Reduced
Prothrombin time	Increased	Increased
Thrombin time	Norm	Increased
Fibrinogen	Norm	Reduced
FDP	Norm	More than 10 mg/ml
PTT	Increased	Increased

Table 5. Laboratory parameters for various hemorrhagic syndromes in infants

Indicators	Healthy	Vitamin K deficiency	Hepatic coagulopathy	DIC syndrome (II, III stages)	Thrombocytopenia without DIC	Hemophilia
Platelet count, $10^9/L$	150–400	Norm	Norm	Reduced	Reduced	Norm
Prothrombin time, sec	12–16	Increased	Increased	Increased	Norm	Norm
Thrombin time, sec	14–21	Norm	Increased	Increased	Norm	Norm
APTT, sec	28–36	Increased	Increased	Increased	Norm	Increased
Fibrinogen, g/L	1,6–4,0	Norm	Norm or slightly reduced	Reduced	Norm	Norm

THERAPEUTIC STRATEGY AND PREVENTION OF HEMORRHAGIC DISEASE OF THE NEWBORN

Goals of treatment:

- Stop bleeding;
- Stabilization of the state (hemodynamics, gas exchange);
- Elimination of vitamin K deficiency.

1. A presumptive diagnosis of VKDB should be made in an infant presenting with bleeding or neurologic symptoms and either prolonged PT or INR, or a history of not receiving vitamin K at birth.

2. Such infants should be treated immediately with parenteral vitamin K (phytonadione), 1 to 2 mg intravenously or subcutaneously. The vitamin K1 (phytomenadion) is lipid – soluble form of vitamin.

3. Because the bleeding in classic vitamin K deficiency bleeding usually is not life threatening, a single dose of parenteral vitamin K dose should normalize the coagulation profile within two to three hours.

4. Fresh frozen plasma may be considered for moderate-to-severe bleeding. If APTT is outside the upper limit of the norm, it is necessary to enter the FFP (Fresh frozen plasma) intravenously for 30 minutes at the rate of 10–15 ml/kg.

5. Re-conduct a study of prothrombin and APPT and while maintaining their violations – repeat the previous dose of FFP.

6. Life-threatening bleeding may also be treated with prothrombin complex concentrates (PCC). It is prepared from large pools of normal donor plasma; the PCCs contain the vitamin K–dependent clotting factors prothrombin, FVII, FIX, and FX, as well as anticoagulant protein C and S. They are isolated from the cryoprecipitate supernatant of large plasma pools after removal of antithrombin and factor XI.

7. If there is no effect after the introduction of FFP, cryoprecipitate is used at the rate of 5 ml/kg for 30 minutes.

8. Re-conduct a study of prothrombin and activated partial thromboplastin time and while maintaining their violations – enter cryoprecipitate at the same dose.

Monitoring

1. If the indications persist, it is necessary to repeat the blood clotting test every 12 hours.

2. It is necessary to identify and treat the cause of coagulopathy: sepsis, shock, hypothermia, hypoxia, etc.

3. If coagulopathy persists for more than 24 hours, consultation with a hematologist is required.

Table 8. Products for Treatment of Coagulopathies

Product	Factor Content	Usual Dose	Indications
Fresh frozen plasma	All factors	10–20 mL/kg	Disseminated intravascular coagulation (DIC); liver disease; protein C deficiency
Exchange transfusion	All factors platelets	Double volume	Severe DIC; liver disease
Factor VIII concentrate	Factor VIII	25–50 U/kg	Factor VIII deficiency (Hemophilia A)
Factor IX concentrate	Factor IX	50–100 U/kg	Factor IX deficiency
Vitamin K	–	1–2 mg	Vitamin K deficiency
Platelet concentrate	Platelets	1–2 units/5 kg	Severe thrombocytopenia
Intravenous gamma globulin	IgG	1–2 g/kg	Severe sepsis; thrombocytopenia due to transplacental antibodies

VKDB preventive measures:

1. Women in pregnancy require higher a nutrient supply, they may experience greater shortages of other nutrients, especially in suboptimal deficiency. Although Vitamin K supplement is not necessary in normal pregnancy, deficiency may occur in epilepsy and other impaired conditions. If pregnant women take drugs that violate the metabolism of Vitamin K, it is recommended to take additional Vitamin K: in the third trimester at a dose of 5 mg/day, or 2 weeks before delivery at a dose of 20 mg/day.

2. Administration of vitamin K1 (phytonadione) immediately after birth is an effective way to prevent classical and late forms of VKDB. Data show that the administration of vitamin K1 compared with placebo improves the biochemical indices of coagulation status during the first week after birth and is more effective in preventing VKDB. Menadione, a synthetic water-soluble form of vitamin K, can cause hemolytic anemia, hyperbilirubinemia, jaundice, and kernicterus in infants [30,31]. Menadione has been used in premature or low birth weight newborns but may precipitate kernicterus in high doses.

Studies have shown that the prophylactic appointment of Phytomenadione (vitamin K1) tenfold reduces the likelihood of bleeding in the early stages after birth and the manifestation of VKDB. The American Academy of Pediatrics (AAP) has recommended that «a single dose of 0.5 mg to 1.0 mg of vitamin K be administered intramuscularly (IM) to all newborns shortly after birth to prevent VKDB» since 1961.

According to the protocol of the Ministry of Health of Ukraine on medical care of a healthy newborn child: «Prevention of early and classic forms

of hemorrhagic disease of newborns is provided by intramuscular administration of vitamin K1 to full-term infants after birth in the maternity hospital at a dose of 1 mg». The dose is administered not earlier than 1 hour after delivery, during the first day of life. «Prevention of the late form of hemorrhagic disease of newborns is provided by taking the enteral form of vitamin K1 from the 8th day of life until the end of 3 months of age, provided only breastfeeding. If at the same age there is a need for simultaneous prevention of vitamin K1 and D3 deficiency, it is provided by enteral administration of these vitamins, starting with 8th day of life».

It is mandatory to obtain informed consent for medical interventions from the child's legal representative. If the parents refuse to take preventive measures, this should be recorded in informed consent. The medical documentation should indicate the dose of vitamin K administered, the route and date of administration of the drug.

In some countries, oral administration of vitamin K has been advocated because it is easier to administer and is less costly. However, even with increasing the oral dose of vitamin K, there remains a risk for intracranial bleeding. In countries where oral vitamin K is the standard, IM rather than oral prophylaxis should be administered to infants who are preterm, receiving antibiotics, or who have liver disease or diarrhea, because they may have decreased absorption of the oral preparation. VKDB may still develop despite IM administration of vitamin K in neonates with liver disease.

The Canadian Paediatric Society and the College of Family Physicians of Canada also recommend routine IM administration of a single dose of vitamin K to all newborns but also proposed that 2.0 mg dose of oral (PO) vitamin K administered within 6 hours of birth, then repeated at 2 to 4 weeks and 6 to 8 weeks of age, was an acceptable alternative. Administering one intramuscular (IM) dose of vitamin K (0.5 mg for infants weighing $\leq 1,500$ g or 1.0 mg for infants weighing $> 1,500$ g) routinely to all newborns within the first 6 hours post-birth and following initial stabilization and appropriate maternal/newborn interaction, is now the recommended best practice. One recent practice review has confirmed that routine administration of IM vitamin K at birth effectively prevents VKDB. However, while clinical decisions should always be based on the best evidence available, potential for harm to the infant must also be considered. The psychological effects of procedural pain on infants (and parents) are unknown. Pain experienced during the neonatal period may have long-term effects.

When parenteral nutrition shows the assignment of the vitamin complex containing Vitamin K. For adequate nutritional support and prevention of hemorrhagic syndrome, it is necessary to focus on the daily need for Vitamin K in premature and full-term newborns (table 9).

Table 9. Adequate Intake (AI) for Vitamin K

Life Stage	Age	Males (µg/day)	Females (µg/day)
Infants	0–6 months	2.0	2.0
Infants	7–12 months	2.5	2.5
Children	1–3 years	30	30
Children	4–8 years	55	55
Children	9–13 years	60	60

Side effects of Vitamin K

These are largely confined to local effects and the side effects of an IM injection. Exacerbation of jaundice and haemolysis does not occur with the doses now used or the naturally occurring lipid soluble vitamin K₁ (Konakion^(R), Kanavit). Many years ago, these were the problems associated with the administration of water-soluble vitamin K in very large doses. Intravenous vitamin administration can produce local reactions. Risks associated with the injection technique include infection, irritation of the injection site or nerve and muscle damage as the Vitamin K injection must be given deeply into the muscle. These are very rare complications.

Contraindications for the appointment of vitamin K₁: hypercoagulability, thromboembolism, hemolytic disease of a newborn, with caution in case of deficiency of G-6-PD. High doses of more than 10 mg or prolonged use increases hemolysis and contributes to the development of jaundice.

Newborns who underwent VKDB after stabilization of the state are transferred to the second stage of nursing for further examination and treatment.

QUESTIONS FOR SELF-CONTROL

1. Types of hemorrhagic disorders in children, classification.
2. Features of the haemostatic system in newborns.
3. Etiology and pathogenesis of hemorrhagic disease of the newborns.
4. Describe vitamin K metabolism.
5. The reasons for the development VKDB and risk factors.
6. Clinical characteristics of VKDB and classification.
7. Types of bleeding in newborns with VKDB. Complications of VKDB.
8. Plan of examination and auxiliary methods of diagnostics of VKDB.
9. Differential diagnosis between different types of hemorrhagic disorders.
10. Emergency care for VKDB in newborns.
11. Prevention of VKDB.

Control tests

1. On the 3rd day after birth, the child had melena, which increased by 4 days. There are numerous petechiae on the skin and mucous membranes, and

in the feces - impurities of crimson blood. During the Apt test, the color of the fecal masses did not change. The blood has a low content of II, VII, IX X blood clotting factors, hemoglobin is 160 g/L, red blood cells $4.5 \times 10^{12}/L$, platelets $250 \times 10^9/L$. What is the most likely diagnosis?

- A. Afbrinogenemia
- B. Hemorrhagic disease of the newborn
- C. Hemolytic disease of newborn
- D. DIC-syndrome
- E. Willebrand's Disease

2. In full-term boy (second physiological pregnancy and uncomplicated childbirth) blood regurgitation, melena was detected at the end of the second day of life. What kind of emergency therapy is needed in this case?

- A. Protease Inhibitors, aminocaproic acid
- B. High doses of vitamin C
- C. Calcium, contrical
- D. Vitamin K₁, fresh frozen plasma
- E. Glucocorticosteroids

3. A full-term newborn on the 2nd day of life had vomiting with small blood content. What study should be conducted for the differential diagnosis of hemorrhagic disease and the syndrome of “swallowing blood” of the mother?

- A. Apt Test
- B. Coagulation
- C. Blood clotting Time
- D. Bilirubin Level
- E. General blood test

4. The child was born on time with an Apgar score of 5–7 points. On 3rd days there was melena. The General condition of the child is not disturbed. The Apt test is negative. A study of the hemostatic system within the capacity of the hospital was prescribed. What indicators are more likely to be obtained?

- A. Prothrombin time is reduced, platelets are normal
- B. Prothrombin time increased, platelets are normal
- C. Prothrombin time and the platelet count are reduced
- D. Prothrombin time and platelets are normal
- E. Prothrombin time - normal, platelets – reduced

5. In a newborn child who was born in a state of severe asphyxia on the 3rd day of life, umbilical bleeding and hemorrhagic rash on the skin and subcutaneous tissue were noted. Lengthening of prothrombin time, violation in the auto-coagulation test, the number of platelets were registered– $250 \times 10^9/L$. What therapy is rational in this case?

- A. The use of corticosteroids IM, IV
- B. Heparin subcutaneously or IV + fresh frozen plasma intravenously drip

- C. The administration of the concentrate PPSB + phytonadione
- D. Platelet mass IV, and etamzilat IV
- E. Fresh frozen plasma IV/drip+ vitamin K1 (phytonadione)

Standards of answers to tasks:

Number	1	2	3	4	5
Answer	B	D	A	B	E

Situational task 1

Full-term boy of three days of life, pregnancy 2, childbirth 2 with a diagnosis of "intestinal bleeding". Mother is 17 years old. The pregnancy proceeded with the threat of termination in the 32–34 weeks. Childbirth at 38 weeks, body weight – 2950 g, Apgar score is 7–8 points. Vitamin K in the hospital was not administered due to the refusal of the mother. On the 3rd day there was a one-time vomiting, dark brown staining of feces. Physical examination: there are single bruises on the skin of the trunk, petechia. There is melena.

Lab findings

TEST	Reference values	3 rd day of life
Hb, g/L	167–240	170
RBC	$(7,5-4,5) \times 10^{12}/L$	4.5
Duration of bleeding on Duke (min)	2–4	2
aPTT (sec)	42.9 (31.3–54.3)	72
Prothrombin time (sec)	13.0 (10.1–15.9)	40
Thrombin time (sec)	18.0	18.0
Factor I Fibrinogen, g/L	283 (167–399)	270
INR, sec	0.8–1.3	24.8
Factor VIII	100	98
Antihemophilic factor, %	(50–178)	
von Willebrand factor, %	153 (50–287)	70
Platelets	$320-290 \times 10^9/L$	310

1. Your preliminary diagnosis.
2. What is the basis of the identified symptoms?
3. Evaluate the results of the additional survey.
4. What conditions or diseases should hemorrhagic disease be differentiated with?

Situational task 2

The newborn boy was born from the 2nd pregnancy at the 38th week of gestation. Body weight at birth is 2820 gr. Apgar score was 8/10 points.

The child was vaccinated according to the calendar (BCG and hepatitis B). Vitamin K was not administered. He was discharged from the maternity home in a satisfactory condition. The child was breastfed. On the 20th day of life there was a slight bleeding in the umbilical wound. There was no treatment. The mother noted bloody discharge from the nose and crust in the nasal passages

of the child at the age of 27th days. The next day there was a hematoma on the back under the shoulder blade about 1.5 cm in size. There was a single vomiting, sluggish sucking on the 29th day of life. He was restless.

On the 30th day the child entered the intensive care unit. The treatment: phytonadione, twice the transfusion of FFP, transfusion of the erythrocyte mass.

Coagulogram data:

TEST	Ref. value	30 rd day of life	32 day of life
aPTT (sec)	42.9 (31.3–54.3)	96	24.4
Prothrombin time, (sec) (A. Quik)	13.0 (10.1–15.9)	581	13.0
Thrombin time, (sec)	18.0	18.3	18.0
Factor I Fibrinogen, g/L	283 (167–399)	276	360
INR, sec	0.8–1.3	74.19	1.16
Factor VIII Antihemophilic factor, %	100 (50–178)	101	176
von Willebrand factor, %	153 (50–287)	74	85
Platelets		165	180

Neurosonography conclusion: Intraventricular hemorrhage, grade 3 on both sides.

1. Make your preliminary diagnosis.
2. What is the basis of the identified symptoms?
3. Evaluate the results of the additional survey.
4. What are the complications identified in this patient?

Etalon of answers to tasks:

Task 1

2.1. Vitamin K deficiency bleeding.

2.2. In this case, hemorrhagic syndrome developed as a result of vitamin K deficiency caused by a number of provocative factors – lack of prevention of vitamin K deficiency, complicated course of pregnancy.

2.3. The lab. findings determine hypocoagulation (extension of the aPTT to 72 and PT to 40, increase INR to 24.8). The levels of fibrinogen, Willebrand factor, Factor VIII, platelets, Hb and RBC remain within the reference values.

2.4. This disease needs to be differentiated from the following disorders: Alloimmune Thrombocytopenia, Consumption Coagulopathy, Hepatobiliary Disease, Maternal Isoimmune Thrombocytopenia, Uncommon Coagulopathies, Congenital coagulopathy, Swallowed blood syndrome.

Task 2

2.1. Hemorrhagic disease of the newborn

2.2. Reduced activity of vitamin-K-dependent coagulation factors

2.3. The results of the coagulogram indicate hypocoagulation (extension of the aPTT to 96 and PT to 581, increase INR to 74). The levels of fibrinogen, Willebrand factor, Factor VIII, platelets remain within the reference values.

2.4. Intraventricular bilateral hemorrhage grade 3.

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