

**Ministry of Healthcare of Ukraine**  
**Poltava State Medical University**

**«Approved»**  
at the meeting of the  
Chair of Internal medicine №1  
Head of the Chair  
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**Methodical instruction  
for the students self-training  
during preparing for practical classes (seminars)**

<b><i>Subject</i></b>	<b>Internal medicine</b>
<b><i>Module №1</i></b>	<b>FUNDAMENTALS OF INTERNAL MEDICINE</b>
<b><i>Topic</i></b>	<b>Hemophilia. Thrombocytopenic purpura</b>
<b><i>Course</i></b>	<b>IV</b>
<b><i>Faculty</i></b>	<b>Medical</b>

### **The subject of the lesson: Hemophilia. Thrombocytopenic purpura**

1. The theme topicality. The theme "Hemophilia" is very important for future doctors in their professional activity; it influences positively on the students in their attitude to the future profession and forms professional skills and experience as well as taking the principle of the knowledge of the subject under study.

2. The main goals:

To have general knowledge of the theme studied

To understand, memorize and use the knowledge received

To learn the etiopathogenesis, classification, clinics, diagnostics, principles of treatment

To be able:

- to derive previous and clinical diagnosis,
- to complete the plan of additional investigation,
- to interpret the results of additional data,
- to prescribe the treatment.

3. Basic knowledge, abilities and skills necessary for studying theme.

#### Interdisciplinary integration

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Subject	To know	To be able to
Previous subject (pathophysiology, propedeutics; pharmacology	Basic terms Pathogenesis Skills Pharmacokinetic-dynamic	To use information gained previously
Following subject	etiopathogenesis, classifications, clinics, diagnostics, principles of treatment	to derive clinical diagnosis, to interpret the results of additional data; to prescribe the treatment

4. Materials for self-training

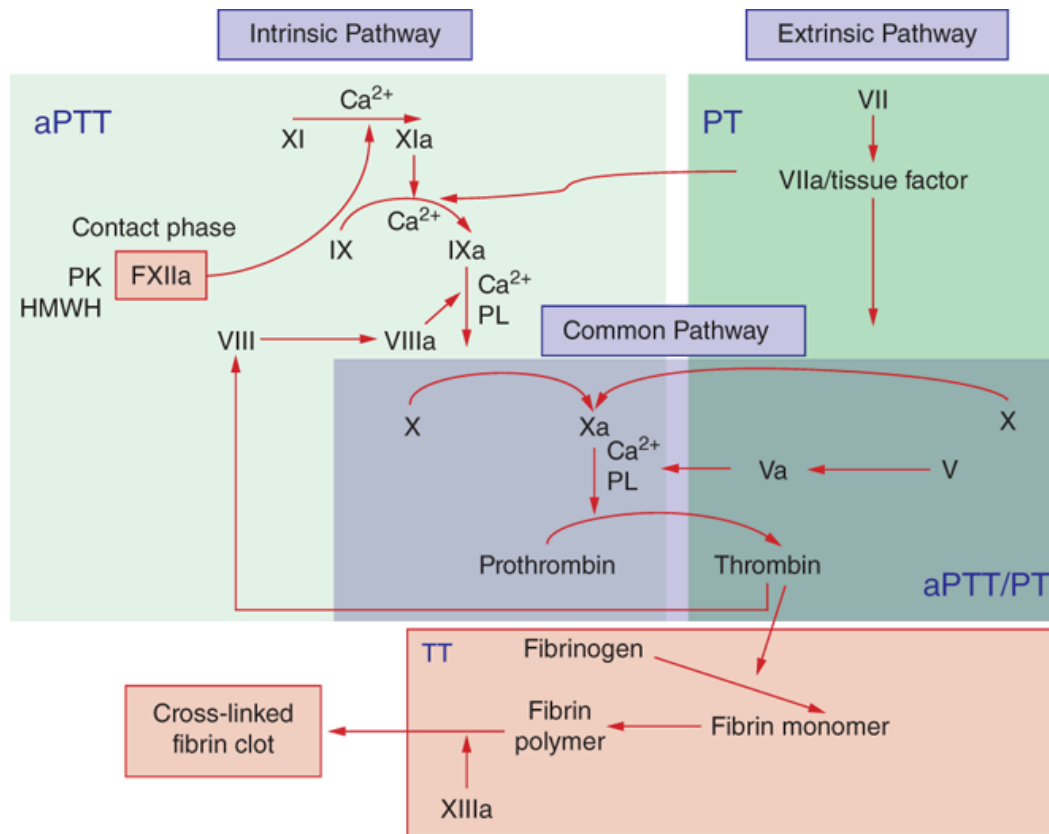
4.1. The main terms, subjects and its introductions

Subject	Introduction
Hemophilia	Congenital blood coagulation disorder, inheritance is sex linked, males are affected while females act as carriers.
Hemophilia A	Occurs as a result of low level or either absence of coagulation factor VIII.
Hemophilia B	(Christmas' disease) occurs as a result of deficiency of coagulation factor IX.
ITP (Immune/idiopathic thrombocytopenic purpura	An acquired thrombocytopenia, defined as decreased platelet count and caused by immune destruction of platelets

4.2. Self preparation at class. Practical skills the student must be able to do:

- 1.To survey a patient.
- 2.To make a differential diagnostic and formulate the clinical diagnosis.
- 3.To estimate the results of lab studies and procedures.
- 4.To write out the recipe: coagulation factor VIII/IX; prednisolone et al.

### Theme contents:



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**Pic.1. Coagulation cascade**

**Hemophilia** is an X-linked recessive hemorrhagic disease due to mutations in the *F8* gene (hemophilia A or classic hemophilia) or *F9* gene (hemophilia B). The disease affects 1 in 10,000 males worldwide, in all ethnic groups; hemophilia A represents 80% of all cases. Male subjects are clinically affected; women, who carry a single mutated gene, are generally asymptomatic.

**CLINIC.** The main clinical syndrome is hemorrhagic, hematoma type. Clinically, hemophilia A and hemophilia B are indistinguishable. The disease phenotype correlates with the residual activity of FVIII or FIX and can be classified:

- severe (<1%).
- moderate (1–5%).
- mild (6–30%).

In the severe and moderate forms, the disease is characterized by bleeding into the joints (hemarthrosis), soft tissues, and muscles after minor trauma or even

spontaneously. Patients with mild disease experience infrequent bleeding that is usually secondary to trauma. Among those with residual FVIII or FIX activity >25% of normal, the disease is discovered only by bleeding after major trauma or during routine presurgery laboratory tests. Early in life, bleeding may present after circumcision or rarely as intracranial hemorrhages. The disease is more evident when children begin to walk or crawl. In the severe form, the most common bleeding manifestations are the recurrent hemarthroses, which can affect every joint but mainly affect knees, elbows, ankles, shoulders, and hips. Acute hemarthroses are painful, and clinical signs are local swelling and erythema. To avoid pain, the patient may adopt a fixed position, which leads eventually to muscle contractures. After a joint has been damaged, recurrent bleeding episodes result in the clinically recognized “target joint,” resulting in progressive joint deformity that in critical cases requires surgery as the only therapeutic option.

## LAB STUDIES

CBC and general coagulation tests are normal, except isolated *prolongation of the aPTT assay*. Patients with hemophilia have normal bleeding times and platelet counts. The diagnosis is made after specific determination of FVIII or FIX clotting activity.

The Lee-White clotting time is also prolonged.

## TREATMENT

Considerations regarding the treatment of bleeding in haemophilia patients include the following:

- signs of bleeding may not appear until several days after well documented trauma. Early treatment is more effective, less costly, and can be lifesaving;
- avoid the use of aspirin or aspirin-containing drugs, which impair platelet function and may cause severe hemorrhage. Cyclooxygenase inhibitors can be used, as they do not impair platelet function.
- treatment should begin as soon as possible.

The goals are to control symptoms, and to prevent recurrent bleeding or other complications. The treatment is based on lifestyle modification and control of blood coagulating level.

- Lifestyle modifications include the following:
  - Very important to change the profession rightly
  - The parents had got full information about disease of their child.
  - Schoolboys had to be free from physical training classes, except swimming (which is highly recommended).

## MEDICATION

The goals of pharmacotherapy are to prevent complications and to reduce morbidity.

Plasma products enriched in factor VIII reduce the degree of orthopedic deformity and permit virtually any form of elective and emergency surgery.

Cryoprecipitate, which contains about half the factor VIII activity of fresh-frozen plasma in one-tenth the original volume, is simple to prepare and is produced in hospital

or regional blood banks. These products should be avoided in hemophilia patients when factor concentrates are available.

Patients with hemophilia should receive either monoclonal purified or recombinant factor VIII/IX to minimize viral infection risk and exposure to irrelevant proteins.

FVIII and FIX are dosed in units.

One unit is defined as amount of FVIII (100 ng/mL) or FIX (5 µg/mL) in 1 mL of normal plasma. One unit of FVIII per kilogram of body weight increases the plasma FVIII level by 2%. One can calculate the dose needed to increase FVIII levels to 100% in a 70-kg severe hemophilia patient (<1%) using the simple formula below. Thus, 3500 units of FVIII will raise the circulating level to 100%.

$$FVIII \text{ dose (IU)} = \frac{\text{Target FVIII levels} - \text{FVIII baseline levels}}{\times \text{body weight (kg)} \times 0.5}$$

The doses for FIX replacement are different from those for FVIII, because FIX recovery after infusion is usually only 50% of the predicted value. Therefore, the formula for FIX replacement is as follows:

$$FIX \text{ dose (IU)} = \frac{\text{Target FIX levels} - \text{FIX baseline levels}}{\times \text{body weight (kg)} \times 1}$$

## PROGNOSIS

- Most patients with hemophilia do well with medications, although a relapse after cessation of medical therapy is common and indicates the need for long-term maintenance therapy.
- Identifying the subgroup of patients who may develop the most serious complications of the disease and surgical treatment is important.

## IMMUNE THROMBOCYTOPENIC PURPURA

*Immune thrombocytopenic purpura* (ITP; also termed *idiopathic thrombocytopenic purpura*) is an acquired disorder in which there is immune-mediated destruction of platelets and possibly inhibition of platelet release from the megakaryocyte.

In children, it is usually an acute disease, most commonly following an infection, and with a self-limited course. In adults, it is a more chronic disease, although in some adults, spontaneous remission occurs, usually within months of diagnosis.

**CLINIC.** The main clinical syndrome is hemorrhagic, the petechial type. ITP is characterized by mucocutaneous bleeding. Patients usually present either with ecchymoses and petechiae, or with thrombocytopenia incidentally found on a routine CBC. Mucocutaneous bleeding, such as oral mucosa, gastrointestinal, or heavy menstrual bleeding, may be present. Rarely, life-threatening, including central nervous system, bleeding can occur. Wet purpura (blood blisters in the mouth) and retinal hemorrhages may herald life-threatening bleeding.

### LAB TESTS:

- CBC – platelets level is  $<150 \times 10^9/L$ ;
- bone marrow examination (BM aspirate) shows increased level of megakaryocytes with poor platelet release;
- presence of circulating plasma autoantibodies against platelet glycoproteins (optional test).

Diagnosis of ITP is generally made by review of peripheral smear and evaluation of history and examination of the patient. The IWG recommended a few additional tests for all patients with ITP, including H pylori testing, HIV, and hepatitis C testing as well as a direct antiglobulin test and blood type.

## MANAGEMENT

Prednisone 1 mg/kg/d per os for 2 to 4 weeks has been the standard first-line treatment for many years. Highdose dexamethasone, rituximab and thrombopoietin receptor agonists may also show good effect as the second-line therapy.

Splenectomy is indicated only if relapse after glucocorticoids develops.

## Test evaluation and situational tasks.

Choose the correct answer/statement:

1. In the pathogenesis of idiopathic thrombocytopenic purpura main role belongs to:

- A. Immune mechanisms
- B. Toxic effects
- C. Reduction of platelet production
- D. Genetic disorders
- E. Mechanical platelets trauma

2. Which of the following manifestations of hemorrhagic syndrome are the most typical for hemophilia?

- A. Hemarthroses
- B. Bleeding from mucous membranes
- C. Hematuria
- D. Stroke
- E. Subcutaneous hematoma

3. Which of the following drugs is fundamental in the treatment of hemophilia A?

- A. Factor VIII concentrate
- B. Cryoprecipitate
- C. Hemostatic sponge
- D. Preserved blood
- E. Factor IX concentrate

4. Which of the following drugs are the primary in conservative treatment of idiopathic thrombocytopenic purpura?

- A. Corticosteroids
- B. Blood transfusion

- C. Heparin
- D. Cryoprecipitate
- E. Dicynonum

5. The diagnosis of thrombocytopenic purpura is confirmed by:

- A. Thrombocytopenia
- B. Leukocytosis
- C. Anemia
- D. Accelerate ESR
- E. Changes in coagulation

6. Which of the following manifestations of hemorrhagic syndrome is the most characteristic of immune thrombocytopenic purpura?

- A. Petechiae
- B. Hemarthroses
- C. Hematuria
- D. Subcutaneous hematoma
- E. Bleeding from mucous membranes

7. Which of the following factors related to the plasma coagulation factors?

- A. Fibrinogen
- B. Heparin
- C. Plasminogen
- D. Platelets
- E. Serotonin

8. Which of the following drugs is fundamental in the treatment of hemophilia A?

- A. Factor VIII concentrate
- B. Aminocaproic acid
- C. Factor IX concentrate
- D. Prednisolone
- E. Heparin

9. The cause of hemophilia B is:

- A. Deficiency of coagulation factor IX
- B. Deficiency of VIII and IX coagulation factors
- C. Deficiency of VII and VIII clotting factors
- D. Deficiency of VI coagulation factor
- E. Deficiency of XII coagulation factor

10. Which of the following manifestations of hemorrhagic syndrome are the most typical for hemophilia?

- A. Post-traumatic and spontaneous bleeding, hemarthrosis
- B. Hemorrhagic petechial rash, abdominal pain, hematuria
- C. Spontaneous bleeding from the mucous membranes

D. Nosebleeds

E. Papular, petechial rash, symmetrically located in the limbs

**Real-life situations to be solved:**

1. A woman aged 42, complains of the bruising on his legs, long menorrhagia, general weakness, noise in my head. Objectively: pale skin, massive punctulate and spotty rash on the legs and body. Tachycardia. Systolic murmur at all points of auscultation. BP -75/50 mm Hg. In blood test: RBC -  $2,9 \times 10^{12}/l$ , HGB - 80 g/l, color index - 0.9, leukocytes -  $6,5 \times 10^9/L$ , platelets -  $20,0 \times 10^9/l$ . ESR- 12 mm / h Duration bleeding by Duke - 12 min. In the bone marrow - the increased number of young immature megakaryocytes no signs of platelet release. Other indicators are normal. Which disease correspond to the data of clinical and laboratory signs?

2. 18-years old patient K. was hospitalized to the therapeutic department with renal bleeding continuing more than a day. From anamnesis it is known that the patient has a hereditary pathology of intrinsic blood clotting pathway, it was diagnosed in childhood, repeatedly treated in the hematology hospital, where he received treatment with cryoprecipitate and fresh frozen plasma. Objectively: skin is pale-pink color, elbow joints, knee and ankle joints are deformed, active and passive movements are severely limited. The complete blood test: erythrocytes –  $4.6 \times 10^{12}/l$ , Hb – 115 g/l, the color index – 0.75; MCV – 80.6 fl, platelets  $224 \times 10^9/l$ , white blood cells –  $4.4 \times 10^9/l$ , bands 4%, segments 60%, eosinophils 1%; basophils 0%, lymphocytes 30%, monocytes 5%, ESR – 3 mm/h. The duration of bleeding by Duke is 4 minutes, the Lee-White clotting time: start – 15 minutes, the end – 25 minutes and continues. The complete urine analysis – red color, 1020, leukocytes 2-4 in the view, the red blood cells are on the whole field of view. In coagulogram: prothrombin time 12.7 sec, fibrinogen 3.9 g/l, APTT – 55.9 sec, blood coagulation factor VIII – 4%, blood coagulation factor IX – 97,8%. What is the most likely diagnosis?

**Recommended literature:**

**I. Main:**

1. Internal Medicine: in 2 books. Book 1. Diseases of the Cardiovascular and Respiratory Systems: textbook / N.M. Seredyuk, I.P. Vakaliuk, R.I. Yatsyshyn et al. Київ, Медицина., 2019. - 664 + 48 кольор. вкл.).
2. Internal medicine: Part 1 (cardiology, rheumatology, haematology): textbook for English-speaking students of higher medical schools / edited by Professor M.A. Stanislavchuk and Professor V.A. Serkova. - Vinnytsia: Nova Knyha, 2019. - 392 p.



3. Медицина за Девідсоном: принципи і практика / Навчальний посібник: пер. 23-го англ. вид.: у 3 т. Т.3 С. Ралстона, Я. Пенмана, М. Стрекена, Р. Гобсона; К.: ВСВ «Медицина», 2021. – 642 с.
4. CURRENT Medical Diagnosis and Treatment 2012, Fifty-First Edition (LANGE CURRENT Series) by Stephen McPhee, Maxine Papadakis and Michael W. Rabow (Paperback - Sep 12, 2011)/
5. Побічна дія ліків – Side Effects of Medications: навчальний посібник у 2 т. / за заг. ред. В.М. Бобирьова, М.М. Потяженка. – Вінниця:
6. Cardiovascular diseases. Classification, standards of diagnosis and treatment / Edited by Academician Kovalenko V.M., Prof. Lutaia M.I., Prof. Sirenko Yu.M., Prof. Sychova O.S. – Kyiv. – 2020.
7. Perederii V.H., Tkach S.M. Principles of internal medicine. – Vol.2 / Textbook for students of higher educational institutions. – Vinnytsia: Nova knyha. – 2018.
8. Internal diseases. The textbook based on the principles of evidentiary medicine, 2018.

## **II. Additional literature:**

1. Recommendations of the Association of Cardiologists of Ukraine for the diagnosis and treatment of chronic heart failure / Voronkov L.H. – moderator, working group of the Ukrainian Association of Heart Failure Specialists. – 2017.
2. Respiratory diseases / Ghanei M. - In Tech, 2012. - 242 p.
3. Clinical respiratory medicine / Spiro S., Silvestri G., Agusti A. - Saunders, 2012. - 1000 p.
4. Principles and practice of interventional pulmonology / Ernst A., Herth F. - Springer, 2012. - 757 p.
5. Clinical respiratory medicine / Spiro S., Silvestri G., Agusti A. - Saunders, 2012. - 1000 p.
6. Petrov Y. The chief symptoms and syndromes in patients with cardiovascular pathology : The practical handbook for medical students / Ye.

Petrov, Yu. Goldenberg, N. Chekalina; UMSA. - Poltava : TexcepBic, 2010. - 143

7. Gastroenterology and Hepatology Board Review: Pearls of Wisdom, Third Edition (Pearls of Wisdom Medicine) by John K. DiBaise (May 11, 2012)
8. Clinical Pulmonology 2012 (The Clinical Medicine Series) by M.D., C. G. Weber (Oct 30, 2011) - Kindle eBook
9. Clinical Nephrology 2012 (The Clinical Medicine Series) by M.D., C. G. Weber (Sep 19, 2011) - Kindle eBook
10. Clinical Nephrology 2012 (The Clinical Medicine Series) by M.D., C. G. Weber (Sep 19, 2011) - Kindle eBook
11. Hematology: Clinical Principles and Applications, 4e by Bernadette F. Rodak MS MLS (Feb 18, 2017)
12. Rheumatology, 2-Volume Set: EXPERT CONSULT - ENHANCED ONLINE FEATURES AND PRINT, 5e by Marc C. Hochberg MD MPH, Alan J. Silman MD, Josef S. Smolen MD and Michael E. Weinblatt MD (Oct 19, 2019)
13. Endocrine Pathology: Differential Diagnosis and Molecular Advances by Ricardo V. Lloyd (Nov 5, 2018)
14. Clinical Endocrinology 2012 (The Clinical Medicine Series) by M.D., C. G. Weber (Sep 19, 2017) - Kindle eBook
15. Williams Textbook of Endocrinology: Expert Consult-Online and Print, 12e by Shlomo Melmed, Kenneth S. Polonsky MD, P. Reed MD Larsen and Henry M. Kronenberg MD (May 27, 2016)
16. Electrocardiography, 3e with Student CD (Booth, Electrocardiography for Health Care Personnel) by Kathryn A. Booth (Jan 27, 2017)
17. Echocardiography Review Guide: Companion to the Textbook of Clinical Echocardiography: Expert Consult: Online and Print, 2e (Expert Consult Title: Online + Print) by Catherine M. Otto (Mar 7, 2017).

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