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FACULTY OF POSTGRADUATE AND PRE-UNIVERSITY EDUCATION

MANAGEMENT OF PATIENTS WITH HEMOPHILIA

Methodological materials for independent study for students

UZHHOROD

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UZHHOROD NATIONAL UNIVERSITY
FACULTY OF POSTGRADUATE AND
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Methodical materials are devoted to issues of pathogenesis, clinical manifestation, diagnosis and treatment of different types of hemophilia. The author tried to highlight modern algorithms of patient management, the most effective methods of prevention and treatment of hemophilia. The methodical materials are intended for senior year students of higher medical educational institutions.

Uzhgorod
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Contents

Hemophilia is a rare X-linked recessive congenital bleeding disorder characterized by a deficiency of coagulation factors.

EPIDEMIOLOGY

Hemophilia affects more than 1.2 million individuals (mostly males) worldwide. Hemophilia A is more common than hemophilia B.

- **Hemophilia A** occurs in approximately 1 in 4000 to 1 in 5000 live male births. The estimated prevalence is 17.1 cases per 100 000 males for all severities of hemophilia A (6.0 cases for severe hemophilia A)
- **Hemophilia B** occurs in approximately 1 in 15,000 to 1 in 30,000 live male births. The estimated prevalence is 3.8 cases per 100 000 males for all severities of hemophilia B (1.1 cases for severe hemophilia B).
- **Hemophilia C** - 1 in 1,000,000 in the general population. However, it is more prevalent in people with Ashkenazi Jewish ancestry (Jews from Eastern Europe), occurring in about 1 in 450 individuals in that population.

Hemophilia usually affects only males who inherit an affected maternal X chromosome. Females with hemophilia are rare; in such cases, both X chromosomes are affected or one is affected and the other is inactive. A female with one affected X chromosome is called a carrier of hemophilia.

Sporadic disease (without a positive family history, presumed due to a de novo mutation) is also common. Studies have demonstrated that sporadic causes account for as much as 55 percent of cases of severe hemophilia A and 43 percent of cases of severe hemophilia B.

Hemophilia occurs in all racial and ethnic groups and throughout the world.

PHYSIOLOGY OF COAGULATION

Hemostasis is the mechanism that leads to the cessation of bleeding from a blood vessel. It is a process that involves multiple interlinked steps. This cascade culminates in the formation of a “plug” that closes up the damaged site of the blood vessel controlling the bleeding.

The mechanism of hemostasis can be divided into four stages:

1. Constriction of the blood vessel.
2. Formation of a temporary “platelet plug."

3. Activation of the coagulation cascade.
4. Formation of “fibrin plug” or the final clot.

Coagulation (secondary hemostasis) (fig.1) includes the two main coagulation pathways, intrinsic or the contact pathway (lasts several minutes) and extrinsic or tissue factor (TF) pathway (completed up to 10 seconds), that meet up at a point to form the common pathway. The common pathway ultimately activates fibrinogen into fibrin. These fibrin subunits have an affinity for each other and combine into fibrin strands that bind the platelets together, stabilizing the “platelet plug”.

The intrinsic pathway of blood coagulation is so named due to the presence of all the required reactants of this pathway in the circulation, with no external protein source required (unlike the extrinsic pathway that requires exposure to extravascular tissue factor for triggering).

Both pathways consist of a series of cascade enzyme activation events that lead to the formation and stabilization of a blood clot by crosslinking of fibrin monomers and activation of platelets. The extrinsic pathway gets triggered by disruption of the endothelium and exposure of tissue factor (TF) in the subendothelium. Tissue factor then binds activated factor VIIa forming a complex, which activates factors IX and X into IXa and Xa, respectively. The intrinsic pathway becomes activated when factor XII, prekallikrein, and high-molecular-weight kininogen in the blood become exposed to an artificial surface. Factor XII undergoes a conformational change resulting in the small generation of factor XIIa, which activates prekallikrein to kallikrein with reciprocal activation of factor XII to XIIa. The resulting generation of factor XIIa activates factor XI to factor XIa, which converts factor IX to factor IXa. Both pathways converge at the production of factor Xa. Factor Xa converts prothrombin (factor II) into thrombin (factor IIa).

Thrombin, in turn, helps release factor VIII from the von Willebrand factor (von Willebrand factor is involved in platelet adhesion to collagen and protects factor VIII from proteolysis) and activates into factor VIIa, activates platelets by exposing phospholipids that bind IXa, and also activates factor XIII into factor XIIIa, which helps to stabilize the clot by cross-linking fibrin monomers. Factor IXa, together with factor VIIa, calcium, and phospholipids, form a tenase complex that recruits large quantities of factor X to activate it. In turn, factor Xa together with the prothrombinase complex calcium and phospholipids, help convert prothrombin into thrombin. Thrombin then helps split fibrinogen into fibrin monomers.

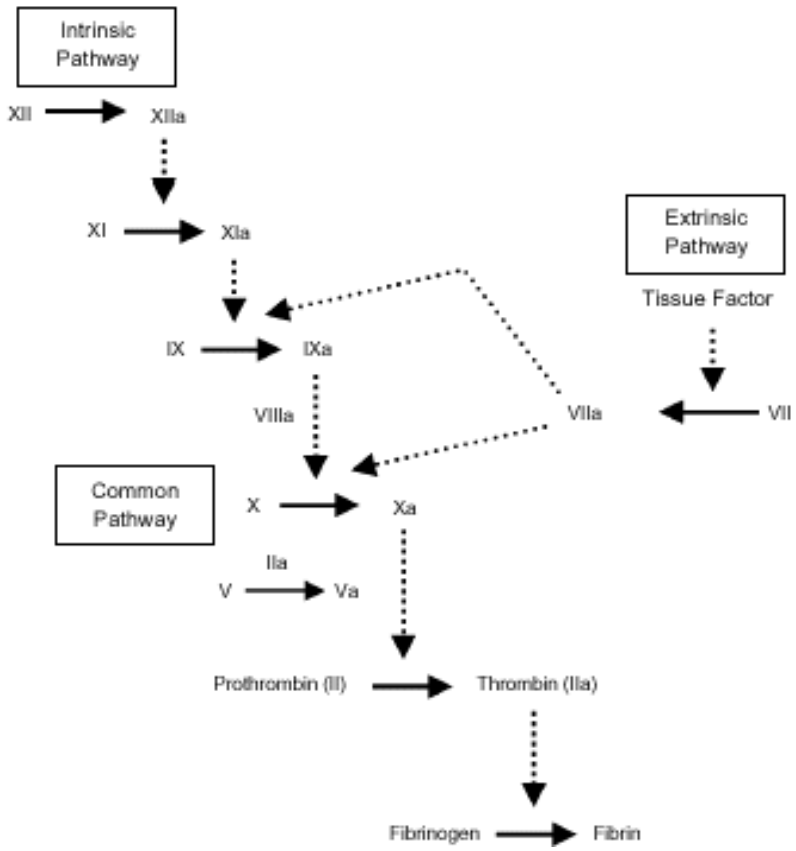

Figure 1. Coagulation cascade

PATHOGENESIS

When either FVIII or FIX are absent, severely decreased, or defective, the clot that forms is insufficient to support normal hemostasis. Outer regions of the clots from patients with hemophilia were stabilized by a fibrin meshwork; whereas, the inner portion of the clot showed little or no fibrin formation. Therefore, hemophilia results from an inability to prolong FIIa generation via the intrinsic pathway owing to absent, decreased, or abnormal production of either FVIII or FIX. Absence of FXI leads to disruption of intrinsic pathway.

CLASSIFICATION

Types of hemophilia according to inheritance

- Congenital hemophilia: an inherited condition with an X-linked recessive pattern of inheritance
- Acquired hemophilia: a rare condition with an autoimmune etiology and no genetic inheritance pattern

Types of hemophilia according to type of factor deficit

- Hemophilia A: reduced or absent factor VIII (antihemophilic factor)

- Hemophilia B: reduced or absent factor IX (plasma thromboplastin component or Christmas factor)
- Hemophilia C: reduced or absent factor XI (plasma thromboplastin antecedent)

Types of hemophilia according to severity

Types of hemophilia according to severity and clotting factor levels are demonstrated in table below (tab.1)

Table 1

Severity of hemophilia A and B based upon plasma levels of factor VIII or IX activity

Severity	Clotting factor level	Bleeding episodes
Severe	<1 IU/dL (<0.01 IU/mL) or <1% of normal	Spontaneous bleeding into joints or muscles, predominantly in the absence of identifiable hemostatic challenge
Moderate	1-5 IU/dL (0.01-0.05 IU/mL) or 1-5% of normal	Occasional spontaneous bleeding; prolonged or delayed-onset bleeding with minor trauma or surgery
Mild	5-40 IU/dL (0.05-0.40 IU/mL) or 5-<40% of normal	Severe bleeding with major trauma or surgery; spontaneous bleeding are rare

CLINICAL MANIFESTATIONS

Clinical manifestations of hemophilia relate to bleeding from impaired hemostasis, sequelae from bleeding, or complications of coagulation factor infusion.

Initial presentation

Age at first bleeding

- Most infants with *severe hemophilia* present within the first year to second year of life with easy bruising, hemarthrosis, bleeding due to oral injury, or after an invasive procedure.
- *Moderate hemophilia* is diagnosed up to 6 years.
- *Mild hemophilia* may go undetected for long periods of time until people experience serious trauma or undergo surgery

Initial site of bleeding

Bleeding may occur anywhere in the body in patients with hemophilia.

- **Infants** – common sites of bleeding in newborns include the central nervous system, extracranial sites such as cephalohematoma, and sites of medical interventions including circumcision, heel sticks, and venipunctures.
- **Children** – bruising, joint bleeds, and other sites of musculoskeletal bleeding become more common once children become mobile (including crawling). Frenulum and oral injuries are also common sites in young toddlers.
- **Older children and adults** – common sites of bleeding in older children and adults include joints, muscles, central nervous system, and oral or gastrointestinal tract.

Frequency of bleeding episodes

- Without prophylactic treatment, individuals with *severe hemophilia* may average up to two to five spontaneous bleeding episodes each month including spontaneous joint bleeds or deep-muscle hematoma.
- The frequency of bleeding episodes for patients with *moderate hemophilia* varies, usually from once a month to once a year. Typically occurs four to six times yearly (more frequent bleeding may occur if the joint becomes *a "target joint" - a joint with ≥3 recurrent bleeding episodes in six months*).
- The frequency of bleeding episodes for patients with *mild hemophilia* varies widely, typically from once a year to once every ten years.

General sites of bleeding

General sites of bleeding are demonstrated in the table below (tab. 2)

Table 2

Serious	• Joints (hemarthrosis) • Muscles, especially deep compartments (iliopsoas, calf, forearm) • Mucous membranes of the mouth, nose, and genitourinary tract
Life-threatening	• Intracranial • Neck/throat • Gastrointestinal

Approximate frequency of bleeding at different sites

Approximate frequency of bleeding at different sites is demonstrated in the table below (tab. 3)

Table 3

Frequency of bleeding at different sites

Site of bleeding	Approximate frequency
Joints • More common in hinged joints: ankles, knees, elbows • Less common in multi-axial joints: shoulders, wrists, hips	70-80%
Muscles	10-20%
Other sites (major bleeds)	5-10%
Central nervous system	<5%

Signs and symptoms

Systemic signs of hemorrhage include the following:

Tachycardia

Tachypnea

Hypotension

Orthostasis

Joints and muscles

- Hemarthrosis (hemorrhage into a joint) (fig.2) is the most common site for bleeding in ambulatory patients.
- *Bleeding* episodes most common in the index *joints* (elbows, ankles, and knees).
- One joint is usually affected at a time, but multiple bleeding sites are not uncommon.
- The ankles are most commonly affected in children, and the knees, elbows, and ankles in adolescents and adults.
- Hemarthrosis is painful and can be physically debilitating, as distension of the synovial space and associated muscle spasm lead to markedly increased intrasynovial pressure.

- Tingling, warmth, pain, stiffness, refusal to use the joint (young children) are the main symptoms.
- Tenderness, pain with movement, decreased range of motion, effusion, and warmth of the joint can be found on the physical examination.
- Once joint damage and inflammation occur, a joint can develop increased susceptibility to further bleeding and become a target joint.

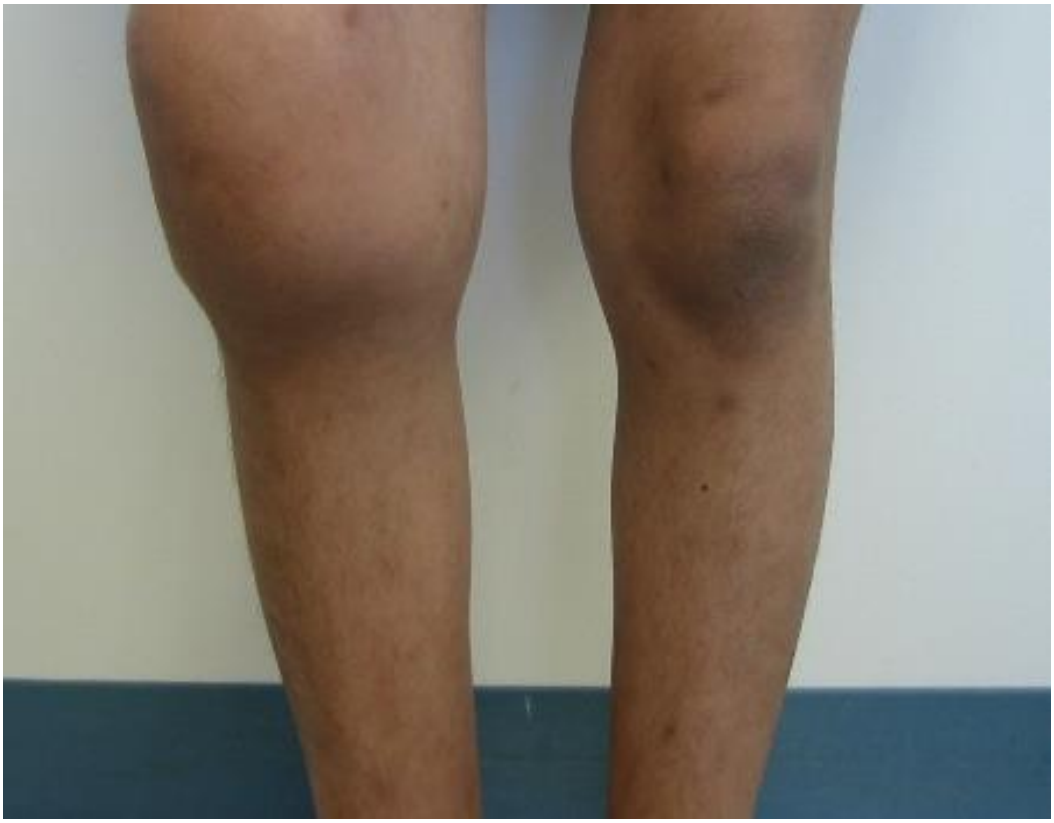

Figure 2. Massive swelling due to acute hemarthrosis of the right knee

- *Bleeding into muscles* with hematoma formation most often affects large muscle groups such as muscles in the leg (quadriceps), hip (iliopsoas), and arm.
- Usual presentation of muscular bleeding includes pain at the site, swelling, increased warmth, erythema, and limitation in range of motion.
- Muscle bleeding may be extensive and may compromise neurovascular structures and produce compartment syndrome (increased pressures in a muscle compartment), especially in the lower leg and forearm.

Epistaxis, oral, gastrointestinal bleeding

- Bleeding can occur from the nose, oral mucosa, gingiva, and frenulum.
- Sometimes follows minor trauma or dental procedures.
- The most common symptoms – hematemesis, melena, frank red blood per rectum, abdominal pain.

- Bleeding can dissect into the neck, which can lead to airway compromise or airway obstruction.
- Bleeding into the abdominal wall can produce severe pain that often is misdiagnosed as an acute abdomen.
- Hematomas of the bowel wall can also occur, producing symptoms that mimic acute appendicitis or produce obstruction or intussusception.

Genitourinary tract

- Hematuria is a frequent manifestation of severe hemophilia; usually, it is benign and not associated with progressive loss of renal function.
- The bleeding can arise from the kidneys or bladder and may persist for days or weeks. Ureteral obstruction with colic may occur when clots form within the ureter.
- On physical examination bladder spasm/distension/pain and costovertebral angle pain can be found.

Intracranial bleeding

- Intracranial hemorrhage (ICH) is relatively rare compared with other sites of bleeding, but it is one of the most dangerous and life-threatening events in individuals with hemophilia.
- Can be spontaneous or post-traumatic.
- Main symptoms - irritability, headache, vomiting, seizures, lethargy and focal neurological deficits, spinal cord syndromes.
- On physical examination can be abnormal neurologic exam findings, altered mental status, and meningismus.

Bleeding in females/carriers

Female carriers of hemophilia are heterozygous for the relevant gene variant (they have one unaffected allele and one allele with the variant in the gene that encodes the relevant factor). Causes of severe hemophilia in females can be inheritance of disease-causing variants from both parents (an affected male and a female carrier). Overall, they are expected to have approximately 50 percent of normal factor activity, which is generally sufficient to prevent clinical bleeding.

However, some hemophilia carriers have symptoms similar to affected males with mild hemophilia or present with menorrhagia and bleeding following surgical procedures or childbirth.

DIAGNOSIS

Patient and family history

The patient should be questioned about:

- History of hemorrhage disproportionate to trauma
- History of spontaneous hemorrhage
- Concomitant illness (especially those associated with acquired hemophilia, such as chronic inflammatory disorders, autoimmune diseases, hematologic malignancies, and allergic drug reactions)

Adults should be asked about all potential hemostatic challenges including menstrual cycles, dental extractions, trauma, and surgical interventions.

Presence of bleeding disorders in the family is another important clue for confirming diagnosis of hemophilia. Males within a family who inherit the familial mutation will all have approximately the same degree of factor deficiency and similar severity of disease because they share the same genetic variant.

While a positive family history is supportive, a negative family history cannot be used as evidence against the diagnosis, since many cases are sporadic.

Screening tests

1. *Prothrombin time* (to evaluate the extrinsic and common pathways of coagulation): normal
2. *Platelet count:* normal
3. *Activated partial thromboplastin time (**aPTT**):* **usually prolonged**

The aPTT may be normal in individuals with milder factor deficiencies (eg, factor activity level >15 percent), especially in hemophilia B (factor IX deficiency), where even individuals with moderate and mild disease may have a normal aPTT. *While a prolonged aPTT is consistent with hemophilia, a normal aPTT does not exclude the possibility of mild hemophilia, especially hemophilia B (factor IX deficiency).* Thus, specific factor analysis is performed regardless of the aPTT result.

- If aPTT prolonged → **mixing study** (incubating patient plasma with normal plasma for 2 hours at 37°C [98.6°F] and aPTT repeated; if the patient suffers from hemophilia, the aPTT will be corrected in the sample with the external plasma).
- If mixing study is positive (or if patient/family history are strongly positive) → **quantitative assessment of factor activity levels.** In general, factor activity levels should be measured in male patients with a known family history of hemophilia, male patients without a known familial variant, who are suspected to have hemophilia

based on clinical history and/or a prolonged aPTT that corrects in mixing studies, females identified as carriers by genetic testing, or females who potentially may be carriers for whom genetic testing is not available.

The normal range is generally considered to be from approximately 50 percent to 150 percent of the normal value; this range may also depend on the laboratory performing the testing and the age of the patient. An individual with mild hemophilia A who undergoes testing when stressed, affected by an inflammatory condition (factor VIII is an acute phase reactant), or pregnant may have a falsely elevated factor level. If this is suspected, factor activity testing should be repeated under conditions of low stress and/or after the inflammatory condition has resolved.

- In **patients with factor VIII deficiency**, it is important to exclude von Willebrand disease (VWD) by **von Willebrand factor (VWF) antigen testing (VWF:Ag)**

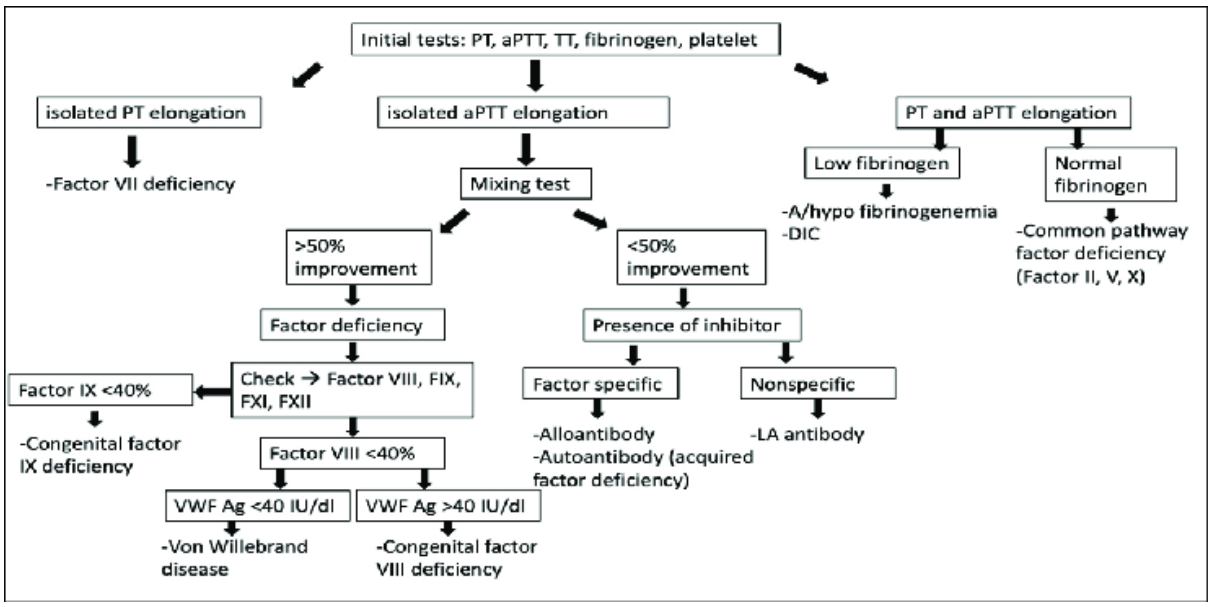

Figure 3. Laboratory diagnosis of hemophilia*.*

PT; prothrombin time, aPTT; activated partial thromboplastin time, TT; thrombin time, VWF; von Willebrand factor, LA; lupus anticoagulant, DIC; disseminated intravascular coagulopathy

Genetic testing

Genetic testing is often performed to identify a familial variant if it has not been identified or to confirm the presence of a known familial gene mutation.

In contrast to patients with suspected hemophilia, suspected female carriers should have genetic testing considered as first-line evaluation, with measurement of factor levels in identified carriers.

Other tests

Other tests that are indicated as part of the differential work-up include:

- *FBC*: to rule out thrombocytopenia as a cause of bleeding and to diagnose anemia (severe or prolonged bleeding);
- *bleeding time and platelet aggregation studies:* to evaluate platelet function;
- *liver aminotransferases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]):* to evaluate for liver dysfunction that can also contribute to prolongation of PT and aPTT;
- *lupus inhibitor screening (in addition to mixing study):* to exclude inhibitor-mediated prolonged aPTT;
- *urinalysis* is *not done routinely*, but if performed it may sometimes (but not always) show microscopic or macroscopic hematuria;
- *imaging studies* or *endoscopy* may be required for evaluation of acute bleeding. Investigations may include:
    - *head CT and/or MRI*: for evaluation of intracranial hemorrhage
    - *neck CT and/or MRI*: for evaluation of bleeding near the airway
    - *abdominal ultrasound or abdominopelvic CT scan*: for evaluation of gastrointestinal bleeding or iliopsoas bleeding. *Ultrasound* also can be used to assess *haemarthrosis*.
    - *upper and/or lower endoscopy*: for evaluation of gastrointestinal bleeding
    - *plain x-rays:* as necessary, for bone evaluation. X-rays have been traditionally used to describe the clinical progression of arthropathy (fig. 4). MRI and ultrasound may detect soft-tissue bleeding at an early stage. MRI may be helpful to evaluate whether a patient is a candidate for surgical procedures including synovectomy, joint fusion, or joint replacement.

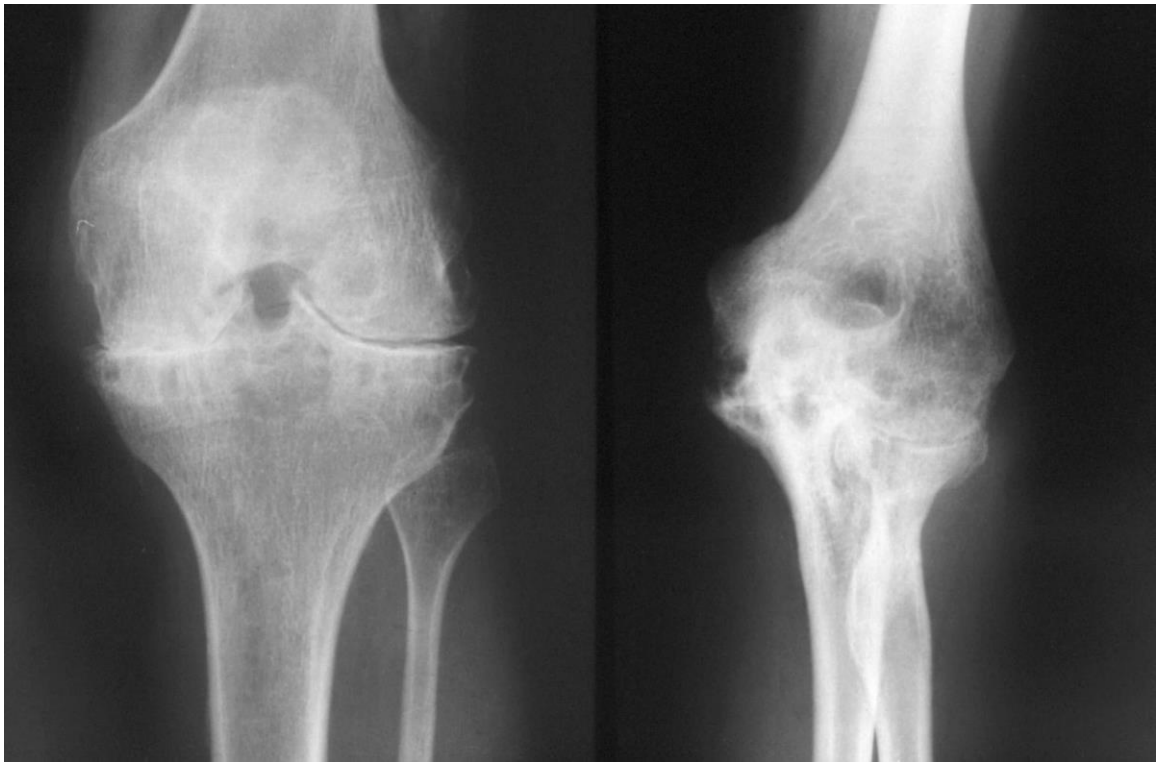

Figure 4. Advanced hemophilic arthropathy of the knee joint. *These images show chronic severe arthritis, fusion, loss of cartilage, and joint space deformities.*

COMPLICATIONS

- Hemophilic arthropathy (also called hemophilic arthritis) refers to persistent joint disease caused by hemarthrosis in a joint.
    - The mechanism of hemophilic arthropathy is multifactorial and includes chronic or episodic synovitis, with loss of cartilage, subchondral cyst formation, bone cysts, erosion, and joint space narrowing.
    - Arthropathy typically develops over time with recurrent hemarthroses, with more advanced arthropathy generally developing in late adolescence.
    - Sequelae can include muscular atrophy and contraction, nerve damage and loss of function from compartment syndrome, loss of bone mineral density with increased risk of fracture, chronic pain and diminished quality of life, need for joint replacement
- Pseudotumour is a potentially limb- and life-threatening condition. The 'tumour' grows as a chronic, encapsulated cystic mass subsequent to inadequate management of recurrent bleeds in soft tissue/muscles or bones. Often occurs in muscle adjacent to bone, which can be secondarily

involved. The pseudotumour can become massive, causing pressure on adjacent vital organ(s) and neurovascular structures and may cause pathological fractures.

- Neurologic sequelae of intracranial hemorrhage are chronic neurocognitive, educational, and behavioral deficits.
- Factor infusion as treatment can lead to complications:
    - infections transmitted from plasma-derived factor products (typically viral; modern procedures significantly reduce the risk of transmission of infectious organism, except prions, hepatitis A virus, parvovirus)
    - development of antibodies to factor (termed inhibitors), that block the activity of the relevant factor. Inhibitors typically develop following factor infusions in patients with severe disease but can also occur in moderate and mild disease, especially in hemophilia A. These inhibitory antibodies develop in response to exogenous factors and complicate bleeding episodes because they decrease responsiveness to factor infusions; in addition, anaphylactoid reactions can occur with factor IX inhibitors.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of hemophilia includes other inherited bleeding disorders and other causes of prolongation of the activated partial thromboplastin time (aPTT) or conditions that can present similarly with bleeding after minor trauma or spontaneous bleeds.

- **Inherited platelet disorders** – a variety of inherited platelet disorders can cause clinical bleeding symptoms. Like hemophilia, some of these may be associated with normal platelet counts. Unlike hemophilia, inherited platelet disorders should have normal coagulation testing, and most of these disorders are autosomal rather than X-linked. Inherited platelet disorders may be characterized by thrombocytopenia, abnormal platelet function, and/or abnormal platelet morphology. Differential diagnosis between platelet disorders and clotting factor deficiencies according to clinical manifestation is demonstrated in the table below (tab. 4)

Table 4

Differential diagnosis between platelet disorders and clotting factor deficiencies

Bleeding characteristics	**Type of bleeding disorder**	
	Thrombocytopenia or platelet function disorders	**Clotting factor deficiencies or inhibitors**
Major sites of bleeding	Mucocutaneous (mouth, nose, gastrointestinal tract, urinary tract, menorrhagia)	Deep tissue (joints, muscles) or soft tissue hematomas
Petechiae	Common	Uncommon
Ecchymoses	Generally small and superficial. May be significant, depending upon the degree of thrombocytopenia.	May develop large ecchymoses
Excessive bleeding after minor cuts	Yes	Not usually
Excessive bleeding with surgery or invasive procedures	Often immediate; severity is variable (no excess bleeding with mild thrombocytopenia, severe bleeding with certain platelet function disorders such as GT)	Often during the procedure. Individuals with factor XIII deficiency may experience delayed bleeding.

- **von Willebrand disease** (deficiency in the quality or quantity of von Willebrand factor) – like hemophilia, von Willebrand disease (VWD) is an inherited bleeding disorder that may be associated with a normal or prolonged aPTT. Unlike hemophilia, VWD transmission is autosomal. Thus, VWD is equally common in male and female patients, and disease severity is similar in both sexes. Most types of VWD present with a different bleeding pattern from hemophilia (eg, mucosal bleeding seen in VWD; joint bleeding seen in hemophilia). Since VWF protects factor VIII from proteolysis, severe form of VWD can manifest with bleeding

into joints and muscles similarly to hemophilia. The measurement of VWF together with the measurement of FVIII helps to distinguish between these two diseases.

Differential diagnosis between hemophilia, von Willebrand disease and platelet defects according to laboratory studies is shown in the table below (tab. 5)

Table 5

Differential diagnosis of hemophilia, von Willebrand disease and platelet defects according to laboratory studies			
Possible diagnosis	PT	APTT	Platelet count
Normal	Normal	Normal	Normal
Hemophilia A or B	Normal	Prolonged	Normal
VWD	Normal	Normal or Prolonged	Normal or reduced
Platelet defect	Normal	Normal	Normal or reduced

- **Factor XIII deficiency** – factor XIII is involved in stabilizing the fibrin clot and protecting it from fibrinolysis. Factor XIII deficiency is an inherited bleeding disorder that can produce severe bleeding in homozygotes and milder bleeding in heterozygotes. Like hemophilia, factor XIII deficiency can present with intracranial hemorrhage around the time of birth or bleeding associated with umbilical cord separation. Unlike hemophilia, the typical presentation is delayed bleeding after initial hemostasis; impaired wound healing and pregnancy loss may also be seen. Unlike hemophilia, factor XIII deficiency is characterized by a normal aPTT and PT, and normal activity levels of factor VIII, IX, and XI.
- **Other factor deficiencies with prolonged aPTT** – other inherited conditions such as deficiencies of factor XII, prekallikrein, or high molecular weight kininogen can cause an isolated prolongation of the aPTT, with a normal prothrombin time (PT). Unlike hemophilia, these deficiencies are not associated with clinical bleeding. Diagnostic testing

will reveal the specific deficiency, with normal factor VIII, IX, and XI levels.

- **Ehlers-Danlos syndrome** – the bleeding is usually mucosal, unlike hemophilia, where it is musculoskeletal. In addition, the skin is hyperextensible, and joints are hypermobile. The diagnosis is usually through clinical features, genetic testing, and tissue biopsy.
- **Fabry disease** – the bleeding is usually mucosal, unlike hemophilia, where it is musculoskeletal. Patients may also have other organs being affected, including kidneys and heart, and have skin lesions called angiokeratomas. They also have pain in the extremities. Fabry disease is usually diagnosed with clinical findings and genetic testing.
- **The antiphospholipid antibody syndrome (APS)** – due to an acquired autoantibody that prolongs the aPTT in vitro, but clinically manifests as a prothrombotic state rather than impaired hemostasis. Patients with APS may have thromboembolism and/or recurrent pregnancy loss. Rarely, APS may be associated with prolongation of the PT and acquired prothrombin deficiency. Unlike hemophilia, the prolonged aPTT in APS does not show correction when patient plasma is mixed with control plasma; additional laboratory findings of APS are presented separately.
- **Disseminated intravascular coagulation (DIC)** – mimics hemophilia, hard to differentiate, but usually, there is an underlying condition in DIC, for example, acute promyelocytic leukemia. Diagnosis is usually carried out by blood tests that show decreased platelet count and the absence of factor VIII autoantibodies.
- **Liver disease** – when liver disease is mild, only the PT may be prolonged due to a predominant effect on factor VII. However, in severe and/or chronic liver disease, both the PT and aPTT may be prolonged. Importantly, liver disease is also associated with decreased production of anticoagulant factors. Thus, a prolonged aPTT does not reflect the overall hemostatic picture.

TREATMENT

ROUTINE/COMPREHENSIVE CARE

The optimal management of people with hemophilia is complex.

- **Immunizations** — recommended immunizations should be given at age-appropriate intervals to individuals with hemophilia. For immunisations, subcutaneous administration may be considered in preference to

intramuscular injection. However, it is not clear if the benefit of reducing the risk of intramuscular haematoma outweighs the potential risk of reduced efficacy for some vaccines. Pneumococcal polysaccharide, inactivated polio, hepatitis A and hepatitis B have been shown to maintain efficacy when administered subcutaneously. Treatment may also be considered before immunization to reduce the risk of haematoma, depending on the patient's factor level.

- **Dental care** — appropriate oral hygiene and regular dental care is essential for individuals with hemophilia to prevent gingival and dental disease, which increase the risk of bleeding.
- **Exercise and athletic participation** — an appropriate exercise regimen should be encouraged as a daily routine. Ideal activities are those that reflect the individual's preferences, abilities, and local resources, and include non-contact sports such as swimming, walking, golf, tennis, bicycling, archery, and table tennis, and supervised group activities.
- **Medicines to avoid** — medicines that increase the risk of bleeding, including anticoagulants, aspirin, and other nonsteroidal anti-inflammatory drugs (NSAIDs) should generally be avoided in patients with hemophilia. Pain can be treated with local measures (cold packs, immobilization, splinting), acetaminophen, or codeine. Use of antithrombotic drugs may be associated with an increased risk of bleeding in patients with hemophilia.
- **Travel** — appropriate planning for travel should occur in individuals with hemophilia regardless of level of severity. At a minimum, an emergency supply of hemostatic replacement therapy should be kept with the patient during travel.

PROPHYLAXIS TO REDUCE BLEEDING EPISODES

Prophylaxis versus on-demand therapy — Prophylactic therapy (factor administration in the absence of bleeding) is highly effective in reducing bleeding and long-term complications of bleeding such as chronic arthropathy in people with hemophilia, especially those with severe factor deficiency or phenotype, in comparison with on-demand therapy. Types of prophylaxis for patients with hemophilia A and B are demonstrated in the table below (tab. 6)

Table 6

Types of prophylaxis for patients with hemophilia A or B

Type of treatment	**Definition**
Episodic (on demand) treatment	Replacement factor given at the time of bleeding
Continuous (regular) prophylaxis	Replacement factor given to prevent bleeding for at least 45 of 52 weeks (85%) of a year
▪ Primary prophylaxis	Continuous prophylaxis started before age three years and before the second large joint bleed or before bleed at all
▪ Secondary prophylaxis	Continuous prophylaxis started after two or more large joint bleeds but before the onset of chronic arthropathy
▪ Tertiary prophylaxis	Continuous prophylaxis started after the onset of arthropathy to prevent further damage
Intermittent (periodic) prophylaxis	Replacement factor given to prevent bleeding for short periods of time such as during and after surgery or patients with moderate or mild disease (factor activity 5 to 40 percent) and more than one bleeding episode

Choice of prophylactic therapy — *factor replacement products* (clotting factor concentrates - CFCs) are available for hemophilia A and B (factor VIII replacement products - concentrates from plasma, recombinant products, and recombinant products with extended half-life, factor IX replacement products - plasma-derived, recombinant, longer-lasting recombinant factor IX).

Individuals with hemophilia A also have the option of prophylactic *emicizumab*.

Age of initiation — it is generally initiated at as young an age as reasonably possible. Dosing is scheduled to maintain sustained, protective factor levels.

However, both age at initiation and dosing frequency need to be balanced against the risks and burdens of therapy that is administered intravenously.

Clotting factor concentrates

Dosing schedule – the goal of dosing has traditionally been to maintain the factor level above 1 to 2 percent, essentially converting the patient from a severe to a moderate hemophilia phenotype, but dosing schedules vary and are dependent on factor deficiency and the patient, their bleeding rate, and ease of IV access. an analysis of bleeding frequency determined that for every 1 percent increase in factor activity level there would be an 18 percent reduction in bleeding frequency. Factor levels are usually measured 15 minutes after the infusion to verify the calculated dose.

- **Hemophilia A** – Factor VIII, 25 to 40 units/kg of body weight, given three times per week (Malmo protocol) or 15 to 30 units/kg three times per week (Utrecht protocol). for extended half-life (long-acting) factor VIII frequency can be once every 5 to 7 days
- **Hemophilia B** – Factor IX, 25 to 40 units/kg of body weight, given two times per week (Malmo protocol) or 15 to 30 units/kg two times per week (Utrecht protocol). Longer lasting products allow for once per week or once every two week dosing.

For patients who are adherent to their prescribed prophylaxis regimen but still experience breakthrough bleeds, escalation of prophylaxis with measurement of factor trough levels, presence of inhibitor and increasing of frequency can be recommended.

For patients with severe phenotype hemophilia A or B in countries with healthcare constraints, is strongly recommended prophylaxis (even when the only option is using lower factor doses) over episodic factor therapy to reduce hemarthroses and other spontaneous and breakthrough bleeding and better preserve joint function.

Emicizumab

Emicizumab is a humanized bispecific monoclonal antibody that binds to both factor IXa and factor X, substituting for the role of factor VIII in hemostasis. It is active in the presence of a factor VIII inhibitor, and is not associated with infectious risk although it has a high price. Emicizumab is administered subcutaneously and has a long half-life (four to five weeks), whereas factor replacement products are administered intravenously several times a week.

Therapy is started with a loading dose of 3 mg/kg subcutaneously once weekly for four weeks. Subsequent maintenance dosing can be done using 1.5 mg/kg subcutaneously once per week, 3 mg/kg subcutaneously once every two weeks, or 6 mg/kg subcutaneously once every four weeks. The subcutaneous administration route increases the ease of use.

Emicizumab is not effective for acute bleeding and hemophilia B prophylaxis.

Emicizumab will interfere with the activated partial thromboplastin time assay, one-stage based assay for clotting factor activity, and factor VIII inhibitor titre.

ACUTE THERAPY FOR BLEEDING

For acute bleeding in patients with hemophilia, the immediate goal is to raise the factor activity to a level sufficient for hemostasis.

Treatment options for most patients with congenital hemophilia consist of factor VIII or factor IX replacement (for hemophilia A and hemophilia B, respectively) by infusion of factor VIII or IX concentrate. The targeted factor activity level depends on the location and severity of the bleeding, the expected half-life of the product administered, and the presence of an associated injury or occurrence in a target joint.

Additional treatments include:

- antifibrinolytic agents (e.g., tranexamic acid, aminocaproic acid);
- pain medications
- desmopressin: patients with mild hemophilia A (with a demonstrated positive response to desmopressin) may benefit.

In patients with hemophilia A receiving emicizumab prophylaxis, factor VIII infusion at the dose expected to achieve haemostasis should be used for breakthrough bleeding.

Life-threatening bleeding

Any patient with hemophilia who presents with a severe acute bleeding episode requires quick recognition of the location and severity of the bleed.

Life-threatening bleeds include those occurring in the following sites:

- central nervous system/intracranial;
- gastrointestinal (GI) tract;
- airway (neck/throat).

Serious bleeding:

- in the hip;
- in the eyes;

- in the muscle (eg, iliopsoas and/or with neurovascular compromise or potential for neurovascular complications);
- any bleeding severe enough to result in anemia and potentially require red blood cell transfusion(s);
- any prolonged bleeding that is not adequately responding to home-based therapy;
- any significant injuries such as motor vehicle accidents or falls from distances of several feet or more.

Urgent treatment is necessary, even before full assessment:

- resuscitation and basic life-support measures (ABC) are important;
- subspecialty consultation, appropriate to the anatomical site of the hemorrhage, may be necessary. Patients with intracranial hemorrhage may require anticonvulsant therapy for management of seizures.
- the factor for the relevant disorder (factor VIII for hemophilia A, factor IX for hemophilia B) should be administered urgently. The specific factor levels need to be monitored, to adjust dose and frequency. Monitoring is usually done by measuring a trough blood factor level before the first dose in the morning. The goal is to maintain peak factor VIII or factor IX levels between 80% and 100% and trough level no less than 40% to 50% for the first 10 to 14 days. The peak factor activity level should be checked approximately 5 to 15 minutes after the first dose of factor. If this was not done, measure a trough factor activity and obtain a peak after the second dose. Dosage of CFCs for treatment of acute major/severe bleeding in patients with hemophilia A and B is illustrated in the table below (tab. 7)

Table 7

Dosage of clotting factor concentrates for treatment of acute major/severe bleeding

	Hemophilia A	Hemophilia B
Major/severe bleeding Raise factor level to 80 to 100%	Factor VIII dose of approximately 40-50 units/kg	Factor IX dose of approximately 100 to 140 units/kg

  - **Calculation for subsequent doses (without inhibitors). Timing of next dose** – Additional doses should be timed to occur when a factor activity level of approximately 50 percent is anticipated (or

documented). It is equivalent to approximately one half-life of the infused product, so the patient's circulating factor level does not drop below 50 percent. These calculations are based on peak and trough factor levels.

- **Hemophilia A** – For life-threatening bleeding, check the trough approximately four to six hours after the first dose of a standard half-life factor VIII product. The next dose is due approximately 8 to 12 hours after the first dose for a standard half-life product. Longer intervals apply for extended half-life products (10 to 20 hours for most products, approximately 48 hours for efanesoctacog alfa, which should be given at a repeat dose of 30 to 50 international units every two to three days as clinically warranted if this product is continued for bleed treatment).
- **Hemophilia B** – For life-threatening bleeding, check the trough approximately 8 to 12 hours after the first dose of a standard half-life factor IX product. The next dose is due approximately 18 to 24 hours after the first dose for a standard half-life product. Longer intervals apply for extended half-life products (from 54 to 104 hours).

- **Subsequent dose calculation** – Subsequent dosing is individual and based on the peak and trough (minimal, just before next infusion) levels after the initial dose, the patient's weight and is calculated by a special formula. The following calculation should be used to determine the appropriate factor dose:

  Dose (units) = % correction x Vd x patient weight (kg)

  For the % correction, use 100 for a desired factor activity of 100 percent. If the patient's trough level is 50 percent and the desired factor activity is 100 percent, then the percent correction is 50%.

  For the Vd:

  -Factor VIII – All products have a Vd of approximately 0.5 dL/kg.

  - Factor IX – The Vd varies by product.

  Sample calculations:

  - Hemophilia A – For a 60 kg patient treated with a recombinant factor VIII product with Vd of 0.5 dL/kg who requires a factor level of 100 percent and has a trough value of 50 percent, the dose is calculated as follows:

50 (% correction) x 0.5 (Vd) x 60 kg (weight) = 1500 international units of recombinant factor VIII concentrate.

- Hemophilia B – For an 80 kg patient treated with Benefix (Vd = 1.3 for age ≥12 years) who requires a factor IX level of 100 percent and has a trough value of 50 percent, the dose is calculated as follows:
  50 (% correction) x 1.3 (Vd) x 80 kg (weight) = 5200 international units of Benefix.

- Do not waste factor (administer excess rather than discarding).
- If the trough factor activity is lower than expected, the dosing interval may be shortened and/or the subsequent dose increased depending on peak levels. If the trough factor activity level is higher than expected, the dosing interval may be increased and/or the subsequent dose may be lowered.

Hemarthrosis

- **Prompt factor infusion** – factor should be infused promptly at the first sign of joint bleeding (eg, at the onset of tingling, pain, or typical symptoms of joint bleeding rather than waiting for reduced range of motion or swelling), preferably within two hours of bleed identification. This should be performed at home whenever possible to avoid delays in infusion. Dosage of CFCs for treatment of hemarthrosis in patients with hemophilia A and B is shown in the table below (tab. 8)

Table 8

Dosage of clotting factor concentrates for treatment of acute hemarthrosis

	Hemophilia A	Hemophilia B
Hemarthrosis Raise factor level to 40 to 50% (80-100% for bleeding into the hip, iliopsoas, or target joint, or bleeding associated with injury)	Factor VIII dose of approximately 25 units/kg	Factor IX dose of approximately 50 to 70 units/kg

The need for additional doses and the duration of therapy are individualized according to the patient's symptoms, affected joint,

concurrent issues (bleeding into the hip, iliopsoas muscle, or a target joint; or bleeding associated with injury), and initial response.

- **Assessment of bleeding** – arthrocentesis is not required to diagnose joint bleeding in patients with hemophilia. If used (eg, to evaluate for suspected infection;if there is neurovascular compromise, severe pain, or other evidence of increased joint pressure that has not improved with other treatment), factor should be administered before the procedure to raise the factor level to 100 percent.
- **Reduce inflammation, pain, and bleeding** – additional interventions to reduce bleeding, pain, and inflammation include avoidance of weight bearing or use of the affected extremity, application of ice packs, immobilization, and/or splinting as recommended. Standard rest, ice, compression, and elevation (RICE) protocols apply.
    - The use of ice without direct skin contact for short periods of 15-20 minutes soon after bleeding occurs is considered acceptable but should not exceed 6 hours
    - Compression may help to reduce the risk of rebleeding.
    - Elevation may help reduce hemarthrosis-related swelling

  Analgesics can be given, generally avoiding agents with antiplatelet activity such as non-selective nonsteroidal antiinflammatory agents (NSAIDs). Selective cyclooxygenase 2 (COX2) inhibitors may be used since they do not have significant anti-platelet activity.
- **Identify other contributing factors** – clinical evaluation is used to distinguish an acute bleed from other conditions such as pain due to chronic arthropathy, acute fracture or sprain, or infection. It may be challenging to distinguish hemarthrosis of the hip from bleeding into the iliopsoas muscle. In general, hemarthrosis of the hip results in severe pain with hip motion, whereas iliopsoas bleeding primarily causes limited hip extension. Iliopsoas bleeding may also cause reduced sensation over the ipsilateral thigh due to compression of the sacral plexus root of the femoral nerve.
- **Hospital admission versus home care** – the majority of hemarthroses are managed at home. Indications for hospitalization include:
    - Hemarthrosis that may be life or limb-threatening, such as suspected bleeding into the hip or iliopsoas muscle
    - Initial delay in therapy, leading to a more severe bleed or a bleed requiring more aggressive initial therapy

    - Suspicion of an infection
    - Need for joint aspiration due to increased joint pressure or possible infection
    - Bleeding in an individual with an inhibitor that is not responding well at home
    - Bleeding episodes that are not responding as expected at home
    - Associated pain that is not controlled with home oral analgesia
    - Inability to adhere to home instructions/bedrest for any reason, including children who cannot be non-weight bearing, adults with significant arthropathy, patients with inhibitors requiring very frequent dosing, and patients with mild disease who have not learned how to use factor infusions
- **Treatment duration** – it can be challenging to determine when acute bleeding into a joint has stopped. Patient report of bleeding is most commonly used, and ultrasound may be helpful as well. The duration of therapy depends on the joint affected, the size of the hemarthrosis, and the ability to avoid weight bearing, which affects the pace of healing. Some experts treat for approximately three to four days after bleeding has stopped; fewer infusions may be needed for patients receiving prophylaxis with emicizumab or an extended half-life product.
- **Joint rehabilitation** – following resolution of a joint bleed, it is important to initiate a rehabilitation program that involves a gradual increased range of motion, weight bearing, and strength training. Individuals who are not receiving routine prophylaxis should consider using prophylaxis, including limited short-term prophylaxis following recurrent target joint hemarthrosis, with factor administration for several weeks to months to reduce or prevent recurrent bleeding, or to use a more aggressive dosing schedule in individuals who are already receiving routine prophylaxis.

Muscle/soft tissue bleeding

- Therapy should be initiated as soon as possible (at the first sign of symptoms or immediately after injury or trauma).
- For severe muscle hematomas, a peak factor activity level of at least 50 percent is appropriate as a minimum, but usually higher peak levels are used for severe muscle bleeding.

- Treatment/factor replacement therapy is required for individuals with any degree of factor deficiency in hemophilia A and B. Dosing is as for joint bleeding.
- For individuals with mild hemophilia A, it may be possible to raise the factor VIII level using desmopressin.
- Severe muscle bleeds require more than one factor infusion.
- Surgical decompression is undertaken only if medical therapy fails to forestall progression.
- Muscle bleeds can result in a significant drop in hemoglobin level, and the hemoglobin should be monitored until it is clear that bleeding has ceased.

Minor bleeding

- Minor bleeding such as epistaxis or skin bleeding may be treated with local measures including ice, pressure, or elevation.
- Topical therapies including antifibrinolytic agents or other adjunctive local therapies may also be helpful.
- At times, episodes of epistaxis may be prolonged or may result in larger volume blood loss that will necessitate replacement therapy.

Resource-poor settings (no access to purified factor)

- Purified factor products (virally inactivated plasma-derived concentrates or recombinant products) should be used whenever possible, to avoid potential transfusion-transmitted infection and transfusion reactions.
- For individuals in resource-poor settings, options include Fresh Frozen Plasma (FFP), or, for those with hemophilia A, Cryoprecipitate. Dosing is based on the factor concentration in the product, patient weight, and the desired factor level. One mL of FFP contains one unit of factor activity. A dose of 15 to 20 mL/kg will raise the factor VIII level by approximately 30 to 40 percent and the factor IX level by approximately 15 to 20 percent.

ADJUVANT THERAPIES

Antifibrinolytic therapy for mucosal bleeding or surgery

Antifibrinolytic agents include tranexamic acid (TXA) and epsilon aminocaproic acid (EACA). These may be used in combination with factor replacement therapy for individuals with a mucosal source of bleeding, or as single agents in settings with mucosal bleeding that is less severe (eg, dental procedures). Topical administration to skin sites is also possible.

These agents are most useful for stabilizing clots in areas of increased fibrinolysis such as the oral or nasal cavity (eg, dental bleeding, epistaxis) or for heavy menstrual bleeding in women with bleeding disorders. Their mechanism of action is to inhibit fibrinolysis by inhibiting plasminogen activation in the fibrin clot, thereby enhancing clot stability.

- **TXA** – The usual oral dose is 25 mg/kg per dose every six to eight hours. The intravenous (IV) dose is 10 mg/kg, administered every six to eight hours.
- **EACA** – The usual dose is 75 to 100 mg/kg per dose every six hours (maximum single dose 3 to 4 g).

These drugs can be administered orally or intravenously. When given orally, they must be given three or four times over a 24-hour period because of their short half-lives.

Antifibrinolytic agents should not be used for urinary tract bleeding (haematuria) due to the risk of obstruction by clots (unlysed clots will behave like stones). Antifibrinolytics should also be avoided in patients with bleeding into the thoracic cavity (as unlysed haematoma may interfere with respiration), hence they are also contraindicated in the setting of thoracic surgery.

Neither TXA nor EACA should be given simultaneously with an activated prothrombin complex concentrate (aPCC), as this will increase the risk of thromboembolism. If an antifibrinolytic agent and an aPCC are used, they should be separated by at least 12 hours.

Adjunctive local therapies

Other adjunctive hemostatic therapies include microfibrillar collagen, especially for bleeding in the oral cavity.

DDAVP for mild hemophilia A

DDAVP (desmopressin) is a synthetic analog of vasopressin (antidiuretic hormone]) that lacks pressor activity and may be effective for minor bleeding or certain elective procedures in patients with mild hemophilia A who have had a documented response to a test dose.

For those who have a response, a typical dose is 0.3 mcg/kg (maximum dose, 20 to 30 mcg), administered intravenously or subcutaneously; or as a nasal spray one puff (150 mcg) in one nostril in patients weighing <50 kg and two puffs (150 mcg in both nostrils) in patients weighing ≥50 kg.

DDAVP can increase the factor VIII level two- to fourfold.

The following caveats apply to DDAVP use:

- DDAVP is **not** effective for patients with severe hemophilia A (factor VIII activity <1 percent) because factor activity level cannot be increased sufficiently, and usually is not used in individuals with moderate hemophilia A (factor VIII activity from 1 to 5 percent) for the same reason.
- DDAVP should **only** be used for mild bleeding for which a 30- to 60-minute delay is acceptable (90-minute delay for nasal spray) and a two- to fourfold factor VIII increase are likely to be sufficient for hemostasis. For more serious bleeding, factor VIII infusion should be used.
- DDAVP is **not** effective for patients with hemophilia B because factor IX is not stored in platelets or endothelial cells.
- DDAVP generally is not used in children under two years of age due to an increased risk of water retention
- DDAVP has antidiuretic activity and can cause hyponatremia, especially with prolonged use or excess free water intake. As a result, doses often are limited to once daily for three consecutive days, and **water intake is restricted**.

HEMOPHILIA C

Hemophilia C - inherited bleeding disorder caused by deficiency of factor XI.

Mechanisms and prevalence

Factor XI is the precursor to a serine protease (factor XIa) important for clot propagation and maintenance. Inherited factor XI deficiency is an autosomal dominant or recessive bleeding disorder that is rare in the general population but common among individuals of Ashkenazi Jewish heritage (carrier rate, 8 to 9 percent).

Clinical features

Factor XI deficiency is a trauma-associated bleeding disorder; spontaneous bleeding is rare. Bleeding can occur with surgery or trauma. Heavy menstrual bleeding can occur. Factor XI levels do not easily predict the likelihood of bleeding.

Evaluation and diagnosis

Factor XI deficiency may be suspected due to family history, excessive bleeding, or a prolonged activated partial thromboplastin time (aPTT). Coagulation testing is typically done first, followed by factor XI activity. Severe disease is defined by factor XI <20 percent (<20 units/dL); partial disease is

defined by factor XI level 20 percent to the lower limit of normal (typically, 60 to 70 percent). Genetic testing is not required but may be done in selected cases.

Bleed treatment

Serious acute bleeding (from trauma) should be treated with a plasma product such as Fresh Frozen Plasma (FFP) or a purified factor XI concentrate, with or without an antifibrinolytic agent. A target factor XI level of 30 to 45 percent is generally sufficient.

Bleed prevention

Routine prophylaxis is not required. Antiplatelet therapy should generally be avoided unless there is a cardiovascular indication. Testing for factor XI inhibitors may be appropriate in some individuals.

ACQUIRED HEMOPHILIA

Acquired hemophilia is a rare but potentially life-threatening bleeding disorder caused by the development of autoantibodies (inhibitors) directed against plasma coagulation factors, most frequently factor VIII (FVIII).

Pathogenesis

Inhibitors (autoantibodies) bind the specific clotting factor and interfere with its function and/or reduce its half-life. In both cases, factor activity is reduced, sometimes to undetectable levels, similar to severe hemophilia. This leads to an increased bleeding risk; serious bleeding is the most common presentation.

Approximately 30 to 50 percent of individuals with acquired hemophilia A have an associated underlying condition. It is unclear whether these conditions cause the inhibitor to develop, trigger expansion of cells producing the inhibitor, or are merely markers of immune dysregulation or autoimmunity.

Common underlying conditions include:

- malignancy (solid tumors [especially adenocarcinomas] and hematologic malignancies);
- autoimmunity or connective tissue disorders (rheumatoid arthritis, systemic lupus erythematosus [SLE]);
- pregnancy or postpartum period (typically within two to three months postpartum, typically following a first pregnancy);
- medications (clopidogrel, omalizumab).

Epidemiology

An incidence of acquired hemophilia A of approximately 1 to 2 per million annually. The incidence increases with age:

- <16 years: 0.045 per million annually
- >85 years: 14.7 per million annually

The female to male ratio for acquired hemophilia A is approximately equal.

Evaluation

Typical presentation and clinical findings. The hallmark of acquired hemophilia A is bleeding. The sudden presence of large hematomas or extensive ecchymoses in an older individual without significant trauma or known bleeding disorder should always raise the clinical suspicion of acquired hemophilia A, and, if an inhibitor of factor VIII is not identified, an inhibitor of a different factor.

- **Reason for coming to medical attention**. Most patients present with unexpected bleeding and abnormal clotting tests, typically a prolonged aPTT. The remaining 10 to 20 percent present with an isolated prolonged aPTT without bleeding.
- **Patient characteristics**. Most individuals are adults, often older. The prevalence of an underlying condition that alters immunity (cancer, autoimmune disorder, postpartum state) is 30-50%.
- **Bleed characteristics:**
    - **timing** - most bleeds occur spontaneously; in some cases, bleeding is first noted during or after a surgical procedure;
    - **location** - subcutaneous bleeding is the most common finding, seen in as many as 80 percent of cases. Visceral bleeding is also common, including retroperitoneal or muscle hematomas. Symptomatic patients often present with large hematomas, extensive ecchymoses or severe mucosal bleeding, including epistaxis, gastrointestinal bleeding, and/or gross hematuria. *Hemarthroses, which are common in hemophilia A and B, are unusual* with acquired factor inhibitors.
    - **severity** – bleeding is often severe, constituting a **medical emergency**. A significant number of patients have repeated bleeding after initial therapy.

Laboratory testing

- **Prolonged aPTT**. Most factor VIII inhibitors are characterized by a prolonged aPTT and a normal prothrombin time (PT). All possible causes of a prolonged aPTT should be reviewed, including factor deficiencies

(factors VIII, IX, XI) and, indirectly, deficiency of von Willebrand factor (VWF), which stabilizes factor VIII.

- **Inhibitor screen and titer**. The next step after identifying a prolonged aPTT is to determine whether it is due to an inhibitor (fig. 5). This is done using a mixing study or inhibitor screen.

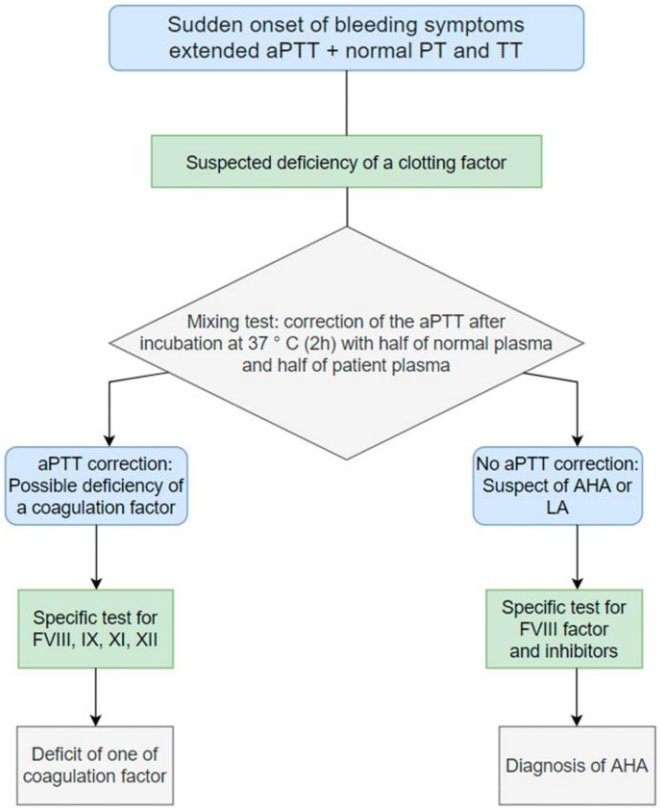

Figure 5. Algorithm of laboratory diagnosis of acquired hemophilia

If an inhibitor is present, the aPTT remains prolonged. If the aPTT does not correct, the Bethesda assay is performed. The Bethesda assay both establishes the diagnosis of a factor VIII inhibitor and quantifies the antibody titer. An inhibitor titer of 5 BU is considered high because it means the inhibitor in 1 mL of blood can inhibit the factor VIII from 5 mL of blood. The stronger the inhibitor, the higher the BU titer.

- **Factor VIII activity level**. For individuals with severe or active bleeding, factor VIII activity level should be obtained without delay. If factor VIII activity is normal, activity levels of other factors can be obtained (for a prolonged aPTT, factor IX, factor XI, and factor XII).

  The diagnosis of an acquired factor inhibitor is confirmed by the finding of factor activity level below the reference range accompanied by an inhibitor in the appropriate clinical setting (typically, bleeding in a patient

without a prior bleeding disorder; less commonly, new onset prolonged clotting times without bleeding).

Features that are **not** consistent with acquired hemophilia A include:

- Positive family history of hemophilia
- Chronic bleeding disorder since childhood or young adulthood
- History of thrombosis rather than bleeding
- Normal coagulation testing
- Low von Willebrand factor (VWF) activity

Management

Initial treatment of acquired factor inhibitors typically requires:

- **Control of bleeding.** Active bleeding may be treated with one or more of the following:
  - bypassing products such as recombinant activated factor VII (rFVIIa) or factor eight inhibitor bypassing activity (FEIBA);
  - factor concentrates, such as factor VIII (human or porcine) for acquired hemophilia A, as long as the inhibitor titer is low;
  - Fresh Frozen Plasma (FFP) or prothrombin complex concentrate (PCC), only if a factor concentrate is not available and the inhibitor titer is low;
  - antifibrinolytic agents for mucosal bleeding.
- **Elimination of the inhibitor**. Most patients are treated with immunosuppression to eliminate (or speed the resolution) the inhibitor. This is especially true for patients with active bleeding or a history of serious bleeding associated with the inhibitor. Prednisone alone is the easiest to manage but can take longer than prednisone plus cyclophosphamide in an individual with a higher titer inhibitor.

Multiple choice question

1. hemophilia A is characterized by the deficiency of…

A. Factor XII
B. Factor V
C. Factor VII
D. Factor VIII

2. Typical clinical manifestation of hemophilia:

A. Petechiae, palpable purpura
B. Bleeding in the joints and muscles
C. Petechiae, easy bruising
D. Subungual hematoma

3. For acquired hemophilia is true everything, EXCEPT:

A. The mixing test doesn't show correction of aPTT
B. The prevalence of acquired hemophilia is about the same between men and women
C. Hemarthrosis is a common clinical manifestation of acquired hemophilia
D. For the treatment of acquired hemophilia can be used recombinant activated factor VII

4. What distinguishes hemophilia C from A:

A. It is congenital disease
B. Bleeding can occur with trauma
C. Prolonged aPTT
D. Deficiency of factor XI

5. For confirming diagnosis hemophilia can be used everything, EXCEPT

A. Mixing study
B. aPTT
C. Urinalysis
D. Factor activity level

6. Choose treatment of acute bleeding for hemophilia B:

A. Desmopressin

B. Recombinant factor IX
C. Emicizumab
D. Ibuprofen

7. Choose treatment of acute bleeding for hemophilia A without inhibitors:
A. Emicizumab
B. Recombinant activated factor VII
C. Recombinant factor VIII
D. Recombinant factor IX

8. Correct about hemophilia everything, EXCEPT:
A. Spontaneous bleeding common for severe hemophilia
B. All women have symptoms of hemophilia
C. Arthropathy is the most common complication
D. Mild hemophilia can be undetected for long period of time

9. Causes of prolonged aPTT, EXCEPT:
A. Disseminated intravascular coagulopathy
B. Factor VII deficiency
C. Factor VIII deficiency
D. Von Willebrand disease

10. If factors are unavailable, what can be used for the treatment of bleeding hemophilia A:
A. Frozen plasma
B. Factor IX
C. Emicizumab
D. Aspirin

1	2	3	4	5	6	7	8	9	10
D	B	C	D	C	B	C	B	B	A

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