METHODOLOGICAL RECOMMENDATIONS FOR STUDENTS

“Thrombocytopenic purpura and hemophilia”

Kharkiv 2012
Module 4. “The basic foundations of diagnostics, treatment and prophylaxis of common hematological diseases”.

Practical lesson N 29
“Thrombocytopenic purpura and hemophilia”

Topicality

The annual incidence of the acute form of idiopathic thrombocytopenic purpura (ITP) is approximately 4 to 5.3 per 100,000 children; however, many times ITP remains undiagnosed because of its transient and self-limiting nature. About 15% to 20% of children with acute ITP will develop chronic ITP. Approximately 80% of pediatric patients will have a complete remission within several weeks to months, regardless of therapy.

The chronic form occurs more often in adults, usually women between 20 and 40 years of age, with a female:male ratio of 3:1.4. Chronic ITP has an insidious onset and a lower rate of acute bleeding. Often, the chronic form is an incidental finding. It is sometimes a secondary disorder, associated with another underlying disease (autoimmune disorders, chronic lymphocytic leukemia, or lymphoma) and is not usually preceded by a viral infection. Chronic ITP undergoes remissions and exacerbations, persisting for more than 6 months and often for years. Only about 20% of patients with chronic ITP will have a spontaneous remission, regardless of therapy. The incidence of chronic ITP in adults has been reported to be 5.8 to 6.6 per 100,000.

The most common hemophilias are hemophilia A and hemophilia B, resulting from a deficiency in coagulation factors VIII and IX, respectively. Both of these hemophilias are X-linked recessive traits, with bleeding tendencies manifesting in male offspring. Hemophilia A is the more common of the disorders, with an incidence of 1 in 5,000 male live births; in the general population, the incidence is 1 in 10,000. Hemophilia B occurs in 1 in 30,000 male live births, or 1 in 60,000 in the general population. Deficiencies in other coagulation factors may also occur but are rare.

Educational goals:
- To give definition of thrombocytopenic purpura and hemophilia;
- To become familiar with etiology and pathogenesis of thrombocytopenic purpura and hemophilia;
- To become acquainted with modern classifications of thrombocytopenic purpura and hemophilia;
- To learn methods of investigations of coagulation abnormalities with special emphasis on indications and contraindications to them;
- To learn how to interpret data of laboratory and instrumental investigations;
- To study how to manage thrombocytopenic purpura and hemophilia.
What student should know?

- The basic etiologic factors and pathogenetic mechanisms of thrombocytopenic purpura and hemophilia;
- The basic clinical syndroms of thrombocytopenic purpura and hemophilia;
- The chief complaints and physical finding in thrombocytopenic purpura and hemophilia;
- The methods of physical examination of patients with thrombocytopenic purpura and hemophilia;
- The diagnostic value of bleeding time and coagulation time in thrombocytopenic purpura and hemophilia;
- The diagnostic meaning of clinical blood analysis in thrombocytopenic purpura;
- The list of instrumental investigations, which allow to identify bleeding and formation of hematomas;
- The complications of thrombocytopenic purpura and hemophilia;
- The particularities of management of patients with thrombocytopenic purpura and hemophilia;
- The particularities of treatment of thrombocytopenic purpura and hemophilia (curative regimen, corticosteroids, replacement therapy by factors of coagulation);
- The prophylaxis of complications in patients with thrombocytopenic purpura and hemophilia.

What student should know how to do?

- the identification of mean clinical syndromes in thrombocytopenic purpura and hemophilia;
- the development of treatment plan of patients with thrombocytopenic purpura and hemophilia;
- the interpretation of laboratory findings in case of thrombocytopenic purpura and hemophilia;
- the clarification of differential diagnosis;
- the drugs prescription to patients with thrombocytopenic purpura and hemophilia;
- the evaluation of prognosis of patients with thrombocytopenic purpura and hemophilia

Practical skills:

- Inspection of skin, its derivatives and visible mucous membranes;
- Tourniquet sign;
- Inspection of abdomen;
- Superficial palpation of abdomen;
- Deep sliding palpation of abdomen;
- Assessment of joints function.
Coagulation Disorders

Hemostasis

Hemostasis is the body's ability to maintain blood in its fluid state while it is within the vasculature and minimize blood loss by promoting clotting when the blood is outside of the vasculature. For this to occur there must be coordination of blood vessels, platelets, coagulation factors, natural inhibitors, and the fibrinolytic proteins existing in an overlapping system of checks and balances.

Normal hemostasis requires three responses: the vascular response, formation of a platelet plug, and formation of a fibrin clot. At the same time, naturally occurring anticoagulant proteins inhibit the action of clotting factors in an attempt to control thrombosis, fibrinolysis, and inflammation. The fibrinolytic system also dissolves and removes excess fibrin deposits to preserve vascular patency.

The Vasculature

The main role of the vasculature is to prevent bleeding. Normal intact vascular endothelium repels platelets and red blood cells (RBCs) and secretes substances to inhibit clotting. The initial vascular response to trauma is vasoconstriction, which shunts blood away from the damaged area. Traumatic disruption of the vessel endothelial lining triggers formation, binding, and/or activation of various substances. Trauma also exposes substrates that facilitate attachment and formation of the platelet plug, which is the primary hemostatic mechanism. The secondary hemostatic mechanism controls the formation of a fibrin clot via the ordered interaction of a series of tissue and blood components or factors. Primary and secondary hemostasis operates simultaneously. During this time, inhibitor systems also operate to prevent propagation of the clot, and fibrinolysis is activated for eventual removal of the clot.

Platelet Pathophysiology

Platelets play a dominant role in the spontaneous prevention of blood loss from damaged blood vessels. Immediately after tissue injury, platelets clump together to form a primary hemostatic plug through a series of overlapping phases, which stops blood flow while maintaining vascular integrity. These phases include adhesion, aggregation, secretion, and elaboration of procoagulant activity. This series of steps ultimately results in the formation of a permanent insoluble fibrin clot that is essential for long-term hemostasis.

Platelets are fragments of megakaryocytes, which are large stem cells that are formed in the bone marrow. A normal platelet concentration is 150,000 to 450,000/mm$^3$ of blood, and production appears to be directly proportional to demand. This allows for the repair of minor ruptures that occur routinely in everyday life. The bone marrow contains a limited quantity of “reserve” platelets. This reserve can be readily exhausted after a noxious intervention resulting in platelet destruction. Platelet cells mature over a 4- to 5-day period and have a typical life span of approximately 9 to 10 days. After formation and release from the bone marrow, approximately 25% to 35% of platelets are found in the spleen.
and the remainder in the circulation. Younger platelets are more physiologically active than older ones.2

**Coagulation And Fibrinolysis**

The nomenclature and characteristics of the factors involved in the coagulation cascade. The Roman numeral designations for clotting factors generally correspond to their order of discovery. Many clotting factors fall into one of two major groups, based on their biochemical properties. Factors XI, XII, prekallikrein, and high-molecular-weight kininogen are known as contact activation factors because they initiate the contact phase of the coagulation pathway. Factors II, VII, IX, and X are vitamin K-dependent coagulation factors synthesized by the liver. Vitamin K is an essential cofactor for hepatic carboxylation of glutamic acid residues. The $t$-carboxyglutamic acid residues allow the calcium binding that is essential for normal clotting activity. Vitamin K-deficient persons continue to produce factors II, VII, IX, and X, but in inactive forms. Factor III (tissue factor) is found in many tissues; factor IV (calcium) comes from diet and bone. No factor VI exists.

The traditional model of coagulation cascade comprises reaction complexes, each including an enzyme, a substrate, and a reaction accelerator. The numerous steps amplify the activation process, which ensures a rapid response at sites of injury. The product of these reactions is the potent enzyme thrombin, which is formed by the catalytic action of factor Xa (activated factor X) on prothrombin. Historically, there have been two classic independent pathways that lead to the generation of factor Xa and subsequently give rise to the common pathway: the extrinsic and intrinsic pathways. More recently, these two independent pathways have been merged into one in order to account for clinical observations not explained by the traditional coagulation cascade, such as why patients with hemophilia, who lack either factor VIII or IX, continue to bleed when neither of these deficiencies affects the extrinsic pathway. Even though this new model of coagulation has been developed, the fundamental principles behind clot formation remain the same.

After the fibrin clot is formed, fibrinolysis is initiated to remove the clot and restore blood flow. Fibrinolysis is mediated by the enzyme plasmin. Plasmin circulates in the inactive form of plasminogen. Tissue plasminogen activators (t-PAs) that are present in endothelial cells and other tissues activate plasminogen to form plasmin, which in turn cleaves fibrin into fibrin degradation products (FDPs).

The intact vessel endothelium and natural anticoagulants continuously maintain normal blood flow. Disruption of endothelial integrity or release of tissue factor after injury activates both the platelet and coagulation systems, resulting in an insoluble fibrin clot that limits further bleeding. Fibrinolysis is then activated, which results in vascular patency by breaking down the fibrin clot. Abnormalities in these systems may occur at virtually any step and may result in bleeding or coagulation disorders.
**Thrombocytopenia**

A normal platelet count ranges from 150,000 to 450,000/mm$^3$. Thrombocytopenia, defined as a decrease in the normal number of blood platelets, is one of the most common causes of abnormal bleeding. A platelet count less than 150,000 per mm$^3$ generally indicates the presence of thrombocytopenia; however, clinical trials evaluating the existence of a reduced platelet count use a variety of values to define thrombocytopenia. Mild thrombocytopenia (50,000 to 150,000/mm$^3$) is associated with few symptoms. Counts less than 50,000/mm$^3$ constitute moderate thrombocytopenia and are associated with some bleeding potential. In severe thrombocytopenia (<10,000 to 20,000/mm$^3$), spontaneous life-threatening bleeding can occur. As platelet counts less than 100,000/mm$^3$ bleeding time becomes progressively longer. However, the actual risk for bleeding depends on both the number of platelets available and how well they function.

Thrombocytopenia has many causes, which may vary with both age and development. The causes of thrombocytopenia should be distinguished to optimize the therapeutic approach. A decrease in the platelet count may occur from a decrease in production of platelets, altered distribution (sequestration) of platelets, or increased destruction of platelets.

A decrease in platelet production may occur from conditions that either alter normal formation of platelets (thrombopoiesis) or decrease the number of marrow megakaryocytes. Examples include marrow injury (e.g., myelosuppressive drugs, chemicals, radiation, or viral infections such as rubella, cytomegalovirus, Epstein-Barr virus, and human immunodeficiency virus), marrow failure (e.g., aplastic anemia and hereditary disorders), or marrow replacement (e.g., leukemia, tumor metastases, and fibrosis). Ineffective thrombopoiesis caused by severe vitamin B$_{12}$ or folate deficiency is characterized by a normal or increased number of megakaryocytes in the bone marrow associated with inadequate availability of platelets in the circulation.

Altered distribution of platelets can result from any disorder that causes splenomegaly (e.g., alcoholic liver disease, congestive heart failure, lymphomas, sickle cell disease, and myeloproliferative diseases). In this situation the actual number of total body platelets is normal, but their distribution in the body is altered.

Increased destruction of platelets can result from increased platelet utilization and from immunologic and nonimmunologic mechanisms. Disseminated intravascular coagulation (DIC) is an example of a nonimmunologic condition that causes increased platelet consumption. Immunologic causes of thrombocytopenia include drug-induced immune thrombocytopenia (e.g., quinidine, quinine, gold, and heparin), autoimmune disorders [e.g., systemic lupus erythematosus (SLE) and autoimmune thrombocytopenic purpura], and autoantibody-produced thrombocytopenia (e.g., placental transfer and history of multiple transfusions).

Massive blood loss may result in dilutional thrombocytopenia when treated with large amounts of fluids having few or no platelets. Other miscellaneous
causes of thrombocytopenia are thrombotic thrombocytopenic purpura (TTP), prosthetic heart valves, extracorporeal perfusion, hemodialysis, and snake envenomation.

The symptoms of thrombocytopenia include symmetric petechiae and purpura on the extremities and trunk, mild to moderate bleeding of mucosal surfaces (oropharynx, nose, and the gastrointestinal, pulmonary, and genitourinary systems), and easy or spontaneous bleeding.

**Immune Thrombocytopenic Purpura**

Immune thrombocytopenic purpura (ITP; also known as idiopathic thrombocytopenic purpura), an autoimmune disorder, is characterized by decreased numbers of circulating platelets, normal or increased numbers of megakaryocytes in the bone marrow, and clinical signs and symptoms related to the low platelet count. Most cases of ITP involve shortened platelet survival due to immune-mediated platelet destruction by antiplatelet autoantibodies of the immunoglobulin (Ig) G or IgM subtypes.

Clinically, ITP is classified as acute (lasting 6 months or less) or chronic. The acute form most commonly occurs in young, previously healthy children 2 to 8 years of age and affects both sexes equally. The onset in most pediatric patients is seen within days to several weeks after an acute viral infection, most often an upper respiratory infection but also varicella, rubeola, or rubella. The syndrome has also been seen after immunizations.

**Clinical Presentation and Diagnosis**

**Signs and Symptoms**

Acute ITP is characterized by an abrupt onset.\textsuperscript{4,5,6} The platelet count is frequently low, between 10,000 and 20,000/mm\textsuperscript{3}. In most patients the physical examination is remarkable only for the hemorrhagic abnormalities associated with the low platelet count. Small punctate red macules (petechiae) and a dark red-purple discoloration of the skin reflecting larger areas of hemorrhage (purpura) are the classic signs of ITP. These can occur anywhere on the external surface of the skin as well as internally, the gastrointestinal tract being the most common internal site. Bleeding of the nasal, oropharyngeal, and vaginal mucosa; easy bruising with ecchymoses; conjunctival hemorrhage; epistaxis; and menorrhagia are common. Hematuria, retinal hemorrhage, and joint bleeding are less common. Splenomegaly is absent. Central nervous system (CNS) bleeding is seen in approximately 1\% of patients. Intracranial hemorrhage occurs early in the acute form of ITP and is most common in patients with platelet counts less than 20,000/mm\textsuperscript{3}. It is considered the most serious risk with ITP, owing to its associated high morbidity and mortality. Manifestations include altered mental status and headache.

Patients with chronic ITP usually have a higher platelet count compared to those with the acute form.\textsuperscript{4,6} Minor skin and mucous membrane bleeding may be the sole manifestations, and some patients are asymptomatic. However, serious bleeding, such as intracranial hemorrhage, can occur in patients with chronic ITP and a low platelet count.
Diagnosis

The diagnosis is usually a process of eliminating other disorders that also cause thrombocytopenia. This is especially true for children with signs and symptoms of acute ITP. The differential diagnosis of ITP includes a wide array of hematologic diseases, including leukemia, marrow hypoplasia, DIC, aplastic anemia, TTP, and lymphoma. Nonhematologic causes of thrombocytopenia include systemic infection, thyroid disease, tuberculosis, and autoimmune diseases such as SLE. Human immunodeficiency virus (HIV) infection should be considered as a possible diagnosis for patients who fit into high-risk categories. Drug-induced thrombocytopenia should also be excluded, and any drug that is capable of causing thrombocytopenia should be discontinued. Splenomegaly, adenopathy, fever, and malaise are uncommon in acute ITP and may suggest other disorders when present.

Laboratory testing reveals isolated thrombocytopenia, unless bleeding has been sufficient to cause anemia. A complete blood examination shows a decreased number of platelets with an elevated mean platelet volume and platelet distribution width. On peripheral smear, the platelets are larger and appear to be less mature than normal. Thrombocytopenia in acute ITP may be severe (platelet count 10,000 to 20,000/mm³), whereas patients with chronic ITP generally have higher counts (30,000 to 75,000/mm³). Bleeding time is prolonged in proportion to the degree of thrombocytopenia. The bleeding time for a given platelet count is shorter than that for thrombocytopenia caused by decreased platelet production, because the circulating platelets are young and “superactive.”

This accounts for the lack of bleeding symptoms in some patients despite severe thrombocytopenia. The prothrombin time (PT), activated partial thromboplastin time (aPTT), and erythrocyte sedimentation rate usually remain normal. Almost all patients have normal hemoglobin, hematocrit, and RBC indices, although chronic gastrointestinal hemorrhage or menorrhagia occasionally causes iron deficiency anemia. Bone marrow examination shows normal or increased numbers of immature megakaryocytes.

Differential Diagnosis

Because an ITP-like syndrome can be seen in patients with HIV or hepatitis C infection, appropriate testing is indicated in at-risk individuals. Secondary ITP may be induced by drugs or occur in patients with collagen vascular disease, lymphoproliferative disorders, immune thyroid disease, or common variable hypogammaglobulinemia. The presence of these disorders is usually suggested by a careful history, physical examination, and CBC findings; the diagnosis can be confirmed by appropriate laboratory and radiologic studies.

Treatment

The major goals in the treatment of ITP are to decrease the risk of hemorrhage and to obtain complete remission of the disease. Traditionally, these goals are met either by suppressing the production of antiplatelet antibodies or by inhibiting platelet phagocytosis. Supportive measures to reduce the risk of bleeding include restriction of physical activity and avoidance of drugs that alter platelet activity; these should be implemented for all patients. For patients with chronic
ITP secondary to another disorder, treatment of the underlying disease will benefit the ITP.

**Acute Immune Thrombocytopenic Purpura**

The initial course of treatment in children with acute ITP is controversial. Part of this controversy is due to the fact that more than 80% of patients with acute ITP will have a complete spontaneous recovery within a few weeks to months of the disease onset, irrespective of the treatment given. Intracranial hemorrhage is the primary concern of clinicians who prefer early treatment. The risk of intracranial hemorrhage, however, is low (incidence of 0.2% to 1%). Others choose not to treat because of adverse effects, cost, the low frequency of CNS bleeding, and the self-limiting nature of the disease. Some clinicians base the decision to treat on the platelet count, electing to treat when the count is less than 20,000/mm$^3$. Recent surveys, however, have shown that the majority of children with acute ITP do not have serious bleeding episodes even with low platelet counts. A “watch and wait” approach is frequently used for initial management of children with acute ITP and mild to moderate symptoms. Platelet counts should be repeated within 7 to 10 days after diagnosis to rule out the development of serious bone marrow disorders.

If treatment is initiated, the goal is to rapidly increase the platelet count to a hemostatically safe level. Prednisone has been considered the drug of choice for treating acute ITP. Dosages range from 1 to 4 mg per kg daily for a maximum of 2 to 3 weeks. Lower doses of prednisone (1 to 2 mg/kg) are effective in raising platelet counts but may not be faster than no treatment. Higher dosages (4 mg/kg) may produce a more rapid rise in platelet count, with a reported median of 4 days to reach a platelet count of greater than 50,000/mm$^3$. Short-term therapy (4 days) at this higher dosage may also be effective. Higher-dose prednisone may be preferred for children with mucous membrane bleeding and more severe cutaneous symptoms. However, the optimal corticosteroid dosage and route of administration have not been established. Adverse effects are minimal at low doses, whereas higher doses have been associated with weight gain, epigastric discomfort, glycosuria, and behavioral changes. High-dose methylprednisolone (30 mg/kg daily for 2 to 3 days) has been used for urgent treatment (e.g., neurologic symptoms, evidence of internal bleeding, or when surgery is needed).

Intravenous high-dose immune globulins (IVIGs) have been shown to shorten the duration of platelet counts less than 20,000/mm$^3$. IVIG has many simultaneous effects on platelet function, which occur through inhibition of Fc receptor-mediated platelet binding in the reticuloendothelial system. IVIG alters T- and B-cell numbers and function. It also produces a reduction in platelet-associated immunoglobulins, which is seen within 3 days. The total dose of IVIG to be administered is 2 g/kg, given as either 0.4 g/kg/day for 5 days or 1 g/kg/day for 2 days. This usually results in a response in 1 to 3 days, with about 80% of patients showing a platelet count greater than 50,000/mm$^3$ at 72 hours after treatment. If the effect is not sustained, repeat doses may be given. Adverse effects of IVIG include nausea, vomiting, headache, and fever, which seem to occur more often (50% to
60%) in patients who receive the total dose over 2 days. However, these symptoms usually abate after about 1 day and are readily managed with acetaminophen. The long-term response to IVIG, assessed as maintenance of a platelet count greater than 20,000/mm$^3$ with no subsequent bleeding, is about 62%. IVIG may be used with methylprednisolone when urgent therapy is needed. This combination has been shown to increase the platelet count more rapidly than either drug alone.

The decision whether to use prednisone or IVIG as initial therapy requires consideration of many factors. IVIG may be preferable because it has a more rapid onset of action compared to traditional doses of prednisone; however, higher prednisone doses may yield a comparable onset of action. Some investigators prefer IVIG, with the belief that it may have a disease-modifying role. Some practitioners consider prednisone to be the gold standard and favor its use because of familiarity with the drug. Much lower cost and concern regarding administration of blood products also favor prednisone, although a shortened hospital stay with IVIG may offset some of the cost. Additional studies are clearly necessary to clarify this clinical decision.

Anti-D immunoglobulin (WinRho) is an Rh$o$ (D) immune globulin made from freeze-dried γ-globulin (IgG) fraction and contains antibodies to Rh$o$ (D). It has been successfully used in the treatment of ITP in nonsplenectomized, Rh$o$ (D)-positive children and adults. When given at a dosage of 25 µg/kg/d for 2 days, the platelet response is slower compared to IVIG. However, higher doses (40 to 75 µg/kg) result in increases in platelet counts similar to those seen with IVIG.4,5 It has some advantages over IVIG, such as cost and method of administration. Anti-D may, however, cause reductions in hemoglobin and, rarely, renal failure.

Splenectomy is generally avoided as a treatment for children with ITP because of the high rate of spontaneous remission of the disorder and the risks associated with the surgery (e.g., postsplenectomy sepsis). If splenectomy is contemplated, pneumococcal and Haemophilus influenzae immunizations should be given before the surgery; prophylaxis with penicillin is needed after surgery, and some clinicians recommend lifetime prophylaxis.

**Chronic Immune Thrombocytopenic Purpura**

Chronic ITP is primarily a disease of adults, but approximately 10% to 20% of children with acute ITP have a poor response to treatment, and their ITP will evolve into the chronic form. The decision to treat patients with chronic ITP depends on a number of factors, including severity of the disorder, platelet count, lifestyle, and adverse effects of treatment.

Studies have suggested that the risk for clinically significant bleeding is low when platelet counts are greater than 10,000/mm$^3$. For patients with nonactive lifestyles, a platelet count greater than 30,000/mm$^3$ is thought to be acceptable. For more active patients, higher platelet counts (>50,000/mm$^3$) are needed. However, bleeding can still occur despite higher platelet counts; other factors (i.e., age, uremia, chronic liver disease) must be considered when assessing the risk of bleeding in patients with chronic ITP. In addition, there are no strict
recommendations as to what a “safe” platelet count is for patients with chronic ITP. Therapy for chronic ITP is usually begun with 1 to 2 mg/kg/day of prednisone. A positive response should be seen in 3 to 7 days, although 2 to 4 weeks may be needed for maximal response. If a response is not seen within 4 weeks, the corticosteroid should be tapered and discontinued. An alternative therapy should be considered in patients who fail to respond to corticosteroids or who cannot be maintained on low-dose or alternate-day therapy.

The initial response rate to steroid therapy may be as high as 50% to 80%, but less than 20% of patients will be able to receive long-term corticosteroid therapy, owing to relapse or adverse reactions. IVIG has been used for chronic ITP, but its effect is transient, with return to pretreatment levels 3 to 4 weeks after therapy. In patients with refractory disease, splenectomy is usually considered next. Nearly 70% of patients who undergo splenectomy respond with a normal platelet count. Postulated mechanisms for efficacy of splenectomy in chronic ITP include a reduction in the phagocytosis of antibody-coated platelets and a reduction of platelet-associated antibody production. It is important that the operative procedure include a search for and removal of all accessory splenic tissues.

The presence of accessory splenic tissues has been associated with relapse following splenectomy. Corticosteroids or IVIG are often given before surgery to boost the platelet count (>30,000/mm³) and reduce the risk of perioperative bleeding. Oral dexamethasone (40 mg/d for 4 days) has also been used preoperatively. Polyvalent pneumococcal vaccine should be administered preoperatively. Some clinicians also advocate daily oral penicillin therapy for several years after surgery. A complete remission of ITP has been reported in up to 80% of patients after splenectomy.

Platelet kinetic studies may be performed to assess the degree of splenic sequestration; this may assist in the decision to perform splenectomy. In one study, a platelet count greater than 120,000/mm³ at the time of discharge, age less than 30 years, preoperative corticosteroid dependence, and splenic sequestration (measured preoperatively) were associated with a more favorable response to splenectomy.

A number of second-line agents have been used to treat patients who are refractory to corticosteroids and splenectomy. Immunosuppressive therapy is usually considered next. Azathioprine, cyclophosphamide, and the vinca alkaloids (vincristine and vinblastine) are the most commonly used agents. Azathioprine is believed to interfere with the response of T cells to antigenic challenge, with an additional more generalized reduction in T-helper activity. About 20% of patients given azathioprine respond with a normal platelet count, which may be sustained for several years. Between 30% and 40% have a partial response. The dosage of azathioprine used is 1 to 4 mg/kg/day (or 100 to 200 mg/day); the dose is reduced if the patient becomes leukopenic. It is usually given in conjunction with steroids and may have a steroid-sparing effect for some patients. Side effects are usually less serious than with cyclophosphamide, bone marrow suppression being the most important. Azathioprine is considered the safest agent for long-term therapy.
Cyclophosphamide is given in an oral dosage of 1 to 2 mg/kg/d or as an intermittent intravenous dose (1 to 1.5 g/m² intravenously every 3 to 4 weeks). Improvement is usually seen in 2 to 10 weeks, with a maximum response in platelet count seen in 8 weeks. Treatment is continued for 4 to 6 weeks after an adequate platelet count is achieved. Studies showing complete remission in 30% to 40% of patients are an advantage with cyclophosphamide. Unfortunately, side effects, including bone marrow suppression, hemorrhagic cystitis, and bladder fibrosis, may limit its use.

Vinca alkaloids have been reported to be beneficial in more than 50% of patients who are refractory to steroids and splenectomy. Vincristine (0.25 mg/kg to a maximum dose of 2 mg) and vinblastine (0.125 mg/kg to a maximum dose of 10 mg) are given intravenously every 2 to 6 weeks. Response occurs more rapidly than with azathioprine or cyclophosphamide, but relapses usually occur in 3 to 4 weeks. These agents are believed to decrease the rate of destruction of platelets by inhibiting phagocytosis and decreasing antibody levels. Vincristine may also bind selectively to platelet tubulin, such that when the antibody-coated platelet is phagocytosed, the macrophages are poisoned. Vincristine and vinblastine have been loaded onto platelets in an attempt to deliver them selectively to macrophages that are responsible for platelet destruction, but this is not commonly done because of its impracticality and lack of advantage over conventional administration. The incidence of side effects is relatively high with the vinca alkaloids. Vincristine may cause transient malaise, fever after injection, temporary jaw pain, alopecia, and a variety of neuropathies. Leukopenia, abdominal pain, and headache are associated with vinblastine.

Danazol, an anabolic steroid, is thought to decrease phagocytosis of platelets by decreasing the number of phagocytic cell IgG Fc-receptors. Dosage is usually 400 to 800 mg per day initially, then tapered to 50 to 200 mg daily. Clinical response is normally seen within 8 weeks, however, treatment should be continued for up to 6 months since response may be slow. Between 30% and 40% of patients have a sustained increase in platelets. Side effect frequency is low; side effects include virilization, fibrinolysis, and hepatic dysfunction. Danazol is contraindicated during pregnancy.

High-dose corticosteroids have also shown some efficacy in patients with refractory disease. Dexamethasone 40 mg per day (oral or intravenous) for 4 days given every 4 weeks for up to six cycles has been reported to result in a complete and sustained response. However, results have not been consistent. Methylprednisolone given at a dosage of 30 mg/kg/d for 3 days tapered to 1 mg per kg increased platelet counts within 3 to 4 days, but the response was transient in some patients.

Rituximab, an anti-CD20 monoclonal antibody, has been successful in some patients with refractory ITP. In one small pilot study, rituximab at a dosage of 375 mg per m² once weekly for 4 weeks resulted in a complete response (defined as normalization of platelet counts for \( \geq 30 \) days) in 5 of 12 patients, with a partial
response (platelet count >30,000/mm$^3$) in 2 of 12 patients. However, relapse after discontinuation of rituximab has occurred.

Other therapies that have been studied in limited numbers of patients include colchicine, dapsone, cyclosporine, and interferon-α. However, no clear consensus exists as to optimal treatment for patients with refractory ITP. A meta-analysis conducted by Vesely et al found azathioprine, cyclophosphamide, and rituximab to be associated with the highest rates of complete response, but these rates were still low, ranging from 17% to 27% of patients.

Although spontaneous complete remission of chronic ITP is unusual, the long-term prognosis is usually favorable. Most patients will have stable, mild to moderate thrombocytopenia. The objective of therapy in chronic ITP is to keep the patient hemostatically safe (i.e., platelet counts >30,000 to 50,000/mm$^3$), not necessarily to obtain a complete remission. A review of the literature on patients with refractory disease showed a median death rate of 5.1%, caused either by uncontrolled bleeding or by complications of therapy. High-risk groups included patients with a history of bleeding, those with the concomitant presence of other bleeding disorders, and those more than 60 years of age.

**Hemophilia**

The hemophilias are a variety of inherited bleeding disorders that involve a deficiency of one or more coagulation factors.

The hemophilias include hemophilia A, caused by a deficiency of clotting protein factor VIII (antihemophilic factor), and hemophilia B, caused by a deficiency of factor IX (also called antihemophilic factor B, plasma thromboplastin component, or Christmas factor, named after an individual with the disease). A deficiency of either of these two intrinsic coagulation pathway components results in inefficient and inadequate generation of thrombin.

Hemophilia A and B affect secondary hemostasis. Factors VIII and IX are necessary for activation of factor X, followed by generation of thrombin; thrombin in turn leads to formation of fibrin. When injury occurs in an individual with hemophilia, platelet function (part of primary hemostasis) is normal, with the formation of a platelet plug. However, stabilization of the formed platelet plug by fibrin does not occur (since thrombin formation is inadequate to generate fibrin), leading to a failure in secondary hemostasis and continued bleeding.

Factor deficiency is not absolute in hemophilia; factor VIII and factor IX procoagulant levels remain relatively constant in a patient and correspond to hemorrhagic frequency and severity. Bleeding can occur spontaneously in patients with severe deficiency or only after trauma in patients with some factor activity. The most common sites for bleeding are muscles and large joints.

Factor VIII or factor IX levels of 100% correspond to factor VIII or factor IX activity of 1.0 U/mL. Factor VIII and factor IX levels in a normal person range from 50% to 200% (0.5 to 2.0 U/mL). Although hemostasis occurs at 25% to 30% of normal factor VIII activity, most symptomatic patients with hemophilia A have factor VIII levels less than 5%. The severity of the deficiency is categorized as
mild, moderate, and severe. Patients with factor levels less than 1% (0.01 U/mL) are classified as having severe hemophilia. Hemorrhagic episodes are more frequent in these patients (20 to 30 or more annually) and often occur without evidence of trauma. Patients with factor levels greater than 5% are considered to have mild hemophilia. These patients usually hemorrhage only after trauma or surgery. Patients with factor levels between 1% and 5% are considered to have moderate hemophilia, with manifestations between the two extremes. Most patients with hemophilia have moderate to severe disease.

**Clinical Presentation and Diagnosis**

The clinical hallmarks of hemophilia A and B are identical and include:

(a) lack of excessive hemorrhage from minor cuts or abrasions, owing to the normalcy of platelet function;

(b) joint and muscle hemorrhages;

(c) easy bruising;

(d) prolonged and potentially fatal postoperative hemorrhage.

The diagnosis of hemophilia is made based on family history (which may not be present in up to 30% of individuals) or bleeding episodes. With severe hemophilia, neonates have a 1% to 4% risk of intracranial hemorrhage. Bleeding tendencies usually become evident in the toddler stage, when the child is learning to crawl or walk. Most children with severe hemophilia have a first bleeding episode prior to age 4. Moderate hemophilia is usually diagnosed slightly later in childhood, whereas mild hemophilia may not be recognized until after some type of trauma.

Bleeding into joints results in hemarthrosis, the most common and often the most disabling manifestation of hemophilia. Repeated exposure of the synovium to blood results in swelling and hypertrophy; blood leukocytes in the joint space erode both the cartilage and bone, with narrowing of the joint space. Continued damage causes loss of joint motion and contracture, leading to disability in target joints (joints with recurrent bleeding). The joints that are most often involved include the knees, elbows, ankles, shoulders, hips, and wrists. The spine and hands are rarely involved.

An aura consisting of joint warmth and tingling often signals the onset of hemorrhage. Mild discomfort gives way to pain, swelling, erythema, and decreased range of motion over the next several hours. Young children often display guarding, irritability, and decreased movement in an affected joint. Classic symptoms in a reliable patient are a sufficient basis for immediate treatment.

There is no cure for hemophilia, and treatment is directed at increasing concentrations of the deficient factor. Joint hemorrhage should be treated when the earliest symptoms appear to limit acute effects and prevent long-term sequelae. Within 8 to 12 hours of treatment, symptoms of hemarthrosis begin to resolve. Initial treatment with factor VIII or factor IX concentrate requires that levels be increased to 30% to 50%. The duration of therapy depends on the severity of bleeding. Once bleeding has stopped, blood is resorbed, and the joint returns to normal over several days to weeks. Use of nonsteroidal anti-inflammatory agents
for joint pain should be avoided because of their disruptive effects on platelet function.

Microscopic and macroscopic hematuria is a common problem among hemophiliac patients. Treatment with factor concentrate to elevate levels to 40% to 50% for 2 to 4 days is necessary if conservative treatment, such as bed rest and increased fluid intake, is unsuccessful. The use of ε-aminocaproic acid should be avoided, since decreasing clot lysis may prevent removal of a clot occluding the ureter.

Spontaneous and posttraumatic hematomas are frequent complications of hemophilia. Although most are small and resolve spontaneously, large soft tissue bleeding episodes may cause anemia and compartment syndromes with ischemic and neurologic complications. Large hematomas require treatment with factor concentrates to increase levels to 50% to 60% or more. Maintenance therapy for several days may be required to reduce rebleeding. Aggressive therapy can reduce the incidence of long-term complications, including pseudocysts, calcifications, and fibrosis.

Spontaneous or posttraumatic intracranial bleeding is an infrequent but serious complication of hemophilia. The annual incidence of intracranial bleeding has been reported to be 54 to 200 per 10,000 individuals with hemophilia. Even with prompt treatment, patients who experience intracranial bleeding are at risk for reduced quality of life due to functional disability. Treatment of intracranial bleeding should be immediate and aggressive. Any patient with a history of head trauma and signs of head injury, including abrasions, lacerations, or scalp hematoma, should be treated. Factor VIII or factor IX concentrates should be given to increase and maintain the level near 100%.

Mucosal bleeding is not uncommon among patients with hemophilia. Factor replacement to a level greater than or equal to 30% is often indicated. Supplementation with ε-aminocaproic acid or tranexamic acid may be advantageous to stabilize clot formation. Temporary restriction of oral intake and repeated treatment may be required if clot dislodgment is a problem.

**Treatment**

Care of patients with hemophilia and related bleeding disorders has improved dramatically over the past several decades, resulting in lower morbidity, increased life expectancy, and significantly better quality of life. Hemophilia treatment centers, established in the mid-1970s, not only provide comprehensive medical care to patients with bleeding disorders, but also provide patients and families with educational and social services to help cope with this lifelong disorder. These centers, along with wider availability of coagulation factor products and early and accurate diagnoses, have substantially reduced mortality among patients with hemophilia.

Treatment of hemophilia consists primarily of administration of products that increase the concentration of deficient clotting factors [e.g., factor concentrates, FFP, cryoprecipitate, or desmopressin (DDAVP)] and inhibiting
fibrinolysis with antifibrinolytics, such as ε-aminocaproic acid and tranexamic acid.

*Fresh-Frozen Plasma*

FFP is the fluid portion of 1 unit of whole blood, taken from a single donor. It contains about 1 U of factor VIII and 1 U of factor IX per mL of plasma (some factor activity may be lost during frozen storage of the plasma). However, because of the large amount of fluid that would be required, FFP is not the optimal means of factor replacement. Several guidelines on the treatment of hemophilia and bleeding disorders recommend the use of FFP for coagulation factor deficiencies for which there is no coagulation factor concentrate available. For patients with hemophilia B, FFP has been recommended for use only in life-threatening emergencies, when factor IX concentrates are not available. Factor IX levels may be increased by up to 15% with FFP, if the volume needed can be tolerated by the patient (up to 18 mL/kg).

*Cryoprecipitate*

Cryoprecipitate is prepared by thawing FFP and removing the cell-free fluid remaining after centrifugation, leaving factor VIII, vWF, and fibrinogen. The amount of factor VIII in cryoprecipitate varies; on average a 10- to 20-mL bag contains about 80 units of factor VIII. Cryoprecipitate contains no factor IX. Because of the risk of viral transmission, availability of factor concentrates, and variability in factor VIII content, cryoprecipitate is not recommended for treatment of hemophilia A.

*Factor VIII Replacement*

Two types of factor VIII concentrate are available: plasma-derived and recombinant. Plasma-derived factor VIII concentrate is produced from factor VIII isolated from pooled plasma generated from thousands of donors. Although plasma-derived concentrates are considered safe, a large percentage of hemophilia patients were infected with hepatitis C or HIV in the mid-1980s, before the risk of transmission of these viruses through human plasma products was recognized, resulting in significant mortality. Today, the safety of plasma-derived concentrates is ensured through strict plasma-donor screening and testing. Factor concentrates also undergo viral removal and inactivation methods to reduce the risk of viral transmission; these include solvent/detergent, heat treatment, pasteurization, vapor heating, and filtration. Chromatographic methods (e.g., immunoaffinity with monoclonal antibodies) are used to purify the concentrate, removing any nonfactor proteins and contaminants.

Recombinant factor VIII concentrates are produced by recombinant technology, using hamster cell lines (kidney or ovary cells) transfected with the human gene for factor VIII. Three generations of recombinant products are currently available. First-generation recombinant factor concentrates use animal and/or human plasma-derived proteins (e.g., albumin) in the cell culture medium and as a stabilizer in the final formulation. With second-generation agents, animal and/or human plasma-derived proteins are used in the cell culture medium but not in the final product. These agents use a sugar (e.g., mannitol or sucrose) as a
stabilizer in the final product. No animal or human plasma-derived proteins are used in third-generation recombinant products. The development of third-generation recombinant products is in keeping with the MASAC recommendation of removing all animal or human protein sources from recombinant products to eliminate the risk of transmission of known or unknown pathogens from human or animal proteins.

Although the viral inactivation and removal methods used during the manufacture of plasma-derived coagulation factor concentrates have made these products safe in regard to transmission of HIV or hepatitis, there is still concern about other potential pathogens, such as new variant Creutzfeldt-Jakob disease and parvovirus. Recombinant factor products have been shown to be safe, with no reports of disease transmission. Whenever possible, recombinant factor concentrates are generally preferred over plasma-derived products for the treatment of hemophilia.

The goal of factor replacement therapy is to achieve hemostasis by maintaining adequate levels of deficient factor. The level of clotting factor to achieve this goal depends on the indication for treatment. Volume of distribution or recovery (ratio of observed peak factor concentration to predicted peak concentration), baseline factor concentration, factor half-life, and the presence of inhibitors can all influence the dose of factor replacement required.

Factor VIII distributes into plasma volume and initially to extravascular space. The volume of distribution is approximately 50 mL per kg. A simple dose calculation based on volume of distribution is that each unit of factor VIII infused per kilogram of body weight yields a 2% increase in plasma level (0.02 U/mL or 2 U/dL). With an average elimination half-life of 12 hours, factor VIII may be dosed every 12 hours, with 50% of the initial dose used as a maintenance dose, every 12 hours. Factor VIII concentrate has also been given as a continuous infusion. This method of administration may reduce the amount of factor needed and maintain a more constant factor concentration to reduce the risk of bleeding from trough concentrations that are too low.

Factor IX Replacement

Bleeding in patients with hemophilia B (deficiency of factor IX) can be treated with factor IX concentrates. As for factor VIII, factor IX is available as a plasma-derived product and as a recombinant product.

Factor IX complexes (prothrombin complex concentrates) have been used for patients with hemophilia B. These concentrates contain not only factor IX, but also significant quantities of the other vitamin K-dependent clotting factors II, VII, and X. Although these agents are effective, they increase the risk of thrombosis, especially when used at high doses.

Because the molecular size of factor IX is one-fifth that of factor VIII, the volume of distribution of factor IX is twice that of factor VIII. A simple dose calculation based on volume of distribution is that each unit of factor IX infused per kg of body weight yields a 1% increase in plasma level (0.01 U/mL or 1 U/dL).
The longer half-life of factor IX allows for every-24-hours dosing, with 50% of the initial dose used as a maintenance dose every 24 hours.

Treatment Complications

One of the major complications of treatment of hemophilia is the development of inhibitors. As many as 50% of patients with hemophilia A and 3% of patients with hemophilia B have been reported to develop inhibitors to the respective factors with repeated administration of the concentrate. Inhibitors are IgG antibodies that bind to and inactivate the coagulation factor, reducing the efficacy of the factor concentrate and therefore the response to treatment. Inhibitors to factor VIII (the more commonly occurring) are expressed as titers called Bethesda units (BU). Low responders (3 to 5 BU) have low inhibitor titers that do not rise after further exposure to factor VIII. High responders (the majority of patients with inhibitors) may have low inhibitor titers initially, but they rise markedly (>1,000 BU) with further exposure to factor VIII (called an anamnestic response). Inhibitor titers usually rise 2 to 3 days after exposure, peak in 7 to 21 days, then decline slowly.

Patients with inhibitors do not bleed more often than patients without inhibitors, but treatment of bleeding is more difficult for these patients and the use of prophylactic therapy is not possible. Options for treatment of patients with inhibitors are to (a) administer sufficient quantities of factor concentrate to overwhelm antibodies that are present with an excess of factor to produce hemostasis, (b) restore hemostasis with factors other than factor VIII (called bypassing agents), and (c) remove antibodies by use of immune tolerance induction therapy. Patients who are low responders can sometimes be successfully treated with higher doses of factor concentrate. However, for most patients with inhibitors, use of bypassing agents or immune tolerance induction (ITI) is often necessary.

Human factor VIII can be used to treat hemorrhages in patients with low or high responses with inhibitor levels <5 BU and in patients with inhibitor levels between 5 and 30 BU after inhibitor removal. To neutralize inhibitors and achieve therapeutic hemostatic concentrations of 30% to 50%, an adult patient can be given an initial factor VIII bolus of 70 to 140 U/kg, followed by an infusion of 4 to 14 U/kg/hour. Factor VIII levels should be monitored regularly to ensure that therapeutic concentrations are maintained. Porcine-derived factor VIII concentrate is another option for patients with inhibitors (titers to human factor VIII <50 or <15 BU to porcine factor VIII).

There is a risk of cross-reactivity to porcine factor VIII (averaging 25%), and inhibitors to the porcine factor should be measured prior to therapy. The recommended dose of porcine factor VIII for patients with low titers to human factor VIII (<5 BU) is 20 to 50 U/kg; for patients with titers 5 to 50 BU, porcine factor VIII can be dosed at 50 to 100 U per kg. Infusion reactions to porcine factor VIII (chills, fever, rash) occur in about 10% of patients; pretreatment with corticosteroids or antihistamines may be beneficial.
Thrombocytopenia and an anamnestic response may also occur with porcine factor VIII. However, as of this writing, porcine factor VIII (Hyate:C, Ipsen) has been discontinued; it is available in limited quantities from the manufacturer while existing supplies last. A recombinant B-domain deleted porcine factor VIII (OBI-1) is currently under investigation by Octagen and is in phase II trials.

When factor VIII inhibitor levels are too high (>30 to 50 BU), bypassing agents may be needed to control bleeding. Anti-inhibitor coagulant complexes [AICC; also known as activated prothrombin complex concentrates (aPCC)] and factor IX complexes [also known as prothrombin complex concentrates (PCC)] have been successfully used to treat bleeding in patients with inhibitors to factor VIII. However, the clinical response with these agents is variable, and there may be a risk of thromboembolic complications and anamnestic response.

Another bypassing agent that has been shown to be effective in patients with inhibitors to factor VIII or factor IX is recombinant factor VIIa. It does not appear to be associated with an anamnestic response and has a low risk for thromboembolic events. However, the response rate is variable and it has a short half-life, requiring frequent dosing (every 2 to 4 hours). Bleeding has been reported to be controlled with a dose of 35 µg/kg; a greater effect was seen with doses of 70 to 90 µg/kg.

The third option for treatment of inhibitors in patients with hemophilia is ITI. Some clinicians have recommended ITI for most patients with hemophilia as a means to eradicate inhibitors. ITI regimens include long-term, regular infusion of factor concentrates with or without immunosuppressive or immunoabsorptive therapies. This approach is most successful when initiated during periods of low inhibitor titers, shortly after the development of inhibitors (i.e., in childhood), and when therapy is uninterrupted. Although costly, the life-long consequences of poorly controlled bleeding episodes in children with hemophilia must be considered. ITI is more effective in patients with inhibitors to hemophilia A (about 85% response); about 50% of patients with inhibitors to hemophilia B respond to ITI. Use of recombinant factor VIIa may be a more effective approach to treatment of patients with inhibitors to hemophilia B.

**Desmopressin**

Desmopressin (DDAVP) is a synthetic analog of the hormone vasopressin. Although its mechanism is unknown, DDAVP produces up to a five-fold increase in factor VIII concentrations in most patients with mild hemophilia. DDAVP does not increase production of factor VIII but stimulates the release of stored factor VIII. DDAVP does not increase the concentration of factor IX, so patients with severe hemophilia A or with hemophilia B do not benefit from this therapy.

To determine whether patients will respond to DDAVP, a plasma factor concentration is obtained after an infusion. Testing for responsiveness should be conducted when a patient is asymptomatic. This prevents a delay in the decision to use more aggressive forms of therapy while the DDAVP response is being assessed.
during a bleeding episode. Most patients with mild hemophilia A and factor VIII levels >10% respond to DDAVP.

For patients who are known to respond and who do not have life-threatening bleeding or who are not undergoing major surgery, DDAVP is the treatment of choice. The recommended intravenous dosage of DDAVP is 0.3 µg per kg, given over 30 minutes. For patients weighing more than 10 kg, the dose should be diluted in 50 mL and in 10 mL for patients less than 10 kg. DDAVP should result in an increase in factor VIII concentrations of three to five times baseline within 1 hour of the infusion. DDAVP may be administered daily for 2 to 3 days, after which tachyphylaxis may develop. If therapy is needed for longer periods, factor VIII concentrate should be considered instead. DDAVP may also be given subcutaneously, but the maximal response is delayed. A dose of 250 µg can be used intranasally, resulting in a 2.5-fold increase in factor VIII levels. Blood pressure, fluids, electrolytes, and heart rate should be monitored in patients receiving DDAVP, because it may cause a slight pressor response and fluid retention. Seizures secondary to hyponatremia have also been reported.

Antifibrinolytic Agents

ε-Aminocaproic acid and tranexamic acid are lysine-derived antifibrinolytic agents that bind to plasminogen at the lysine binding site, inhibiting fibrinolysis and stabilizing a formed fibrin clot. The primary role of these antifibrinolytic agents is as a single-dose prophylactic agent after dental procedures.

ε-Aminocaproic acid is administered orally as a loading dose of 200 mg/kg (maximum 10 g) followed by maintenance doses of 50 to 100 mg/kg every 6 hours (maximum 24 g over 24 hours) for 5 to 7 days. Tranexamic acid is administered orally at 25 mg/kg every 6 to 8 hours for 5 to 7 days. The two agents are generally well tolerated, gastrointestinal complaints being the most reported complication.

Prophylaxis

In addition to “on demand” therapy (i.e., use of factor concentrates for control of active bleeding), factor concentrates have been used for prophylaxis of bleeding. When initiated early, prophylactic factor VIII or factor IX infusions can eliminate or minimize disabling arthropathies. Prophylaxis has been described as primary (initiation of therapy prior to the age of 2 years or before any significant joint bleeding occurs) or secondary (treatment started after the age of 2 years or after two or more joint bleeds have occurred). Both types of prophylaxis are effective in improving joint function and quality of life, although more data are available for primary prophylaxis. The optimal duration of prophylaxis is unknown.

Current guidelines recommend the use of prophylactic factor concentrates for patients with severe hemophilia A or B (factor concentrations <1%). The goal of regular administration is to keep factor VIII or factor IX trough concentrations >1% between dosing.175 Dosages of factor VIII concentrate of 25 to 40 U/kg three times weekly or every other day and 40 to 100 U/kg of factor IX concentrate twice weekly have been suggested. Although prophylactic therapy is nearly 100% effective in preventing bleeding, considerations in its use include cost, need for
venous access, availability of factor concentrates, and patient and family acceptability.

**Future Therapies**

No cure for hemophilia currently exists. Liver transplantation has been reported to be successful in returning factor production to normal in a few patients with hemophilia A and end-stage liver disease.

The most promising therapy under investigation is likely to be gene therapy. One feature of hemophilia that makes gene therapy or gene transfer a viable approach is the need to raise factor concentrates by a very small amount (1% to 5% of normal) for a clinical effect to be seen. Beneficial effects of gene therapy have been seen in early phase I trials; however, the potential risks of gene therapy must also be considered.

**QUESTIONS**

**Task 1**

A 64-year-old male is hospitalized with a transient ischemic attack and is evaluated for carotid disease. Physical exam is normal. CBC on admission is normal. The patient is started on heparin. A repeat CBC 1 week later shows an Hgb of 14 g/dL (normal is 13 to 18 g/dL), WBC of 9,000/μL, and platelet count of 10,000/μL. You should

a. Obtain a bone marrow study
b. Obtain a liver-spleen scan
c. Suspect drug-induced thrombocytopenia
d. Begin corticosteroids for idiopathic thrombocytopenia purpura

**Task 2**

You are asked to consult on a 34-year-old male with thrombocytopenia. He sustained a motor vehicle collision 10 days ago, resulting in shock, internal bleeding, and acute renal failure. An exploratory laparotomy was performed that showed a ruptured spleen requiring a splenectomy. He also underwent an open reduction and internal fixation of the left femur. The platelet count was 260,000 cells/mL on admission. Today it is 68,000 cells/mL. His medications are oxacillin, morphine, and subcutaneous heparin. On examination the vital signs are stable. The examination is significant for an abdominal scar that is clean and healing. The patient’s left leg is in a large cast and is elevated. The right leg is swollen from the calf downward. Ultrasound of the right leg shows a deep venous thrombosis. Antiheparin antibodies are positive. Creatinine is 3.2 mg/dL. What is the most appropriate next management step?

A. Discontinue heparin.
B. Stop heparin and start enoxaparin.
C. Stop heparin and start argatroban.
D. Stop heparin and start lepirudin.
E. Observe the patient.
Task 3
Which of the following statements is true?
A. Factor VIII deficiency is characterized clinically by bleeding into soft tissues, muscles, and weightbearing joints.
B. Congenital factor VIII deficiency is inherited in an autosomal recessive fashion.
C. Factor VIII deficiency results in prolongation of the prothrombin time.
D. Factor VIII complexes with Hageman factor, allowing for a longer half-life.
E. Factor VIII has a half-life of nearly 24 h.

Task 4
A 16-year-old male has recurrent thigh hematomas. He has been active in sports all of his life and has had 3 episodes of limb-threatening bleeding with compartment syndrome. A family history is notable for a maternal grandfather with a similar bleeding history. Paternal family history is not available. Laboratory analysis in clinic reveals a normal platelet count, a normal activated partial thromboplastin time (22 s) and a prolonged prothrombin time (25 s). He takes no medications. What is the most likely reason for his coagulation disorder?
A. Factor VIII deficiency
B. Factor VII deficiency
C. Factor IX deficiency
D. Prothrombin deficiency
E. Surreptitious warfarin ingestion

Task 5
All the following are vitamin K–dependent coagulation factors except
A. factor X
B. factor VII
C. protein C
D. protein S
E. factor VIII

Task 6
A 31-year-old male with hemophilia A is admitted with persistent gross hematuria. He denies recent trauma or any history of genitourinary pathology. The examination is unremarkable. Hematocrit is 28%. All the following are treatments for hemophilia A except
A. desmopressin (DDAVP)
B. fresh-frozen plasma (FFP)
C. cryoprecipitate  
D. recombinant factor VIII  
E. plasmapheresis

Task 7  
During a pre-employment physical and laboratory evaluation, a 20-year-old male is noted to have a prolonged activated prothromblastin time (aPTT). On review of systems, he denies a history of recurrent mucosal bleeding and has never had an issue with other major bleeding. He has never had any major physical trauma. A family history is limited because he does not know his biologic family history. Mixing studies correct the aPTT when normal serum is used. You suspect an inherited hemorrhagic disease such as hemophilia. Which other laboratory abnormality would you most likely expect to find if this patient has hemophilia?  
A. Low Factor VIII activity  
B. Low factor IX activity  
C. Prolonged bleeding time  
D. Prolonged prothrombin time  
E. Prolonged thrombin time

Task 8  
Which one of the following drugs is LEAST likely to result in thrombocytopenia?  
(A) Heparin  
(B) Quinine  
(C) Quinidine  
(D) Estrogen  
(E) Heroin

Task 9  
All of the following statements regarding platelet abnormalities are TRUE, EXCEPT  
(A) bleeding complications may arise if platelets are < 50,000/µL  
(B) patients are at risk for spontaneous bleeding if platelet counts are < 10,000/µL  
(C) when platelets drop below 10,000/µL, the patient should receive a platelet transfusion  
(D) patients with idiopathic thrombocytopenic purpura respond well to platelet transfusion  
(E) each unit of platelets transfused should raise the platelet count by about 10,000/µL

Task 10  
All of the following antibiotics are associated with drug-induced deficiencies of vitamin K–dependent factors EXCEPT:
(A) cefotaxime  
(B) trimethoprim  
(C) cefoperazone  
(D) moxalactam  
(E) cefamandole

**Further reading:**