Hemostasis is the process of blood clot formation and represents a coordinated response to vessel injury. It requires an orchestrated response from platelets, the clotting cascade, blood vessel endothelium, and fibrinolysis. Thrombin-stimulated clot formation and plasmin-induced clot lysis are closely related and regulated. This dynamic process is often viewed in phases: formation of a platelet plug, propagation of the coagulation cascade, formation of a clot, and fibrinolysis of the clot.

Most hemostatic abnormalities are acquired and result from drugs (e.g., aspirin or warfarin [Coumadin]), from associated disease (e.g., hepatic insufficiency), or from iatrogenic causes (e.g., multiple transfusions).

Hemostasis depends on normal function and integration of the vasculature, platelets, and coagulation pathway.

Vascular integrity is maintained by a lining of nonreactive overlapping endothelial cells supported by a basement membrane, connective tissue, and smooth muscle. These cells are important in maintaining a barrier to macromolecules and, when injured, in contributing to the metabolic response and local vasoconstriction. The vascular endothelium is an important contributor to hemostasis.1

The endothelium contributes to both clot formation and regulation by producing substances such as von Willebrand’s factor (vWF), antithrombin III, heparin sulfate, prostacyclin, nitric oxide, and tissue factor pathway inhibitor.

Platelets have multiple and ever-expanding roles in our understanding of hemostasis. They are complex cytoplasmic fragments released from bone marrow megakaryocytes under the control of thrombopoietin. Platelets contain lysosomes, granules, a trilaminar plasma membrane, microtubules, and a canalicular system. Granules are an important component of hemostasis and contain platelet factor 4, adhesive and aggregation glycoproteins, coagulation factors, and fibrinolytic inhibitors. Each participates in the process of coagulation. The platelet’s role is termed primary hemostasis, and it serves as the initial defense against blood loss.1,2 A fibrin clot that incorporates coagulation factors usually reinforces a platelet clot. Platelet activity is summarized in Box 122-1. Any of the steps listed may be absent, altered, or inhibited by inherited or acquired disorders.

Coagulation Pathway

The coagulation pathway is a complex system of checks and balances that results in controlled formation of a fibrin clot. Coagulation factors have been given standard Roman numerals matching their order of discovery (Box 122-2).

A simplified version of the coagulation pathway is presented in Figure 122-1. The clotting cascade is traditionally depicted as consisting of intrinsic and extrinsic pathways. The intrinsic pathway is initiated by exposure of blood to a negatively charged surface, such as a glass surface in the activated partial thromboplastin clotting time. The extrinsic pathway is activated by tissue factor exposed at the site of vessel injury or thromboplastin. Both pathways converge to activate factor X, which then activates prothrombin to thrombin. The primary physiologic event that initiates clotting is exposure of tissue factor at the injured vessel site. Tissue factor is a critical cofactor that is required for activation of factor VII. Activated factor VII activates factor X directly as well as indirectly by activating factor IX.

Because of limited amounts of tissue factor and rapid inactivation by tissue factor pathway inhibitor, the extrinsic pathway initiates the clot process. Sustained generation of thrombin and clot formation depend on the intrinsic pathway through activation of factor IX by activated factor VII, which helps explain the bleeding problems associated with hemophilia.3 Intrinsic, extrinsic, and common pathways function normally for hemostasis to occur, and each may be evaluated with laboratory tests. The clinically important groups of coagulation factors are as follows:

Thrombin-sensitive factors contributing to the metabolic response and local vasoconstriction: I, V, VIII, XIII
Vitamin K-sensitive factors: II, VII, IX, X
Sites of heparin activity: IIa, IXa, Xa (major site), XIa, platelet factor 3
Thrombin-sensitive factors are activated by thrombin and may give rise to a bleeding disorder if defective synthesis occurs. Vitamin K–sensitive factors may also cause bleeding from defective synthesis, as occurs with liver disease and warfarin anticoagulants. Heparin in combination with antithrombin III affects the coagulation pathway at multiple sites.

Coagulation Control

All the components of the coagulation reaction are necessary to prevent excessive bleeding. Hemostasis is a balance between the
excessive bleeding state and thrombosis. Once coagulation is initiated, controls are necessary to prevent local or generalized thrombosis. These controls include the following: Removal and dilution of activated clotting factors through blood flow, which also mechanically opposes growth of the hemostatic plug Modulation of platelet activity by endothelium-generated nitric oxide and prostacyclin

Adhesion to subendothelial connective tissue: collagen, basement membrane, and noncollagenous microfibrils; serum factor VIII (von Willebrand’s) permits this function; adhesion creates the initial bleeding arrest plug Release of adenosine diphosphate, the primary mediator and amplifier of aggregation; release of thromboxane A, another aggregator and potent vasoconstrictor; release of calcium, serotonin, epinephrine, and trace thrombin Platelet aggregation over the area of endothelial injury Stabilization of the hemostatic plug by interaction with the coagulation system: Platelet factor 3, a phospholipid that helps accelerate certain steps in the coagulation system Platelet factor 4, a protein that neutralizes heparin Pathway initiation and acceleration by thrombin production Possible secretion of active forms of coagulation proteins Stimulation of limiting reactions of platelet activity

Removal of activated coagulation components by the reticuloendothelial system Regulation of the clotting cascade by antithrombin III, protein C, protein S, and tissue factor pathway inhibitor Activation of the fibrinolytic system

**CLINICAL FEATURES**

**Out-of-Hospital Treatment**

The out-of-hospital treatment of bleeding problems presents no special concerns. Local pressure and volume repletion are the...
Clinical Evaluation of a Bleeding Patient

Box 122-3

<table>
<thead>
<tr>
<th>History</th>
<th>Physical Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nature of bleeding</td>
<td>Vital signs</td>
</tr>
<tr>
<td>Petechiae</td>
<td>Skin: nature of bleeding, signs of liver disease</td>
</tr>
<tr>
<td>Purpura</td>
<td>Mucosa: oral or nasal</td>
</tr>
<tr>
<td>Ecchymosis</td>
<td>Lymphadenopathy</td>
</tr>
<tr>
<td>Significant bleeding episodes</td>
<td>Abdomen: liver size and shape, splenomegaly</td>
</tr>
<tr>
<td>Sites of bleeding</td>
<td>Joints: signs of previous bleeding</td>
</tr>
<tr>
<td>Skin</td>
<td>Other sites of blood loss: pelvic, rectal, urinary tract</td>
</tr>
<tr>
<td>Mucosa: oral or nasal</td>
<td></td>
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<tr>
<td>Muscle</td>
<td></td>
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<tr>
<td>Gastrointestinal</td>
<td></td>
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<tr>
<td>Genitourinary</td>
<td></td>
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<td>Joints</td>
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<td>Patterns of bleeding</td>
<td></td>
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<tr>
<td>Recent onset or lifelong</td>
<td></td>
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<tr>
<td>Frequency and severity</td>
<td></td>
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<tr>
<td>Spontaneous or after injury</td>
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<td>Challenges to hemostasis</td>
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<td>Tooth extraction</td>
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<tr>
<td>Operative procedures</td>
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<tr>
<td>Association with medication, particularly aspirin</td>
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<tr>
<td>Medications</td>
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<tr>
<td>Associated diseases</td>
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<td>Uremia</td>
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<tr>
<td>Liver disease</td>
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<tr>
<td>Infection</td>
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<tr>
<td>Malignant neoplasm</td>
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<tr>
<td>Previous transfusion</td>
<td></td>
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<tr>
<td>Family history</td>
<td></td>
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</tbody>
</table>

Ancillary Evaluation

A definitive diagnosis depends on laboratory evaluation. Tests pertinent to the ED are discussed in the following sections and listed in Box 122-4.

Coagulation Studies

Box 122-4

| Complete blood count and smear (EDTA—purple top) |
| Platelet count (EDTA—purple top) |
| Bleeding time |
| Prothrombin time (citrate—blue top) |
| Partial thromboplastin time (citrate—blue top) |
| Other coagulation studies: fibrinogen level, thrombin time, clot solubility, factor levels, inhibitor screens |
| As necessary: electrolyte values; glucose, BUN, and creatinine concentrations; type and crossmatch |

BUN, blood urea nitrogen; EDTA, ethylenediaminetetraacetic acid.

Complete Blood Count and Blood Smear

The complete blood count assesses the degree of anemia associated with the bleeding episode. Reductions in hemoglobin and hematocrit often lag behind the actual loss of red blood cells (RBCs) in acute hemorrhage because of a slow equilibration time. The peripheral blood smear may demonstrate schistocytes or fragmented RBCs in disseminated intravascular coagulation (DIC). Teardrop-shaped or nucleated RBCs may reflect myelophthisic disease. A characteristic white blood cell morphologic condition is seen with thrombocytopenia associated with infectious mononucleosis, folate or vitamin B12 deficiency, or leukemia.

Platelet Count

The platelet count may be estimated from the smear. Normally, one platelet is present per 10 to 20 RBCs. Often, the count is automated, the normal range being 150,000 to 400,000/mm³. Platelet counts less than 100,000/mm³ define thrombocytopenia. With normal platelet function, the bleeding time increases in direct relation to a decrease in the platelet count below 100,000/mm³. Levels below 20,000/mm³ may be associated with serious spontaneous hemorrhage. However, the count gives no information about the functional capability of platelets.

Bleeding Time

Bleeding time is the best test to determine both vascular integrity and platelet function that can be performed in the ED. The test is performed after two standard incisions, 1 mm deep and 1 cm long, are made on the volar aspect of the forearm under 40 mm Hg pressure by a blood pressure cuff with use of a template to ensure appropriate incisions. The time is measured from the incision to the moment when the blood oozing from the wound is no longer absorbed by filter paper. Some institutions have replaced the traditional bleeding time with a platelet function analyzer instrument, which is just as accurate and more convenient. A normal time is 8 minutes, a time of 8 to 10 minutes is borderline, and a time longer than 10 minutes is typically abnormal. Because of the high incidence of drug-induced platelet dysfunction, ask the patient about medications, particularly aspirin and other antiplatelet medications (e.g., clopidogrel). Platelet function testing is independent of the coagulation pathways. As mentioned previously, the bleeding time is prolonged with platelet counts below 100,000/mm³, but such prolongation does not represent platelet dysfunction. However, a prolonged bleeding time associated with platelet counts above 100,000/mm³ suggests impaired function.

Prothrombin Time

The prothrombin time (PT) tests the factors of the extrinsic and common pathways. The patient’s anticoagulated plasma is
combined with calcium and tissue factor prepared from rabbit or human brain tissue. Sensitivity to factor deficiencies depends on the source of the tissue factor. The PT detects deficiencies in fibrinogen, prothrombin (factor II), factor V, factor VII, and factor X. It is used to test the extrinsic pathway. A normal control sample is simultaneously run, and the clotting times of both are recorded. The time in seconds is usually given over the normal control time, for example, 12.5/11.5. A PT of 2 seconds or more above the control time is considered significant. Results are usually reported as the international normalized ratio (INR), which compensates for differences in sensitivity of various thromboplastin reagents to the effects of warfarin. The test is helpful in monitoring the use of coumarin anticoagulants, and the time may be prolonged in patients with liver disease and other abnormalities of vitamin K–sensitive factors.

Partial Thromboplastin Time

The partial thromboplastin time (PTT) tests the components of the intrinsic and common pathways, that is, essentially all factors but VII and XIII in the entire clotting cascade. In this test, a phospholipid source and a contact-activating agent (kaolin) are added to anticoagulated citrate plasma. After an incubation period that allows factor XII to become activated, calcium is added and the clotting time is recorded. A normal control sample is run simultaneously. Normal ranges may vary, and each hospital laboratory should be checked. The average time is 25 to 29 seconds. The sensitivity of the test varies from factor to factor, but factor levels usually are less than 40% before the PTT is prolonged. The test may be altered by clotting factor inhibitors of external origin (e.g., heparin) or internal origin (e.g., anti-VIII antibody). Inappropriately high values may occur if the plasma is too turbid or icteric. The activated PTT is most sensitive to abnormalities in the sequence of the coagulation cascade that precedes activation of factor X.

Fibrinogen

Fibrinogen is present in sufficient concentration to be measured directly. Because it is the final coagulation substrate, its level reflects the balance between production and consumption. It may be decreased by low production, as in severe liver disease, or by overconsumption, as in DIC. Low levels and altered function increase the PT, PTT, and thrombin clotting time. Because fibrinogen is an acute-phase reactant, certain conditions, including malignant disease, sepsis, inflammation, and pregnancy, may alter the test result.

Thrombin Time

Measurement of the thrombin clotting time bypasses the intrinsic and extrinsic pathways by directly converting fibrinogen to fibrin. It is a useful screening test for both qualitative and quantitative abnormalities of fibrinogen and inhibitors such as heparin and fibrin split products.

Clot Solubility

The result of clot solubility testing may be the only abnormality in disorders involving factor XIII deficiency and some abnormal fibrinogen. A washed clot is incubated in acetic acid or urea. If the clot is not properly cross-linked, it dissolves.

Factor Level Assays

Factor levels are determined either by bioassay, in which the ability of the sample of plasma to normalize controlled substrate-deficient plasma is evaluated, or by immunologic assay. Inhibitor screening tests reveal antibodies in plasma that prolong the normal plasma clotting time when mixed.

**DIFFERENTIAL DIAGNOSIS AND MANAGEMENT**

When a bleeding disorder is diagnosed or suggested, the assessment initially includes stabilization, which may necessitate volume, RBC, and coagulation factor replacement. If the disorder is known, clinical complications associated with its underlying pathophysiologic condition needs to be considered. If the disorder is unknown, a rapid differential diagnosis must be made. A clinically useful scheme approaches bleeding disorders in terms of three constituents: vascular integrity, platelets, and coagulation factors. This differential diagnostic approach can be further divided into inherited and acquired disorders.

**Vascular Disorders**

Vascular disorders have signs and symptoms similar to those of thrombocytopenic states. The inherited forms are rare. Acquired forms are usually associated with connective tissue changes or endothelial damage. The differential diagnosis of vascular disorders is listed in Box 122-5.

**Platelet Disorders**

**General Approach**

Platelet abnormalities can be caused by congenital disorders, but most are from acquired conditions. The bleeding source is usually capillary, with resultant cutaneous and mucosal petechiae or ecchymosis. Epistaxis, menorrhagia, and gastrointestinal bleeding are common initial symptoms. The bleeding is generally mild and occurs immediately after surgery or dental extractions. Petechiae and purpura may be noted on physical examination, and superficial ecchymoses may be found around a venipuncture site. The purpura associated with platelet disorders is typically asymptomatic and not palpable. This is in contrast to purpura associated with vasculitis, which can burn or itch and is palpable. Deep muscle hematomas and hemorrhages are not aspects of the clinical picture. The bleeding time is prolonged, and the platelet count may be low, normal, or high. The differential diagnosis of platelet disorders is listed in Box 122-6.
Thrombocytopenia

Decreased Production. Thrombocytopenia from decreased bone marrow production is usually caused by the effects of chemotherapeutic drugs, myelophthisic disease, or direct bone marrow effects of agents such as alcohol or thiazides.

Splenectomy. Splenic sequestration is rare. It is seen primarily with hypersplenism resulting from hematologic malignant disease, portal hypertension, or disorders involving increased splenic RBC destruction, such as hereditary spherocytosis or autoimmune hemolytic anemia.

Increased Destruction

Immune Thrombocytopenia. Thrombocytopenia associated with increased peripheral destruction of platelets and shortened platelet survival caused by an antiplatelet antibody is seen in a number of diseases. In most cases a cause is identifiable.

Collagen vascular diseases, particularly systemic lupus erythematosus, may cause an antiplatelet antibody-related platelet decrease. Similar associations have been noted with leukemia and lymphoma, particularly lymphocytic lymphoma. All evaluations of suggested immune thrombocytopenia should include a complete blood count, peripheral smear, antinuclear antibody test, and bone marrow examination. A number of drugs have been associated with thrombocytopenia of immunologic origin. Quinine and quinidine are common offenders that affect platelets through an “innocent bystander” mechanism. The platelet is coated with a drug-antibody complex, complement is fixed, and intravascular platelet lysis occurs. Because of its relatively high frequency, heparin is an important cause of drug-induced thrombocytopenia in hospitalized patients. Platelets are activated by the formation of an immunoglobulin G (IgG)–heparin complex.

Low-molecular-weight heparin may be associated with less thrombocytopenia than standard, unfractionated heparin is; however, both forms of heparin demonstrate cross-reactivity.

Heparin-induced thrombocytopenia (HIT) is a serious immune-mediated side effect associated with heparin. A meta-analysis including 7287 patients determined the incidence of HIT to be 2.6% for unfractionated heparin and 0.2% for low-molecular-weight heparin. It usually occurs 5 to 7 days after the initiation of heparin treatment. Thrombus develops in approximately half the patients with HIT. The thrombotic complications can lead to loss of a limb in up to 20% and death in as many as 30%. The diagnosis is suggested in the presence of absolute thrombocytopenia or a greater than 50% reduction in platelets after the initiation of heparin. The most specific diagnostic tests for HIT are serotonin release assays, heparin-induced platelet aggregation assays, and solid-phase immunoassays. Platelet-associated IgG levels are commonly elevated, but this finding is less specific or sensitive than the other diagnostic tests. More concerning to the emergency physician is delayed-onset HIT. This form of HIT occurs a median of 14 days after the initiation of heparin, but it has been reported to occur up to 40 days after heparin is started. Arterial or venous thrombosis typically develops in patients with HIT after they receive heparin. The administration of heparin can result in the development of antibodies to the heparin and platelet factor 4 complex. The heparin–platelet factor 4–antibody complex is removed from the circulation, resulting in thrombocytopenia; however, this complex also results in the generation of microparticles that have procoagulant properties, which can lead to thrombus formation. Treatment of thrombotic complications in these patients involves the use of direct thrombin inhibitors (lepirudin, argatroban), factor Xa inhibitors (fondaparinux), or heparinoids (danaparoid).

Digitoxin, sulfonamides, phenytoin, and aspirin are other drugs that may be associated with a thrombocytopenia. The patient has usually ingested the medication within 24 hours. An idiopathic thrombocytopenic purpura type of syndrome has been reported in intravenous cocaine users. Clinical trials with platelet glycoprotein IIb/IIIa antagonists suggest that intravenous glycoprotein IIb/IIIa inhibitors may confer an increased risk for associated thrombocytopenia, independent of heparin therapy. The platelet count may fall below 10,000/mm³ and be complicated by serious bleeding. Laboratory testing may confirm the presence of antibody, especially with the use of quinine and quinidine. After administration of the drug is stopped, the platelet count improves slowly during a period of 3 to 7 days. A short course of corticosteroid therapy, such as prednisone in a dose of 1 mg/kg with rapid tapering, may facilitate recovery.

Postinfectious immune thrombocytopenia is usually associated with viral diseases such as rubella, rubeloa, and varicella. Although many cases associated with sepsis have a mechanical origin, some immune mechanisms have been demonstrated.

Post-transfusion thrombocytopenia is a rare disorder that causes a precipitous fall in platelets approximately 1 week after the transfusion. In 90% of cases, its origin is linked to the 98% of the population carrying a PLA1 antigen on platelets. Despite the fact that 2% of blood recipients are mismatched with respect to this antigen, it is fortunately a rare occurrence. On transfusion into a PLA1–negative patient, the platelets with attached PLA1 antibodies provoke an anamnestic response, but the actual mechanism of platelet destruction remains unknown. The platelet count often falls precipitously below 10,000/mm³, with a significant risk for major bleeding. Intracranial hemorrhage occurs in approximately 10% of such cases. Patients are usually middle-aged women with a history of pregnancy who may have been previously pregnant recently.
sensitized to the PLA1 antigen during pregnancy. Plasma exchange therapy is an effective intervention.\textsuperscript{12,13}

\textit{Idiopathic Thrombocytopenic Purpura.} Autoimmune idiopathic thrombocytopenic purpura (ITP) is considered after other causes of thrombocytopenia have been excluded. ITP is associated with an IgG antiplatelet antibody that has proved difficult to detect. The two clinically important forms are acute and chronic.\textsuperscript{15}

The acute form of ITP is seen most often in children 2 to 6 years of age. A viral prodrome commonly occurs within 3 weeks of its onset. The platelet count decreases, usually to less than 20,000/mm\textsuperscript{3}. The course is self-limited, with a greater than 90% rate of spontaneous remission. Morbidity and mortality rates are low, although full recovery may take several weeks. Treatment of acute ITP is supportive. Steroids and intravenous immune globulin therapy are reserved for patients with active bleeding.\textsuperscript{13}

The chronic form of ITP is primarily an adult disease found three times more often in women than in men. The onset of chronic ITP is insidious, without a prodrome, and it is manifested as easy bruising, prolonged menses, and mucosal bleeding. The patient may have petechiae or purpura, and platelet counts between 30,000/mm\textsuperscript{3} and 100,000/mm\textsuperscript{3} are common. Bleeding complications are of unpredictable frequency and severity, although the long-term mortality rate is approximately 1%.\textsuperscript{16} Spleenomegaly is unusual in either acute or chronic ITP.

Associated diseases, such as lymphoma and systemic lupus erythematosus, needs to be ruled out before the diagnosis of ITP can be made. Quantitative laboratory tests of antiplatelet antibody may differentiate between patients who will favorably respond to therapy and those who will not. Hospitalization is recommended during the initial evaluation because the differential diagnosis is complex and the risk of bleeding is significant. Management includes stopping of all nonessential drugs, particularly those that inhibit platelet function (e.g., aspirin). The initial treatment of chronic ITP is typically corticosteroids (prednisone 1 mg/kg per day). Intravenous immune globulin and anti-D immunoglobulin, in conjunction with steroids, have also been used as first-line therapy. However, these therapies are best used after consultation with a hematologist. Splenectomy, monoclonal antibody therapy, and immunosuppressives are considered in steroid-failure cases.\textsuperscript{13}

A thrombopoietin-receptor agonist, eltrombopag, has recently been shown in a well-designed trial to increase platelet counts in a patient with a hematologist. Splenectomy, monoclonal antibody therapy, and immunosuppressives are considered in steroid-failure cases.\textsuperscript{13}

A thrombopoietin-receptor agonist, eltrombopag, has recently been shown in a well-designed trial to increase platelet counts.\textsuperscript{12,13}

The representative adhesion disorder is von Willebrand’s disease, which is a factor VIII problem more than a platelet dysfunction. Platelets are normal in terms of their morphologic condition, number, release, and aggregation. The factor VIII component (vWF) that permits platelet adhesion.\textsuperscript{23}

Release Defects. Release defects include “storage pool” syndromes in which release is normal but amounts of adenosine deposits of fibrin and platelet aggregates in capillaries and arterioles. Hemolytic-uremic syndrome is considered to be similar to TTP; however, hemolytic-uremic syndrome is associated with less central nervous system and more renal involvement than TTP. Although the initiating event is unclear, prostacyclin and abnormal platelet aggregation are believed to play a central role in pathogenesis of the disease. The disease may affect patients of any age or sex, but the majority are 10 to 40 years of age, and 60% of cases occur in women. Most cases of TTP are idiopathic. However, TTP can be associated with medications. Quinine is the most common drug associated with the disease. The antiplatelet drugs ticlopidine and clopidogrel, which are used to treat a variety of cardiovascular and cerebrovascular disorders, have also been associated with TTP. It is classically seen as the constellation of thrombocytopenic purpura, microangiopathic hemolytic anemia, fluctuating neurologic symptoms, renal disease, and fever.

The platelet count in TTP ranges from 10,000/mm\textsuperscript{3} to 50,000/mm\textsuperscript{3}, and generalized purpura and bleeding complaints are common. Anemia is universal, and hematocrit levels are commonly less than 20%. The hemolysis may cause jaundice or pallor, and the blood smear characteristically contains numerous schistocytes and fragmented RBCs. Neurologic symptoms include stroke, seizures, paresthesias, altered levels of consciousness, and coma, all of which characteristically fluctuate in severity. The renal component varies from hematuria and proteinuria to acute renal failure. Fever is present in 90% of patients.

Before the availability of plasma exchange, TTP followed a progressive and fatal course, with 90% mortality rate 1 to 3 months after diagnosis. Therapy has included corticosteroids, splenectomy, anticoagulation, exchange transfusion, and dextran. However, plasma exchange with fresh frozen plasma (plasmapheresis) is the current treatment of choice and has reduced the mortality to below 20%.\textsuperscript{21} In addition to plasma exchange, initial therapy may also include steroids, such as prednisone, and antiplatelet agents, such as aspirin and dipyridamole. If TTP is suspected in the ED, a hematologist should be consulted before any therapy is initiated. With the exception of life-threatening bleeding, platelet transfusion is avoided because platelets may cause additional thrombi in the microcirculation.\textsuperscript{21,22}

\textit{Dilutional Thrombocytopenia.} Dilutional thrombocytopenia occurs in cases of massive transfusion, exchange transfusion, or extracorporeal circulation. Volume replacement with stored bank blood is platelet poor because platelets have a life span of only 9 days. The number of transfusions directly correlates with the degree of thrombocytopenia. Current transfusion practice is to monitor platelet counts for every 10 units of RBCs and to transfuse once the platelet count approaches 50,000/mm\textsuperscript{3}.\textsuperscript{23,24}

\textbf{Thrombocytopenia}

Knowledge of abnormal platelet function as a clinical disorder has grown rapidly in recent years. The drug-induced form may be one of the most commonly seen causes of abnormal bleeding.\textsuperscript{15} Defects may occur at any level of platelet function, including adhesion, release, and aggregation.

\textit{Adhesion Defects.} The representative adhesion disorder is von Willebrand’s disease, which is a factor VIII problem more than a platelet deficiency. Platelets are normal in terms of their morphologic condition, number, release, and aggregation. The abnormal adhesion results not from the platelet but from an endothelium-based plasma deficiency of a factor VIII component (vWF) that permits platelet adhesion.\textsuperscript{23}

\textit{Release Defects.} Release defects include “storage pool” syndromes in which release is normal but amounts of adenosine
diphosphate, calcium, and serotonin are decreased. Release defects may be congenital or acquired, as in systemic lupus erythematosus, alcoholism, or lymphoma. Drugs induce the most common release problem. Aspirin and related drugs block the enzyme cyclooxygenase, which participates in thromboxane A₂ formation. Decreased release of thromboxane A₂ results in decreased aggregation and less local vasoconstriction. Both may contribute to an increased risk of bleeding. Testing for this risk has been suggested by development of the post-aspirin bleeding time as a screening test for hemostatic disorders. Aspirin is unique in that it permanently poisons this reaction for the life of the platelet in doses of only 300 to 600 mg. Phenylbutazone and indomethacin affect function only while they are present in the circulation. A similar problem may occur in patients with uremia or dysproteinemia and as a rare inherited form.

**Aggregation Defects.** Primary aggregation defects are associated with the rare recessive trait thrombasthenia. This platelet membrane abnormality may be detected by the lack of clot retraction during a 2-hour clot retraction test.

**Platelet Transfusions.** Most platelet function disorders are not treated by platelet transfusion because its efficacy is questionable and alloimmunization may occur. Platelet transfusions are commonly indicated for primary bone marrow disorders (e.g., aplastic anemia or acute leukemia). Assessment of the risk for spontaneous bleeding by platelet counts is an imprecise science. Less mature platelets associated with peripheral consumption or sequestration are less likely to allow spontaneous hemorrhage than those associated with primary bone marrow involvement. An estimate of functionality is combined with the platelet count for a better predictor of primary hemostasis potential. At counts below 40,000 to 50,000/mm³, a variable degree of risk exists, especially that associated with trauma, ulcers, or invasive procedures. At counts higher than 50,000/mm³, hemorrhage caused by platelet deficiency is unlikely. Spontaneous bleeding in the absence of surgery, trauma, or other risk factors may occur in patients with platelet counts below 5000 to 10,000/mm³, and prophylactic platelet infusions should be reserved for this level of thrombocytopenia.²⁶

**Thrombocytosis**

Thrombocytosis is a platelet count higher than 600,000/mm³; Box 122-6 presents the list of potential causes. It is often caused by infection or iron deficiency, in which case it is not generally associated with complications related to the platelet count.²⁷ The primary or autonomous state may be associated with bleeding or thrombosis. It is often an associated finding in patients with polycythemia vera, myelofibrosis, or chronic myelogenous leukemia. Suggested autonomous thrombocytosis requires a full hematologic evaluation.

**Disorders of the Coagulation Pathway**

The coagulation system accomplishes secondary hemostasis through a complex enzymatic cascade. The clinically significant disorders have a number of characteristic features that help differentiate them from platelet disorders, including the following: The bleeding source is often an intramuscular or deep soft tissue hematoma from small arterioles. The congenital form of the disease occurs predominantly in men, often as a sex-linked inheritance. Bleeding may occur after surgery or trauma but is delayed in onset up to 72 hours. Epistaxis, menorrhagia, and gastrointestinal sources of bleeding are rare, whereas hematuria and hemarthrosis are common in severe cases. The bleeding time is normal except in patients with von Willebrand’s disease.

The PT and PTT are the basic laboratory diagnostic tools for the evaluation of coagulation disorders and can be used to organize the approach to their diagnosis.

**Abnormal Prothrombin Time and Other Test Results Normal**

An elevated PT reflects an extrinsic pathway abnormality mediated through deficiency of factor VII. The hereditary form is caused by a rare autosomal recessive gene. The acquired form is commonly seen and may be a result of vitamin K deficiency, warfarin use, or liver disease. Because factor VII has the shortest half-life (3-5 hours) of the coagulation factors, it is the first to manifest a deficiency when its active form is underproduced. The PT is a sensitive gauge of hepatic function and the efficacy of warfarin administration. INRs calculate the prothrombin ratio raised to the power of an international sensitivity index for specific thromboplatin reagents. It is recommended with most warfarin therapy that the INR be maintained between 2.0 and 3.0, except in the setting of cardiac valvular disease, in which the target INR is 2.5 to 3.5.

**Abnormal Partial Thromboplastin Time and Other Test Results Normal**

Two groups of inherited disorders manifest an isolated elevation in the PTT. The first group consists of the contact factors (e.g., XII [Hageman factor]), prekallikrein (Fletcher factor), and high-molecular-weight kininogen. They cause a benign disorder in which the PTT is elevated but the patient has no bleeding diathesis. These deficiencies exist as isolated laboratory abnormalities, and thus they should not be invoked as a cause of the patient’s bleeding problem. They may be specifically assayed when a precise diagnosis is necessary.

The second group causes significant bleeding problems resulting from deficiencies of factors within the intrinsic coagulation system. They are the most common inherited abnormalities of the entire clotting system. Deficiencies of factors VIII, IX, and XI account for 99% of inherited bleeding disorders. Patients with active life-threatening bleeding who are thought to have a congenital bleeding disorder can be supported with fresh frozen plasma, 15 mL/kg, while diagnostic studies are being performed. The risk of transmission of hepatitis B or C virus or human immunodeficiency virus (HIV) should be considered.

In a patient with a prolonged PTT and a lifelong history of bleeding, the most important test is assay of factor VIII and factor IX. This test measures the ability of the patient’s plasma to correct the prolonged PTT of plasma deficient in factor VIII. This ability is compared with that of normal plasma, and the result is given as a percentage of normal. The test measures the procoagulant activity of factor VIII but does not discriminate between abnormal activity resulting from abnormal factor VIII and low levels of normal factor VIII. The two forms of this deficiency are hemophilia A and von Willebrand’s disease.

**Hemophilia A.** Hemophilia A is caused by a variant form of factor VIII that is present in normal levels but lacks a clot-promoting property. The incidence is 60 to 80 persons per million population. Of known cases, 70% have been found to have a sex-linked recessive nature; that is, the disease is carried on the X chromosome at location Xq28. Factor VIII circulates in plasma in very low concentration and is normally bound to vWF. The source of factor VIII production is uncertain, but the liver is thought to be a significant source because hemophilia A can be corrected by liver transplantation. A female carrier mating with a normal man is predicted to pass the disease to half her sons. Likewise, a male hemophilic would have all normal sons and all carrier daughters. The remaining 25 to 30% of cases of the disease are believed to
result from a spontaneous genetic abnormality. The familial form has a remarkable consistency of severity from generation to generation, although the degree of severity has considerable variation. This severity may be directly related to the level of factor VIII coagulant (factor VIII:C) activity. Cases with less than 1% activity are severe, with a tendency toward spontaneous bleeding. Cases with 1 to 5% activity are moderate, with rare spontaneous bleeding but increased problems with surgery or trauma. Cases with 5 to 10% activity and above are considered mild, with little risk of spontaneous bleeding but still with hazards after trauma and surgery. A number of hemophiliacs may have activity above 10% but have few problems under normal conditions. The PTT may lack sensitivity for this group because it is significantly prolonged only at factor VIII:C levels less than 35 to 40%.28,29

The disease is seen as a disorder of secondary hemostasis with a characteristic pattern of bleeding. Bleeding can occur anywhere, but deep muscles, joints, the urinary tract, and intracranial sites are the most common. Recurrent hemarthrosis and progressive joint destruction are major causes of morbidity in hemophilia. Intracranial bleeding is the major cause of death in all age groups of hemophiliacs. Mucosal bleeding, such as epistaxis and oral bleeding, or menorrhagia is rare unless the disease is associated with von Willebrand’s disease or platelet inhibition, such as with aspirin use. Gastrointestinal bleeding is rare unless peptic ulcer disease is also present. Trauma is a common initiator of bleeding in all stages of severity. This potential hazard should be viewed expectantly in all hemophiliacs because late bleeding may occur, usually by 8 hours but potentially up to 1 to 5 days and, rarely, even longer after traumatic injury.30,31

Management of Hemophilia A. Comprehensive management of hemophilia involves a team effort of physicians, specialized nurses, physical therapists, social workers, the patient, and the patient’s family. The therapeutic responsibility of the emergency physician consists of three areas: preparation for and identification of the problem, initial evaluation, and admission of new bleeders; replacement therapy for bleeding episodes; and anticipation of potential life threats and admission of known bleeders for observation in selected circumstances. At one time, treatment of hemophilia-associated bleeding was a relatively common emergency medicine activity, but since 1975, hemophilia home therapy has increasingly been instituted. Therefore, many hemophiliacs now come to the ED only with complicated problems or trauma-related difficulties, and most are knowledgeable about their disease.

Preparation. ED management of patients with hemophilia is best accomplished with advanced planning that includes protocols developed with a hematologist for ordering and administration of factor VIII and maintenance of a file of known hemophiliacs in the area who are monitored at the hospital. The file should include the primary physician, diagnosis, factor VIII activity level, blood type, presence of anti-hemophilic factor antibodies, and time of last hospitalization.

Replacement Therapy. The accepted therapy for hemophilia A is factor VIII replacement with cryoprecipitate or factor VIII:C concentrates. These concentrates are exposed to heat treatment or solvent-detergent mixtures to decrease transmission of hepatitis B virus, hepatitis C virus, and HIV. In the past, the concentrate was made from fractionated freeze-dried antihemophilic factor and contained 250 to 1500 IU of factor VIII:C in a reconstituted volume. Factor VIII is also produced by recombinant DNA techniques and is considered to be the replacement product of choice.32,33 Recombinant-derived factor VIII is comparable to plasma-derived factor VIII in terms of characteristics and control of bleeding, but it has no discernible side effects. Factor VIII:C concentrates are commonly used in severe hemophilia and for home therapy. Cryoprecipitate is the cold precipitable protein fraction derived from fresh frozen plasma thawed at 1 to 6°C. It was once the mainstay of hemophilia A therapy and may be used when noninfected factor VIII concentrates are not available.34

Before 1985, plasma-derived replacement therapies posed risk for transmission of hepatitis C virus, hepatitis B virus, and HIV. However, with the current methods of donor screening, antiviral techniques, and safety testing and with the availability of recombinant clotting factors, the risk of viral transmission is extremely low.35

Therapy for a bleeding episode includes a number of considerations: the circumstances in which factor VIII is given, the dosage, the timing of maintenance, the duration of the dosage, the presence of antibodies, and the means of gauging effectiveness. As a general rule, 1 U/kg of factor VIII will increase the circulating factor VIII level by 2%. The dose of factor VIII needed is the desired percentage increase in factor VIII activity × 0.5 × the weight in kilograms. The typical percentage factor VIII activity goals are 25 to 40% for minor bleeding or trauma, greater than 50% for moderate bleeding, and 80 to 100% for serious, life-threatening bleeding or trauma.35 Tables 122-1 and 122-2 include guidelines for the recommended treatment in a variety of circumstances. Most important, the emergency physician should believe patients who say that they are bleeding and institute early therapy.

The response to therapy can be monitored by clinical improvement, a decreasing PTT, and, optimally, serial factor VIII:C activity levels. The lack of a response to factor VIII administration should raise the possibility of circulating antibodies. All hemophiliacs should be screened for the development of these antihemophilic factor antibodies when they are given in-hospital therapy or if their condition becomes refractory to home therapy. The 7 to 20% of patients in whom these IgG antibodies develop usually have a severe deficiency necessitating multiple factor VIII transfusions. The treatment may be complex, and hospitalization is necessary. A variety of therapies have been considered, including “overwhelming” factor VIII doses, exchange plasmapheresis, immunosuppressive therapy, and the infusion of prothrombin complexes containing activated clotting factors. Other recommended therapies include porcine factor VIII, which has less cross-reactivity with the human product, and recombinant activated factor VIIa.36,37 Recombinant factor VIIa used in hemophilia complicated by alloantibody inhibitors has been shown to stop bleeding in 93% of cases.38 Serious or intractable bleeding may be improved in some nonhemophiliac patients with the use of recombinant factor VIIa. However, no improvement in survival has been proved, and the incidence of thromboembolism may be increased.39 Until more data are available, the role of recombinant factor VIIa in settings outside of congenital coagulation disorders remains to be determined. Acquired IgG antihemophilic factor antibodies may exist in nonhemophiliac patients. They can occur in the postpartum period; as immunologic reactions to penicillin or phenytoin; and in association with systemic lupus erythematosus, rheumatoid arthritis, or inflammatory bowel disease. The diagnosis is made by the occurrence of an acquired hemophilia-like syndrome with positive antibody titers in the appropriate setting.

Desmopressin acetate has been shown to increase levels of factors VIII:C and VIII:Ag in patients with hemophilia A and in some with von Willebrand’s disease. It is given intravenously at 0.3 μg/kg per dose. Benefits are primarily noted in patients with mild to moderate disease, and the effects of a single dose last for 4 to 6 hours.40 Use of desmopressin in the ED is probably best reserved for patients who have been successfully treated with it in the past.

Prophylaxis. The anticipation of delayed bleeding in patients with hemophilia may necessitate admission and observation for a variety of trauma-related injuries. Candidates for prophylactic admission are patients with deep lacerations; those with soft tissue injuries in areas where the pressure from a developing hematoma could be destructive, such as in the eye, mouth, neck, back, and
spinal column; and patients with a history of major trauma forces without injury. Head trauma is potentially life-threatening to hemophiliacs, and central nervous system bleeding is the major cause of death for patients in all age groups. Studies find a 3 to 13% risk of intracranial hemorrhage; in a prospectively studied cohort of 37 patients with severe disease who sustained head trauma, no patient given replacement therapy within 6 hours had intracranial bleeding. It is recommended that patients who sustain head trauma but who have normal computed tomography scans have factor VIII therapy initiated to greater than 50% activity level. All hemophiliacs with head trauma should be considered for admission with early hematology consultation.

Gene therapy represents a potential development in the treatment of hemophilia. With cloning of the genes encoding factor VIII, the possibility exists for either a partial or complete cure of hemophilia. The goal of gene therapy is not to restore factor levels to normal but rather to convert from a severe to a mild phenotype.

Table 122-1 Recommended Factor VIII Therapy for Specific Problems in Hemophilia

<table>
<thead>
<tr>
<th>TYPE OF BLEEDING</th>
<th>INITIAL DOSAGE</th>
<th>DURATION</th>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abrasion</td>
<td>Usually none; if necessary, treat as minor</td>
<td>None</td>
<td>Treat with local pressure and topical thrombin</td>
</tr>
<tr>
<td>Laceration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial</td>
<td>Minor bleeding (25 mg/kg)</td>
<td>Single-dose coverage</td>
<td>May need hospitalization for observation; repeated dose may be necessary for suture removal</td>
</tr>
<tr>
<td>Deep</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal epistaxis</td>
<td>Usually none; may need to be treated as mild bleeding</td>
<td>None</td>
<td>Uncommon; consider platelet inhibition; treat in usual manner</td>
</tr>
<tr>
<td>Spontaneous</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Traumatic</td>
<td>Moderate bleeding (25 mg/kg)</td>
<td>Up to 5-7 days</td>
<td>Trauma-related bleeding can be significant</td>
</tr>
<tr>
<td>Oral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucosa or tongue bites</td>
<td>Usually none; treat as minor if persists</td>
<td>Single dose</td>
<td>Commonly seen</td>
</tr>
<tr>
<td>Traumatic (laceration) or dental extraction</td>
<td>Moderate (25 U/kg) to severe (50 U/kg)</td>
<td>Single dose; may need more</td>
<td>Saliva rich in fibrinolytic activity; oral ε-aminocaproic acid (Amicar) may be given at 100 mg every 6 hr for 7 days to block fibrinolysis; check contraindications; hospitalize patients with severe bleeding</td>
</tr>
<tr>
<td>Soft tissue or muscle hematomas</td>
<td>Moderate (25 U/kg) to severe (50 U/kg)</td>
<td>2-5 days</td>
<td>May be complicated by local pressure on nerves or vessels (e.g., iliopsoas, forearm, calf)</td>
</tr>
<tr>
<td>Hemarthrosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td>Mild (25 mg/kg)</td>
<td>Single dose</td>
<td>Treat at earliest symptom (pain); knee, elbow, ankle more common</td>
</tr>
<tr>
<td>Late or unresponsive cases of early hemarthrosis</td>
<td>Mild to moderate (25 U/kg)</td>
<td>3-4 days</td>
<td>Arthrocentesis rarely necessary and only with 50% level coverage; immobilization is critical point of therapy</td>
</tr>
<tr>
<td>Hematuria</td>
<td>Mild (12.5 U/kg)</td>
<td>2-3 days</td>
<td>Urokinase, the fibrinolytic enzyme, is in urine; with persistent hematuria, an organic cause should be ruled out</td>
</tr>
<tr>
<td>Major or life-threatening bleeding</td>
<td>Major bleeding (50 U/kg)</td>
<td>7-10 days or 3-5 days after bleeding ceases</td>
<td>In head trauma, therapy should be given prophylactically; early computed tomography scan of head is recommended for all</td>
</tr>
</tbody>
</table>

Table 122-2 Dosage of Factor VIII (Antihemophilic Factor)

<table>
<thead>
<tr>
<th>BLEEDING RISK</th>
<th>DESIRED FACTOR VIII LEVEL (%)</th>
<th>INITIAL DOSE (U/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>5-10</td>
<td>12.5</td>
</tr>
<tr>
<td>Moderate</td>
<td>20-30</td>
<td>25</td>
</tr>
<tr>
<td>Severe</td>
<td>50 or greater</td>
<td>50</td>
</tr>
</tbody>
</table>

Standard Calculation
1. Patient’s plasma volume (50 mL/kg × weight in kg) × (desired level of factor VIII [percent]) – (present level of factor VIII [percent]) = number of units for initial dose.
2. In emergency therapy, the present level of factor VIII is assumed to be zero.
3. One unit is the activity of the coagulation factor present in 1 mL of normal human plasma.
4. Because the half-life of factor VIII is 8 to 12 hours, the desired level is maintained by giving half the initial dose every 8 to 12 hours.
5. Cryoprecipitate is assumed to have 80 to 100 U of factor VIII:C per bag; factor VIII:C concentrates list the units per bottle on the label.

von Willebrand’s Disease. To understand von Willebrand’s disease, it is helpful to review the nomenclature used to refer to factor VIII in some centers. Factor VIII has at least three activities. First is its antihemophilic, or coagulant, activity, VIII:C. All references to factor VIII in this chapter thus far have been to this activity. A second activity supports platelet adhesion and in vitro aggregation with the antibiotic ristocetin; it is called von Willebrand’s factor activity, or VIII/vWF. A third component reacts with rabbit antibodies to factor VIII; it is termed the factor VIII antigen, or VIII:Ag, and relates to the measured plasma level rather than to the activity of factor VIII. The antigen and cofactor activity for platelet function are structurally related. von Willebrand’s disease has both decreased factor VIII:Ag levels and decreased VIII:C activity secondary to underproduction. The patient’s platelets are normal in number, morphologic condition, and other functions, but in the absence of circulating factor VIII/vWF,
their adhering properties are diminished. von Willebrand’s disease is the most common hereditary bleeding disorder, with an estimated prevalence of 1%. The disease occurs in 5 to 10 persons per million population as an autosomal dominant trait with a variable penetrance pattern. A rare X-linked inheritance has been described.

Manifestations of von Willebrand’s disease are usually milder and less crippling than those of hemophilia. The factor VIII:C level is in the 6 to 50% range. Bleeding sites are predominately mucosal (e.g., epistaxis) and cutaneous. Hemarthroses are rare, but menorrhagia and gastrointestinal bleeding are common. Laboratory differentiation from hemophilia A includes abnormal bleeding time, decreased level of factor VIII:Ag, and abnormal platelet aggregation with ristocetin. In patients with severe disease, replacement therapy with factor VIII in the form of intermediate purity factor VIII concentrate is the method of choice. The initial dose is 25 to 50 IU/kg every 12 hours to keep vWF levels at 50% or to control bleeding. A unique response to the transfusion of plasma components in patients with von Willebrand’s disease is the stimulation of a progressive increase in VIII:C activity that lasts 12 to 40 hours. After the initial dose, fewer units are necessary, and longer dosage schedules may be followed by a clinical response and a combination of factor VIII:C activity and serial bleeding times. Cryoprecipitate is no longer recommended because of the risk of viral transmission.

In extreme circumstances without alternatives, fresh frozen plasma may be used. A factor VIII concentrate (Humate-P) has also demonstrated sufficient VIII:vWF to treat the disease. Drug therapy with desmopressin is of benefit in patients with mild to moderately severe von Willebrand’s disease. It is most useful in the common form of the disease and is ideally given in consultation with a hematologist.

Hemophilia B (Christmas Disease). Hemophilia B is a deficiency of factor IX activity. Its genetic pattern and clinical findings are indistinguishable from those of hemophilia A, but its incidence is only a fifth that of hemophilia A. Factor IX is a vitamin K–dependent glycoprotein. Its deficiency is diagnosed by a factor IX assay, usually after the factor VIII:C assay is found to be normal. The replacement schedule for factor IX is similar to that for hemophilia A, but a purified factor IX concentrate or recombinant factor IX preparation is used. The plasma prothrombin complex (factors II, VII, IX, and X) and fresh frozen plasma are also useful, but they pose a higher risk of viral transmission and venous or arterial thrombosis. The maintenance dosage schedule is increased to every 24 hours because of the longer half-life of factor IX. Clinical concerns and treatment strategies associated with hemophilia A also apply to hemophilia B.

Similar to hemophilia A, gene testing and counseling are available. Gene therapy in animals has demonstrated promising results, and preliminary results from a human study suggest that the severity of hemophilia B can be altered and improved by gene manipulation.

Miscellaneous Coagulation Disorders

A number of other disorders may be caused by a deficiency in the common coagulation pathway. An altered fibrinogen level or abnormal function is a relatively common cause. Patients with this deficiency also have an abnormal thrombin time. The inherited forms are rare. The acquired forms have been related to fibrin-blocking substances and hypofibrinogenemia, which are found most often in cases of DIC and dysfibrinogenemia associated with macroglobulinemia, multiple myeloma, and hepatitis. In the context of emergency medicine, fibrinogen’s most important role relates to its activity in DIC.

The other components of the common pathway (factors II, V, and X) have rare inherited deficiencies. The acquired forms are far more common and relate to vitamin K deficiency (decreased factor II, VII, IX, and X activity), warfarin use (same factors as with vitamin K deficiency), hepatic insufficiency (potentially all factors except VIII), and massive transfusion of stored blood (low in factors V and VIII and platelets).

Excessive anticoagulation from warfarin occurs from a number of causes, including interactions between warfarin and other drugs or foods and accompanying diseases that interfere with the absorption or metabolism of warfarin. Management of excessive anticoagulation from warfarin depends on the degree of elevation of the INR and if bleeding accompanies the excessive anticoagulated state. If the INR is below 5.0 and not accompanied with bleeding, treatment consists of withholding of additional warfarin. If the INR is between 5.0 and 9.0 without bleeding, in addition to withholding of additional warfarin, 1.0 to 2.5 mg of oral vitamin K therapy is recommended. Patients presenting with an INR above 9.0 but not bleeding are treated with 5 mg of oral vitamin K. Patients presenting with an elevated INR and bleeding require 10 mg of vitamin K and the administration of fresh frozen plasma. Vitamin K can be administered orally, intravenously, or subcutaneously. A meta-analysis demonstrated that oral dosing is superior to other routes of administration and that subcutaneous dosing is the least desirable method of administration. In cases of excessive anticoagulation with warfarin that is accompanied by serious or life-threatening bleeding, vitamin K is often administered intravenously. Vitamin K given intravenously should be administered as an infusion during 20 to 30 minutes and not given as a bolus injection.

Bleeding from heparin therapy is less of an issue in the ED but still can be a problem. In addition to discontinuation of the heparin, the administration of protamine sulfate can urgently reverse the effects of heparin. The full neutralizing effect of unfractionated heparin is achieved with 1 mg of protamine for every 100 units of heparin. Protamine can also be used to reverse the effects of low-molecular-weight heparin; however, it does not completely abolish the anticoagulant effects as it does with unfractionated heparin. When it is used for bleeding caused by low-molecular-weight heparin, the dose of protamine is 1 mg for every 1 mg of low-molecular-weight heparin. Because rapid injection of protamine results in hypotension, the recommended rate of administration is no more than 50 mg during 10 minutes. Recombinant factor VIIa may be considered in resistant forms of bleeding from anticoagulation; however, it is not a substitute for vitamin K, protamine, or blood product transfusions.

Disseminated Intravascular Coagulation. DIC is a relatively common acquired coagulopathy. Its ubiquitous nature, multiple origins, and potentially devastating sequelae, balanced by an effective mode of therapy, make early diagnosis of this hematologic process critical. It is most often encountered in the critical care setting. Hemostasis is achieved by a fine balance between procoagulants and inhibitors and thrombus formation and lysis. The balance may be disturbed by pathologic processes that result in an out-of-control coagulation and fibrinolytic cascade within the systemic circulation. The following occurs in this abnormal clotting sequence:

Platelets and coagulation factors are consumed, especially fibrinogen and factors V, VIII, and XIII.

Thrombin is formed, and it overwhelms its inhibitor system and acts to accelerate the coagulation process and directly activate fibrinogen.

Fibrin is deposited in small vessels in multiple organs.

The fibrinolytic system by means of plasmin may lyse fibrin and impair thrombin formation.

Fibrin degradation products are released and affect platelet function and inhibit fibrin polymerization.

Coagulation inhibition levels (e.g., antithrombin III, protein C, and tissue factor pathway inhibitor) are decreased.
The clinical consequence of these processes is the life-threatening combination of a bleeding diathesis from loss of platelets and clotting factors, fibrinolysis, and fibrin degradation product interference; small-vessel obstruction and tissue ischemia from fibrin deposition; and RBC injury and anemia from fibrin deposition. The condition needs to be considered in any patient in whom purpura, a bleeding tendency, and signs of organ injury, particularly of the central nervous system and kidney, develop. This broad description is further confused clinically by the variable acuteness and intensity of intravascular clotting, the effectiveness of fibrinolysis, and other systemic manifestations of the initiating disease. The clinical diagnosis of DIC is confirmed by laboratory tests (Table 122-3).

Two conditions that may simulate DIC are severe liver disease and primary fibrinolysis. Liver disease of this severity is usually manifested by clinical jaundice and splenomegaly. Primary fibrinolysis is a rare disorder that affects fibrinogen and fibrin but generally leaves the coagulation components (platelets, factor V, and factor VIII) in the low-normal range. Additional laboratory tests can be used to confirm the diagnosis of primary fibrinolysis, but these are not typical tests obtained in the ED and are best ordered in conjunction with a hematologist.

When planning therapy, the emergency physician needs to remember that DIC is secondary to a serious underlying pathologic process. Once the diagnosis is confirmed, the initial treatment is focused on reversal of the triggering mechanism. Many episodes of DIC are self-limited, such as in a transfusion reaction, or compensated, such as in association with a tumor mass, and do not require intervention other than support.

Replacement therapy is usually instituted simultaneously with attempts to control the primary process. The goal is to avoid depletion of clotting factors. Treatment is partially based on which of the two major pathologic components of DIC dominates the clinical picture. If active bleeding is present, replacement therapy with platelets, fresh frozen plasma, and cryoprecipitate (I, V, VIII) is recommended. Selective replacement therapy can be based on the laboratory and clinical response. Retardation of bleeding, a decrease in fibrin degradation products, and a rise in platelet counts and fibrinogen levels are useful monitors. Normalization of clotting times occurs too late to be of value in monitoring.

Heparin has selective use in the treatment of DIC when fibrin deposition and thrombosis dominate the pathologic picture. Certain disease states are associated more with fibrin deposition, in which case heparin therapy should be considered. Examples include purpura fulminans, retained dead fetus before delivery, giant hemangioma, and acute promyelocytic leukemia. Heparin therapy is of little benefit in cases of meningococcemia, abruptio placentae, severe liver disease, and trauma. Low doses of heparin (300-500 units/hr) as a continuous infusion are currently recommended. Low-molecular-weight heparin may also be used instead of unfractionated heparin. Continuous monitoring of the clinical response, heparin levels, and bleeding status is necessary.

Other therapeutic agents, such as antithrombin III and activated protein C, have been evaluated. However, none has demonstrated an improved outcome in DIC, and only recombinant activated protein C (drotrecogin alfa) has been associated with improved outcomes in septic shock, regardless of whether DIC was present.

The goals of emergency care of patients with DIC include initial recognition, aggressive pursuit of the diagnosis, understanding of potential life-threatening complications, and only rarely initiation of therapy.

### DISPOSITION

All patients with bleeding disorders of unknown cause or of a significant degree should be admitted to the hospital for further evaluation. The circumstances in which a patient with a known bleeding disorder may be discharged for home care are discussed in earlier sections on individual disease states. Transfer of these patients may be necessary, particularly if hematologic consultation is not readily available. The standard criteria of hemodynamic stability, appropriate monitoring, and full knowledge and understanding on the part of the family and accepting physician should be met before transfer. Because of the delayed bleeding pattern in hemophiliacs, it may be especially hazardous to transfer them long distances. Therefore, the importance of advance knowledge and preparation is reemphasized. Outpatients are usually treated under the auspices of the hematologic consultant. Early notification and appropriate follow-up arrangements should be made with these specialists.

### KEY CONCEPTS

- Although hemostatic disorders are confirmed by specific patterns of laboratory test results, a careful history and focused physical examination are often the key to the diagnosis of hematologic diseases.
- The frequency of hemostatic disorders seen in the ED is unknown; however, they are likely to be more common than thought. Although classic diseases such as hemophilia and DIC are uncommon, the use of antiplatelet and anticoagulation agents is common in other disease states, such as cardiovascular diseases.
- Hemophilia patients are often highly informed about their disease. Patient input should be solicited and respected, and early consultation with the patient's hematologist is encouraged. Early treatment with replacement factor while diagnostic testing proceeds is encouraged.
- Platelet dysfunction is often equated with low platelet counts. Even though critical thrombocytopenia increases the risk of bleeding, particularly with trauma and surgery, dysfunction can occur at normal platelet counts. For example, antiplatelet therapy and renal disease can alter platelet function without reducing blood counts.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.