CHAPTER 33

Coagulopathies

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Coagulopathies include hemorrhage, thrombosis, and embolism, and represent common clinical manifestations of hematological disease. Normally, bleeding is controlled by a fibrin clot formation, which results from the interaction of platelets, plasma proteins, and the vessel wall. The fibrin clot is ultimately dissolved through fibrinolysis. A derangement of any of these components may result in a bleeding or thrombotic disorder. In this chapter, individual disease states are examined under the broad headings of coagulation factor deficiencies, disorders of platelets, mixed disorders, acquired thrombophilias, and inherited thrombophilias.

ANATOMY, PHYSIOLOGY, AND PATHOLOGY

Coagulation is initiated after blood vessels are damaged, enabling the interaction of blood with tissue factor, a protein present beneath the endothelium (Figure 33.1). Small amounts of Factor VII present in plasma bind to tissue factor, and this tissue factor–Factor VII complex activates Factor X. Activated Factor X, in the presence of Factor V, activates prothrombin (II) to thrombin (IIa), which subsequently cleaves fibrinogen to fibrin. The fibrin polymerizes into an insoluble gel. This is stabilized by the action of Factor XIII. This process constitutes the extrinsic pathway.

Coagulation is consolidated by the intrinsic pathway. Factor XI is activated (possibly by thrombin generated in the extrinsic pathway), resulting in the activation of Factor IX, which then activates Factor X in the presence of Factor VIII. Activated Factor X produces a fibrin clot, as outlined in the description of the extrinsic pathway. Decreased levels of clotting factors may be caused by defective synthesis, excessive use, circulating inhibitors of clotting factors, or excessive proteolysis by the fibrinolytic system.

The coagulation pathway is controlled by a number of endogenous anticoagulants. Protein C is a plasma protein that is vitamin K dependent. It requires activation by a complex of thrombin and thrombomodulin, an endothelial cell protein, to inhibit activated Factors V and VIII, thus inhibiting the activation of Factors IX and X, respectively. Activated protein C (APC) inhibition is catalyzed by protein S, another vitamin K–dependent plasma protein, and also requires the presence of platelet phospholipid and calcium. Antithrombin III (AT III) primarily inhibits the activity of thrombin and Factor X by binding to the factors and blocking their activity. This inhibition is greatly enhanced by heparin. Loss of function and/or decreased concentrations of these proteins result in uninhibited coagulation and hence a predisposition to spontaneous thrombosis otherwise known as a hypercoagulable state.

Fibrinolysis is a mechanism for dissolving fibrin clots. Plasmin, the activated form of plasminogen, cleaves fibrin to produce soluble fragments. Fibrinolytics, such as tissue plasminogen activator, streptokinase, and urokinase, activate plasminogen, resulting in dissolution of a fibrin clot.

CLASSES OF BLEEDING DISORDERS

Vascular defects usually cause bleeding only into the skin and mucous membranes. Congenital causes include Osler–Weber–Rendu syndrome and Ehlers–Danlos disease. Acquired causes of vascular purpura include infections, drugs, uremia, connective tissue disorders, and dysproteinemias. Treatment is directed to the primary illness.

Inherited Coagulation Disorders

Hereditary bleeding disorders are extremely rare. The most common bleeding disorders include hemophilia A, hemophilia B, and von Willenbrand disease (vWD). The worldwide incidence of hemophilia A is 1 case per 5,000 live male births. Hemophilia B occurs at an even lower rate, with 1 case per 50,000 live male births (Soucie, Evatt, & Jackson, 1998). vWD is the most common of the three bleeding disorders across all ethnic groups, affecting 1% of the population. Up to 80% of affected patients have Type I vWD (Zimmerman & Valentino, 2013).

Deficiencies of any of the known coagulation factors could be present from birth. Deficiencies may be inherited

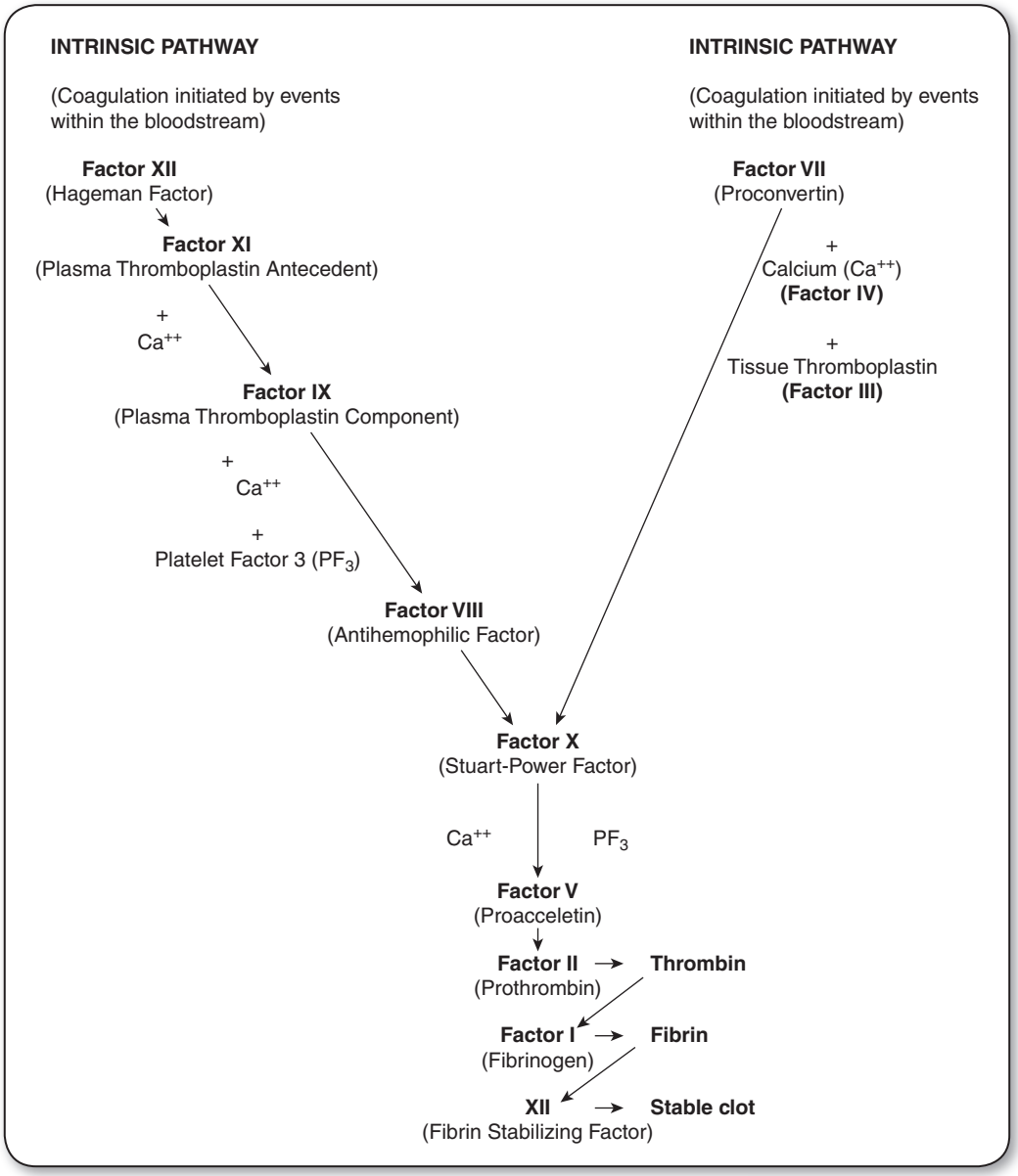

FIGURE 33.1
The coagulation cascade is initiated by the extrinsic pathway and consolidated by the intrinsic pathway. Coagulation is controlled by the inhibition of Factor VIII and Factor V by activated protein C (APC), and by antithrombin III (AT III) inhibition of Factors II and X.

or result from a spontaneous disruption in the associated coagulation factor genes. The more common deficiencies of Factors VIII and IX, as well as vWD, are discussed in this chapter (Table 33.1).

HEMOPHILIA

Hemophilia is an X-linked recessive disorder associated with a congenital deficiency of Factor VIII or Factor IX. Factor VIII deficiency is known as hemophilia A and Factor IX deficiency is known as hemophilia B. Hemophilia B was first diagnosed by Steven Christmas and thus is also called Christmas disease. Hemophilia is suspected in any male who has excessive bleeding after trauma, or spontaneous bleeding into joints or soft tissues (Table 33.1). Patients with severe hemophilia (factor level: <1%) are at risk for spontaneous hemarthrosis and soft-tissue bleeding. Patients who have moderate disease (factor level: 1%–4%) or mild hemophilia (factor level: 5%–25%) are at a reduced risk of spontaneous hemorrhage, but may bleed excessively after trauma or surgery (Wagenman, Townsend, Mathew, & Crookston, 2009).

VON WILLEBRAND DISEASE

von Willebrand factor (vWF) is a plasma protein that is required for the adhesion of platelets to sites of vascular damage. In persons with von Willebrand disease, deficiency of vWF is called Type I; qualitative abnormality of vWF is called Type II. vWD is an autosomally inherited hemostatic disorder of variable severity, characterized by mucosal and cutaneous bleeding, similar to patients with platelet disorders (see Table 33.2). Patients may have a prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT).

TABLE 33.1 Overview of Coagulopathies

BLEEDING DISORDER	FACTOR	FREQUENCY	CLINICAL PRESENTATION	LAB TESTING
Hemophilia A	VIII	1 in 5,000 live male births	Eccymosis Hemathrosis Muscle hemorrhage Wound bleeding	Prolonged aPTT Decreased Factor VIII Decreased Factor IX
Hemophilia B	IX	1 in 50,000 live male births	Eccymosis Hemathrosis Muscle hemorrhage Wound bleeding	Prolonged aPTT Decreased Factor IX
von Willebrand disease	vWF	1%	Minor bleeding Epistaxsis Increased postoperative bleeding	Decreased von Willebrand factor-antigen (vWF:Ag), Factor VIII
CLOTTING DISORDER	**FACTOR**	**FREQUENCY**	**CLINICAL PRESENTATION**	**LAB TESTING**
Factor V Leiden	V	5%	Thromboembolism	Positive genotypic assay APC resistance
Prothrombin G20210A	II	3%	Thromboembolism	Positive genotypic assay
Protein C deficiency	Protein C	<1%	Thromboembolism	Decreased protein C activity
Protein S deficiency	Protein S	<1%	Thromboembolism	Decreased protein S activity
Antithrombin III deficiency	ATIII	<1%	Thromboembolism	Decreased AT III activity

APC, activated protein C; aPTT, activated partial thromboplastin time; AT III, antithrombin III.

Mixed Coagulation Disorders

Mixed coagulation disorders are a group of acquired diseases. They usually involve multiple elements of the hemostatic system and are often associated with a particular disease or clinical syndrome.

DISSEMINATED INTRAVASCULAR COAGULATION

Disseminated intravascular coagulation (DIC) can be caused by the activation of either the coagulation or fibrinolytic system, resulting in excessive bleeding or thrombosis. Conditions associated with DIC include gram-negative sepsis infections, meningococcemia, Rocky Mountain spotted fever, typhoid fever, obstetric complications (abruptio placentae, eclampsia, retained dead fetus), massive trauma, surgery, shock, and certain malignancies.

LIVER DISEASE

Coagulation disorders are common in patients with acute and chronic hepatic diseases. These may arise from malabsorption of vitamin K, decreased synthesis of clotting proteins, abnormal synthesis of clotting proteins, or decreased clearance of activated factors. Fibrin degradation products may be elevated because of poor hepatic clearance, resulting in impaired coagulation resembling DIC. Liver disease associated with hypersplenism may result in thrombocytopenia.

VITAMIN K DEFICIENCY

Factors II, VII, IX, and X are vitamin K–dependent coagulation factors that are synthesized in the liver. Vitamin K is naturally synthesized by intestinal bacteria. Vitamin K is a lipid-soluble vitamin, which is absorbed only in the presence of bile salts. Depletion of vitamin K–dependent factors may occur in patients receiving certain antibiotics; in obstructive jaundice, malabsorptive states, or hepatic parenchymal disease; and in patients receiving warfarin therapy. Patients have an elevated PT resulting in an increased international normalized ratio (INR).

Platelet Disorders

Platelet disorders include thrombocytopenia, which may be caused by diminished platelet production, enhanced platelet destruction, or sequestration of platelets (Table 33.2). Qualitative platelet disorders are more commonly acquired, but could be congenital. Congenital disorders affect platelet adhesion, aggregation, or secretion, and are rare. Acquired qualitative platelet disorders are secondary to uremia, myeloproliferative disorders, drugs, and dysproteinemias.

IMMUNE THROMBOCYTOPENIC PURPURA

Immune thrombocytopenic purpura (ITP), the autoimmune destruction of platelets, usually presents as bruising, petechiae, or bleeding. The differential diagnosis includes

TABLE 33.2 Causes of Thrombocytopenia

Diminished platelet production
Marrow infiltration with tumor, fibrosis, infection
Aplastic/hypoplastic anemia
Exposure to environmental toxins (arsenic, pesticides)
Ionizing radiation
Nutritional deficiencies (B12, folate)
Viral infections
Drugs (thiazides, alcohol, myelosuppressive agents)
Paroxysmal nocturnal hemoglobinemia
Splenic sequestration
Lymphoproliferative disorders
Portal hypertension
Myeloproliferative disorders
Infections (bacterial, viral, parasitic)
Increased platelet destruction
Nonimmune
Vascular prosthesis DIC
Sepsis/infection
TTP
Immune
Drug-induced antibodies
ITP

DIC, disseminated intravascular coagulation; ITP, immune thrombocytopenic purpura; TTP, thrombotic thrombocytopenic purpura.

aplastic anemia, sepsis, DIC, acute leukemia, drug-induced thrombocytopenia, and infiltrative bone marrow disorders. The diagnosis is made by excluding other causes of thrombocytopenia, after a careful history, physical examination, and peripheral smear. An HIV test should be performed in those patients with risk factors. Bone marrow aspiration may be indicated in elderly patients or patients with atypical findings.

ITP may be acute (short term) or chronic. Acute ITP occurs primarily in children and usually lasts <6 months. Chronic ITP usually occurs in adults and lasts for >6 months, with a 3:1 ratio of females to males. It is common in patients between the ages of 20 and 50 years. ITP may also be associated with HIV infection, systemic lupus erythematosus, lymphoproliferative disorders, ulcerative colitis, and carcinoma. The thrombocytopenia is often chronic and unremitting, requiring definitive therapy.

DRUG-INDUCED THROMBOCYTOPENIA

Drug-induced thrombocytopenia is diagnosed after excluding other causes, and by noting a temporal relation between the onset of thrombocytopenia and the administration of the drug, as well as resolution upon discontinuation of the drug. Although many drugs can be implicated, alcohol, thiazide diuretics, quinine, quinidine, penicillins, gold, sulfa, and heparin are the most common. Myelosuppressive drugs used to treat malignancies and other disorders can produce thrombocytopenia by suppressing platelet production.

Heparin-induced thrombocytopenia is associated with an early nonimmune clinical syndrome and a later immune-mediated thrombocytopenia that occurs 5 to 7 days after the initiation of heparin. This type of thrombocytopenia may be associated with paradoxical thrombosis instead of bleeding.

In all cases, the offending drug should be discontinued and switched to an alternative if possible.

THROMBOTIC THROMBOCYTOPENIC PURPURA

Thrombotic thrombocytopenic purpura (TTP) is a complex clinical syndrome characterized by a formation of blood clots under the skin. Patients may present with headaches, blurred vision, seizures, profound coma, purpura, and petechiae from thrombocytopenia, jaundice, hemolytic anemia, fever, or renal dysfunction. TTP may be acquired or congenital. The causes of TTP are unknown, although this disease has been associated with certain drugs, pregnancy, malignancy, and HIV infection.

Laboratory findings include anemia, thrombocytopenia, fragmented red blood cells seen on peripheral smear, elevated blood urea nitrogen and creatinine levels, proteinuria, hematuria, and an elevated level of lactic dehydrogenase. The PT/INR and aPTT are usually normal.

CLASSES OF THROMBOTIC DISORDERS

Acquired Thrombophilias

Thrombophilia refers to a tendency to have venous thromboembolisms (VTEs) and to be at risk for recurrent episodes. Acquired causes of thrombosis include malignancy, myeloproliferative disorders, use of certain drugs, surgery, trauma, prolonged immobilization, pregnancy, antiphospholipid antibodies with or without systemic lupus erythematosus, and hyperhomocysteinemia (see discussion on Virchow's triad in Chapter 74 for additional information).

ANTIPHOSPHOLIPID ANTIBODIES

The antiphospholipid antibodies—anticardiolipin antibody, lupus anticoagulant, and antib2-glycoportein 1—are directed against different phospholipids. The lupus anticoagulant is an antibody against the phospholipid moiety of prothrombin activator complex, which interferes with and prolongs the aPTT and less commonly increases the INR. Despite the prolonged aPTT, this disorder is not associated with bleeding, but it may be associated with thrombosis. The lupus anticoagulant most highly predicts thrombosis. Antiphospholipid antibody syndrome is a term used for patients with persistent antiphospholipid antibodies who experience at least one clinical manifestation, such as a vascular thrombosis and/or pregnancy morbidity (Ruiz-Irastorza, Crowther, Branch, & Khamashta, 2010).

HYPERHOMOCYSTEINEMIA

A high level of homocysteine, an amino acid produced from methionine metabolism, causes an increased risk of venous and arterial thrombosis when it undergoes autooxidation. Normal metabolism of homocysteine relies on adequate stores of folic acid and vitamins B_6 and B_{12}. Thus, hyperhomocysteinemia is not a coagulation cascade issue but a defect in metabolism and/or increase in production. Hyperhomocysteinemia can be precipitated by acquired medical conditions, including vitamin deficiencies, or by genetic defects.

Inherited Thrombophilias

Inherited thrombophilias should be considered in patients who have a VTE and who are <45 years old, have a family history of VTEs, have had recurrent spontaneous episodes of VTEs, have had thrombosis in an unusual site (e.g., mesenteric vein, cerebral vein), and/or have had recurrent fetal losses and acquired causes have been excluded. All of the inherited thrombophilias discussed here are transmitted as an autosomal dominant trait, meaning that carriers, or heterozygotes, are affected.

The prevalence of inherited thrombophilias in the general population is relatively low. The two most common thrombophilias are Factor V Leiden (FVL) and prothrombin G20210A mutation. Both of these are more prevalent in Caucasians, with a prevalence of about 5% for Factor V Leiden and 3% for prothrombin G20210A mutation. A majority of those with either disease are heterozygote carriers. Being a carrier for both Factor V Leiden and prothrombin mutation is rare, with a prevalence of about 0.1% (Lijfering et al., 2010). Deficiencies of the natural anticoagulants have a prevalence of <1% in the general population. The least common is antithrombin deficiency (Seligsohn & Lubetsky, 2001). People can be carriers of multiple thrombophilia disorders, each of which further increases a person's lifetime risk for a VTE.

FACTOR V LEIDEN

A mutation of a single DNA base pair found on the Factor V gene causes the production of defective Factor V proteins. This single base change, where guanine is substituted with adenine, leads to the replacement of arginine by guanine at position 506, creating Factor V Leiden. These defective Factor V proteins resist APC. In other words, this mutation causes resistance of Factor V to the endogenous anticoagulation effects of protein C and causes an imbalance of the clotting cascade favoring thrombosis. The Factor V Leiden mutation was discovered by researches in Leiden, Netherlands, and is the most commonly diagnosed thrombophilia. Heterozygote carriers of Factor V Leiden are at a five-fold increased risk for a first-time VTE, and homozygote carriers are at an 18-fold increased risk, compared to the general population (Lijfering et al., 2010).

PROTHROMBIN G20210A MUTATION

Prothrombin G20210A mutation is a single base pair mutation on the 3'-untranslated region of the prothrombin gene. At position 20210 in this region, guanine is substituted with adenine. This substitution leads to increased production of prothrombin and thus thrombin. Both heterozygote and homozygote carriers have elevated levels of prothrombin. Heterozygote carriers of prothrombin G20210A mutation are at a threefold increased risk for a first-time VTE compared to the general population (Lijfering et al., 2010).

ANTITHROMBIN DEFICIENCY

Lack of antithrombin activity enables the coagulation cascade to continue uninterrupted. Antithrombin deficiency results from a quantitative or qualitative defect and is divided into two different types depending on its origin. Type I antithrombin deficiency is quantitative and occurs when production of normally functioning antithrombin is decreased. Type II antithrombin deficiency is qualitative and occurs when dysfunctional antithrombin molecules are produced. Certain conditions can induce a state of antithrombin deficiency. Such conditions associated with acquired antithrombin deficiency include heparin therapy, liver and/or renal disease, and DIC (Seligsohn & Lubetsky, 2001).

PROTEIN C DEFICIENCY

Protein C deficiency results from either a quantitative or a qualitative defect and is divided into two different types depending on its origin. Type I protein C deficiency is quantitative and occurs when production of normally functioning protein C molecule is decreased. Type II is qualitative and occurs when defective protein C molecules are produced, leading to low activity of protein C. Type I defect predominates in protein C deficiency. Certain conditions can cause protein C deficiency and/or induce further deficiency. Such conditions associated with acquired protein C deficiency include liver disease, vitamin K deficiency, use of vitamin K antagonists (VKAs), and DIC (Seligsohn & Lubetsky, 2001).

PROTEIN S DEFICIENCY

As with the other deficiencies, protein S deficiency results from a quantitative or qualitative defect; Type I and Type II, respectively. However, protein S deficiency has another category, Type III. Type III protein S deficiency is due to decreased amounts of free protein S molecules. Approximately 60% of protein S is bound to C4b-binding protein, an acute phase reactant, and the remaining free portion of protein S has the ability to be the cofactor that helps activate protein C. Free protein S can be decreased due to increased C4b-binding proteins or due to a divergence between protein S and C4b-binding protein to complex. Types I and III predominate in protein S deficiency. As with the other deficiencies, certain situations can cause protein S deficiency. Situations associated with acquired protein S deficiency include pregnancy, oral contraceptive therapy, inflammatory conditions, liver

disease, vitamin K deficiency, use of VKAs, and DIC (Marlar & Gausman, 2011; Seligsohn & Lubetsky, 2001).

HISTORY AND PHYSICAL EXAMINATION

Bleeding Disorders

Any recurrent bleeding, especially if it begins in early childhood or includes a family history of bleeding, is suggestive of an inherited bleeding disorder. Spontaneous hemarthroses or hematomas are associated with severe hemophilia A or B but may be observed with other severe coagulopathies. Abnormal bruising and mucosal bleeding, including epistaxis, gingival bleeding, and menorrhagia, are typical of abnormalities of platelets or vascular endothelium. Neonatal umbilical cord bleeding and defective wound healing may indicate Factor XIII deficiency, afibrinogenemia, or rarely dysfibrinogenemia.

A patient of European Jewish descent with postsurgical and mucosal bleeding may have a deficiency of Factor XI, which occurs predominantly in this population. Deficiencies of the intrinsic contact factors (Factor XII, prekallikrein, or high-molecular-weight kininogen) do not produce abnormal bleeding.

A detailed drug history (notably aspirin, nonsteroidal anti-inflammatories, anticoagulants, and antibiotics) and an evaluation for underlying medical conditions such as liver disease, cancer, uremia, or collagen vascular disorders are essential. A careful history of every previous surgical, dental, or traumatic event should be taken, noting the amount of blood loss and measures needed to control the bleeding.

Thrombotic Disorders

The primary clinical manifestations of thrombophilias are thromboembolisms, especially in the deep venous system of the lower extremities; in other words, deep venous thrombosis (DVT) with or without pulmonary embolisms (PEs). Other locations of thrombosis that have been associated with thrombophilias include cerebral veins and arteries, mesenteric veins, hepatic veins, and renal veins. Following a DVT, patients can present with post-thrombotic syndrome (PTS). PTS occurs due to damaged valves in the venous system and causes discoloration, ulceration, swelling, and chronic pain. See Chapter 74 on venous thromboembolisms for further discussion.

DIAGNOSTIC CRITERIA

Basic tests to diagnose a bleeding disorder include a bleeding time, which tests quantitative and qualitative platelet disorders; an INR, which examines the extrinsic pathway of the coagulation cascade (i.e., a deficiency or inhibition of Factors VII, X, V, II, I); an aPTT, which examines the intrinsic pathway of the coagulation cascade (i.e., a deficiency or inhibition of prekallikrein, high-molecular-weight kininogen, and Factors XII, XI, IX, VIII, X, V, II, I); and the thrombin time, which tests for deficiencies or inhibitors of thrombin and fibrinogen. A complete blood count will determine if there is a quantitative platelet deficiency.

DIAGNOSTIC TESTS

If a patient with a bleeding history has an increased PT/INR or a prolonged aPTT, then a mixing study should be performed using a 50:50 mix of patient plasma and control plasma (Figure 33.2). The PT/INR or aPTT would correct to normal with a coagulation factor deficiency, whereas plasma with an inhibitory antibody would not correct in mixing studies.

In a patient with a bleeding history and normal screening tests, one should suspect vWD. Repeated determinations of the bleeding time and activity of vWF may be necessary to establish the diagnosis. The laboratory workup may include the functional ristocetin cofactor assay to determine the plasma level of vWF, and characterization of the multimeric structure of the vWF molecule by gel electrophoresis.

If these tests are normal in a patient with a bleeding history, testing for Factor XIII should be performed by testing for increased solubility of the fibrin clot in urea. Further testing should rule out deficiencies of plasminogen activator inhibitor, or $\alpha 2$ antiplasmin. These latter tests are seldom necessary unless a positive history of bleeding and negative screening laboratory tests indicate a high probability of such disorders.

Platelet function can be evaluated in vitro by platelet aggregation studies, in which light transmission through turbid platelet-rich plasma increases as platelets aggregate after the addition of an agonist. Laboratory findings in DIC include thrombocytopenia, an increased INR, prolonged aPTT and thrombin time, increased levels of fibrin degradation products, and hypofibrinogenemia.

Laboratory abnormalities in hemophilia include a variable prolongation of the aPTT and reduced Factor VIII activity (Wagenman et al., 2009). Inhibitory antibodies are present in about 10% of patients with hemophilia A and 2% of patients with hemophilia B. Inhibitory antibodies in hemophiliacs should be suspected when mixing studies with normal plasma fail to normalize the factor level in vitro.

Patients who demonstrate thrombophilia should be evaluated for all of the different inherited thrombophilias. Genotypic assays are used to diagnose Factor V Leiden and prothrombin G20210A mutation. For Factor V Leiden, an APC resistance assay is also helpful in diagnosis. Factor V Leiden accounts for 90% to 95% of cases of APC resistance. In a plasma sample from a person with Factor V Leiden, the addition of APC will cause a slight increase in aPTT. In comparison, a sample of plasma from a control or a person without this mutation, the addition of APC will cause a prolonged aPTT because Factors V and VIII do not resist the anticoagulant effects of protein C. Evaluating the concentrations of protein C, protein S, and antithrombin helps to diagnose these deficiencies. The concentrations of these proteins are expressed as percentages. When assessing

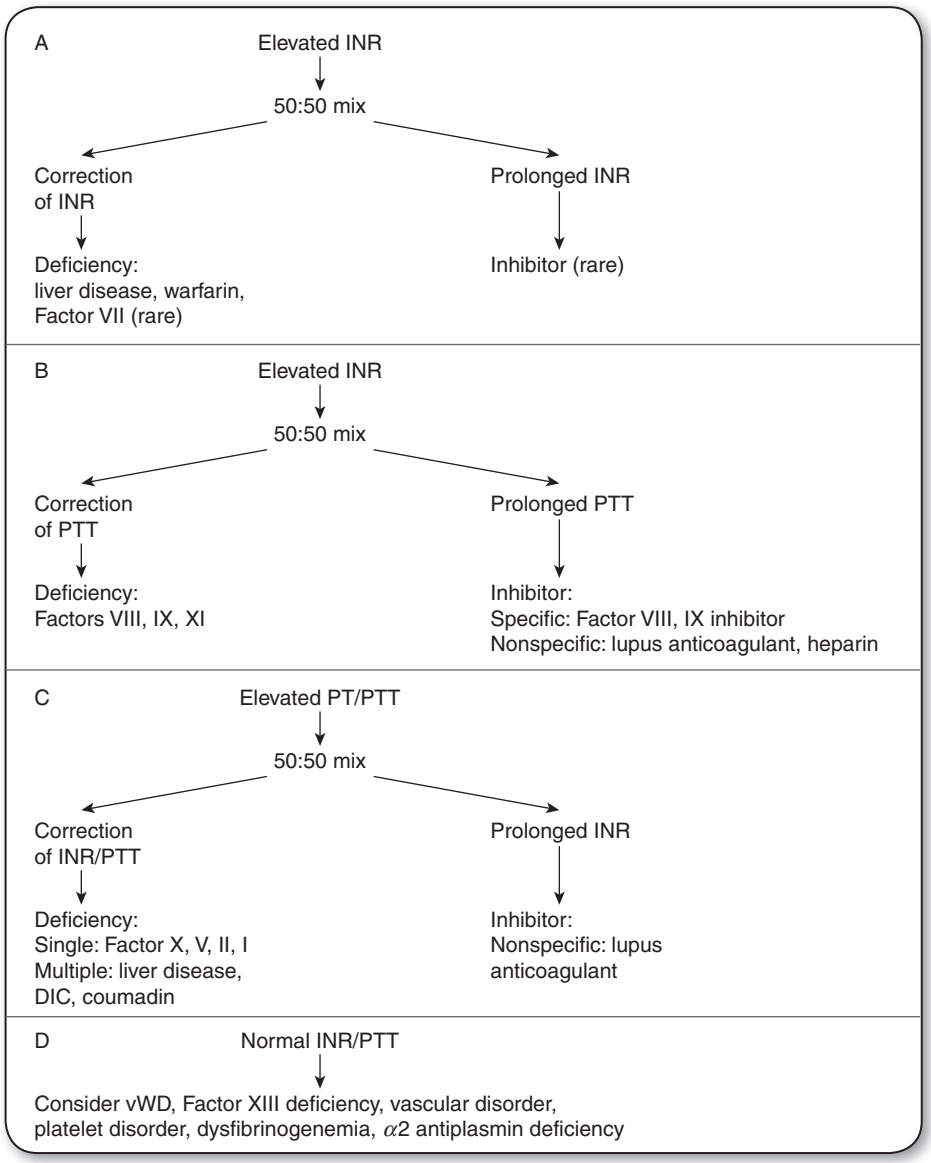

FIGURE 33.2
An algorithm for the evaluation of a bleeding patient.

INR, International Normalization Ratio; PTT, partial thromboplastin time; vWD, von Willebrand disease.

these laboratory results, factors that can lead to decreased concentrations must be considered.

Clinical Pearls

- Because protein C and protein S are vitamin K–dependent factors, assays of these factors as well as APC resistance should be performed when the patient has not been receiving warfarin for at least two weeks. Similarly, patients who are receiving heparin may have decreased levels of AT III.
- During an acute VTE, the concentrations of these proteins are also decreased. However, if a result is normal and obtained during a scenario associated with decreased concentration and/or activity, the deficiency can be ruled out. If the result is low, repeat testing should be performed prior to diagnosing a patient with one of the deficiencies. The different subtypes of these deficiencies are determined by functional assays.

Patients should also be evaluated for the evidence of hyperhomocysteinemia and antiphospholipid antibodies. The diagnosis of antiphospholipid antibodies is confirmed by performing the dilute Russell viper venom time and an anticardiolipin antibody assay.

TREATMENT OPTIONS, EXPECTED OUTCOMES, AND COMPREHENSIVE MANAGEMENT

Hemophilia

In patients with mild hemophilia A, desmopressin (DDAVP), which stimulates the release of both Factor VIII and vWF, can be used for the control of bleeding and as prophylaxis before some surgical procedures (Bolton-Maggs & Pasi, 2003). DDAVP should not be used as therapy in patients with life-threatening bleeding or in patients with severe deficiencies of

Factor VIII. DDAVP is administered as an intravenous infusion (0.3 mg/kg) and can be repeated every 8 to 12 hours. Prolonged administration of DDAVP may result in tachyphylaxis.

Von Willebrand Disease

The two primary treatments for vWD are DDAVP and transfusion therapy. Replacement therapy with cryoprecipitate or intermediate-purity Factor VIII concentrates containing functional vWF have been used. These therapies are reserved for patients with severe Type I disease and the majority of Type II vWD patients.

Clinical Pearls

- In patients undergoing dental procedures, oral antifibrinolytic mouthwashes may be used to control bleeding. Tranexamic acid and aminocaproic acid mouthwashes have been compounded and administered for hemophilia patients undergoing dental procedures. Additionally epsilonaminocaproic acid (EACA), an inhibitor of fibrinolysis, can be used to control bleeding. One regimen is to administer EACA on the day before the dental procedure and for 5 to 7 days afterward, along with a single 50% factor replacement dose immediately before the procedure.
- Severe hemophilia A is treated with Factor VIII concentrates (Mannucci, 2008). Hemophilia B is usually treated with high-purity Factor IX concentrate. Minor cuts and abrasions for all types usually require no therapy. Recombinant Factor VII has also been used for the treatment of hemophilia for patients who have developed inhibitors to replacement coagulation factors (Mannucci, 2005).
- Uncomplicated hemarthrosis and symptomatic hematomas in noncritical locations can be managed by administering Factor VIII or IX intravenously to achieve levels of about 50% of normal for 2 to 4 days. A single dose administered by the patient at home at the onset of symptoms is often sufficient therapy for a hemarthrosis. Prompt initiation of therapy can minimize bleeding and subsequent joint deformity. Immobilization of the joint for 2 to 3 days is important. Needle aspiration of blood from the joint space is performed only if severe pain and swelling are present. Life-threatening hemorrhage, hematomas in critical locations, and major surgery require achievement of factor levels of 100% and longer courses of therapy. Therapy is monitored by assaying Factor VIII or IX activity after a replacement dose.
- With replacement therapy, the average life expectancy now exceeds 60 years. Unfortunately, 70% to 90% of patients treated with factor concentrates before 1985 were infected with the HIV and hepatitis viruses. Heat and other treatments are now used to inactivate these viruses.

DDAVP, administered at 0.3 mg/kg by intravenous infusion, can elevate vWF activity for 6 to 8 hours in most cases of Type I vWD. The response to DDAVP in Type II vWD is variable and in some cases potentially harmful. Some authorities recommend testing certain Type II vWD patients with DDAVP well in advance of surgery to assess if they will respond. The concomitant use of antifibrinolytics, such as tranexamic and aminocaproic acids, is recommended, particularly for dental procedures and minor mucosal bleeding.

Disseminated Intravascular Coagulation

The treatment of DIC is aimed primarily at the underlying disease process and secondarily at the coagulopathy that results in the thrombotic or hemorrhagic manifestation. In patients with severe bleeding, fresh-frozen plasma (FFP), cryoprecipitate, or platelets can be used. In patients with thrombosis, heparin may be useful, usually at lower-than-normal doses, to reduce the risk of bleeding (e.g., 500 units/hr intravenous infusion). However, unless the thrombotic or hemorrhagic complications are serious, specific therapy for DIC is probably of no benefit.

Liver Disease

Patients with liver disease and a prolonged INR should empirically be given vitamin K 10 mg/d subcutaneously for 3 days, although only a minority of patients will respond. Patients who are actively bleeding may be given FFP, which may temporarily replace the deficient coagulation factors. Usually 2 to 4 units of FFP are administered every 4 to 6 hours. Care must be taken to avoid fluid overload with this therapy. Recombinant Factor VII and prothrombin complex concentrate (PCC) have also been used to control bleeding in patients with liver disease.

Vitamin K Deficiency

Intravenous administration of vitamin K (1 mg/d) results in faster normalization of a prolonged PT than oral administration (5–10 mg/d). Parenteral vitamin K should be administered slowly due to the risk of anaphylaxis. In patients with severe hemorrhage, immediate replacement of coagulation factors can be achieved by the administration of FFP, 2 to 4 units every 4 to 6 hours.

Thrombocytopenia

In general, patients who are bleeding with thrombocytopenia associated with platelet counts of <50,000/mL should be treated with platelet transfusions. A dose of platelets is 0.1 units/kg and is expected to raise the platelet count by 30,000 to 50,000/mL. Asymptomatic patients with a platelet count <10,000/mL should receive similar prophylaxis.

Patients with thrombocytopenia from platelet destruction rarely benefit from platelet transfusions, and treatment is directed at the cause of the thrombocytopenia. Patients

with thrombocytopenia from platelet sequestration may require far greater quantities of platelets than normal. Occasionally, a splenectomy may be indicated to correct the thrombocytopenia.

Acquired qualitative platelet disorders are generally treated with platelet transfusions. Uremic bleeding associated with qualitative platelet abnormalities can be treated with DDAVP or dialysis, however.

Treatment for chronic ITP includes prednisone, 1 to 2 mg/kg daily. Splenectomy should be considered for patients who need an excessively high dose of prednisone to maintain an adequate platelet count, or for patients whose disease does not respond to steroid treatment.

Intravenous immune globulin, 400 mg/kg daily for 5 days, usually increases the platelet count more rapidly than steroids alone and can be used in actively bleeding patients. Transfused platelets are cleared rapidly and are therefore rarely beneficial. Patients who suffer relapses after splenectomy may be treated with a variety of drugs, including cyclophosphamide, azathioprine, vincristine, or danazol, with variable success.

Without appropriate treatment, TTP is almost universally fatal. However, 70% of patients will survive with expediently administered exchange transfusions with FFP (3 to 4 L/d) and in some cases prednisone daily. Plasma exchange is continued until the clinical status has improved and the platelet count and level of lactic dehydrogenase are normal for several consecutive days.

The cryosupernatant fraction of plasma may be used in patients whose disease does not initially respond to plasma exchange with FFP. Approximately, 20% of patients whose disease initially responds suffer a relapse and require retreatment. Platelet transfusions should be withheld in patients with TTP, except for patients with severe hemorrhage.

Prevention

Patients with severe thrombocytopenia should be warned against taking aspirin or nonsteroidal anti-inflammatories, which interfere with platelet function and could increase the risk of bleeding.

Prenatal testing for both hemophilia A and B can be performed via chorionic villous sampling on women who are carriers of the gene and who are pregnant with a male fetus. As with any postconception screening, moral and emotional issues may make this diagnostic tool unacceptable for some people. Excellent genetic counseling should be given to persons considering this test.

Thrombophilias

Lifelong prophylaxis should not be considered for asymptomatic persons with inherited thrombophilia who are not exposed to thrombotic risk factors. However, prophylactic measures should be implemented when the patient is exposed to transient clinical risk factors (e.g., surgery, prolonged immobilization, pregnancy, and the postpartum period).

CLINICAL WARNING:

Patients with thrombophilia should be counseled about the high risk of venous thrombosis associated with oral contraceptive use. Because pregnancy and the 4 weeks after delivery are times associated with high thrombotic risk, the administration of unfractionated heparin, 5,000 units three times a day, or a low-molecular-weight heparin (LMWH) is recommended.

Before and after surgery, patients should receive subcutaneous unfractionated heparin (UFH), 5,000 units three times a day, or LMWH. When the risk is exceptionally high, as in certain orthopedic procedures, transfusion of AT III or protein C concentrates may be considered as additional therapy for patients with AT III or protein C deficiency, respectively.

A patient with a documented first episode of VTE and no previous venous thrombosis with or without a history of thrombophilia should receive at least 3 months of anticoagulation therapy and consider extended duration of therapy if the VTE was unprovoked and the patient's risk of bleeding is low to moderate (Kearon et al., 2012). If treatment with VKA is started in patients with protein C or protein S deficiency, patients should be bridged with heparin or LMWH to prevent further deficiency in proteins C and S.

See Chapter 74 for further discussion on venous thromboembolism treatment.

Clinical Pearls

- Patients should use compression stockings with a 30 to 40 mmHg compression to help prevent PTS.
- The true incidence of recurrence in patients with thrombophilia who discontinue anticoagulant therapy after a single episode of venous thrombosis is unknown. Thus, the risks and benefits of lifelong anticoagulation should be individualized. Most authorities would offer lifelong anticoagulation to thrombophilic patients who have had more than one episode of venous thrombosis. Usually, lifelong anticoagulant therapy is not offered after the first thrombotic episode, especially if it developed in association with surgery, pregnancy, or other circumstances associated with a high risk of thrombosis. If the first thrombotic event was life-threatening or if there are multiple inherited genetic defects, lifelong oral anticoagulant therapy may be considered. For such patients treated with VKAs, the recommended therapeutic INR range is 2 to 3 rather than lower, <2, or higher, >3 (Holbrook et al., 2012). In addition, for patients with hyperhomocysteinemia, administration of folate 1 mg/d, pyridoxine 100 mg/d, and cobalamin 0.4 mg/d reduce the level of serum homocysteine; however, such supplements do not reduce the risk of recurrent VTE or cardiovascular events, in those with coronary artery disease or stroke (Anderson & Weitz, 2011).

TEACHING AND SELF-CARE

Patient and family education focuses on the particular features of the bleeding and/or thrombotic disorder in question. General guidelines for counseling include the following:

- Physical exercise that is safe and aerobic in nature is strongly encouraged. Being in good physical condition can reduce the number and minimize the damage of bleeding complications. The physical regimen should be planned to reduce the chance of potential bleeding from trauma; contact sports are discouraged.
- All patients should be taught to detect warning signs and to seek immediate treatment should those signs occur. This is especially important for the patient with thrombocytopenia. Bruising, nosebleeds, oral bleeding, or petechiae may indicate danger. For patients with thrombotic disorders, pain, swelling, warmth, and redness in the extremities may indicate a DVT and shortness of breath, difficulty breathing, and chest pain may indicate a PE.
- Bleeding disorders can be treated with blood transfusions. Patients with bleeding disorders who have not been exposed to hepatitis B should receive the hepatitis B vaccine series.
- Genetic counseling is important for patients with inherited diatheses.
- Patients with thrombophilias and plans to travel for an extended period of time (e.g., flights 4 hours in duration or longer) should be counseled on wearing loose-fitting clothing, getting up and walking around, drinking lots of fluids, stretching legs, and wearing compression stockings.

COMMUNITY RESOURCES

- National Hemophilia Foundation: www.hemophilia.org/NHFWeb/MainPgs/MainNHF.asp?menuid=180&contentid=45&ptname=bleeding
- National Heart, Lung, and Blood Institute: What is immune thrombocytopenia; www.nhlbi.gov/health-topics/topics/itp
- Lupus Foundation of America; www.lupus.org
- Community Outreach Health System: What is coagulation, platelet disease information; http://web.bu.edu/COHIS/cardvasc/cdv.htm
- National Heart, Lung, and Blood Institute Information Center, P.O. Box 30105, Bethesda, MD 20824-0105 (301-592-8574); NHLBIinfo@nhlbi.nih.gov, www.nhlbi.nih.gov
- National Blood Clot Alliance, Stop the Clot; www.stoptheclot.org
- Clot Care Online Resource; www.clotcare.org
- Anticoagulation Forum; www.acforum.org

Referral Points and Clinical Warnings

The care of patients with severe bleeding diatheses should be supervised by a hematologist experienced in hemostatic disorders. Referrals should be made to a hematologist for such patients before surgical procedures and in the event of significant hemorrhagic episodes. Hemophiliacs with inhibitory antibodies are especially difficult to treat and should be evaluated by a hematologist. Patients with thrombocytopenia should be evaluated by a hematologist, especially if the cause is not immediately evident, if the platelet count is <50,000/mL, or if the patient is actively bleeding. Management of patients receiving VKA for treatment and secondary prophylaxis of thrombosis should be under the care of an anticoagulation clinic.

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