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121 Coagulation Disorders

Gomez K: Advances in the diagnosis of heritable platelet disorders.

Blood Rev 56:100972, 2022. James PD et al: ASH ISTH NHF WFH 2021 guidelines on the diagnosis of von Willebrand disease. Blood Adv 5:280, 2021. Jiang D et al: Changing paradigms in ITP management: Newer tools for an old disease. Transfus Med Rev 36:188, 2022. Jokiranta TS: HUS and atypical HUS. Blood 129:2847, 2017. May J et al: Heparin-induced thrombocytopenia: An illustrated review. Res Pract Thromb Haemost 7:100283, 2023. Skeith L et al: A practical approach to evaluating postoperative thrombocytopenia. Blood Adv 4:776, 2020. Vayne C et al: Pathophysiology and diagnosis of drug-induced immune thrombocytopenia. J Clin Med 9:2212, 2020. Zheng XL et al: ISTH guidelines for the diagnosis of thrombotic thrombocytopenic purpura. J Thromb Hemost 18:2486, 2020. Jean M. Connors

Coagulation Disorders PART 4 Oncology and Hematology Deficiencies of coagulation factors have been recognized for centuries. Patients with genetic deficiencies of plasma coagulation factors exhibit lifelong recurrent bleeding episodes into joints, muscles, and closed spaces, either spontaneously or following an injury. The most common inherited factor deficiencies are the hemophilias, X-linked diseases caused by deficiency of factor (F) VIII (hemophilia A) or FIX (hemophilia B). Rare congenital bleeding disorders due to deficiencies of other factors, including FII (prothrombin), FV, FVII, FX, FXI, FXIII, and fibrinogen, are commonly inherited in an autosomal recessive manner (Table 121-1). Disease phenotype often correlates with the level of factor activity. While patients can have a congenital deficiency of FXII accompanied by a significant prolongation in the activated partial thromboplastin time (aPTT), FXII deficiency is not accompanied by a bleeding phenotype, likely due to redundant paths to activation of the intrinsic pathway of the coagulation cascade, including direct activation of FXI by thrombin generated through the extrinsic pathway (Fig. 121-1). Advances in characterization of the molecular basis of clotting factor deficiencies have contributed to better understanding of the disease phenotypes allowing the development of more targeted

TABLE 121-1 Genetic and Laboratory Characteristics of Inherited Coagulation Disorders					
CLOTTING FACTOR DEFICIENCY	INHERITANCE	PREVALENCE IN GENERAL POPULATION	LABORATORY ABNORMALITY ^a	MINIMUM HEMOSTATIC LEVELS	TREATMENT
Fibrinogen	AR	1 in 1,000,000	++	100 mg/dL	Cryoprecipitate 2–4 d
Prothrombin	AR	1 in 2,000,000	++	20–30%	FFP/PCC 3–4 d
Factor V	AR	1 in 1,000,000	+/-	+/-	15–20% FFPc 36 h
Factor VII	AR	1 in 500,000	-	15–20%	FFP/PCC 4–6 h
Factor VIII	X-linked	1 in 5000	+	-	30% FVIII concentrates 8–12 h
Factor IX	X-linked	1 in 30,000	+	-	30% FIX

concentrates 18–24 h Factor X AR 1 in 1,000,000 +/- +/- – 15–20% FFP/PCC 40–60 h Factor XI AR 1 in 1,000,000 + – – 15–20% FFP 40–70 h Factor XII AR ND + – – b b 60 h HK AR ND + – – b b 150 h Prekallikrein AR ND + – – b b 35 h Factor XIII AR 1 in 2,000,000 – – +/- 2%–5% Cryoprecipitate/FXIII concentrates aValues within normal range (–) or prolonged (+). bNo risk for bleeding; treatment is not indicated. cSince platelets contain FV, platelet transfusion can be used as therapy. Abbreviations: aPTT, activated partial thromboplastin time; AR, autosomal recessive; FFP, fresh-frozen plasma; HK, high-molecular-weight kininogen; ND, not determined; PCC, prothrombin complex concentrates; PT, prothrombin time; TT, thrombin time.

therapeutic approaches, including the use of small molecules, recombinant proteins, or cell- and gene-based therapies. The two most commonly used tests of hemostasis, the prothrombin time (PT) and the aPTT, were designed to perform the first screen for clotting factor deficiency (Fig. 121-1). An isolated prolonged PT suggests FVII deficiency, whereas a prolonged aPTT indicates an intrinsic pathway factor deficiency, most commonly hemophilia A or B (FVIII or FIX, respectively) or FXI deficiency (Fig. 121-1). The prolongation of both PT and aPTT suggests a deficiency of FV, FX, FII, or fibrinogen abnormalities. A mixing study, in which the addition of normal pooled plasma to the patient's plasma, will correct a prolonged aPTT or PT due to a factor deficiency, and is the next step in determining if there is a coagulation factor deficiency. If the clotting time does not correct, it suggests the presence of an inhibitor, an antibody to a specific factor; however, a mixing study will also detect the presence of anticoagulants. Many labs have testing methods for detecting inhibitors that neutralize anticoagulants. If the mixing study corrects with normal plasma, individual factor activity assays are performed to determine which factor is deficient. Acquired deficiencies of plasma coagulation factors are more frequent than congenital disorders; the most common disorders include hemorrhagic diathesis of liver disease, disseminated intravascular coagulation (DIC), and vitamin K deficiency. In these disorders, blood coagulation is hampered by the deficiency of more than one clotting factor, and the bleeding episodes are the result of perturbation of both primary (e.g., platelet and vessel wall interactions) and secondary (coagulation) hemostasis. The development of alloantibodies to coagulation plasma proteins, clinically termed inhibitors, is a relatively rare disease that often affects hemophilia A or B and FXI-deficient patients on repetitive exposure to the missing protein to control bleeding episodes. Inhibitory autoantibodies also occur among subjects without genetic deficiency of clotting factors and, although rare, can be seen in the postpartum setting, as a manifestation of underlying autoimmune or neoplastic disease, or idiopathically. Rare cases of acquired inhibitors to thrombin or FV have been reported in patients receiving topical bovine thrombin preparation as a local hemostatic agent in complex surgeries. A mixing study that does not correct with the addition of normal plasma indicates the presence of an inhibitor, requiring additional tests to identify the specificity of the inhibitor and measure its titer. Inhibitor detection in patients with hemophilia is of particular importance, with yearly screening performed at most hemophilia treatment centers. The treatment of coagulation factor deficiencies in the setting of bleeding requires replacement of the deficient protein(s) using recombinant or purified plasma-derived products or fresh-frozen plasma 11–14 d

Intrinsic Pathway Extrinsic Pathway Ca²⁺ aPTT PT XIa XI IX IXa Ca²⁺ Contact phase FXIIa PK HMWH VIII VIIIa Xa X Ca²⁺ Cross-linked fibrin clot FIGURE 121-1 Coagulation cascade and laboratory assessment of clotting factor deficiency by activated partial thromboplastin time (aPTT), prothrombin time (PT), thrombin time (TT), and phospholipid (PL). (FFP). Prothrombin complex

concentrates (PCCs) are intermediate purity plasma-derived factor concentrates initially used as sources of FVIII or FIX for hemophilia patients, but because they contain the vitamin K-dependent factors, they are also used for warfarin reversal. Three-factor PCC (3F-PCC) is less frequently used now for warfarin reversal because these preparations contain low levels of FVII, requiring FFP as a source of FVII. Four-factor PCC (4F-PCC), especially the one used in the United States, contains FII, FIX, FX, higher levels of FVII than 3F-PCC, and protein S and protein C. HEMOPHILIA A AND B ■

■ PATHOGENESIS AND CLINICAL MANIFESTATIONS Hemophilia is an X-linked recessive hemorrhagic disease due to mutations in the F8 gene (hemophilia A or classic hemophilia) or F9 gene (hemophilia B). The disease affects 1 in 10,000 males worldwide, in all ethnic groups; hemophilia A represents 80% of all cases. The large size of the F8 gene makes it more susceptible to mutation events than the smaller F9 gene. Male subjects are clinically affected; women, who carry a single mutated gene, are generally asymptomatic. However, increased bleeding tendencies with procedures are now more commonly appreciated based on F8 or F9 level. Family history of the disease is absent in ~30% of cases, and in these cases, 80% of the mothers are carriers of the de novo mutated allele. More than 500 different mutations have been identified in the F8 or F9 gene. One of the most common hemophilia A mutations results from an inversion of the intron 22 sequence, and it is present in 40% of cases of severe hemophilia A. Advances in molecular diagnosis now permit precise identification of mutations, allowing accurate diagnosis of women carriers of the hemophilia gene in affected families. Clinically, hemophilia A and hemophilia B are indistinguishable. The disease phenotype correlates with the activity of FVIII or FIX and can be classified as severe (<1%), moderate (1–5%), or mild (6–30%). In the severe and moderate forms, the disease is characterized by bleeding into the joints (hemarthrosis), soft tissues, and muscles after minor trauma or even spontaneously. Patients with mild disease experience infrequent bleeding, usually secondary to trauma. Among those with baseline FVIII or FIX activity >25%, the disease is discovered only with bleeding after major trauma or during routine laboratory tests, usually an isolated prolongation of the aPTT that requires mixing study

VII VIIIa/tissue factor Ca^{2+} PL Common Pathway X V Va PL Prothrombin Thrombin aPTT/PT Fibrinogen TT Fibrin polymer Fibrin monomer CHAPTER 121 XIIIa Coagulation Disorders evaluation. FVIII has a short circulating half-life of 25–30 min that is extended to roughly 12 h when complexed with its carrier protein von Willebrand factor (VWF). In patients without a known history of hemophilia, a diagnosis of von Willebrand disease (VWD) needs to be excluded in patients with a prolonged aPTT and low FVIII activity. Early in life, bleeding may present after circumcision or rarely as intra cranial hemorrhages. The disease is more evident when children begin to walk or crawl. In the severe form, the most common bleeding manifestations are recurrent hemarthroses, affecting primarily the knees, elbows, ankles, shoulders, and hips. Acute hemarthroses are painful, and clinical signs are local swelling and erythema. To avoid pain, the patient may adopt a fixed position, which leads eventually to muscle contractures. Very young children unable to communicate verbally show irritability and a lack of movement of the affected joint. Chronic hemarthroses are debilitating with synovial thickening and synovitis in response to the intraarticular blood. After a joint has been damaged, recurrent bleeding episodes result in the clinically recognized “target joint,” which then establishes a vicious cycle of bleeding, resulting in progressive joint deformity that in critical cases requires surgery as the only therapeutic option. Hematomas into the muscle of distal parts of the limbs may lead to external compression of arteries, veins, or nerves that can result in compartment syndrome. Bleeding into the oropharyngeal spaces, central nervous system (CNS), or retroperitoneum is life-threatening and

requires immediate therapy. Retroperitoneal hemorrhages can accumulate large quantities of blood with formation of masses with calcification and inflammatory tissue reaction (pseudotumor syndrome) and also result in damage to the femoral nerve. Pseudotumors can also form in bones, especially long bones of the lower limbs. Hematuria is frequent among hemophilia patients, even in the absence of genitourinary pathology. It is often self-limited and may not require specific therapy. **TREATMENT Hemophilia** Without treatment, severe hemophilia may limit life expectancy. Advances in the blood fractionation industry during World War II resulted in the realization that plasma could be used to treat hemophilia, but the volumes required to achieve even modest elevation

of circulating factor levels limit the utility of plasma infusion as an approach to disease management. The discovery in the 1960s that the cryoprecipitate fraction of plasma was enriched for FVIII, and the eventual purification of FVIII and FIX from plasma, led to the introduction of home infusion therapy with factor concentrates in the 1970s. The availability of factor concentrates resulted in a dramatic improvement in life expectancy and quality of life for people with severe hemophilia. However, the contamination of the blood supply with hepatitis viruses and HIV resulted in transmission of these bloodborne infections within the hemophilia population. The introduction of viral inactivation steps in the preparation of plasma-derived products in the mid-1980s greatly reduced the risk of HIV and hepatitis; the risks were further reduced by the production of recombinant FVIII and FIX proteins in the 1990s. It is uncommon for hemophilic patients born after 1985 to have contracted either hepatitis or HIV, and for these individuals, life expectancy is now ~65 years. In fact, since 1998, new infections with viral hepatitis or HIV have not been reported in hemophilia patients.

Factor replacement for hemophilia has been the mainstay of therapy for half a century; however, advances including uniquely functioning molecules and gene therapy have expanded treatment approaches. Factor replacement has been provided either in response to a bleeding episode or as prophylactic treatment. Primary prophylaxis is defined as maintaining the missing clotting factor at levels ~1% or higher on a regular basis to prevent bleeds, especially the onset of hemarthroses. Hemophilic boys receiving regular infusions of FVIII (3 days/week) or FIX (2 days/week) can reach puberty without detectable joint abnormalities. Therefore, prophylactic treatment has become more common. The Centers for Disease Control and Prevention reported that >51% of children with severe hemophilia who are aged <6 years receive prophylaxis, increasing considerably from 33% in 1995. Although prophylaxis with factor concentrates is the standard care for children and adults with severe hemophilia, teenagers and young adults do not always maintain treatment due to high cost and lifestyle factors including difficulties accessing peripheral veins for infusions that occur two to three times a week or potential infectious and thrombotic risks of long-term central vein catheters. **PART 4 Oncology and Hematology Treatment of hemophilia bleeds** requires the following: (1) prompt initiation of factor replacement as symptoms often precede objective evidence of bleeding, especially for classic symptoms of bleeding into the joint in a reliable patient, headaches, or major trauma; and (2) avoidance of antiplatelet drugs. FVIII and FIX are dosed in units. One unit is defined as the amount of FVIII (100 ng/mL) or FIX (5 µg/mL) in 1 mL of normal plasma. One unit of FVIII per kilogram of body weight increases the plasma FVIII level by 2%. One can calculate the dose needed to increase FVIII levels to 100% in a 70-kg severe hemophilia patient (<1%) using the simple formula below. Thus, 3500 units of FVIII will raise the circulating level to 100%.
$$\text{FVIII dose (IU)} = \text{Target FVIII levels} - \text{FVIII baseline levels} \times \text{body weight}$$

(kg) $\times$ 0.5 unit/kg The doses for FIX replacement are different from those for FVIII, because FIX recovery after infusion is usually only 50% of the predicted value. Therefore, the formula for FIX replacement is as follows: FIX dose (IU) = Target FIX levels - FIX baseline levels $\times$ body weight (kg) $\times$ 1 unit/kg The FVIII half-life of 8–12 h requires injections twice a day to maintain therapeutic levels, whereas the FIX half-life is longer, $\sim$ 24 h, so that once-a-day injection is sufficient. In specific situations such as after surgery, continuous infusion of factor may be desirable because of its safety in achieving sustained factor levels at a lower total cost. Cryoprecipitate is enriched with FVIII protein bound to VWF (each bag contains $\sim$ 80 IU of FVIII). This product should be used

only in emergencies when factor concentrates are not available, although cryoprecipitate may be the only source of FVIII in developing countries. Mild bleeds such as uncomplicated hemarthroses or superficial hematomas require achieving an initial factor level of 30–50%. Additional doses to maintain levels of 15–25% for 2 or 3 days are indicated for severe hemarthroses, especially when these episodes affect the “target joint.” Large hematomas, or bleeds into deep muscles, require factor levels of 50% or even higher if the clinical symptoms do not improve, and factor replacement may be required for a period of 1 week or longer. The control of serious bleeds, including those that affect the oropharyngeal spaces, CNS, and the retroperitoneum, requires sustained protein levels of 50–100% for 7–10 days. Prophylactic replacement for surgery is aimed at achieving normal factor levels (100%) for a period of 7–10 days; replacement can then be tapered depending on the extent of the surgical wounds. Oral surgery is associated with extensive tissue damage that usually requires factor replacement for 1–3 days coupled with oral antifibrinolytic drugs.

NONTRANSFUSION THERAPY IN HEMOPHILIA

DDAVP (1-Amino-8-D-Arginine Vasopressin) DDAVP is a synthetic vasopressin analogue that causes a transient rise in FVIII and VWF, but not FIX, by release from stores in vascular endothelial cells. Patients with moderate or mild hemophilia A should be tested to determine if they respond to DDAVP before use. DDAVP at doses of 0.3 μ g/kg body weight, over a 20-min period, is expected to raise FVIII levels by two- to threefold over baseline, peaking between 30 and 60 min after infusion. DDAVP does not improve FVIII levels in severe hemophilia A patients because no stores are available to release. Repeated dosing of DDAVP results in tachyphylaxis as storage pools are depleted. After three consecutive doses, if further therapy is indicated, exogenous FVIII is required.

Antifibrinolytic Drugs Bleeding in the gums, the gastrointestinal tract, and during oral surgery can be treated with oral antifibrinolytic drugs such as ϵ -aminocaproic acid (EACA) or tranexamic acid to prevent fibrin degradation by plasmin. The duration of the treatment depending on the clinical indication is 1 week or longer. Tranexamic acid is given at doses of 25 mg/kg three to four times a day. EACA treatment requires a loading dose of 200 mg/kg (maximum of 10 g) followed by 100 mg/kg per dose (maximum 30 g/d) every 6 h. These drugs are not indicated to control hematuria because of concern for forming an occlusive clot in the lumen of genitourinary tract structures.

COMPLICATIONS

Inhibitor Formation The formation of alloantibodies to FVIII or FIX is the major complication of hemophilia treatment. The prevalence of inhibitors to FVIII is estimated to be $\sim$ 30% in severe hemophilia A patients and 10% among patients with nonsevere hemophilia A. Inhibitors to FIX are detected in only 3–5% of all hemophilia B patients. The high-risk group for inhibitor formation includes severe deficiency ($>$ 80% of all cases of inhibitors), familial history of inhibitor, African descent, mutations in the FVIII or FIX gene resulting in deletion of large coding regions, or gross gene rearrangements. Inhibitors usually appear early in life, at a median of 2 years of age, and after 10 cumulative days of exposure. However, intensive replacement therapy such as for major surgery, intracranial bleeding, or trauma increases the risk of inhibitor formation for patients of all ages and severity; all patients require close laboratory

monitoring following these events. The clinical diagnosis of an inhibitor is suspected when patients do not respond to factor replacement at therapeutic doses. Inhibitors increase both morbidity and mortality in hemophilia. Because early detection of an inhibitor is critical to a successful correction of the bleeding or to eradication of the antibody, most hemophilia centers perform annual screening with aPTT and mixing studies. The Bethesda assay uses a similar principle as a mixing study and

defines the specificity of the inhibitor and its titer. The results are expressed in Bethesda units (BU), in which 1 BU is the amount of antibody that neutralizes 50% of the FVIII or FIX present in normal plasma after 2 h of incubation at 37°C. Clinically, inhibitor patients are classified as low responders or high responders, with response defined as increase in antibody titer; knowledge of responder type guides therapy. Therapy for inhibitor patients has two goals: the control of acute bleeding episodes and the eradication of the inhibitor. For the control of bleeding episodes, low responders, those with titer <5 BU, respond well to high doses of human FVIII (50–100 U/kg), with minimal or no increase in the inhibitor titers. However, high-responder patients, those with initial inhibitor titer

“ 5 BU or an anamnestic response with increase in the antibody titer to >5 BU, even if low titer initially, do not respond to FVIII. The control of bleeding episodes in high-responder patients can be achieved by using concentrates enriched for prothrombin, FVII, FIX, FX (PCCs but usually activated PCCs [aPCCs]), and recombinant activated FVII (FVIIa), known as “bypass agents” because they activate coagulation downstream of the inhibited/absent factor or through a different pathway (Fig. 121-1). For FIX inhibitor patients, high doses of FIX can be used (<5 BU); however, allergic or anaphylactic reactions are common in FIX inhibitor patients; thus, bypass products should be used to treat or prevent bleeding as well as for those cases of high titer inhibitors. For eradication of the inhibitory antibody, immunosuppression alone is not effective. The most effective strategy is immune tolerance induction (ITI) based on daily infusion of the missing protein until the inhibitor disappears, typically requiring periods >1 year, with success rates of ~60%. The management of patients with severe hemophilia and inhibitors resistant to ITI is challenging. The use of anti-CD20 monoclonal antibody (rituximab) combined with ITI was thought to be effective, but although it reduces the inhibitor titers in some cases, sustained eradication is uncommon. Other Therapeutic Approaches for Hemophilia A and B Engineered clotting factors, using fusion to polyethylene glycol (FVIII, FIX), IgG1-Fc (FVIII, FIX), or albumin (FIX) or other strategies, extend the plasma half-life of the coagulation factor. A number of products have been approved for use. These extended half-life products (for FVIII and FIX) facilitate prophylaxis with fewer weekly injections to maintain circulating levels >1%, decreasing injections from 3 to 2 days a week in hemophilia A and to once a week for hemophilia B. Novel approaches to manipulating the coagulation cascade components, including targeting the natural anticoagulants and inhibitors of activation of coagulation, have shown promising clinical trial results but do not yet have regulatory

approval. Emicizumab is an asymmetric bispecific antibody with one immunoglobulin variable chain region that binds FIXa and another that binds FX bringing them in close contact and resulting in activation of FX by FIXa. FXa subsequently cleaves prothrombin to thrombin—without the need for FVIII (Fig. 121-2). It is effective in patients with severe hemophilia A with or without inhibitors. Similar molecules are in development. After initial once-a-week subcutaneous injections (an improvement over intravenous administration of factors) for 4 weeks, patients can usually be maintained with once-a-month dosing to prevent spontaneous bleeds, an overwhelmingly dramatic improvement in quality of life when compared to even the twice-weekly infusion schedule of “long-acting” FVIII compounds. Breakthrough bleeds can occur, however, and need to be carefully managed, as a small number of patients with inhibitors treated with aPCC or recombinant FVIIa developed thrombotic events or fatal thrombotic microangiopathy. Routine aPTT and FVIII activity measurements are inaccurate when emicizumab is present; to detect endogenous or infused FVIII activity, a chromogenic FVIII activity assay using bovine factor substrates is required. These X-linked disorders are ideally suited for gene therapy as small increases in plasma factor level will result in significant clinical improvement. FIX has been the most studied as the gene is smaller

Bispecific antibody Factor X Factor IXa EGF2 EGF2 EGF1 EGF1 Gla Gla Factor Xa CHAPTER 121 PS-exposed PL membrane Coagulation Disorders FIGURE 121-2 Mechanism of action of emicizumab. Emicizumab is a bifunctional antibody; the two binding sites recognize different protein sequences, unlike normal antibodies where both variable regions recognize the same antigen. One arm of emicizumab recognizes factor IXa and the other factor X. It functions to bring these two factors in proximity so that factor IXa can activate factor X to factor Xa, which then cleaves prothrombin to thrombin and activates the clotting cascade. (From T Kitazawa, M Shima: Emicizumab, a humanized bispecific antibody to coagulation factors IXa and X with a factor VIIIa-cofactor activity. *Int J Hematol* 111:20, 2020.) and easier to package in the viral vectors used. In one approach, the sequence of a known spontaneous FIX gain-of-function mutation that has marked increase in specific activity, FIX Padua, is used so that small increments in plasma level of FIX are also accompanied by even greater increase in functional activity. The larger FVIII gene has also been successfully transferred through an adeno-associated viral vector to a few patients with hemophilia A. The early results appear promising. Complications include transaminitis and loss of gene expression for a variety of reasons. Gene therapy using adenoviral vector approaches have now been approved for patients with hemophilia A or B. Details on how to implement gene therapy, selection of appropriate patients, and follow-up monitoring are still being developed (Chap. 483). INFECTIOUS DISEASES Hemophilia patients treated with clotting factor concentrates before the development of recombinant factors in the 1990s were almost universally infected with hepatitis C virus (HCV) and HIV, which became the second leading cause of death. Co-infection of HCV and HIV, present in almost 50% of hemophilia patients, is an aggravating factor for the evolution of liver disease as correction of both genetic and acquired (secondary to liver disease) factor deficiencies may be needed. Effective treatments for both HIV and HCV have altered the

devastating prognosis. In some select cases with cirrhosis, liver transplant has been performed, which also is curative for hemophilia. **EMERGING CLINICAL PROBLEMS IN AGING**

HEMOPHILIA PATIENTS Patients with hemophilia now live well into adulthood, with life expectancy of patients with severe hemophilia now only ~10 years shorter than the general male population and near normal in patients with mild or moderate hemophilia. The older hemophilia

population has distinct needs relating to more severe arthropathy, chronic pain, and high rates of HCV and/or HIV infections.

Although mortality from coronary artery disease is lower in hemophilia patients with hypocoagulability decreasing thrombus formation, atherogenesis is not prevented. Typical cardiovascular risk factors such as age, obesity, and smoking, along with physical inactivity, hypertension, and chronic renal disease, are seen in these patients as in the general population. Management of an acute ischemic event and coronary revascularization should include collaboration among hematologists, cardiologists, and internists. Cancer due to HIV- and HCV-related malignancies is also a concern in this population, with hepatocellular carcinoma (HCC) the most common cause of death in HIV-negative patients. The recommendations for cancer screening for the general population should be the same for age-matched hemophilia patients, including routine screening for HCC. Hemophilia patients benefit from the same preventive and therapeutic approaches to minimize the risk of cardiovascular disease and malignancy as the general population.

MANAGEMENT OF CARRIERS OF HEMOPHILIA Women carriers of hemophilia with factor levels ~50% of normal may not have an increased risk for bleeding. However, a wide range of factor activity (22–116%) due to random inactivation of the X chromosome (lyonization) can occur and lead to unexpected bleeding in women with low levels. The factor level of carriers should be measured to optimize perioperative management. During pregnancy, FVIII levels increase approximately two- to three fold in most carriers compared to nonpregnant women, whereas the FIX increase is less pronounced. After delivery, a rapid fall in the pregnancy-induced rise of maternal clotting factor levels occurs, resulting in increased risk for postpartum hemorrhage that can be prevented by infusion of factor concentrate to levels of 50–70% for 3 days for vaginal delivery and up to 5 days for cesarean delivery. In mild cases, the use of DDAVP and/or antifibrinolytic drugs is recommended.

PART 4 Oncology and Hematology ■ ■ FACTOR XI DEFICIENCY FXI deficiency, also known as hemophilia C, is a rare autosomal bleeding disorder that occurs at a frequency of one in a million. However, it is highly prevalent among Ashkenazi and Iraqi Jewish populations, reaching a frequency of 6% heterozygotes and 0.1–0.3% homozygotes. More than 65 mutations in the FXI gene have been reported, whereas fewer mutations (two to three) are found among affected Jewish populations. Normal FXI clotting activity levels range from 70–150 U/dL. Levels vary depending on the presence of heterozygous, homozygous, or double heterozygous mutations with levels <1 U/dL seen in the latter two. Patients with FXI levels <10% of normal have a high risk of bleeding, but the phenotype does not always correlate with FXI clotting activity. The family history is informative, with the bleeding risk based on bleeding in kindreds. Clinically, spontaneous bleeding is rare, but mucocutaneous bleeding such as bruises, gum bleeding, epistaxis, hematuria, and menorrhagia are common, especially following trauma. This hemorrhagic phenotype suggests that tissues rich in fibrinolytic activity are more susceptible to FXI deficiency. Postoperative bleeding is common but not always present, even among patients with very low FXI levels. FXI replacement is indicated in patients with severe disease for major

surgical procedures. A negative history of bleeding complications following invasive procedures does not exclude the possibility of an increased risk for hemorrhage. **TREATMENT** Factor XI Deficiency Sources of FXI are limited to FFP in the United States, whereas a plasma-derived FXI concentrate is available in other countries. FFP at doses of 15–20 mL/kg to increase levels by 10–20% can be

given every other day in the setting of bleeding or major surgery as FXI has a half-life of 40–70 h. Antifibrinolytic drugs can be used for minor bleeds and as adjunctive treatment with FXI replacement with the exception of genitourinary tract bleeding. The development of an FXI inhibitor can be seen in 10% of severely FXI-deficient patients. Although inhibitors are not associated with spontaneous bleeding, bleeding with surgery or trauma can be severe; treatment with PCC/aPCC or recombinant activated FVII is effective. Data for use of a single very low dose of recombinant activated FVII (10–15 µg/kg) and an antifibrinolytic agent before surgery in patients with severe FXI deficiency are good, avoiding the need for plasma products. **RARE BLEEDING DISORDERS** Inherited disorders resulting from deficiencies of clotting factors other than FVIII, FIX, and FXI (Table 121-1) occur infrequently. Bleeding manifestations vary from generally asymptomatic as with dysfibrinogenemia or FVII deficiency to life-threatening as with FX or FXIII deficiency. In contrast to hemophilia, hemarthroses are rare, but bleeding in the mucosal tract or after umbilical cord clamping is common. Individuals heterozygous for plasma coagulation deficiencies are often asymptomatic. The laboratory assessment for the specific deficient factor following screening with general coagulation tests (Table 121-1) identifies the diagnosis. Replacement therapy using FFP or PCCs for deficiencies provides adequate hemostasis for bleeds or prophylactic treatment, although specific concentrates for FX and fibrinogen are available. Cryoprecipitate or FXIII concentrate is needed for FXIII deficiency. FVII deficiency, like FXI, has an increased prevalence in the Ashkenazi Jewish population and is best treated with recombinant FVIIa rather than FFP or PCCs depending on the severity of bleeding or type of surgery. It should be noted that deficiency of FXII is associated with significant prolongation of the aPTT but no bleeding phenotype. ■ ■ **FAMILIAL MULTIPLE COAGULATION DEFICIENCIES** Several bleeding disorders are characterized by the inherited deficiency of more than one plasma coagulation factor. To date, the genetic defects in two of these diseases have been characterized, and they provide new insights into the regulation of hemostasis by gene-encoding proteins outside blood coagulation. **Combined Deficiency of FV and FVIII** Patients with combined FV and FVIII deficiency exhibit ~5% of residual clotting activity of each factor, yet have a mild bleeding tendency, often following trauma. A mutation in the lectin mannose binding 1 (LMAN1) gene, a mannose-binding protein localized in the Golgi apparatus that functions as a chaperone for both FV and FVIII, is responsible. In other families, mutations in the multiple coagulation factor deficiency 2 (MCFD2) gene have been defined; this gene product forms a Ca²⁺-dependent complex with LMAN1, providing cofactor activity for intracellular mobilization of both FV and FVIII. Replacement therapy to control or prevent bleeding consists of FFP to maintain FV levels and DDAVP or FVIII concentrate to achieve FVIII levels of 20–40%. Alternatively, platelets, which contain FV, can also be used. **Multiple Deficiencies of Vitamin K-Dependent Coagulation Factors** Two enzymes involved in vitamin K metabolism have been associated with combined deficiency of all vitamin K-dependent proteins, including the procoagulant proteins prothrombin (II), VII, IX, and X and the anticoagulant proteins C and S. Vitamin K, a fat-soluble vitamin, is a cofactor for carboxylation of the gamma carbon of the glutamic acid residues in the vitamin K-dependent factors, a critical step for calcium and phospholipid binding (Fig. 121-3). The enzymes γ-glutamylcarboxylase and epoxide reductase are critical for the metabolism and regeneration of

vitamin K. Mutations in the genes encoding the γ -carboxylase (GGCX) or vitamin K epoxide reductase complex 1 (VKORC1) result in defective enzymes and thus in vitamin K-dependent factors with reduced activity, varying from 1–30%

Warfarin Epoxide reductase Vitamin K epoxide Vitamin K reduced Carboxylase γ -Carboxyglutamic acid Glutamic acid

FIGURE 121-3 The vitamin K cycle. Vitamin K is a cofactor for the formation of γ -carboxyglutamic acid residues on coagulation proteins. Vitamin K-dependent γ -glutamylcarboxylase, the enzyme that catalyzes the vitamin K epoxide reductase, regenerates reduced vitamin K. Warfarin blocks the action of the reductase and competitively inhibits the effects of vitamin K. of normal. Patients can have mild to severe bleeding episodes present from birth. Some patients respond to oral vitamin K1 (5–20 mg/d) or parenteral vitamin K1 at doses of 5–20 mg/week. For severe bleeding, replacement therapy with PCC may be necessary. ■

■DISSEMINATED INTRAVASCULAR COAGULATION In 2001, the International Society on Thrombosis and Haemostasis (ISTH) defined DIC as “an acquired syndrome characterized by the intravascular activation of coagulation with loss of localization arising from different causes that can originate from and cause damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction.” Many disparate processes are associated with DIC (Table 121-2). The most common causes are bacterial sepsis, although viral and fungal sepsis can also cause DIC; trauma; obstetric causes such as abruptio placentae or amniotic fluid embolism; and malignant disorders, especially mucin-producing adenocarcinomas and acute promyelocytic leukemia. Activation of inflammatory pathways in response to infectious pathogens results in increased expression of tissue factor, activation of neutrophils and monocytes with release of cytokines and development of neutrophil extracellular traps, and release of poly phosphates that engage in cross-talk with the coagulation system to cause thrombin generation; this process is known as thrombo-inflammation. Damage to vascular endothelial cells results in the loss of their native antithrombotic properties; such damage especially occurs with sepsis and trauma. Systemic inflammatory response syndrome (SIRS) and cytokine storm are cytokine-mediated exuberant inflammatory responses often in the setting of infection that are associated with increased mortality and DIC. Purpura fulminans is a severe form of DIC resulting in thrombosis of extensive areas of the skin; it affects predominantly young children following viral or bacterial infection, particularly those with inherited or acquired hypercoagulability due to deficiencies of the components of the protein C pathway. Neonates homozygous for protein C deficiency can develop neonatal purpura fulminans with or without thrombosis of large vessels. Red blood cell damage and hemolysis Ischemic tissue damage Failure of multiple organs The central mechanism of DIC is the uncontrolled generation of thrombin by multiple mechanisms

(Fig. 121-4). Simultaneous disruption of the physiologic anticoagulant mechanisms and abnormal fibrinolysis further accelerate the process. These abnormalities contribute to systemic fibrin deposition in small and midsize vessels. The duration and intensity of the fibrin deposition can compromise Vessel patency FDP D-dimer

FIGURE 121-4 The pathophysiology of disseminated intravascular coagulation (DIC). Interactions between coagulation and fibrinolytic pathways result in bleeding and thrombosis in the microcirculation in patients with DIC. FDP, fibrin degradation product.

TABLE 121-2 Common Clinical Causes of Disseminated Intravascular Coagulation SEPSIS

IMMUNOLOGIC DISORDERS • Bacterial: Staphylococci, streptococci, • Acute hemolytic transfusion

reaction • Organ or tissue transplant rejection • Immunotherapy • Graft-versus-host disease pneumococci, meningococci, gram-negative bacilli • Viral • Mycotic • Parasitic • Rickettsial TRAUMA AND TISSUE INJURY DRUGS • Brain injury (gunshot) • Extensive burns • Fat embolism • Rhabdomyolysis • Fibrinolytic agents • Aprotinin • Warfarin (especially in neonates with protein C deficiency) • Prothrombin complex concentrates • Recreational drugs (amphetamines) VASCULAR DISORDERS ENVENOMATION • Giant hemangiomas (Kasabach- • Snake • Insects CHAPTER 121 Merritt syndrome) • Large vessel aneurysms (e.g., aorta) OBSTETRICAL COMPLICATIONS LIVER DISEASE • Abruptio placentae • Amniotic fluid embolism • Dead fetus syndrome • Septic abortion • Fulminant hepatic failure • Cirrhosis • Fatty liver of pregnancy Coagulation Disorders CANCER MISCELLANEOUS • Adenocarcinoma (prostate, • Shock • Respiratory distress syndrome • Massive transfusion pancreas, etc.) • Hematologic malignancies (acute promyelocytic leukemia) the blood supply of many organs, especially the lung, kidney, liver, and brain, with consequent organ failure; for example, pulmonary microvascular thrombosis is a component of adult respiratory distress syndrome (ARDS). The sustained activation of coagulation and formation of fibrin can result in consumption of clotting factors and platelets, which in turn leads to systemic bleeding that can be aggravated by secondary hyperfibrinolysis that occurs in late stages of DIC. DIC Uncontrolled thrombin generation Fibrin deposits in the microcirculation Consumption of platelets and coagulation factors Secondary fibrinolysis Diffuse bleeding

TABLE 121-3 International Society on Thrombosis and Haemostasis Criteria for Overt Disseminated Intravascular Congestion (DIC) PARAMETER VALUE POINTS Platelets

“ 100,000 × 10 ⁹ /L
“ 50–<100 × 10 ⁹ /L

<50 × 10⁹/L

d-Dimera Normal

Moderate increase

Severe increase

Prothrombin time (PT) prolonged <3 s

3–<6 s

“ 6 s

Fibrinogen

“ 1 g/L

<1 g/L

Total Score <5 Low-grade DIC

“ 5 Overt DIC ad-Dimer assays are not standardized and have different ranges of normal. Check your institution range of normal to assess degree of increase. Note: A score of <5 suggests nonovert DIC/low-grade DIC and should be repeated every 1–2 days. A score of >5 suggests overt DIC; lab values should be repeated daily to assess critical changes. Not to be used in pregnant patients. PART 4 Oncology and Hematology Clinical manifestations of DIC are related to the magnitude of the imbalance of hemostasis, to the underlying disease, or to both. The most common clinical findings include petechiae, ecchymoses, and bleeding ranging from oozing from venipuncture sites to severe hemorrhage from the gastrointestinal tract, lung, or into the CNS. In chronic DIC, the bleeding symptoms are discrete and restricted to skin or mucosal surfaces. The hypercoagulability of DIC manifests as the occlusion of vessels in the microcirculation resulting in organ failure. Thrombosis of large vessels and cerebral embolism can also occur. Hemodynamic complications and shock are common among patients with acute DIC, due to the underlying disease, with mortality ranging from 30 to >80%. Making the diagnosis of DIC can be difficult. The ISTH has developed a validated scoring tool to aid in the diagnosis of overt DIC with a separate tool for pregnant women. It incorporates platelet count, d-dimer level, PT, and fibrinogen level, and assigns points for different levels of each with the aggregate score helping to make the diagnosis of DIC (Table 121-3). The peripheral smear should be assessed for schistocytes. The laboratory diagnosis of DIC should prompt a search for the underlying disease if not already apparent. In critically ill patients, these tests should be repeated over a period of 6–8 h as patients can rapidly deteriorate. Chronic DIC Low-grade, compensated DIC can occur in clinical situations including giant hemangioma, metastatic carcinoma, or late gestation fetal demise. Plasma levels of fibrin degradation product or d-dimers are elevated. aPTT, PT, and fibrinogen values are within the normal range or high. Mild thrombocytopenia or normal platelet counts are also common findings. Red cell fragmentation is often detected but at a lower degree than in acute DIC. Differential Diagnosis Distinguishing between DIC and severe liver disease is challenging and requires serial measurements of the laboratory parameters of DIC. Patients with severe liver disease manifest laboratory features including thrombocytopenia due to platelet sequestration, portal hypertension, or hypersplenism; decreased synthesis of coagulation factors and

natural anticoagulants; and elevated levels of d-dimer. However, in contrast to DIC, these laboratory parameters in liver disease do not change rapidly. Although microangiopathic disorders such as immune thrombotic thrombocytopenic purpura present with acute onset accompanied by thrombocytopenia, red cell fragmentation, and multiorgan failure, the clinical presentation and laboratory findings including presence of an inhibitor to ADAMTS13 assist in diagnosis (Chap. 120).

TREATMENT Disseminated Intravascular Coagulation The morbidity and mortality associated with DIC are primarily related to the underlying disease. Management of the underlying disease is required to control and eliminate DIC; however, support with platelets and coagulation factors may be needed until the inciting cause is under control. Many patients with overt DIC are critically ill, usually requiring management in the intensive care unit to treat shock physiology and other manifestations of the underlying illness. **MANAGEMENT OF HEMORRHAGIC SYMPTOMS** Patients with active bleeding or at high risk of bleeding during invasive procedures or after chemotherapy require transfusion support; however, transfusion solely to correct mildly to moderately abnormal coagulation parameters is not indicated. Platelet transfusion for platelet counts $<10,000\text{--}20,000/\mu\text{L}$ and replacement of fibrinogen and coagulation factors with FFP, cryoprecipitate, or fibrinogen concentrate as a source of fibrinogen are indicated with amounts determined by the degree of abnormal PT, aPTT, and fibrinogen levels, as well as severity of bleeding or bleeding risk with invasive procedures. For these situations, fibrinogen level should be maintained at $>150\text{ mg/dL}$ and PT prolonged no more than 3 s above the upper limit of normal. Vitamin K should be given. Patients should be frequently monitored, and transfusion support adjusted as the patient's condition changes and dictates. **REPLACEMENT OF COAGULATION OR**

FIBRINOLYSIS INHIBITORS Anticoagulants such as heparin, concentrates of antithrombin and thrombomodulin, and antifibrinolytic drugs have all been tried in the treatment of DIC. Low doses of continuous-infusion heparin (5–10 U/kg per h) may be effective in patients with low-grade DIC associated with solid tumors, acute promyelocytic leukemia, or in a setting with recognized thrombosis. Heparin is also indicated for the treatment of purpura fulminans. In acute hemorrhagic DIC, the use of heparin is likely to aggravate bleeding. The use of heparin in patients with severe DIC, although demonstrating improved coagulation parameters, is not associated with a survival benefit; professional society recommendations for use vary widely. Although the use of concentrates of the serine protease inhibitors, antithrombin and thrombomodulin, for sepsis demonstrated little efficacy in all treated patients, post hoc analyses of those with sepsis and confirmed DIC suggest a survival advantage and require further study. Activated protein C treatment for septic shock was withdrawn from the market years ago as findings in clinical practice did not replicate the mortality advantage seen in the clinical trial; impact on DIC was not evaluated. In patients who have DIC characterized by a primary hyperfibrinolytic state with concomitant severe bleeding, the administration of antifibrinolytics may be considered. However, concern for increasing the risk of thrombosis has led to consideration of concomitant use of heparin. Patients with acute promyelocytic leukemia or those with chronic DIC associated with giant hemangiomas are among the few patients who may benefit from this therapy. ■ ■ **VITAMIN K DEFICIENCY** Vitamin K-dependent proteins are a heterogeneous group, including clotting factor proteins and proteins

found in bone, lung, kidney, and placenta. Vitamin K mediates posttranslational modification of glutamate residues to γ -carboxylglutamate, which is necessary for calcium binding and proper assembly on phospholipid membranes (Fig. 121-3). Inherited mutations with decreased functional activity of the enzymes GGCX or VKORC1 (see above) result in bleeding disorders. Vitamin K

in the diet is often limiting for the carboxylation reaction; thus, recycling of the vitamin K by these enzymes is essential to maintain normal levels of vitamin K-dependent proteins. In adults, severe

vitamin K deficiency due to low dietary intake is rare but is common in

association with the use of broad-spectrum antibiotics or with disease or surgical interventions that affect the ability of the intestinal tract to absorb vitamin K, through anatomic alterations or by changing the fat content of bile salts and pancreatic enzymes in the proximal small bowel. Chronic liver diseases such as primary biliary cirrhosis also deplete vitamin K stores. Neonatal vitamin K deficiency and the resulting hemorrhagic disease of the newborn have been almost entirely eliminated by routine administration of vitamin K to all neonates. Prolongation of PT values is the most common and earliest finding in vitamin K-deficient patients due to the short half-life of FVII and occurs before prolongation of the aPTT. Parenteral administration of 10 mg of vitamin K is sufficient to restore normal levels of clotting factor within 8–10 h. More rapid correction of the coagulopathy requires replacement with FFP or PCC, with the choice depending on patient intravascular volume status and need for rapidity of correction. The reversal of excessive anticoagulant therapy with vitamin K antagonists, such as warfarin, can be achieved by minimal doses of vitamin K

(1 mg orally or by intravenous injection) for asymptomatic patients. This strategy can diminish the risk of bleeding while maintaining therapeutic anticoagulation for an underlying prothrombotic state. For emergent reversal of warfarin in the setting of life-threatening bleeding or need for emergency surgery, use of 4F-PCC is the standard of care. In patients with underlying vascular disease, vascular trauma, atrial fibrillation, and other comorbidities, re-initiation of anticoagulation needs to be carefully considered to prevent subsequent thromboembolic complications. ■

■ COAGULATION DISORDERS ASSOCIATED

WITH LIVER FAILURE The liver is the site of synthesis and clearance of most procoagulant and natural anticoagulant proteins and of essential components of the fibrinolytic system. Acute liver failure is associated with a high risk of bleeding due to deficient synthesis of procoagulant factors and enhanced fibrinolysis; hepatologists refer to this as accelerated intravascular coagulation and fibrinolysis (AICF). Thrombocytopenia is common in patients with liver disease and may be due to decreased thrombopoietin that is synthesized in the liver, congestive splenomegaly (hypersplenism), or immune-mediated shortened platelet life span (primary biliary cirrhosis). In addition, several anatomic abnormalities secondary to underlying liver disease further increase the risk of bleeding (Table 121-4). Dysfibrinogenemia is a relatively common finding in patients with liver disease due to impaired fibrin polymerization. The development of DIC in patients with chronic liver disease is not uncommon and may enhance the risk for bleeding. Laboratory

TABLE 121-4
Coagulation Disorders and Hemostasis in Liver Disease
Bleeding
Portal hypertension
Esophageal varices
Thrombocytopenia
Splenomegaly
Chronic or acute DIC
Decreased synthesis of clotting factors
Hepatocyte failure
Vitamin K deficiency
Systemic fibrinolysis
DIC
Dysfibrinogenemia

Thrombosis Decreased synthesis of coagulation inhibitors: protein C, protein S, antithrombin
Hepatocyte failure Vitamin K deficiency (protein C, protein S) Failure to clear activated coagulation proteins (DIC) Dysfibrinogenemia Abbreviation: DIC, disseminated intravascular coagulation.

evaluation is mandatory for an optimal therapeutic strategy, either to control ongoing bleeding or before invasive procedures. Typically, these patients present with prolonged PT, aPTT, and thrombin time (TT) depending on the degree of liver damage, thrombocytopenia, and normal or slight increase in d-dimer. Fibrinogen levels are low only in fulminant hepatitis, decompensated cirrhosis, advanced liver disease, or in the presence of DIC. The presence of prolonged TT and normal fibrinogen and d-dimer levels suggests dysfibrinogenemia. FVIII levels are often normal or elevated in patients with liver failure, and decreased levels suggest superimposed DIC. FV is only synthesized in the hepatocyte and is not a vitamin K-dependent protein; therefore, reduced levels of FV may be an indicator of liver failure. Normal levels of FV and low levels of FVII suggest vitamin K deficiency. Vitamin K levels may be reduced in patients with liver failure due to compromised storage in hepatocellular disease, changes in bile acids, or cholestasis that can diminish the absorption of vitamin K. Replacement with intra venous vitamin K may improve hemostasis.

Patients with chronic stable liver disease are now recognized to have rebalanced hemostasis with simultaneous changes in both pro coagulant and anticoagulant proteins. Although traditional clinical laboratory tests may suggest increased bleeding risk, these patients in fact do not have spontaneous bleeding and often do not need treatment for minor to moderate bleeding risk procedures. If the patient is bleeding, treatment with FFP was the standard approach to correcting hemostasis in patients with acute liver failure; however, the use of 4F-PCC is now favored due to lower volume, less increase in portal pressure, reduced risk of circulatory overload, and other complications associated with FFP transfusion. As in any clinical situation, treatment should not be given simply to correct laboratory abnormalities in a patient who is not bleeding or with no need for invasive procedures. Platelet concentrates are indicated when platelet counts are $<10,000$ – $20,000/\mu\text{L}$ to control bleeding or immediately before an invasive procedure if counts are $<50,000/\mu\text{L}$. Cryoprecipitate is indicated only when fibrinogen levels are <100 – 150 mg/mL unless the patient is bleeding, in which case a higher target is used. The use of antifibrinolytic drugs as adjuncts to control bleeding in patients with liver failure is not thought to result in an increased risk of thrombosis; however, their impact on acute thrombosis propagation is not well studied.

CHAPTER 121 Coagulation Disorders Liver Disease and Thromboembolism Bleeding in patients with stable liver disease is often mild or even asymptomatic. However, as the disease progresses, the hemostatic balance is precarious and easily disturbed; comorbid complications such as infections and renal failure can rapidly upset this balance (Fig. 121-5). Past assumptions based on abnormal coagulation tests have been that patients with liver disease have a decreased risk of thrombosis; however, multiple factors contribute to hypercoagulability, including decreased levels of the natural anticoagulant proteins S and C, as well as endothelial cell changes and hemodynamic changes that result in stasis such that portal vein thrombosis is common. Patients with liver disease can also develop deep-vein thrombosis and pulmonary embolism; those with cirrhosis appear to have a 1.5- to 2-fold increase in the rate of venous thromboembolism (VTE). Patients with compensated cirrhosis do not appear to have increased bleeding with the use of VTE prophylaxis or even therapeutic dose heparin to treat acute portal vein thrombosis when carefully managed. In the outpatient setting, warfarin is avoided, but low-molecular-weight heparin and direct oral anticoagulants have been safely used to treat thrombosis. Acquired Inhibitors of

Coagulation Factors An acquired inhibitor is an immune-mediated disease characterized by the presence of an autoantibody against a specific clotting factor. Almost half of patients with an acquired factor inhibitor will have an underlying autoimmune or immunoproliferative disorder, have a malignancy, or be peripartum. FVIII is the most common target of antibody formation and is often referred to as acquired hemophilia A, but inhibitors to prothrombin (FII), FV, FIX, FX, and FXI are also reported. Acquired inhibitor to FVIII occurs predominantly in older adults (median age of 60 years) but occasionally in pregnant or postpartum women with

BLEEDING THROMBOSIS Thrombocytopenia Increased levels of VWF Abnormal platelet function
Primary hemostasis Low production of thrombopoietin Decreased levels of ADAMTS-13 Increased production nitric oxide and prostacyclin
EQUILIBRIUM Reduced levels of factors II, V, VII, IX, X, XI
Elevated levels of FVIII
Coagulation Decreased levels of protein C, protein S, antithrombin and heparin cofactor II Vitamin K deficiency Disfibrinogenemia Inherited thrombophilia Low levels of α 2-antiplasmin, FXIII and TAFI
Fibrinolysis Low levels of plasminogen Elevated level of t-PA
Hemodynamic changes (reduced portal blood flow) Comorbidity
PART 4 Oncology and Hematology
Vascular damage (esophageal varices) Portal hypertension; bacterial infection and renal diseases
FIGURE 121-5 Balance of hemostasis in liver disease. TAFI, thrombin-activated fibrinolytic inhibitor; t-PA, tissue plasminogen activator; VWF, von Willebrand factor. no previous history of bleeding. Bleeding episodes occur commonly in soft tissues, the gastrointestinal or urinary tracts, and skin. In contrast to congenital hemophilia, hemarthrosis is rare in these patients. Retroperitoneal hemorrhages and other life-threatening bleeding may appear suddenly. The overall mortality in untreated patients ranges from 8–22%, and most deaths occur within the first few weeks after presentation. The diagnosis is based on the prolonged aPTT with normal PT and TT and a mixing study that does not correct with normal pooled plasma. The Bethesda assay using factor-specific deficient plasma as performed for inhibitor detection in hemophilia will confirm the diagnosis. Treatment of acquired inhibitors of coagulation factors requires control of bleeding and eradication of the inhibitor. Many patients can have life-threatening bleeding. The use of activated “bypass products” such as aPCC or recombinant FVIIa is required. The use of recombinant porcine FVIII can be effective for acquired inhibitors of FVIII. The use of emicizumab to treat acquired FVIII inhibitors has been reported, and trials in this population are underway in Europe. In contrast to inhibitors in patients with congenital factor deficiencies, acquired inhibitors are typically responsive to immune suppression, and treatment should be initiated early for most cases. High-dose intravenous γ -globulin and anti-CD20 monoclonal antibody are reported to be effective in patients with autoantibodies to FVIII; however, no firm evidence confirms that these alternatives are superior to the first line of immunosuppressive drugs (glucocorticoids and cyclophosphamide), effective in 70% of patients. Relapse of an inhibitor to FVIII is relatively common (up to 20%) within the first 6 months following withdrawal of immunosuppression; patients should be followed up regularly for relapse. Topical plasma-derived bovine and human thrombin are commonly used during major cardiovascular, thoracic, neurologic, and pelvic surgeries as well as in trauma patients with extensive burns. Antibody formation to the xenoantigen or its contaminant (bovine clotting protein) has the potential to cross-react with human clotting factors, particularly FV and thrombin, and can result in bleeding that can be life-threatening. The development of antibodies to FV with the use of topical preparations of recombinant human thrombin has also been

reported. The clinical diagnosis of these acquired coagulopathies is rare but is often complicated by the fact that the bleeding episodes may be detectable during or immediately following major surgery and could be assumed to be due to the procedure itself. Primary hemostasis The risk of

developing a cross-reacting antibody is increased by repeated exposure to topical thrombin preparations. Thus, a careful medical history of previous surgical interventions that may have occurred even decades earlier is critical to assessing risk. Coagulation The laboratory abnormalities include a combined prolongation of the aPTT and PT that often fails to improve by transfusion of FFP and vitamin K, and a mixing study that does not correct with normal pooled plasma. The specificity of the antibody is determined by the measurement of the residual activity of human FV or other suspected human clotting factor. No assays specific for bovine thrombin coagulopathy are commercially available. Fibrinolysis No treatment guidelines have been established. Platelet transfusions have been used as a source of FV replacement for patients with FV inhibitors. FFP and vitamin K supplementation may function as co-adjuvants rather than as effective treatments for the coagulopathy itself. Experience with recombinant FVIIa as a bypass agent is limited, and outcomes have been generally poor. Specific treatments to eradicate the antibodies based on immunosuppression with glucocorticoids, intravenous immunoglobulin, or serial plasmapheresis have been sporadically reported. Patients should be advised to avoid any topical thrombin sealant in the future. The presence of lupus anticoagulant can be associated with venous or arterial thrombotic disease. However, bleeding has also been reported rarely with lupus anticoagulants due to antibodies to prothrombin, resulting in hypoprothrombinemia. Both disorders show a prolonged aPTT that does not correct on mixing. To distinguish acquired inhibitors from lupus anticoagulant, note that the dilute Russell viper venom time (dRVVT) and the hexagonal-phase phospholipids test will be negative in patients with an acquired inhibitor and positive in patients with lupus anticoagulants. Moreover, lupus anticoagulant interferes with the clotting activity of many factors (FVIII, FIX, FXI, FXII), which can be assessed in the clinical laboratory; acquired inhibitors are specific to a single factor. Acknowledgment Valder Arruda and Katherine High wrote this chapter in prior editions and some material from their chapter is included here. ■ ■ FURTHER READING Kitazawa T, Shima M: Emicizumab, a humanized bispecific antibody to coagulation factors IXa and X with a factor VIIIa-cofactor activity. *Int J Hematol* 111:20, 2020. Levi M, Scully M: How I treat disseminated intravascular coagulation. *Blood* 131:845, 2018. Menegatti M et al: Management of rare acquired bleeding disorders. *Hematology Am Soc Hematol Educ Program* 2019:80, 2019. Pipe S et al: Delivery of gene therapy in haemophilia treatment centres in the United States: Practical aspects of preparedness and implementation. *Haemophilia* 29:1430, 2023. Roberts LN: How to manage hemostasis in patients with liver disease during interventions. *Hematology Am Soc Hematol Educ Program* 2023:274, 2023. Srivastava A et al: WFH guidelines for the management of hemophilia, 3rd edition. *Haemophilia* 26:1, 2020.

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