disorders and the deep tissue or joint bleeding classically associated with coagulation factor deficiencies.

The diagnosis of congenital afibrinogenemia or dysfibrinogenemia can be established by screening assays (see E-Table 51-2), laboratory assays to measure fibrinogen levels, and tests such as the thrombin time that are designed to measure fibrinogen function. Treatment depends on replacement of fibrinogen by infusion of cryoprecipitate or a fibrinogen concentrate (discussed later).

Acquired Coagulation Factor Disorders

Factor Inhibitors in Congenital Factor Deficiencies

About 25% of patients with hemophilia A develop alloantibodies to transfused factor VIII. An inhibitor acts functionally and can be measured in the laboratory as Bethesda units (BU); 1 BU is defined as the amount of inhibitor that neutralizes 50% of factor activity. High-level inhibitors (>10 BU) completely neutralize the activity of infused factor concentrates, negating their effectiveness in bleeding episodes.

Bleeding requires therapeutic regimens with factor VIII inhibitor bypass activity (FEIBA) or recombinant factor VIIa. For long-term treatment, suppression of an inhibitor is accomplished by a combination of IVIG, immunosuppressive therapy, plasmapheresis, and induction of immune tolerance using high-dose concentrate infusions. Patients with hemophilia B have a lower incidence of inhibitors (2% to 6%), but bleeding in the setting of these inhibitors is treated in a similar fashion with high-dose FEIBA or recombinant VIIa; similar strategies for long-term suppression of the antibody are typically employed.

Acquired Factor Inhibitors

Acquired inhibitors to factor VIII (and rarely to other coagulation factors) occasionally are found in patients (usually older) who do not have a history of bleeding. In contrast to the antibodies in patients with severe congenital hemophilia, acquired inhibitors are typically autoantibodies.

Acquired factor VIII inhibitor titers can be extremely high and are sometimes associated with pregnancy, autoimmune disorders, and malignant diseases, especially lymphoproliferative disorders. Association with these underlying disorders implies some form of immune dysregulation, but the mechanisms underlying acquired factor inhibitors remain poorly understood.

The diagnosis of an acquired inhibitor can be made by laboratory techniques similar to those detailed for patients with congenital hemophilia. For the treatment of bleeding, patients with acquired inhibitors to factor VIII are administered factor VIIa or FEIBA to promote hemostasis. Intensive immunosuppressive therapy with rituximab, an anti-CD20 agent, has become the mainstay of successful treatment and should be started as soon as possible to eradicate the inhibitor.

Vitamin K Deficiency

Bleeding in inpatients and outpatients who are severely ill may be caused by acquired coagulation factor deficiencies resulting from nutritional deficiencies. Foremost among these is vitamin K deficiency, which has several causes. Biliary tract disease can interfere with enterohepatic circulation, leading to decreased absorption of vitamin K. Drugs, especially antibiotics, can sterilize the gut and reduce bacterial sources of vitamin K or other drugs (e.g., cholestyramine) that directly block vitamin K absorption; this category also includes cephalosporins, which interfere with intrahepatic metabolism of fat-soluble vitamin K. Vitamin K deficiency also may reflect poor nutritional status due to malabsorption, chronic disease, or reduced oral intake in patients who are acutely ill.

Factors II, VII, IX, and X are vitamin K–dependent procoagulant factors, as are the natural anticoagulants proteins C and S. In addition to disease-associated vitamin K deficiency, the anticoagulant warfarin blocks vitamin K–dependent γ-carboxylation of factors II, VII, IX, and X and causes an acute decrease in functional factor VII levels because factor VII has the shortest half-life (6 hours) of all vitamin K–dependent factors in vivo. Individuals who experience bleeding while on warfarin may be treated by repletion of vitamin K.

Dilutional Coagulopathy

As with platelets, coagulation factors can be depleted through the dilutional effects of a pure red blood cell transfusion or with the administration of massive amounts of volume expanders or saline solutions. For every 10 units of red cells acutely transfused, there is a concomitant increase in the international normalized ratio (INR) to greater than 2. This also occurs in conjunction with depletion and consumption of circulating coagulation factors due to acute bleeding.

In the setting of trauma, it is important to maintain adequate coagulation factor activity through plasma transfusion. Evidence from the trauma literature suggests that transfusion ratios of red cells to plasma should approach 1 : 1 to optimize hemostasis. The effects of dilutional coagulopathy should be monitored by repeated testing of PT and aPTT with a liberal plasma transfusion strategy.

Liver Disease

Unlike patients with vitamin K deficiency or those receiving warfarin, patients with liver disease have low levels of most factors, not just the vitamin K–dependent factors; the exception is factor VIII. Although liver transplantation increases factor VIII levels in patients with hemophilia, factor VIII levels are usually normal or increased with liver disease, a finding corresponding to RES and megakaryocytic sources of factor VIII production. If factor VIII levels are decreased in patients with liver disease, consideration should be given to superimposed DIC.

When a prolonged PT is evaluated for its cause, measurement of factor VII and a non–vitamin K–dependent factor, such as factor V, is useful. In vitamin K deficiency, the level of factor VII is low, and that of factor V is normal; levels of both factors are low in patients with generalized liver disease. The PT is a sensitive measure of liver function and becomes prolonged in patients with even mild liver disorders; elevation precedes a significant decrease in the albumin or prealbumin levels and is usually coincident with transaminase changes. In patients with mild to moderate liver disease, the PT is prolonged, but the aPTT usually remains within the normal range. In severe liver disease, the PT