becomes even more prolonged, and the aPTT also becomes abnormal.

Other causes of bleeding in liver disease include decreased clearance of fibrin split products or associated DIC, inhibition of platelet function, and increased levels of tissue plasminogen activator. Treatment of bleeding associated with liver disease is based primarily on replacement of coagulation factors by plasma transfusions, although they only temporarily correct abnormalities. Liver transplantation is the only definitive treatment for these synthetic defects.

Fibrinogen Loss or Acquired Defects

Low fibrinogen levels are most commonly seen with consumptive disorders such as DIC, the pathophysiology of which was described earlier. Dysfibrinogenemia, which is occasionally a congenital disorder, is much more often acquired with liver disease. In this setting, diseased hepatocytes produce abnormal fibrinogen molecules arising from defects in post-translational modifications. The abnormal fibrinogen molecules cannot undergo normal cross-linking or polymerization, resulting in bleeding disorders.

The PT and aPTT are prolonged by abnormalities of fibrinogen quantity or function (see E-Table 51-2). A prolonged thrombin time is diagnostically more specific for a low fibrinogen level or abnormal molecule, although inhibitors such as heparin and fibrin split products also prolong the thrombin time. The reptilase time, which is insensitive to heparin, can be used to eliminate the possibility of an increased thrombin time resulting from heparin contamination of the sample and can help to confirm a diagnosis of dysfibrinogenemia.

BLEEDING IN PATIENTS WITH NORMAL LABORATORY VALUES

Some patients with factor- or platelet-dependent bleeding disorders do not exhibit any abnormalities in screening laboratory assays (e.g., PT, aPTT). Vascular purpuras and other bleeding variants follow this pattern. Patients with bleeding caused by mild vWD may have a normal aPTT, but additional studies usually show mild decreases in factor VIII, vWF antigen, or vWF Rcof. Multimeric analysis may demonstrate abnormal levels in patients with mild type 2A vWD. Similarly, mild deficiencies of factor II, V, VII, VIII, IX, or XI may not prolong the PT or aPTT, but specific-factor assays demonstrate levels lower than the normal range.

Mild bleeding, often with a delayed onset after surgery or trauma, may occur in patients with clot instability resulting from factor XIII deficiency or dysfibrinogenemia. In neonates, factor XIII deficiency manifests with late umbilical stump bleeding. Factor XIII deficiency is diagnosed in the laboratory by screening for increased clot solubility in urea; if the clot dissolves abnormally quickly in 8 mol/L of urea, an enzyme-linked immunosorbent assay for the precise XIII level should be performed. Factor XIII deficiency is treated with cryoprecipitate transfusion or an approved factor XIII concentrate. Because of the long half-life of factor XIII, prophylactic therapy for severe deficiency need be provided only in single doses on a 3- to 4-week recurring schedule.

Plasma and Coagulation Factor Transfusion Therapy

For patients with one or multiple defects in coagulation proteins, there are several options for replacement therapy. The most widely used product for replacement of coagulation factors is FFP (E-Fig 51-2). It is collected from the whole blood of healthy donors and is frozen within 8 hours of collection. It contains normal (i.e., therapeutic) levels of all coagulation factors necessary to maintain hemostasis. FFP is the best choice for replacement of coagulation factors for many conditions, including liver failure and deficiencies of factors II, V, X, and XI.

FFP is commonly used with vitamin K therapy for the reversal of warfarin therapy before invasive procedures or with the onset of bleeding. The appropriate dose of FFP is weight based and does not depend on the extent of prolongation in coagulation studies alone. Administration of FFP at 10 to 15 mL/kg should be sufficient to replace deficient coagulation factors and correct abnormal coagulation values. Assuming a volume of about 200 mL per unit of FFP, a reasonable dose for a 70-kg individual is 3 to 4 units of FFP. Administration is time sensitive because coagulation factors degrade at standard half-lives on infusion, and FFP should be provided immediately before an intended procedure to ensure adequate hemostasis.

In some cases, patients may not be able to tolerate the infusion of the large volumes of FFP required to reverse coagulopathic states, and other treatment modalities are available. Prothrombin complex concentrate (PCC) quickly reverses prolonged PTs without the need for large volumes of FFP. PCC is a concentrated, lyophilized, human-derived concentrate containing factors II, VII, IX, and X that can be reconstituted in small volumes and provided by intravenous bolus injection. A true four-factor PCC was approved for clinical use in 2013 by the U.S. Food and Drug Administration (FDA). A variant, human-derived PCC, FEIBA, contains factors II, IX, and X and factor VII that has been modified to be in its active form; FVIIa is the major difference between FEIBA and standard PCC. FEIBA is typically administered in doses of 50-100 U/kg every 8 to 12 hours.

PCC is a good alternative to FFP for bleeding in the setting of warfarin anticoagulation, and FEIBA is primarily used to overcome bleeding in the setting of a coagulation factor inhibitor. Vitamin K should also be considered as an alternative to plasma infusion. Oral or parenteral replacement of vitamin K (1 to 10 mg/day for 3 days) restores coagulation factor synthesis in patients with normal liver function and the vitamin deficiency.

For patients with hemophilia A or B, several virally inactivated, human-derived or recombinant factor VIII and IX concentrates are available. These products were developed because of the high morbidity and mortality rates caused by HIV and hepatitis virus contamination of the pooled products used during the 1980s.

For hemophilia, factor replacement is the key to effective therapy. Patients with severe hemophilia often infuse themselves with low doses of prophylactic factor on a regular basis (25 to 40 U/kg three times per week) and boost their dose or frequency of infusion when they sense internal bleeding, sustain trauma, or undergo dental procedures (E-Table 51-3). Patients with mild