

Patients with congenital Factor XII deficiency have no bleeding symptoms despite their having a prolonged aPTT, and do not require replacement therapy.

Severe Factor XIII deficiency is a bleeding disorder that often presents with umbilical stump bleeding. It is also associated with a high risk of spontaneous intracranial hemorrhage. PT, aPTT, and fibrinogen assays are normal, and specific tests of Factor XIII function will confirm a diagnosis. Replacement is achieved with pasteurized plasma-derived concentrate (Corifact, CSL Behring, King of Prussia, PA) or, in appropriate patients, a recombinant Factor XIII A-subunit preparation (Tretten, Novo Nordisk, Plainsboro, NJ).<sup>58</sup> Although Cryoprecipitated AHF also contains Factor XIII,<sup>42</sup> it is no longer the preferred replacement but would be acceptable in an urgent setting should the above-mentioned products be unavailable.<sup>12,54</sup> Factor XIII has a long half-life (5-11 days). Levels should be maintained above 5% to 10% to prevent spontaneous intracranial hemorrhage, but higher levels (at least 10% to 25%) are suggested for surgery.

Inherited disorders of fibrinogen may be quantitative or qualitative. In patients with congenital defects, fibrinogen replacement therapy may be indicated to treat or prevent surgical bleeding, improve wound healing, or prevent recurrent pregnancy loss. The FDA has licensed a heat-treated fibrinogen concentrate (RiaSTAP, CSL Behring) for patients with congenital fibrinogen deficiency, while Cryoprecipitated AHF remains the only FDA-licensed product for use in other settings.<sup>42,59</sup> Fibrinogen has a long half-life (55-120 hours) and suggested minimum target levels are 50 mg/dL to prevent recurrent pregnancy loss, and over 100 to 150 mg/dL in surgical settings.<sup>54</sup> However, in settings of consumptive hypofibrinogenemia, as occurs with complications of pregnancy or trauma, levels over 150 to 200 mg/dL are recommended.<sup>60</sup>

### **Alpha<sub>2</sub>-Plasmin Inhibitor**

Deficiency of alpha<sub>2</sub>-plasmin inhibitor, the primary circulating plasmin inhibitor, is associated with a severe hemorrhagic disorder.

der. Diagnosis requires a specific assay for this inhibitor. Therapy consists of replacement by plasma transfusion and/or oral antifibrinolytic agents such as epsilon aminocaproic acid (EACA).<sup>61</sup>

---

## Acquired Bleeding Disorders

---

### Vitamin K Deficiency and Vitamin K Antagonists

Vitamin K is a fat-soluble vitamin that is necessary for synthesis in the liver of coagulation Factors II, VII, IX, and X; protein C; and protein S. Nutritional deficiency states can occur in patients in the intensive care unit, those who have chronic disease and are receiving antibiotics, and those with general fat-malabsorption states, such as celiac disease, pancreatic insufficiency, or obstructive jaundice. The dose and route of vitamin K administration depend on the clinical situation. Oral administration is preferred over subcutaneous administration because of the delayed and unpredictable response to subcutaneously administered vitamin K.<sup>62</sup> Historically, intravenous infusion of vitamin K has been associated with anaphylaxis, but a slow infusion rate reduces the risk for patients in whom the oral route is unavailable. The full effect of vitamin K is achieved only after 12 to 24 hours; thus, urgent correction of deficiencies of the vitamin-K-dependent factors requires factor infusion in addition to vitamin K replacement (see below).

Vitamin K antagonists such as warfarin are still commonly used for outpatient anticoagulation therapy, interfering with the vitamin-K-dependent synthesis of coagulation Factors II, VII, IX, and X. Despite their effectiveness, vitamin K antagonists are plagued with problems, including a narrow therapeutic window, considerable dose-response variability between patients, interactions with both drugs and dietary factors, and difficulty in maintaining a therapeutic degree of anticoagulation [as monitored by

the international normalized ratio (INR)]. In rare cases, warfarin-induced skin necrosis can develop about 1 to 4 days after initiation of therapy, which is related to the drug's early effect on protein C synthesis. Patients with congenital deficiency of protein C or its cofactor (protein S) are at increased risk for the development of this complication of warfarin therapy and may warrant coverage with heparin-based therapy until the full warfarin effect is achieved. Warfarin overdose is treated by withdrawal of the drug and/or the administration of vitamin K. In the absence of bleeding, 0.5 to 2 mg of oral vitamin K may be sufficient, but 2.5 mg or higher doses are recommended. The optimal dose of vitamin K has not been evaluated through clinical trials.<sup>62</sup> Urgent replacement of vitamin-K-dependent coagulation factors is addressed below.

#### **Other Anticoagulant Drugs: Heparins and Directed Oral Anticoagulants**

Heparin-based drugs [either conventional unfractionated heparin (UFH) or lower-molecular-weight derivatives] are among the most frequently prescribed medications to treat or prevent thromboembolism. Heparin markedly enhances the ability of antithrombin to neutralize serine proteases. Even slight contamination of a diagnostic sample with UFH (eg, the flush volume in a subclavian catheter) can prolong the TT and the aPTT, which can lead to confusion in diagnosis. The risk of bleeding in patients taking heparin drugs is modified by many factors, including comorbid conditions (such as recent surgery, trauma, or renal failure), the patient's age and gender, and the use of concomitant antiplatelet drugs.<sup>63</sup> UFH therapy is monitored by either using the aPTT or by directly assessing heparin activity via the anti-Factor Xa assay. Plasma is not effective in reversing heparin effect, and acute UFH reversal is accomplished with protamine sulfate.<sup>64</sup> At the completion of cardiac bypass surgery, algorithms or point-of-care instruments can be used to estimate the quantity of circulating heparin in order to select an appropriate

protamine dose; 1 mg of protamine sulfate neutralizes 80 to 100 units of UFH. Protamine has a shorter half-life than UFH, and “rebound” heparin effect or initial underestimation of the protamine dose should be considered in a patient with unexplained bleeding after protamine therapy.<sup>41</sup> Low-molecular-weight heparin (LMWH) is derived by enzymatic or chemical depolymerization of UFH. FDA-approved indications and dose schedules differ between the various approved LMWH preparations, but as a class they share most attributes. LMWH drugs have less anti-Factor IIa activity (and therefore less effect on the aPTT) than does UFH, but they retain the ability to accelerate antithrombin effect against Factor Xa, and thus they remain potent anticoagulant drugs. Compared to UFH, LMWH produces a more predictable anticoagulant response, has a longer plasma half-life (3 to 12 hours), and fewer interactions with osteoclasts and platelets. These qualities translate into weight-based dosing on a once- to twice-daily time frame, no need to monitor levels in most patient settings, and a reduced risk for HIT. The aPTT is not an appropriate monitor of LMWH effect, and specific drug levels (via anti-Factor Xa assay) are required if monitoring is desired. LMWH is cleared mainly through a renal mechanism, and dose adjustment is required in patients with significant renal impairment. If excessive bleeding occurs, protamine may be helpful but is not a completely effective antidote.

Fondaparinux (Arixtra, GlaxoSmithKline, Research Triangle Park, NC) is a synthetic pentasaccharide that strongly binds antithrombin and acts as a selective inhibitor to Factor Xa. It is administered parenterally, has a half-life of 17 to 21 hours, and is cleared primarily through renal excretion. Clinical licensing has been for thromboprophylaxis in the orthopedic setting and for initial treatment of venous thrombotic disease; dose schedules are weight-based and do not rely on drug level monitoring. Fondaparinux is not neutralized by protamine and is not easily removed via dialysis. Case reports suggest that off-label use of rFVIIa has been helpful in patients who develop severe bleeding complications while on fondaparinux.<sup>65</sup>