triad, hemodynamic changes and damaged vasculature may also be a contributing factor, and both processes may potentially also occur in patients with liver disease. Liver-related thrombosis, in particular, thrombosis of the portal and mesenteric veins, is common in patients with advanced cirrhosis. Hemodynamic changes, such as decreased portal flow, and evidence that inherited thrombophilia may enhance the risk for portal vein thrombosis in patients with cirrhosis suggest that hypercoagulability may play a role as well. Patients with liver disease develop deep vein thrombosis and pulmonary embolism at appreciable rates (ranging from 0.5 to 1.9%). The implication of these findings is relevant to the erroneous exclusion of thrombosis in patients with advanced liver disease, even in the presence of prolongation of routine clotting times, and caution should be advised on overcorrection of these laboratory abnormalities.

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. FVIII is the most common target of antibody formation, and is sometimes referred to as acquired hemophilia A, but inhibitors to prothrombin, 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 no previous history of bleeding. In 50% of patients with inhibitors, no underlying disease is identified at the time of diagnosis. In the remaining patients, the causes are autoimmune diseases, malignancies (lymphomas, prostate cancer), dermatologic diseases, and pregnancy. Bleeding episodes occur commonly in soft tissues, the gastrointestinal or urinary tracts, and skin. In contrast to 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 to 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. The aPTT remains prolonged after mixture of the test plasma with equal amounts of pooled normal plasma for 2 h at 37°C. The Bethesda assay using FVIII-deficient plasma as performed for inhibitor detection in hemophilia will confirm the diagnosis. Major bleeding is treated with bypass products such as PCC/aPCC or recombinant FVIIa. In contrast to hemophilia, inhibitors in nonhemophilic patients are typically responsive to immune suppression, and therapy should be initiated early for most cases. The first choice includes steroid or a combination of steroid with cytotoxic therapy (e.g., cyclophosphamide), with complete eradication of the inhibitors in more than 70% of patients. High-dose intravenous γ-globulin and anti-CD20 monoclonal antibody have been reported to be effective in patients with autoantibodies to FVIII; however, there is no firm evidence that these alternatives are superior to the first line of immunosuppressive drugs. Notably, relapse of the inhibitor to FVIII is relatively common (up to 20%) within the first 6 months following withdrawal of immunosuppression. Thus, after eradication, patients should be followed up regularly for early therapeutic intervention when indicated or prior to invasive procedure.

Topical plasma-derived bovine and human thrombin are commonly used in the United States and worldwide. These effective hemostatic sealants are used during major surgery such as for cardiovascular, thoracic, neurologic, pelvic, and trauma indications, as well as in the setting of extensive burns. The development of antibody formation to the xenoantigen or its contaminant (bovine clotting protein) has the potential to show cross-reactivity with human clotting factors that may hamper their function and induce bleeding.

Clinical features of these antibodies include bleeding from a primary hemostatic defect or coagulopathy that sometimes can be life threatening. The clinical diagnosis of these acquired coagulopathies 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.

Notably, the risk of this complication is further 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.

The laboratory abnormalities are reflected by combined prolongation of the aPTT and PT that often fails to improve by transfusion of FFP and vitamin K. The abnormal laboratory tests cannot be corrected by mixing a test with equal parts of normal plasma that denotes the presence of inhibitory antibodies. The diagnosis of a specific antibody is obtained by the determination of the residual activity of human FV or other suspected human clotting factor. There are no commercially available assays specific for bovine thrombin coagulopathy.

There are no established treatment guidelines. Platelet transfusions have been used as a source of FV replacement for patients with FV inhibitors. Frequent injections of FFP and vitamin K supplementation may function as co-adjuvant rather than an effective treatment of 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 steroids, intravenous immunoglobulin, or serial plasmapheresis have been sporadically reported. Patients should be advised to avoid any topical thrombin sealant in the future.

Novel plasma-derived and recombinant human thrombin preparations for topical hemostasis have been approved by the U.S. Food and Drug Administration. These preparations have demonstrated hemostatic efficacy with reduced immunogenicity compared to the first generation of bovine thrombin products.

The presence of lupus anticoagulant can be associated with venous or arterial thrombotic disease. However, bleeding has also been reported in lupus anticoagulant; it is due to the presence of antibodies to prothrombin, which results in hypoprothrombinemia. Both disorders show a prolonged PTT that does not correct on mixing. To distinguish acquired inhibitors from lupus anticoagulant, note that the dilute Russell's viper venom test 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, FXII, FXI), whereas acquired inhibitors are specific to a single factor.

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OVERVIEW OF THROMBOSIS

GENERAL OVERVIEW

Thrombosis, the obstruction of blood flow due to the formation of clot, may result in tissue anoxia and damage, and it is a major cause of morbidity and mortality in a wide range of arterial and venous diseases and patient populations. In 2009 in the United States, an estimated 785,000 people had a new coronary thrombotic event, and about 470,000 had a recurrent ischemic episode. Each year, approximately 795,000 people have a new or recurrent stroke. It is estimated that 300,000–600,000 people each year have a pulmonary embolism or deep venous thrombotic event. In the nondiseased state, physiologic hemostasis reflects a delicate interplay between factors that promote and inhibit blood clotting, favoring the former. This response is crucial as it prevents uncontrolled hemorrhage and exsanguination following injury. In specific settings, the same processes that regulate normal hemostasis can cause pathologic thrombosis, leading to arterial or venous occlusion. Importantly, many commonly used therapeutic interventions may also alter the thrombotic–hemostatic balance adversely.

Hemostasis and thrombosis primarily involve the interplay among three factors: the vessel wall, coagulation proteins, and platelets. Many prevalent acute vascular diseases are due to thrombus formation within a vessel, including myocardial infarction, thrombotic cerebrovascular events, and venous thrombosis. Although the end result is vessel occlusion and tissue ischemia, the pathophysiologic processes