clinical severity, which requires close laboratory monitoring in the following weeks.

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 for inhibitors. The laboratory test required to confirm the presence of an inhibitor is an aPTT with a mix (with normal plasma). In most hemophilia patients, a 1:1 mix with normal plasma completely corrects the aPTT. In inhibitor patients, the aPTT on a 1:1 mix is abnormally prolonged, because the inhibitor neutralizes the FVIII clotting activity of the normal plasma. The Bethesda assay uses a similar principle 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, which provides guidelines for optimal 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 or porcine FVIII (50–100 U/kg), with minimal or no increase in the inhibitor titers. However, high-responder patients, those with initial inhibitor titer >10 BU or an anamnestic response in the antibody titer to >10 BU even if low titer initially, do not respond to FVIII or FIX concentrates. The control of bleeding episodes in high-responder patients can be achieved by using concentrates enriched for prothrombin, FVII, FIX, FX (prothrombin complex concentrates [PCCs] or activated PCCs [aPCCs]), and more recently recombinant activated factor VII (FVIIa) known as "bypass agents" (Fig. 141-1). The rates of therapeutic success have been higher for FVIIa than for PCC or aPCC. For eradication of the inhibitory antibody, immunosuppression alone is not effective. The most effective strategy is the immune tolerance induction (ITI) based on daily infusion of missing protein until the inhibitor disappears, typically requiring periods longer than 1 year, with success rates of approximately 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. Although this therapy may reduce the inhibitor titers in some cases, sustained eradication is uncommon and may require two to three infusions weekly of clotting factor concentrates.

Novel Therapeutic Approaches in Development for Hemophilia Clinical studies using long-acting clotting factors with prolonged half-lives are in the late phase of clinical testing, and these new-generation products (for FVIII and FIX) may facilitate prophylaxis by requiring fewer injections to maintain circulating levels above 1%.

The use of recombinant interleukin 11 in patients with moderate or mild hemophilia A unresponsive to DDAVP has been tested in early-phase clinical trials and may be an alternate therapeutic strategy for clinical situations that require transient increases in FVIII levels.

Gene therapy trials for hemophilia B using adeno-associated viral vectors are ongoing, and initial data are promising (Chap. 91e).

INFECTIOUS DISEASES

Hepatitis C virus (HCV) infection is the major cause of morbidity and the second leading cause of death in hemophilia patients exposed to older clotting factor concentrates. The vast majority of young patients treated with plasma-derived products from 1970 to 1985 became infected with HCV. It has been estimated that >80% of patients older than 20 years of age are HCV antibody positive as of 2006. The comorbidity of the underlying liver disease in hemophilia patients is clear when these individuals require invasive procedures; correction of both genetic and acquired (secondary to liver disease) deficiencies may be needed. Infection with HIV also swept the population of patients using plasma-derived concentrates two decades ago. Co-infection of HCV and HIV, present in almost 50% of hemophilia patients, is an aggravating factor for the evolution of liver disease. The response to HCV antiviral therapy in hemophilia is restricted to <30% of patients and even poorer among those with both HCV and HIV infection. End-stage liver disease requiring organ transplantation may be curative for both the liver disease and for hemophilia.

EMERGING CLINICAL PROBLEMS IN AGING HEMOPHILIA PATIENTS

There has been continuous improvement of the management of hemophilia since the increase in the population of adults living beyond middle age in the developing world. The life expectancy of a patient with severe hemophilia is only ~10 years shorter than the general male population. In patients with mild or moderate hemophilia, life expectancy is approaching that of the male population without coagulopathy. Elderly hemophilia patients have different problems compared to the younger generation; they have more severe arthropathy and chronic pain, due to suboptimal treatment, and high rates of HCV and/or HIV infections.

Early data indicate that mortality from coronary artery disease is lower in hemophilia patients than the general male population. The underlying hypocoagulability probably provides a protective effect against thrombus formation, but it does not prevent atherogenesis. Similar to the general population, these patients are exposed to cardiovascular risk factors such as age, obesity, and smoking. Moreover, physical inactivity, hypertension, and chronic renal disease are commonly observed in hemophilia patients. In HIV patients on combined antiretroviral therapy, there may be a further increase in the risk of cardiovascular disease. Therefore, these patients should be carefully considered for preventive and therapeutic approaches to minimize the risk of cardiovascular disease.

Excessive replacement therapy should be avoided, and it is prudent to slowly infuse factor concentrates. Continuous infusion of clotting factor is preferable to bolus dosing in patients with cardiovascular risk factors undergoing invasive procedures. The management of an acute ischemic event and coronary revascularization should include the collaboration of hematologists and internists. The early assumption that hemophilia would protect against occlusive vascular disease may change in this aging population. Cancer is a common cause of mortality in aging hemophilia patients because they are at risk for HIV- and HCV-related malignancies. Hepatocellular carcinoma (HCC) is the most prevalent primary liver cancer and a 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. Among those with high-risk HCV, a semiannual or annual ultrasound and α fetoprotein are recommended for HCC. Screening for urogenital neoplasm in the presence of hematuria or hematochezia may be delayed due to the underlying bleeding disease, thus preventing early intervention. Multidisciplinary interaction should facilitate the attempts to ensure optimal cancer prevention and treatment recommendations for those with hemophilia.

MANAGEMENT OF CARRIERS OF HEMOPHILIA

Usually hemophilia carriers, with factor levels of ~50% of normal, have not been considered to be at risk for bleeding. However, a wide range of values (22–116%) have been reported due to random inactivation of the X chromosomes (*lyonization*). Therefore, it is important to measure the factor level of carriers to recognize those at risk of bleeding and to optimize preoperative and postoperative management. During pregnancy, both FVIII and FIX levels increase gradually until delivery. FVIII levels increase approximately two- to threefold compared to nonpregnant women, whereas an FIX increase is less pronounced. After delivery, there is a rapid fall in the pregnancy-induced rise of maternal clotting factor levels. This represents an imminent risk of bleeding that can be prevented by infusion of factor concentrate to levels of 50–70% for 3 days in the setting of vaginal delivery and up to 5 days for cesarean section. In mild cases, the use of DDAVP and/or antifibrinolytic drugs is recommended.