TREATMENT HEMOPHILIA

Without treatment, severe hemophilia has a limited life expectancy. Advances in the blood fractionation industry during World War II resulted in the realization that plasma could be used to treat hemophilia, but the volumes required to achieve even modest elevation of circulating factor levels limit the utility of plasma infusion as an approach to disease management. The discovery in the 1960s that the cryoprecipitate fraction of plasma was enriched for FVIII, and the eventual purification of FVIII and FIX from plasma, led to the introduction of home infusion therapy with factor concentrates in the 1970s. The availability of factor concentrates resulted in a dramatic improvement in life expectancy and in quality of life for people with severe hemophilia. However, the contamination of the blood supply with hepatitis viruses and, subsequently, HIV resulted in widespread transmission of these bloodborne infections within the hemophilia population; complications of HIV and of hepatitis C are now the leading causes of death among U.S. adults with severe hemophilia. The introduction of viral inactivation steps in the preparation of plasma-derived products in the mid-1980s greatly reduced the risk of HIV and hepatitis, and the risks were further reduced by the successful production of recombinant FVIII and FIX proteins, both licensed in the 1990s. It is uncommon for hemophilic patients born after 1985 to have contracted either hepatitis or HIV, and for these individuals, life expectancy is approximately 65 years. In fact, since 1998, no evidence of new infections with viral hepatitis or HIV has been reported in patients using blood products. Factor replacement therapy for hemophilia can be provided either in response to a bleeding episode or as a prophylactic treatment. Primary prophylaxis is defined as a strategy for maintaining the missing clotting factor at levels ~1% or higher on a regular basis in order to prevent bleeds, especially the onset of hemarthroses. Hemophilic boys receiving regular infusions of FVIII (3 days/week) or FIX (2 days/week) can reach puberty without detectable joint abnormalities. Prophylaxis has become gradually more common in young patients. The Centers for Disease Control and Prevention reported that 51% of children with severe hemophilia who are younger than age 6 years receive prophylaxis, increasing considerably from 33% in 1995. Although highly recommended, the high cost and difficulties in accessing peripheral veins in young patients and the potential infectious and thrombotic risks of long-term central vein catheters are important limiting factors for many young patients. Emerging data show that prophylaxis is also increasing among adults with severe hemophilia.

General considerations regarding the treatment of bleeds in hemophilia include the following: (1) Treatment should begin as soon as possible because symptoms often precede objective evidence of bleeding; because of the superior efficacy of early therapeutic intervention, classic symptoms of bleeding into the joint in a reliable patient, headaches, or automobile or other accidents require prompt replacement and further laboratory investigation. (2) Drugs that hamper platelet function, such as aspirin or aspirin-containing drugs, should be avoided; to control pain, drugs such as ibuprofen or propoxyphene are preferred. FVIII and FIX are dosed in units. One unit is defined as amount of FVIII (100 ng/mL) or FIX (5 μg/mL) in 1 mL of normal plasma. One unit of FVIII per kilogram of body weight increases the plasma FVIII level by 2%. One can calculate the dose needed to increase FVIII levels to 100% in a 70-kg severe hemophilia patient (<1%) using the simple formula below. Thus, 3500 units of FVIII will raise the circulating level to 100%.

$$\text{FVIII dose (IU)} = \text{Target FVIII levels} - \text{FVIII baseline levels} \times \text{body weight (kg)} \times 0.5 \text{ unit/kg}$$

The doses for FIX replacement are different from those for FVIII, because FIX recovery after infusion is usually only 50% of the predicted value. Therefore, the formula for FIX replacement is as follows:

$$\text{FIX dose (IU)} = \text{Target FIX levels} - \text{FIX baseline levels} \times \text{body weight (kg)} \times 1 \text{ unit/kg}$$

The FVIII half-life of 8–12 h requires injections twice a day to maintain therapeutic levels, whereas the FIX half-life is longer, ~24 h, so that once-a-day injection is sufficient. In specific situations such as after surgery, continuous infusion of factor may be desirable because of its safety in achieving sustained factor levels at a lower total cost.

Cryoprecipitate is enriched with FVIII protein (each bag contains ~80 IU of FVIII) and was commonly used for the treatment of hemophilia A decades ago; it is still in use in some developing countries, but because of the risk of bloodborne diseases, this product should be avoided in hemophilia patients when factor concentrates are available.

Mild bleeds such as uncomplicated hemarthroses or superficial hematomas require initial therapy with factor levels of 30–50%. Additional doses to maintain levels of 15–25% for 2 or 3 days are indicated for severe hemarthroses, especially when these episodes affect the "target joint." Large hematomas, or bleeds into deep muscles, require factor levels of 50% or even higher if the clinical symptoms do not improve, and factor replacement may be required for a period of 1 week or longer. The control of serious bleeds including those that affect the oropharyngeal spaces, CNS, and the retroperitoneum require sustained protein levels of 50–100% for 7–10 days. Prophylactic replacement for surgery is aimed at achieving normal factor levels (100%) for a period of 7–10 days; replacement can then be tapered depending on the extent of the surgical wounds. Oral surgery is associated with extensive tissue damage that usually requires factor replacement for 1–3 days coupled with oral antifibrinolytic drugs.

NONTRANSFUSION THERAPY IN HEMOPHILIA

DDAVP (1-Amino-8-D-Arginine Vasopressin) DDAVP is a synthetic vasopressin analog that causes a transient rise in FVIII and von Willebrand factor (VWF), but not FIX, through a mechanism involving release from endothelial cells. Patients with moderate or mild hemophilia A should be tested to determine if they respond to DDAVP before a therapeutic application. DDAVP at doses of 0.3 μg/kg body weight, over a 20-min period, is expected to raise FVIII levels by two- to threefold over baseline, peaking between 30 and 60 min after infusion. DDAVP does not improve FVIII levels in severe hemophilia A patients, because there are no stores to release. Repeated dosing of DDAVP results in tachyphylaxis because the mechanism is an increase in release rather than de novo synthesis of FVIII and VWF. More than three consecutive doses become ineffective, and if further therapy is indicated, FVIII replacement is required to achieve hemostasis.

Antifibrinolytic Drugs Bleeding in the gums, gastrointestinal tract, and during oral surgery requires the use of oral antifibrinolytic drugs such as ε-amino caproic acid (EACA) or tranexamic acid to control local hemostasis. The duration of the treatment depending on the clinical indication is 1 week or longer. Tranexamic acid is given at doses of 25 mg/kg three to four times a day. EACA treatment requires a loading dose of 200 mg/kg (maximum of 10 g) followed by 100 mg/kg per dose (maximum 30 g/d) every 6 h. These drugs are not indicated to control hematuria because of the risk of formation of an occlusive clot in the lumen of genitourinary tract structures.

COMPLICATIONS

Inhibitor Formation The formation of alloantibodies to FVIII or FIX is currently the major complication of hemophilia treatment. The prevalence of inhibitors to FVIII is estimated to be between 5 and 10% of all cases and ~20% of severe hemophilia A patients. Inhibitors to FIX are detected in only 3–5% of all hemophilia B patients. The high-risk group for inhibitor formation includes severe deficiency (>80% of all cases of inhibitors), familial history of inhibitor, African descent, mutations in the FVIII or FIX gene resulting in deletion of large coding regions, or gross gene rearrangements. Inhibitors usually appear early in life, at a median of 2 years of age, and after 10 cumulative days of exposure. However, intensive replacement therapy such as for major surgery, intracranial bleeding, or trauma increases the risk of inhibitor formation for patients of all ages and degree of