A Practical Guide to the Evaluation and Treatment of Hemophilia

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DESPITE CONSIDERABLE advances in the treatment of hemophilia, clinical expertise in hemophilia care is often concentrated within hemophilia treatment centers. These centers directly and indirectly care for most patients with hemophilia, and provide sophisticated services to this patient population. Much as bone marrow transplantation (BMT) and transfusion medicine have earned a special niche in hematology as sub-specialties of the discipline of hematology, hemophilia care is often categorized similarly. Despite the centralization of hemophilia care, hematologists are often called on to deal with the emergency treatment of hemophilia and with the routine aspects of hemophilia treatment. Furthermore, understanding of the treatment of hemophilia is an integral component of hematology training. This review should be construed as a guide to current management issues in hemophilia treatment, to provide all hematologists with a basic foundation in this field.

ELEMENTS OF HEMOPHILIA

Hemophilia A is caused by the deficiency of factor VIII, hemophilia B is caused by the deficiency of factor IX. After activation of factor IX to factor IXa, this enzyme interacts with the active cofactor form of factor VIII, factor VIIIa, to form a complex on membrane surfaces. This complex converts factor X to factor Xa. Thus, both factor IX and factor VIII are critical components of the blood coagulation pathways. Each individual case of hemophilia is characterized by a series of unique parameters, emphasizing the variability and heterogeneity of this disease. These parameters include the mode of initial presentation, the baseline level of the clotting factor, and the presence or absence of a relevant family history. Major acute and chronic complications are often secondary to recurrent bleeding. Joint deformities, with attendant limitations of the range of motion, are among the most common problems. Patients, particularly those who have required long-term intensive therapy who have been treated with the older generation of factor concentrates, have been exposed to numerous viruses, including hepatitis and human immunodeficiency virus (HIV), and may have the infectious consequences of these exposures. The development of an inhibitor greatly influences the treatment plan, the success of treatment, and the cost of treatment. The bleeding frequency and the frequency of the need for therapeutic intervention establishes a pattern for an individual case. In adults, analgesic use and abuse occur because of chronic joint pain. The education, motivation, and professional attainment of a patient provide insight concerning the degree to which the hemophilia disability has impacted on the career growth and societal contributions. Work or school absenteeism play an important role in impairing the success of an otherwise highly capable individual. Other patients with severe hemophilia are nonetheless able to reach the pinnacle of their professions and contribute significantly to society.

TYPICAL CRISIS BLEEDING IN HEMOPHILIA

Because of its high cost, prophylactic treatment of hemophilia A or hemophilia B is not commonly practiced in the United States. Treatment is provided following a bleeding episode, preferably as early as possible to minimize complications from bleeding.

Hemarthrosis

The most common bleeding problem of the hemophiliac population is spontaneous bleeding into a joint. The most frequently affected joints are the elbow and the knee, but involvement of any joint can occur. Many patients develop "target joints" that bleed more frequently. The bleeding episode is associated with the development of significant pain. Swelling and erythema can occur subsequently, but diagnosis and treatment of an acute hemarthrosis does not require well-developed signs. Indeed, an x-ray of the joint is most likely to show chronic changes from prior bleeding episodes, but is unlikely to provide a clue to the current diagnosis. Therefore, radiograms are not routinely obtained with every incident. Because of the significant benefits of early treatment, classic symptoms in a reliable patient are a sufficient basis for immediate treatment. Irritability, guarding, and lack of movement of the affected joint are signs of probable hemarthrosis in young children who are unable to articulate pain. Diagnosis and early treatment in this group is difficult. Chronic deformity of the joint, with swelling and chronic pain, is the sequelae of recurrent or inadequately managed joint bleeds. Within 8 to 12 hours of treatment, patients can note the effects of restoration of hemostasis by decreased pain and pressure. The joint should be initially rested (ie, immobilized), but mobilization within the first several days is a requirement for the rapid restoration of baseline range of motion of the joint. Initial therapy with factor VIII or factor IX requires that the factor level be raised to about 30% to 50%. A sustained minimal level of 15% to 25% for a longer period of time may be required for severe bleeding episodes, particularly if the bleeding involves a weight-bearing joint. If the bleeding episode requires physical therapy, prophylactic therapy may be indicated to avoid bleeding during efforts to mobilize the joint.

Hematoma

Hematomas, both spontaneous and secondary to minor trauma, are frequent complications of hemophilia. Usually,
hematuria is persistent. Patients with hemophilia can develop evidence of long-term complications, including pseudocysts, of the compartment. Aggressive therapy can reduce the incidence of significant, serious bleeding episodes. Therapy for major bleeding episodes may be required for a week or more to allow resorption of the hematoma and to avoid rebleeding within the compartment. Aggressive therapy can reduce the incidence of long-term complications, including pseudocysts, calcification, and significant fibrosis.

Hematuria

Hematuria, both macroscopic and microscopic, is a common problem in the management of hemophilia. Treatment is controversial and typically has included increased fluid intake, correction of the coagulation deficiency, and corticosteroids. Treatment with factor concentrates for multiple days may be necessary if more conservative measures fail. Defining the underlying cause can be difficult, particularly if the hematuria is spontaneous and painless. A search for the cause of hematuria, especially if secondary to trauma, is warranted in the proper clinical setting, especially if the hematuria is persistent. Patients with hemophilia can develop a second independent disease. Therefore, it is critical that the primary diagnosis of hemophilia be considered with any new symptom complex, but that unrelated diagnoses be entertained as well.

Gastrointestinal (GI) Bleeding

GI bleeding is not a common problem of the hemophilia population. When it occurs, it deserves the same diligent evaluation that obtains in otherwise normal individuals. Because of the hemophilia, an anatomic lesion of the stomach or bowel may give rise to excessive bleeding. During the evaluation, treatment with replacement therapy to achieve factor levels of greater than 50% is indicated. The severity of the bleeding and the nature of the lesion will impact on the duration of treatment.

Laceration

Lacerations, particular minor lacerations caused by a sharp instrument or glass, are relatively easily managed by conservative methods. Because of their superficial location, application of a pressure dressing and the maintenance of pressure will resolve bleeding with time and patience. Although specific therapy to raise the factor level to 30% to 50% should be used for the more serious lacerations, minor lacerations do not require replacement therapy unless bleeding cannot be controlled by conservative measures. Falls, with mucosal lacerations to the mouth, are common among toddlers. Application of pressure and ice to the area of injury is helpful, but is difficult to sustain. Factor replacement to 40% to 50% is usually indicated; this may be supplemented by epsilon amino caproic acid or tranexamic acid. In the most refractory cases, where the formed clot is continuously dislodged, restriction of oral intake and repeated treatment with factor concentrates may be necessary.

Head Trauma

Head trauma or spontaneous intracranial hemorrhage represent one of the most important challenges in the management of hemophilia. Hemorrhagic deaths in the hemophilic population are often caused by intracranial bleeds. Given the consequences of delayed or absent treatment, the general rule of thumb is to treat patients who have incurred even minor head trauma. Any patient with a history of head trauma and signs of head injury, including abrasions, laceration, or scalp hematoma, should be immediately treated with therapy that will raise the plasma factor VIII or factor IX level to 100%. If treatment is justified, then treatment should be complete and not partial. In the face of the history of minor head trauma and no signs of head injury, the decision not to treat is more difficult. If there is concern about an intracranial bleed or a subdural hematoma forming, it may be impossible to predict on the basis of history and physical. It is too late to await the development of headache or neurologic signs. Therefore, in doubt, treat. After rapid initial therapy, a computed axial tomography (CAT) scan of the head may be warranted, particularly if additional therapy is under consideration. However, because of the risk of treatment delays while awaiting radiographic testing, infusion should be administered as a priority before diagnostic evaluation. If intracranial bleeding is confirmed then levels should be monitored closely to maintain trough levels of at least 60% to 70%, and levels preferably around 100%. Therapy should be continued until resolution of the intracranial bleed.

Emergency Care

The appearance of a hemophiliac in the emergency room after an automobile accident can be unsettling to the physicians in charge. A conscious patient will convey the critical elements of his history: that he has hemophilia, that his factor deficiency is of a particular level of severity, whether he has factor VIII or factor IX deficiency (or even von Willebrand disease [vWD]), because some patients with vWD will unfortunately only know it as “hemophilia”), and the presence or absence of an inhibitor. The unconscious patient will hopefully carry identifying medical information, such as a MediAlert bracelet or the like.

Assessment of the need for treatment. The balance between rapid, albeit “broad-spectrum,” treatment for the most serious injuries and their attendant bleeding complications and a delayed treatment response to allow for a comprehensive diagnostic assessment or for the delivery of appropriate pharmaceuticals depends on the initial assessment and the urgency for treatment. After serious trauma in a patient without a history of an inhibitor, including significant blood loss or obvious head injury, maintenance of the blood pressure by transfusion of packed red blood cells and fresh-
TREATMENT OF HEMOPHILIA

frozen plasma (FFP) is indicated as soon as possible. FFP contains about 1 U of factor VIII and 1 U of factor IX per mL of plasma. Thus, 1 U of FFP (250 mL) contains an estimated 200 to 300 U of factor VIII and 200 to 300 U of factor IX. Although FFP is not the optimal source of concentrated factor VIII or factor IX necessary to restore the missing factor upwards of 100% of normal from the patient’s baseline, each unit of FFP will raise the factor level by about 5% to 10% in a 60-kg man. Every emergency room has rapid access to FFP. In the most urgent situations and in the absence of contraindications, FFP represents appropriate initial emergency therapy if factor concentrates are not available. The situation to be avoided is one in which treatment is delayed in a hemophilic with serious internal or external bleeding or obvious head trauma while factor VIII or factor IX concentrate is sought from other institutions, from a central facility, or from the patient’s home, precluding immediate treatment. Therapy can begin with FFP until the appropriate factor concentrate is available.

INHIBITORS OF FACTOR VIII OR FACTOR IX

About 10% to 15% of patients with hemophilia have inhibitors, antibodies that arise in response to “immunization” with a “foreign” protein. The presence of an inhibitor to factor VIII or factor IX, particularly a high-titer inhibitor associated with an anamnestic response, greatly complicates treatment. Stabilization of the patient’s hemodynamic status remains a priority. However, the administration of FFP may not even partially correct the clotting defect and often will stimulate a significant increase in the antibody titer. To rapidly ascertain whether FFP is associated with an increase in the plasma factor VIII or factor IX level, measurement of the partial thromboplastin time by the routine clinical pathology laboratory can permit an estimate of any correction by monitoring the shortening of the partial thromboplastin time (PTT). When the factor VIII or factor IX level is above 30% to 40% of normal, the PTT is usually normal. The best option for treating hemophiliacs with bleeding and an inhibitor is to use conservative measures, if possible, because infusion of products containing the missing protein may elicit an anamnestic response. Therapies for the acute treatment of patients with hemophilia A and inhibitors include intermediate purity factor IX concentrates (also known as prothrombin complex concentrates), activated factor IX concentrates (Autoplex [Baxter], FEIBA [Immuno, Vienna, Austria]), porcine factor VIII, recombinant factor VIII, and human factor VIII itself. Inhibitors to factor IX are much less common than factor VIII inhibitors. Patients with these inhibitors may be treated with activated factor IX concentrates or recombinant factor VIII. The role of intravenous Ig, immuno-suppressants, or extracorporeal circulation to remove inhibitors with Staph A is less well established.

If possible, the hemophilic with an inhibitor and significant bleeding should be treated in a center that specializes in this type of care. The approach to the treatment of the patient with hemophilia A and an inhibitor is challenging, and without clear practice guidelines. Salient issues include (1) the titer of the inhibitor (as expressed in Bethesda units), (2) the temporal pattern of inhibitor induction and decay, (3) the severity of bleeding and the indication for therapy, and (4) the cost of therapy. In patients with low-titer factor VIII inhibitors (<3 to 5 Bethesda units), particularly of the non-inducible type, factor VIII therapy is predictably effective, albeit expensive. Activated intermediate purity factor IX is also effective, and considerable experience has accrued in use of these preparations. Porcine factor VIII should be considered if the inhibitor is poorly reactive or unreactive to human factor VIII. This can be measured in the laboratory using a modification of the factor VIII inhibitor assay; such measurement should be performed before the in vivo use of porcine factor VIII. Recombinant factor VIIa is currently experimental therapy, and available on experimental protocol. Patients with hemophilia B and inhibitors are treated with activated factor IX concentrates.

OPTIONS FOR THE THERAPY OF FACTOR VIII DEFICIENCY

When the clinical situation permits, specific therapies of hemophilia A should be considered. Factor VIII deficiency may be treated with factor VIII, cryoprecipitate, 1-amino-8-D-arginine vasopressin (DDAVP), or FFP. The relative specific activity of factor VIII compared with other plasma proteins is about 1 in FFP, 30 in cryoprecipitate, and 300,000 in highly purified factor VIII preparations. High-purity concentrates are the treatment of choice by many because of their purity and the minimal protein load associated with factor VIII of high specific activity. Each unit of FFP or cryoprecipitate is derived from a single blood donor, and thus carries the same risk of viral disease transmission as a single unit of blood. Purified factor VIII is isolated from pooled plasma generated from thousands of donors. With the advent of new sterilization techniques (including pasteurization, chemical treatment, and filtration), donor screening, and protein purification methodologies, the incidence of transmission of hepatitis B, hepatitis C, or HIV is negligible. Alternatively, recombinant factor VIII derived from cultured Chinese hamster ovary cells or baby hamster kidney cells transfected with the human factor VIII gene can serve as a source of highly purified factor VIII. DDAVP, a vasopressin analog, is a synthetic peptide that indirectly leads to the rapid release of von Willebrand factor (vWF) into the blood; the increase in vWF, a carrier protein for factor VIII, leads concomitantly to an increase in factor VIII. Sometimes no therapy may be needed or indicated, and thus represents the best therapy. For example, a small laceration or bruise may be treated conservatively by the application of pressure dressing and compresses after cleaning of the wound. This avoids the cost and minimal risk associated with therapy.

In a patient who is known to respond to DDAVP and who does not have a life-threatening bleeding problem, DDAVP is the treatment of choice. It is particularly safe in adults, but should not be used in children under 1 year of age. Relatively inexpensive, this synthetic agent does not carry with it the risk of transmission of infectious disease, in contrast to factor VIII derived from human plasma. Most mild hemophilia A patients, with factor VIII levels greater than 10%, respond to DDAVP. In a test setting, an infusion study
is performed by the intravenous administration of 0.3 μg/kg of DDAVP over 20 minutes. In those that are responsive, the factor VIII level typically increases by about fourfold within 30 to 60 minutes. DDAVP may be administered daily for 2 to 3 days, after which tachyphylaxis may develop. If a longer duration of factor VIII therapy is required, then factor VIII concentrate should be considered. We will inform patients of their DDAVP responsiveness and provide them with written instructions to be presented elsewhere in the event of an emergency. However, DDAVP has no role in the treatment of patients who are but marginally responsive, nor should it be used as primary treatment in a serious or life-threatening bleeding emergency (ie, head injury with the possibility of intracranial bleeding) where immediate and definitive correction of the factor VIII deficiency is required. Rather, factor VIII-containing products should be transfused. Although there is little risk with the use of DDAVP in older children and adults, seizures caused by hyponatremia secondary to fluid retention have been reported with its use in infants. In young children, fluid intake and electrolytes should be monitored closely.

The quantity of factor VIII to administer to treat crisis bleeding depends on the location and magnitude of the bleed. Given that the level of factor VIII in normal individuals varies between 60% and 150%, the most serious bleeding problems require efforts to achieve factor VIII peak levels above 70% to 100% by the infusion of factor VIII. For less serious injuries or spontaneous hemarthroses, peak levels of 30% to 50% will usually suffice. One unit of factor VIII is the amount of factor VIII activity contained in 1 mL of normal plasma. The intravascular plasma volume, which is also the volume of distribution of factor VIII, is about 50 mL/kg. Thus, to increase the factor VIII level from 0% to 100% in a 70-kg hemophiliac, 3,500 U of factor VIII must be administered. Factor VIII vials are labeled with the assayed quantity of factor VIII. The amount of factor VIII in a unit of FFP and in a unit of cryoprecipitate can be estimated as about 200 to 300 U and about 80 to 100 U, respectively.

Regardless of the source of factor VIII, the theoretical plasma levels of factor VIII that are calculated are usually about 30% higher than those actually achieved. For this reason, a generous dose of factor VIII is usually selected and a full vial of factor VIII consumed. The half-life of infused factor VIII is about 12 hours. Thus, at 12 hours the plasma factor VIII level will decrease to one half of the initial level; infusion of one half of the initial dose will restore the plasma factor VIII to the initial level (Fig 1). The duration of therapy depends on the magnitude and severity of bleeding as well as the location. Hemarthroses usually require about 2 to 3 days of therapy whereas 5 to 7 days of therapy may be required after surgery.

OPTIONS FOR THE THERAPY OF FACTOR IX DEFICIENCY

Factor IX deficiency may be treated with purified factor IX or FFP. Cryoprecipitate does not contain factor IX and DDAVP does not lead to an elevation of factor IX in plasma. Hemophilia B had been treated with factor IX concentrates that contain other vitamin K-dependent proteins and their activation products. These agents have been associated with thrombosis and myocardial infarction, particularly when used in high doses. Recently, high-purity factor IX preparations have become available. Although more costly, these preparations are the preferred source of factor IX for the treatment of hemophilia B. As with hemophilia A, the quantity of factor IX needed to treat crisis bleeding depends on the location and magnitude of the bleed. The factor IX level in normal individuals varies between 60% and 150%. The most serious bleeding problems require efforts to achieve factor IX levels of about 70% to 100% by the infusion of factor IX concentrates. For less serious injuries or spontaneous hemarthroses, levels of 30% to 50% will usually suffice. One unit of factor IX is the amount of factor IX activity contained in 1 mL of normal plasma. As indicated above, the amount of factor IX required for transfusion can be calculated based on the intravascular plasma volume. However, one critical difference characterizes factor IX compared with factor VIII: factor IX, with a molecular weight of 56,000, is not restricted to the intravascular space, unlike factor VIII, with a molecular weight 330,000; rather, it exchanges into the extravascular space. For this reason, the volume of distribution for factor IX is twice that of factor VIII. A 70-kg hemophili B patient requires 7,000 U of factor IX to increase his plasma factor IX level from 0% to 100% (Fig 2). The half-life of infused factor IX is about 24 hours. Thus, at each half-life it is necessary to re-infuse one half the amount of factor IX initially infused to maintain a peak level of 100% and a trough level of 50%.
HIV infection within the hemophiliac population, factor VIII, previously purified exclusively from human plasma, is now available as an isolate from cell culture of heterologous mammalian cells transfected with the factor VIII cDNA. In parallel, high-purity plasma-derived factor VIII has been developed. Both high-purity plasma-derived factor VIII and recombinant factor VIII are highly efficacious, apparently safe, and represent important improvements of earlier factor VIII products. However, plasma-derived factor VIII is theoretically less safe than recombinant factor VIII in that parvovirus and hepatitis A can be transmitted with contaminated preparations, quality control breakdown during manufacture carries a risk of contamination in plasma-derived products, and as-yet-unknown viruses that are not inactivated by the current pasteurization processes may lurk. On the other hand, experience with recombinant factor VIII is more limited and an issue of increased incidence of factor VIII inhibitors has been raised but not proven. Currently, health reform and economics have delayed the widespread use of recombinant factor VIII in the United States. Recombinant factor VIII is currently sold at a 50% premium to purified plasma-derived factor VIII, which is already about fourfold to sixfold more expensive than the intermediate purity concentrates of factor VIII. The concerns raised about recombinant factor VIII relate primarily to cost, not efficacy or therapeutic complications. As the cost of factor VIII decreases, therapy will switch from crisis-based treatment to prophylaxis. In addition, as more factor VIII is consumed, recombinant sources will increasingly be critical because the amount of human plasma available is finite. Worldwide prophylaxis, only possible with recombinant products, will make for a healthier hemophiliac population.

Given the current realities of the higher cost of recombinant factor VIII and the economic pressure to provide factor VIII therapy at the lowest possible cost, we use the following guidelines. Previously untreated patients (usually children or very mild adult hemophiliacs not responsive to DDAVP) receive recombinant factor VIII. Mild hemophiliacs who are HIV-negative should also receive recombinant factor VIII for their occasional needs, including elective surgery and posttrauma (assuming that DDAVP can be used for minor bleeds but not for surgery or trauma).

Moderate to severe hemophiliA patients who are HIV-negative can receive either product. HIV-positive patients receive high-purity plasma-derived factor VIII, as do patients with frank acquired immunodeficiency syndrome. However, others have argued that a new infectious agent in an HIV-positive hemophiliac could have devastating consequences, and thus these patients should also be treated with recombinant factor VIII.

The good news is that there are excellent factor VIII and factor IX products currently available. This is in marked contrast to the intermediate purity concentrates that lacked heat or detergent treatment, thus assuring hepatitis exposure and, between 1979 and 1984, infecting over half of hemophiliacs with HIV. Low-price recombinant factor VIII and, hopefully, low-price recombinant factor IX (currently under development) hold the promise for the institution of prophylactic therapy.

**Surgical Management of Hemophilia**

Most patients with hemophilia undergo elective surgery under the supervision of expert caregivers in a hemophilia treatment center. Because the potential complications of inadequate treatment are significant, no surgery can truly be considered minor in a patient with hemophilia.

**Major Elective Surgery**

The goal of hemophilia care during elective surgery is to correct the factor deficiency during surgery and during the postoperative course so as to permit the patient to undergo an operation with the same risks as an individual without a coagulation disorder. Unless a hemophilia A patient has very mild hemophilia or is unusually responsive to DDAVP, infusion of factor VIII is indicated. To assure that the patient is fully responsive to therapy, a plasma factor level should be obtained after infusion to ascertain whether a therapeutic level has been reached. If the level is suboptimal, the presence of an inhibitor or accelerated clearance of the infused factor IX or factor VIII may have occurred. Surgery should not proceed until therapeutic levels are obtained and unless there are adequate amounts of factor concentrate to support the surgical procedure and the postoperative course is available. Uncomplicated surgery requires factor infusion to maintain a minimum of 50% to 70% levels at all times for about 2 to 7 days, then therapy may be tapered depending on the type of surgery.
Tooth Extraction

Tooth extraction in a patient with hemophilia should always be performed with the involvement of a hematologist knowledgeable in the management of hemophilia. Usually, hospitalization is not necessary. Administration of factor concentrate or DDAVP in those who are responsive immediately precedes surgery. To assure that the patient is fully responsive to therapy, a plasma factor level is obtained after infusion to ascertain whether a therapeutic level has been reached. Because this surgery is characterized by considerable tissue damage, we aim to obtain normal hemostasis with factor levels of 70% to 100%. After postsurgical observation, the patient is monitored at home. Infusion therapy may be continued for 3 or more days and is individualized depending on the complexity of the extraction. Communication between the hematologist and an experienced oral surgeon is a necessity. To decrease the amount of factor VIII or factor IX required for tooth extraction, ε-amino caproic acid (Amicar) or tranexamic acid (Cyclokapron) (inhibitors of fibrinolysis) is administered orally during this period.29 ε-Amino caproic acid is administered as a loading dose of 200 mg/kg orally (maximum 10 g) followed by maintenance doses of 100 mg/kg/dose (maximum 30 g over 24 hours) orally every 6 hours for 5 to 7 days. Tranexamic acid is administered at 25 mg/kg orally 3 to 4 times per day over the same period. If DDAVP is used to increase the factor VIII level to therapeutic levels, DDAVP should be administered daily. Although the duration of responsiveness to DDAVP is variable, this agent usually becomes less effective or ineffective after 2 to 3 daily doses.

Medical Consideration of Patient Family Members

Mothers and sisters of hemophiliacs may be asymptomatic carriers of the hemophilia gene, and thus may have partial deficiency of either factor VIII or factor IX. In the absence of trauma or the challenge of surgery, a deficiency in these women will not likely have been detected. Therefore, special attention should be taken before elective surgery. Although carriers with factor levels above 50% should not have a bleeding tendency, those with levels of 10% to 30% are likely to show excessive bleeding. Patients suspected of carrier status should be tested for the presence of factor VIII or factor IX deficiency. If a significant deficiency exists, prophylactic therapy will be necessary.

Prophylaxis

Prophylaxis of factor VIII deficiency or factor IX deficiency, with the chronic and periodic infusion of factor VIII or factor IX, can eliminate or minimize most of the bleeding manifestations and sequelae of the bleeding episodes in patients who are begun on prophylaxis before joint disease.30 Once joint disease is present the efficacy of prophylactic therapy in preventing its progression has not been shown. In addition, prophylactic therapy—the ultimate prophylactic therapy being gene therapy—can today eliminate the morbidity of hemophilia so that patients can live completely normal lives. All in all, in the competition for health care dollars, full investment in the treatment of hemophilia is associated with an excellent return: normal healthy patients who contribute fully to society.

Gene Therapy

Gene therapy holds the greatest promise for inexpensive prophylactic therapy, and considerable effort is underway to develop gene therapy for treatment of hemophilia A and hemophilia B. The experimental methods vary, but in general the factor VIII or factor IX gene is introduced via infection with retroviral vectors or transfected with plasmids into patient cells (either hepatocytes, myoblasts, fibroblasts, epithelial cells, or bone marrow). The challenge is to obtain sufficiently high expression of factor VIII, a protein encoded by an unusually large gene, and of factor IX, a protein that requires critical posttranslational processing to express biologic activity. Nonetheless, solution of these problems is anticipated and gene therapy may become a standard treatment of hemophilia in the future.

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This review is dedicated to the memory of James H.X. Barrett (1949-1993): patient, advisor, and friend of the Hemophilia Center at NEMC.

REFERENCES


A practical guide to the evaluation and treatment of hemophilia [see comments]

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