

Management of Hemophilia

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The management of hemophilia begins with accurate diagnosis. A well-standardized coagulation laboratory is needed to measure clotting factor levels accurately and to distinguish among causes of bleeding problems. For sex-linked hemophilia A (factor VIII deficiency) and B (factor IX deficiency), factor levels of carriers and possible carriers should be tested because half of true carriers have levels below the normal range and may be at risk of excess bleeding from trauma, surgical operations, or the like. Analysis of DNA from the factor VIII or IX gene of a male with hemophilia may allow determination of the causative mutation or, at least, may identify markers of the mutant gene (restriction fragment length polymorphism, RFLP, technology) so that comparisons may be made to the DNA of females who may be carriers. Definitive determination of the presence or absence of the carrier state often is possible, as is prenatal diagnosis and even diagnosis of early embryos formed *in vitro* before implantation. Major hemophilia centers typically provide diagnosis of hemophilia and follow factor levels, but rely on a few very expert laboratories for DNA analysis.

Management of the hemorrhagic tendency in hemophilia entails replacement of the deficient clotting factor, either on a regular prophylactic schedule or as soon as each hemorrhage is detected. Clotting factor levels need to be raised to, or above, the minimal levels needed for formation of a strong clot to stop bleeding; levels needed may depend on the site and size of the hemorrhage. Patients with severe hemophilia tend to bleed into the large joints of the limbs and, less often, into the muscles of the limbs. Prophylactic muscle-building helps prevent hemorrhages in joints and muscles. After a joint or muscle hemorrhage has subsided on clotting factor replacement, physical therapy is needed to regain range of motion of the joint and strength of the muscles.

Options for clotting factor replacement vary from one country to another. Simple products such as plasma or cryoprecipitate may be made in local blood banks. Concentrates made from pooled plasma are fractionated in larger facilities with varying levels of sophistication. Recombinant factor VIII is now available, and other recombinant factors are being developed.

Safety from transmission of blood-borne viruses is a major concern. The first defense is selection of healthy donors who are seronegative for the pathogens of major concern, which are, for most of the world, HIV, hepatitis B (HBV) and hepatitis C (HCV). Serologic testing will not detect all infectious donors, in particular those recently infected, a problem of particular concern to countries with expanding epidemics. Testing for viral genomes by polymerase chain reaction (PCR) is economically feasible on small pools (e.g., 100 liters) of plasma destined for fractionation if well-controlled PCR tests are available. Such tests may be available to sophisticated large-scale fractionation facilities, whereas the greatest current need is in countries dependent on simple local plasma products.

Viral inactivation can be carried out for small-scale pooled plasma products by treating with heat or with a solvent-detergent combination. In large-scale fractionation, the same modalities of viral inactivation may be applied with greater refinement, variety

and quality control. Lipid-enveloped viruses (HIV, HBV, HCV) are very sensitive to solvent-detergent treatment. HIV is vulnerable to modest heat inactivation measures; HBV and HCV are vulnerable to more intensive heat inactivation. Non-enveloped viruses such as hepatitis A and B-19 parvovirus are not inactivated by solvent-detergent treatment and are somewhat resistant to heat. Ultrafiltration and new methods of viral inactivation are of great interest. Since any inactivation method can be overwhelmed if the viral load is too large, donor selection and testing cannot be neglected

Recombinant clotting factor concentrates are made by transfecting hamster cells with normal human genes, using retroviral vectors. The cells are cultured in a medium containing bovine serum; substitutes for animal serum are being introduced. The clotting factor is extracted from the culture medium with affinity chromatography and stabilized with human albumin; substitutes for human albumin also are being sought. Recombinant technology offers the opportunity to alter the clotting factor molecule to try to decrease antigenicity, improve plasma half-life, or confer some other advantage. Recombinant products may offer the lowest chance of transmitting a human pathogen, but microbial contamination is not impossible.

For patients with factor IX deficiency, another safety issue is freedom from excessive thrombogenicity. Less purified concentrates also contain prothrombin and factors VII and X. Their use has been associated with occasional thrombotic complications in vulnerable patients such as those undergoing surgery, those with massive injuries, or those with severe liver dysfunction including newborns. More highly purified factor IX concentrates with only trace contamination with the other factors of the “prothrombin complex” are now available and are used for vulnerable patients. In some countries, they are becoming commonly used for all children or all patients with hemophilia B. Recombinant factor IX is in clinical trials.

Patients with congenital clotting factor deficiencies transmitted in an autosomal recessive pattern, such as deficiency of factors V, VII, X, XI or XIII, are few. Clotting factor concentrates of some of these factors are made in a few fractionation plants but availability is limited, primarily by the difficulties of licensing such orphan drugs.

A common complication of hemophilia A and a rare complication of hemophilia B is the development of an inhibitor antibody to the therapeutic clotting factor. In a few patients, levels of inhibitors are low and not raised by further exposure to the clotting factor. Such patients are easily managed by increased doses. In most patients, exposure to the therapeutic factor stimulates higher inhibitor levels. For hemorrhages, such patients may be treated with “bypassing agents”—concentrates containing some activated clotting factors that trigger coagulation at a point beyond the usual action of factor VIII or IX. Such agents include ordinary prothrombin complex, which contains some activated clotting factors, with extra-activated prothrombin complex or, where it is licensed, with recombinant activated factor VII (rVIIa). The latter product requires tissue factor to trigger coagulation, and tissue factor may be exposed primarily at the site of injury. In patients with inhibitors to factor VIII who have very serious hemorrhages, porcine factor VIII concentrate often is useful for it interacts well in the human coagulation mechanism but is inactivated by human antibodies far less efficiently than is human factor VIII.

Suppression of inhibitors by induction of immune tolerance is now common practice in the developed world. The deficient clotting factor is given in very large doses,

exceeding usual therapeutic doses, usually on a daily schedule over many months. In some protocols, immune suppressive drugs such as prednisone, cyclophosphamide or intravenous gamma globulin also may be given. Such protocols are very expensive. Successful suppression is more likely to be achieved in patients with low to moderate inhibitor levels than in those with very high ones.

Patients with frequent bleeding into joints often develop synovial inflammation and hypertrophy leading to chronic synovitis, effusion, and more bleeding. When damage to the articular surface is still minimal, synovitis and bleeding usually can be reduced markedly by intra-articular injections of beta-emitting short-lived isotopes on large colloid particles that do not escape the joint capsule. When the synovium is exceptionally thick, surgical removal may be necessary. Halting synovitis helps delay joint deterioration.

In developed countries, the severity of hemophilic arthropathy and crippling has lessened progressively with punctilious plasma product use over the past four decades. Patients with severe hemophilia, including those who have had early treatment of hemorrhages but have not had prophylactic treatment, still may develop advanced arthritis by early adulthood. Such patients benefit from the attention of physical therapists, physiatrists and orthopedic surgeons. Orthotic and other assistive devices may be needed. Prosthetic replacements of severely arthritic hips and knees usually relieves severe chronic pain and improves function. Severely arthritic, painful ankle and subtalar joints may be treated by surgical fusion. Inability to rotate the forearm often occurs if the radial head enlarges in response to the stimulus of hemorrhages during childhood growth; excision of the radial head relieves much of the disability. A few patients develop pseudotumors, that is, cysts filled with old blood, gradually expanding over years in or adjacent to bones apparently originally stimulated by hemorrhage. When such growths threaten bone stability or appear on the verge of rupture, surgical extirpation is needed. Surgical operations should be attempted only at expert hospitals with the ability to monitor factor levels.

Heavy personal and family burdens are occasioned by this chronic, lifelong, expensive, unpredictable disorder, which is often complicated, in patients who now are adolescents or adults, by concurrent chronic infection with HIV, HCV or, less often, HBV. Psychological support and counseling are needed. Consumer groups offer practical support and personal encouragement, and also may lobby governments for adequate hemophilia care.

Good hemophilia management requires the cooperation and education of patients and their families as well as frequent, lifelong attention from expert health care personnel, usually at designated academic centers.