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HEREDITARY PLASMA CLOTTING FACTOR DISORDERS AND THEIR MANAGEMENT

Fifth Edition

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Treatment of Hemophilia Monographs
Series Editor
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Hereditary Plasma Clotting Factor Disorders and Their Management

Carol K. Kasper

Hemophilia A (Classic Hemophilia)

Hemophilia A is a sex-linked genetic disorder resulting in deficiency of plasma factor VIII (FVIII) coagulant activity. The incidence is about one in every 5,000 male births. The level of FVIII is similar in all affected males in a given family. Hemophilia is defined as severe (<1% FVIII), moderate (1-5%) or mild (5 -30%). The average normal plasma level of FVIII (and of other plasma clotting factors) is defined as 100% (one "unit" (U) per mL or 100 U/dL of plasma) and the normal range is about 40-180%.

Patients with severe hemophilia tend to bleed frequently with minimal, often unrecognized trauma, especially into the large joints of the limbs (the knees, ankles and elbows) and, to a lesser extent, into the hips, shoulders, and large muscles. Bruising or mucosal bleeding occurs with trauma. Patients with moderate hemophilia bleed into similar areas with moderate trauma. Patients with mild hemophilia bleed with definite trauma. All hemophilia patients may have excess bleeding during and after surgical operations including dental extractions.

Patients with hemophilia A have prolonged activated partial thromboplastin times (APTT), but normal prothrombin times, bleeding times and platelet function tests.

FVIII takes part in the activation of factor X (FX), leading to the formation of a fibrin clot. Its function is commonly measured by the FVIII activity assay in which the end point is the formation of fibrin strands. (In a less common assay using chromogenic reagents, the endpoint is the formation of activated FX.) The FVIII molecule also can be detected as FVIII antigen (FVIII:Ag) by specific antibodies in immunologic tests. Levels of FVIII:Ag may exceed levels of FVIII activity in some mild or moderately affected patients who make a dysfunctional molecule.

The site of FVIII synthesis is not yet proven. FVIII circulates bound to von Willebrand factor (VWF), which stabilizes it.

Inhibitory antibodies may develop after exposure to exogenous FVIII. The incidence in severe hemophilia A is about 20% and is much lower in mild hemophilia.

Genetic transmission

Hemophilia A is transmitted by a gene on the X chromosome. The son of a hemophilic man and a normal woman cannot inherit or transmit hemophilia because he receives a Y, not an X chromosome from his father. The daughter of such a union is an "obligate" carrier because she received the paternal X chromosome with the mutant FVIII gene.

A carrier has two X chromosomes, one with a normal FVIII gene and one with a mutant gene. If an ovum with the X chromosome bearing the mutant gene is fertilized, a hemophilic son or a carrier daughter will result. If an ovum with the X chromosome bearing the normal gene is fertilized, an unaffected son or daughter will result. A carrier has equal chances with each pregnancy of having a normal or hemophilic son or a normal or carrier daughter.

The range of FVIII levels in carriers is very wide, from the lowest seen in affected males to the highest seen in normal persons, as would be expected from Lyon's hypothesis of X-chromosome inactivation [1]. Lyon hypothesized that, at a very early morula stage in a female embryo, one of the two X chromosomes in each nucleus is chosen at random to remain functional while the other becomes inactive (seen as the dense Barr body at the edge of the nucleus.) The same X chromosome remains active in all the daughter cells from that time on. Because X chromosome inactivation is usually random, the average female is likely to have the paternal X chromosome active in half her cells and the

maternal X chromosome active in the other half. In a carrier, one X chromosome bears the mutant gene. If that X chromosome is active in half her cells, then those cells cannot make FVIII. Her plasma FVIII level is likely to be half that of normal women.

Bias, however, can occur. Sometimes X chromosome inactivation favors one chromosome over the other. Alternatively, some cells of the morula may replicate better than others, leading to predominance of their X chromosomes. If the chromosome with the mutant FVIII gene remains active in most cells, then the female will have a low level of FVIII, whereas if the chromosome with a normal FVIII gene remains active in most cells, then the female will have a normal level of FVIII.

Most carriers have FVIII levels between 30% and 70%. Factor levels should be measured in all females who are or might be carriers, since those with lower levels are at risk for excessive bleeding with trauma or surgery.

X chromosome inactivation does not affect the ova. Regardless of the carrier's plasma FVIII level, half the ova contain the paternal X chromosome and half contain the maternal X chromosome. A carrier's chance of having a hemophilic son is not related to her plasma FVIII level.

Carrier detection by phenotype

Assays of FVIII and of VWF have been used to predict whether a given woman, related to a male with hemophilia in the maternal line, such as his sister, is a carrier. If such a woman has a FVIII level that is definitely sub-normal, she is strongly suspected of being a carrier.

The level of VWF is controlled by autosomal genes and is usually normal in carriers. In normal women, the levels of FVIII and of VWF are approximately equal. In carriers, the level of VWF may be higher. If the level of VWF (usually measured by an immunologic test such as VWF:Ag) is definitely higher than the FVIII level, then the carrier state is strongly suspected. However, the accuracy of predictions from these tests is so dependent on excellent calibration in the test laboratory that they have fallen out of favor.

With phenotypic tests, it is sometimes possible to show that a woman is very probably a carrier, but it is impossible to prove that she is not a carrier.

Carrier detection by genotype

The specific mutation causing hemophilia can be identified in the FVIII gene of the affected male (or, when the male is not available, in a known carrier.) A great many different mutations cause hemophilia. About 40% of severe hemophilia A is caused by inversion of the tip of the X chromosome, a change easily detected. Mild hemophilia usually is caused by missense mutations, that is, substitution of one nucleotide for another, coding for a different amino acid in the FVIII molecule. Severe hemophilia sometimes is caused by missense mutations, but more often by mutations that truncate the molecule.

If the family mutation is identified, the FVIII genes from the white blood cells of a female relative can be screened for the mutation to determine whether or not she is a carrier. Nearly all carrier diagnosis today is done with mutation analysis.

Alternatively, the gene associated with hemophilia can be traced through the family by identifying normal variations in the gene or adjacent chromosome using "restriction fragment length polymorphisms" (RFLPs). Restriction enzymes cleave DNA at specific nucleotide configurations. cDNA probes are then used to measure DNA fragment lengths after cleavage. If a certain configuration is absent at a given site, the corresponding restriction enzyme will not cleave the DNA and that fragment of DNA will remain long. If the configuration is present at that site, the enzyme will cleave the DNA and short fragments will result. If a certain nucleotide configuration is present in one of a woman's two FVIII genes but not in the other, she is "polymorphic" at that site. RFLPs can be used to trace hemophilia through a family and determine carrier status.

Sporadic hemophilia

When hemophilia first appears in a family, it is called "sporadic". New mutations causing hemophilia occur frequently, especially in rapidly-dividing cells such as the progenitors of sperm and the cells of embryos. Mutations also

may occur in ova. A very large majority of mothers of sporadic cases of hemophilia are somatic mutants, that is, they have the mutation in all their cells. The most probable origin of a woman's mutation is a mutant sperm from her father. Alternatively, the origin could have been a mutant ovum in her mother. Or, a mutation could have arisen in one cell in either of her parents when they were embryos, and the mutant cell developed into a gonad or part of a gonad. Some mothers of sporadic cases can be shown to have the mutation in some, but not all, of her cells; that is, she is clearly a mosaic, having suffered a mutation as an embryo in a cell that developed, in part, into an ovary as well as into some of the white blood cells (which are used for testing). Some mothers may not have the mutation in the white blood cells but may have more than one mutant ovum. All mothers of sporadic cases of hemophilia should be considered carriers who might have additional mutant ova; that is, they are at risk for having another hemophilic son or carrier daughter. It is not possible to prove otherwise.

Conclusive carrier diagnosis can be carried out by testing for the mutation in the white blood cells of other female relatives, such as sisters and maternal aunts of the patient. RFLP analysis may not be conclusive. One can sometimes determine that a female relative has no FVIII gene with the same RFLP pattern as the person with hemophilia and is, therefore, not a carrier. If, however, one of her genes does have the same RFLP pattern, she may or may not be a carrier.

Prenatal diagnosis

Fetal cells from a chorionic villus biopsy (CVB) at eight weeks' gestation or amniotic fluid obtained later can be analyzed for the mutant gene or for the associated RFLP pattern. In carriers with low levels of FVIII (below 30%), midline amniocentesis often is preferred as less bleeding is provoked.

Preimplantation diagnosis

If conception is carried out by *in vitro* fertilization, one cell may be plucked from each embryo at the eight-cell stage, without harm, to screen for the mutation and determine gender. Embryos without the mutation may then be implanted into the uterus. This procedure has been gaining in popularity for carriers of various genetic disorders, including hemophilia, over the past two decades.

Hemophilia B (Christmas disease)

Hemophilia B is a sex-linked genetic disorder resulting in deficiency of factor IX (FIX) coagulant activity. Severe, moderate and mild forms exist in different families. The clinical and genetic features are similar to those of hemophilia A. The incidence is about one-quarter that of hemophilia A.

Patients with hemophilia B have prolonged APTTs, but normal prothrombin times. FIX takes part in the activation of FX, leading to formation of a fibrin clot. Its function is measured by a FIX assay in which the end point is the formation of fibrin strands. The molecule also can be detected in an immunologic test as FIX:Ag. Levels of FIX:Ag exceed those of FIX activity in a third of patients, including some with severe hemophilia B who make dysfunctional FIX molecules. The site of FIX synthesis, which is vitamin-K dependent, is the liver.

Inhibitory antibodies occur after exposure to exogenous FIX in about 3% of patients with severe hemophilia B, especially in those with large gene deletions.

Genetic transmission patterns are the same as in hemophilia A. Carriers have a wide spectrum of FIX levels. Optimal carrier testing is based on mutation analysis, but may also be based on RFLPs.

von Willebrand Disease (VWD)

VWD is an autosomally inherited disorder in which there is deficiency or dysfunction of von Willebrand factor (VWF). VWF is made in endothelial cells and secreted into the plasma, and made in megakaryocytes and found in platelets. While still within the cell, subunits of VWF form huge multimers. VWF functions are as follows: (1) to attach to subendothelial collagen and to platelets at the GPIb receptor, promoting formation of a platelet plug at the site of small vessel injury, and, (2) to bind and transport FVIII. The plasma level of FVIII is reduced if VWF levels are reduced. The first

function, of platelet attachment, is best performed by the largest multimers, whereas FVIII binding does not require large multimers. In the plasma, an enzyme, ADAMTS13, breaks down large multimers.

Patients with VWD tend to bleed from mucosal surfaces in the nose and mouth, from small cuts, and from the gastrointestinal tract. Females often have menorrhagia and bleeding with miscarriages. Levels of VWF may rise with pregnancy but hemorrhaging occasionally occurs with deliveries. The prevalence of symptomatic patients, who require occasional transfusion therapy, is about one in 5,000-10,000 persons. Some people carry a mutant gene but are asymptomatic. The prevalence of severe VWD in Europeans is about one in two million persons.

Laboratory tests for VWF include an immunologic test for its overall level, VWF:Ag, and functional tests reflecting its ability, in diluted plasma, to aggregate normal platelets in the presence of ristocetin (ristocetin cofactor, VWF:RCo); to bind collagen (VWF:CB); and to bind FVIII (VWF:FVIIIB). Ristocetin-induced platelet aggregation (RIPA) is a test of VWF's ability, in the patient's undiluted, fresh, platelet-rich plasma, to support aggregation by ristocetin. Size distribution of multimers can be demonstrated by electrophoresis of VWF:Ag. The bleeding time (BT) or the closure time (CT) with a platelet-function analyzer, such as the PFA-100®, may be prolonged. The VWF:FVIIIB test and multimer analysis are usually performed at reference laboratories. The single test most likely to be abnormal in VWD is VWF:RCo, which is low in all but type 2N VWD.

VWD types

VWD is very heterogeneous. Type 1 and Type 3 are mild and severe quantitative deficiencies of VWF, respectively. Type 2 variants are qualitative deficiencies; that is, the VWF molecule is abnormal. Type 2 variants are caused by mutations in the VWF gene that correspond with the function lost.

Type 1 is a mild to moderate quantitative deficiency of VWF. Levels of FVIII, VWF:Ag, VWF:RCo and VWF:CB tend to be similar. Multimers of all sizes are produced, but the total quantity is low. RIPA is usually normal. VWF:FVIIIB is normal. The BT may be normal or prolonged. Inheritance is dominant, with highly variable expression. Mutations are scattered throughout the gene. A few are null mutations coding for no production of VWF by that allele; a few are dominant-negative mutations in which production of VWF by the normal allele is impeded. Some persons with a given mutation may have obvious VWD and others may have a normal phenotype.

Some mild Type 1 VWD is not related to a VWF gene mutation. Several inherited determinants, other than mutations, may depress the level of VWF. They include normal variations (single nucleotide polymorphisms) of the VWF molecule, and the level of glycosylation of the molecule. The latter is reflected in the great variation in VWF (and FVIII) levels according to ABO blood group, with the lowest levels in group O, in which glycosylation is lower than in other blood groups. Caucasians have lower levels of VWF (and FVIII) than do black Africans. Thyroid hormones, epinephrine, estrogen, and progesterone all increase VWF levels. Persons with borderline or mildly deficient levels of VWF without a VWF gene mutation are indistinguishable from persons with similar levels due to a Type 1 gene mutation. Diagnosis of mild Type 1 VWD is often ambiguous.

In **Type 3**, levels of VWF and of FVIII are very low. A few patients have joint hemorrhages, as in hemophilia A. Affected patients are homozygotes or heterozygotes for "null" mutations, coding for no VWF production. Such mutations are scattered throughout the gene. Patients homozygous for large gene deletions are susceptible to development of inhibitors to VWF. Most heterozygotes for null mutations are asymptomatic, but a few have a type 1 VWD phenotype.

Type 2 is further subdivided. In **Type 2A,** large multimers are not found in the plasma. With some mutations, large multimers are not formed at all. With other mutations, they are vulnerable to rapid proteolysis. Levels of VWF:RCo and VWF:CB are low, but levels of VWF:Ag and FVIII may be low-normal to normal. RIPA usually is below normal. The BT is usually prolonged. VWF:FVIIIB is not affected. Inheritance is dominant with some variability of

expression. Most causative mutations are in the A1 and A2 domains of the gene.

In **Type 2B,** a gain-of-function mutation (in the A1 domain) increases the affinity of large multimers to the platelet GP1b receptor. On multimer analysis, large multimers are absent. Large multimers are constantly removed from circulation; platelets also may be removed. Levels of VWF:RCo and VWF:CB are low, but levels of VWF:Ag and FVIII usually are higher. In RIPA, the patient's platelet-rich plasma aggregates at lower-than-normal concentrations of ristocetin. The BT is usually prolonged. VWF:FVIIIB is not affected. Inheritance is dominant with some variability of expression.

In **Type 2M**, multimers of all sizes are present in the plasma, but the VWF affinity for platelet GPIb is decreased. The level of VWF:RCo is decreased, but the level of VWF:CB is less affected. Levels of VWF:Ag and FVIII usually are higher. Inheritance is dominant with variable expression. The mutation is in the A1 domain, or, in the case of some patients with super-large multimers, in the D3 domain.

In **Type 2N**, the major defect is in FVIII binding. The level of FVIII is low and the level of VWF:FVIIIB is very low. Other tests for VWF function may be normal or mildly deficient. There may be mild mucosal bleeding. The inheritance is recessive, with mutations in the D' to D3 domains. Heterozygotes have intermediate levels of VWF:FVIIIB, but normal levels of FVIII.

In **pseudo-VWD**, there is a gain-of-function mutation in the gene governing the platelet GP1b receptor, which has increased affinity for large multimers of VWF. Large multimers and platelets are constantly removed from the circulation. Pseudo-VWD is inherited in a dominant fashion. Hemorrhages are treated with platelet infusions.

Factor XI Deficiency (Hemophilia C)

Factor XI (FXI) is controlled by autosomal genes. Severe deficiency results from homozygous or doubly heterozygous gene mutations. In FXI deficiency, the APTT is prolonged and the prothrombin time is normal. Persons with severe or moderately-severe deficiencies bleed only with trauma or surgical operations, like patients with mild to moderate hemophilia A or B. Some deficient patients do not bleed excessively. The decision to treat a patient with plasma products before surgery depends on his own past history of bleeding and that of family members. Heterozygotes may have mild deficiencies, e.g. 25-50% levels of FXI, but usually are asymptomatic. The gene is especially predominant in persons of European Jewish descent and the incidence varies in different countries accordingly. Concentrates of FXI are made in England by BPL and in France by LFB.

Rare Clotting Factor Deficiencies

Other clotting factor deficiencies, all autosomal, are primarily symptomatic in homozygotes or compound heterozygotes. All are more common in countries with a high rate of consanguineous marriages, as in the Middle East, than in countries with more random mating.

Deficiency of **factor I (fibrinogen)**, causing afibrinogenemia or hypofibrinogenemia, occurs as a rare recessive trait that may be mildly symptomatic in heterozygotes. A specific test for fibrinogen expresses levels in mg/dL, the only plasma clotting factor routinely measured by weight. In women with severe deficiency, implantation of the embryo in the uterine wall may be difficult, or, miscarriage may be frequent. Several concentrates of fibrinogen are available. Dysfibrinogenemia, that is, production of an abnormal fibrinogen molecule, occurs as a dominant condition affecting heterozygotes. In dysfibrinogenemia, bleeding is the predominant symptom, but excess thrombosis also can occur.

Deficiency of **factor II (prothrombin)** occurs as a very rare recessive trait (the rarest in this list) that may be mildly symptomatic in heterozygotes. The prothrombin time and the APTT are prolonged. Plasma or prothrombin complex concentrate (PCC, see page 9) may be used for treatment.

Deficiency of **factor V (FV)** occurs as a rare recessive trait that may be mildly symptomatic in heterozygotes. The prothrombin time and the APTT are prolonged. There is no concentrate

containing factor V. Whole plasma is the only clotting factor replacement option.

Mild combined deficiency of **FV and FVIII** occurs as the result of a mutation of *ERGIC-53*, which governs the production of a protein that chaperones intracellular transport of these two factors. Both the prothrombin time and the APTT may be prolonged. The combined deficiency occurs in the Mediterranean basin and the Middle East as a very rare recessive trait, expressed primarily in homozygotes. Patients may be treated with plasma or with FVIII concentrates.

Deficiency of **factor VII (FVII)** is twice as common as any of the other rare deficiencies in this list. It is inherited as a recessive trait with intermediate expression in heterozygotes. The prothrombin time is prolonged, but the APTT is normal. Thrombosis has been reported, predominantly after surgical operations. FVII concentrates are made by Baxter in Austria, BPL in England and LFB in France. In the U.S.A., recombinant activated factor VII (NovoSeven®) is licensed for congenital factor VII deficiency.

Deficiency of **factor X (FX)** is a rare recessive trait that may be mildly symptomatic in heterozygotes. Both the prothrombin time and the APTT are prolonged. No specific concentrate is available. Patients are treated with plasma or PCC.

Deficiency of **factor XIII (FXIII)** is a rare recessive trait expressed in homozygotes. The prothrombin time and APTT are normal. FXIII deficiency must be demonstrated with a specific screening test, i.e., instability of the fibrin clot in 5 molar urea. A large majority of patients suffer bleeding from the umbilical stump and a significant minority have CNS bleeding. The half-life of infused FXIII is long, about 6 days. A concentrate of FXIII is made by CSL Behring in Germany and a recombinant FXIII concentrate from NovoNordisk is in clinical trials. Most patients are on prophylaxis with plasma or concentrate given about once a month.

Comprehensive Hemophilia Care

Special treatment centres for persons with congenital bleeding disorders exist in large cities. The complications of bleeding disorders (e.g. joint damage, anemia, social and personal problems) and of their treatment (inhibitors, hepatitis or HIV infections from earlier non-viral-inactivated products) necessitate coordinated interdisciplinary care. Personnel may include hematologists, infectious disease specialists, orthopedic surgeons, nurses, physiotherapists, dentists, social workers, psychologists, genetic counselors, and so on.

Facilities needed include in- and out-patient treatment areas and an expert coagulation laboratory. Comprehensive treatment centres often provide total medical care for patients with bleeding disorders living within a reasonable traveling distance, and provide consultation for patients from a wider area. Information about hemophilia care and lists of hemophilia centres in the U.S.A. may be obtained from the National Hemophilia Foundation at 116 West 32nd Street, 11th Floor, New York NY 10001; *www.hemophilia.org*. Information about treatment around the world, and lists of hemophilia centres, can be obtained from the World Federation of Hemophilia, 1425 René Lévesque Blvd West, Suite 1010, Montréal, Québec, H3G 1T7, Canada; *www.wfh.org*.

General care

Vaginal delivery of a hemophilic infant rarely provokes bleeding; however, if bleeding does occur, it may be in the central nervous system or subgaleal region. Vacuum extraction (ventouse) is contraindicated. Caesarian section is considered for a large fetus or difficult labor, at indications more liberal than with delivery of a normal infant. Beware of umbilical stump bleeding, especially in infants with factor XIII deficiency.

Newborns who may have hemophilia should not be circumcised until the diagnosis is excluded. If circumcision is performed in an infant with hemophilia, he should have clotting factor replacement or be treated with local hemostatic agents such as fibrin glue. Heel pricks to obtain blood for routine tests should be small and pressure should be applied afterwards for several minutes. Femoral or jugular venipuncture should not be attempted. Venipuncture in the superficial veins of the limbs is safe if pressure is applied for several minutes afterwards. Routine intramuscular

immunizations should be given, including vaccination against hepatitis A and B, with pressure on the site for several minutes afterwards.

Parents of a baby with a bleeding disorder often need extensive counseling to cope with their emotional reactions to the diagnosis, to learn about the disorder, and to plan care for their child. At home, they can take a few precautions to improve the safety of the environment – for example, carpets help cushion floors. Trousers and long-sleeved shirts can be padded internally at the levels of the knees and elbows to protect those joints from the inevitable falls. Over-protection should be avoided to allow normal emotional and social growth. Children with bleeding disorders need to play with other children. They also need approval and attention from both parents to develop normal self-esteem.

Sensible physical exercise is encouraged because strong muscles help support joints. A daily exercise program should be followed from early childhood and encouraged with as much enthusiasm as other medical care. Ideal exercise strengthens muscles and preserves joint motion without putting excessive pressure on the joints. Swimming is ideal. Contact sports and jogging are discouraged. If a child is determined to pursue a sport that entails some risk of physical injury, the risk is lower if he is in good physical condition, is trained how to perform the motions of the sport correctly, and wears appropriate safety gear. Boys taking concentrate prophylactically engage in sports with greater safety.

Persons with bleeding disorders need regular, good dental care. Minor bleeding from the gums after vigorous brushing or professional cleaning is easy to control.

Safety of Therapeutic products

Donor infections

Persons needing frequent blood product infusions sometimes have been at high risk of contracting blood-borne viral infections. Fresh-frozen plasma and cryoprecipitate usually are not viral inactivated. (Some pooled, lyophilized plasma available in Europe is viral inactivated; some pooled lyophilized cryoprecipitate is viral inactivated in a few parts of the world.) Donors may be tested serologically for hepatitis B and C (HBV, HCV) and for HIV, as well as for other viruses, but may be in the window period between infection and the appearance of antibodies. Direct nucleic acid testing (NAT) of individual donors for HCV is now an expected standard. In developed countries, other individual NAT tests may be performed. When repeat plasma donors are used, a given donation of plasma can be frozen and stored until the donor returns and again tests negative.

In the mid-1970s, nearly 100% of persons with severe hemophilia had serologic evidence of current or previous HBV infection. HCV infection was near-universal until the late 1980s or 90s. HIV seroconversion started around 1979, accelerated in the early 1980s and halted by 1987 with the use of donor-screened, viral-inactivated concentrates. HIV has not been transmitted by concentrates in the U.S.A. since 1987. Transmission of HCV stopped in the 1990s with serologic screening and the widespread adoption of effective viral inactivation. CDC surveillance in the U.S.A. has confirmed the non-transmission of hepatitis A (HAV), HBV and HCV by concentrates.

Donor screening

In the U.S.A., HBV antigen screening began in 1972, exclusion of donors at high risk for HIV in 1983, HIV antibody screening in 1985, transaminase screening in 1987, HCV antibody screening of plasma in 1992, and p-24 antigen (an HIV antigen) screening in 1996. NAT screening of pooled plasma destined for concentrate manufacture for HIV, B-19 parvovirus, HAV, HBV, and HCV, is now routine, as is NAT of individual blood donors for HCV.

Viral separation and inactivation

All concentrates made in the U.S.A. and in other developed countries have been viral inactivated since the mid-1980s. The first method developed was heat treatment. Concentrates may be heated after lyophilization and bottling ("dry") at 60-100° C, or in steam vapor at 60-80° C after lyophilization but before bottling, or in solution at 60° C before lyophilization pasteurization. Stabilizers are added to enable the clotting factors to withstand heat.

Plasma can also be treated with solvents and detergents to dissolve the lipid envelopes of HIV, HBV, and HCV. Non-enveloped viruses, such as HAV and B-19 parvoviruses, are not killed. A few patients have contracted hepatitis A from solvent-detergent treated concentrates. Nowadays, many FVIII concentrates are treated with both heat and solvent-detergent combinations. Nanofiltration is a popular second step for FIX concentrates; FIX is a small molecule and can be physically separated from viruses.

Finally, viral load can be reduced by greater purification (separation) of clotting factors from other components of plasma.

Recombinant concentrates

Clotting factors also are produced in cell culture to avoid the issue of human donor viral contamination. Hamster cells are transfected with human clotting factor genes by recombinant DNA technology. First-generation recombinant FVIII concentrates contained human albumin stabilizer in the final vial. Current products are stabilized in sugars.

Specific Therapeutic Products

Whole plasma

The frozen plasma from one donation of whole blood usually consists of 175-225 mL, containing 70-90 U/dL of FVIII, FIX, VWF and other plasma clotting factors. Although fresh average normal plasma contains 100 U/dL of each factor by definition, minor deterioration is expected during processing and storage. Use of whole plasma is limited by the amount of intravascular volume expansion the patient can tolerate. Young lean patients with normal heart and lung function may tolerate as much as 18 mL/kg given over an hour, but middle-aged or overweight patients, or those with any degree of cardiac or respiratory compromise, may tolerate very little plasma volume expansion. At the maximum dosage suggested, plasma clotting factor levels typically are raised by less than 20 U/dL. Allergic reactions are common in patients who have received plasma often.

Plasma is used to treat deficiencies of clotting factors for which no concentrate is available. If intensive transfusion is intended for a patient with A, B, or AB blood group, compatible but not cross-matched plasma is chosen. If a high level of a clotting factor is needed, plasma can be given by exchange-plasmapheresis to avoid volume overload.

To minimize the risk of viral infection, one well-screened designated donor can be repeatedly plasmapheresed to supply the needs of one patient. Pooled solvent-detergent treated plasma is available in Europe. Other methods of viral-inactivation have been used from time to time.

Cryoprecipitate

A bag of cryoprecipitate contains the few millilitres of cold-insoluble material remaining after slow thawing of frozen plasma. A typical bag is made from the plasma recovered from one donation of whole blood and contains on average about 80 U of FVIII and VWF and 200-300 mg of fibrinogen in a volume of 10-20 mL. Cryoprecipitate also can be made from plasma obtained by plasmapheresis. A single designated donor can be plasmapheresed repeatedly to supply plasma for one recipient. The donor may be pre-treated with DDAVP to elevate his level of FVIII and VWF.

Cryoprecipitate is transported and stored frozen. Allergic reactions may occur in sensitive persons. Some persons not of blood group O who are sensitive to hemolysis may require ABO compatible cryoprecipitate. Individual bags of frozen cryoprecipitate are not viral inactivated. In some countries, cryoprecipitate is pooled, freeze-dried and viral inactivated.

Human FVIII concentrates

Plasma-derived FVIII concentrates are prepared from plasma pooled from many donors (maximum 60,000). FVIII may be initially separated by cryoprecipitation and further purified by precipitating agents or chromatography. Levels of purification are described according to "specific activity," the amount of FVIII per milligram of protein. Added albumin stabilizer usually is discounted. Current recombinant FVIII concentrates are not stabilized in albumin.

VWF is not present in immuno-affinity purified ("monoclonal") or recombinant FVIII concentrates. Large multimers of VWF are well-preserved in certain concentrates, e.g. Humate-

P®, made in Germany by CSL Behring and Biostate®, made in Australia by CSL. VWF may be present in other brands.

FVIII concentrates are the mainstay of therapy for moderate to severe hemophilia A and are suitable for home infusion programs. Allergic reactions are rare. Most lyophilized concentrates are stable at normal room temperatures. Reconstituted concentrate is stable for 12 or more hours and can be used for continuous infusion.

Prothrombin complex concentrate (PCC/ FIX complex)
Concentrates of prothrombin and FIX with various levels of factors VIIand X are made from pooled human plasma. It is intended primarily for treatment of hemophilia B. Activated forms of these factors may be present. PCC is either heat-treated or solvent-detergent-treated. It is stable in storage at room temperature and is infused immediately after reconstitution. Allergic reactions are rare.

PCC use is associated with an increased risk of thrombotic events, such as disseminated intravascular coagulation (DIC), deep vein thrombosis, and pulmonary embolism. Patients especially vulnerable to those events include those undergoing surgical operations, those with massive injuries, those with serious liver dysfunction, and infants with immature livers. Thromboses can also occur in other patients.

PCC has been used to treat hemophilia B, and also to treat deficiencies of prothrombin, of FVII, and of FX. Its use for hemophilia B is being superceded by FIX concentrate and, for FVII deficiency, by FVII concentrate (where available) or recombinant activated factor VII (rVIIa).

Coagulation FIX concentrate
Highly purified concentrates of plasma FIX now are commonly and preferentially used to treat hemophilia B. They do not promote thrombosis. Recombinant FIX concentrate, stabilized in sugars, also is available.

Activated prothrombin complex concentrates (APCC)
Prothrombin complex concentrate is deliberately activated for treatment of patients with inhibitors. Activated FVII and FX tend to "bypass" FVIII or FIX and may trigger clotting. The only brand currently available is FEIBA®, made in Austria and distributed by Baxter. It has a unique unitage system based on *in vitro* inhibitor-neutralizing capacity. Single doses are about 75-125 U/kg and are not dependent on the inhibitor level.

The efficacy of a single dose given for a joint hemorrhage is about 50%. Thrombotic complications are occasionally reported.

Recombinant activated factor VII (rVIIa)
A recombinant concentrate of activated factor VII (NovoSeven® or Niastase®, made in Denmark by NovoNordisk) is used as a bypassing agent for treatment of patients with inhibitors. The dose currently advocated is 90 µg /kg, repeated every 2-3 hours as needed. NovoSeven® is preferred over APCC for patients with inhibitors to FIX, because the interaction of FIX in APCC with the inhibitor may provoke a severe allergic reaction.

Other concentrates
Human plasma-derived fibrinogen concentrates are available from CSL Behring in Germany, LFB in France, and companies in Japan.

Concentrates of human plasma-derived FVII are made by LFB in France and by Baxter in Austria and are available in Europe and elsewhere (but not in the U.S.A.) for congenital FVII deficiency.

Concentrates of human plasma-derived FXI are made by BPL in England and by LFB in France and are available in Europe and elsewhere (but not in the U.S.A.) for congenital factor XI deficiency. The half-life of FXI is 2-3 days, so the dosage needed for surgical operations is low. FXI, when activated, can be thrombogenic. Restraint in dosage is advised.

A human plasma-derived FXIII concentrate, Fibrogammin P®, is made in Germany by CSL Behring.

Desmopressin (DDAVP)
A synthetic analog of natural vasopressin, 1-deamino-8-D-arginine vasopressin (DDAVP), mediates the immediate release of FVIII, VWF, and plasminogen activator from storage sites. It

is used for mild hemophilia A and VWD. It is given intravenously or by subcutaneous injection in a standard dose of 0.3 µg /kg or by nasal spray in a standard adult dose of 300 µg (half in each nostril). Some clinicians give an antifibrinolytic agent at the same time, to inhibit plasminogen activator. Typical peak levels of FVIII and VWF are 2-3 times higher than baseline levels. A second dose given less than 48 hours after the first dose may not provoke a maximal response because stores have been depleted. The response to a single dose is fairly consistent from one occasion to the next in a given patient, and from patient to patient in a given kindred, but varies from kindred to kindred.

Side effects are mild and transient, and may include facial flushing, mild headaches and nausea. Water retention occurs on occasion; fluids should be restricted.

DDAVP is the treatment of choice for mild hemophilia A or type 1 VWD, if the rise in FVIII and VWF is sufficient to halt a hemorrhage or prevent excess bleeding in a surgical procedure. DDAVP is fairly effective in Type 2A VWD and may be used for acute hemorrhages. The use of DDAVP in Type 2B VWD is debated. It releases new large multimers, which aggregate platelets and drop the platelet count. Disaggregation appears to occur, however, and the platelets are not damaged.

Antifibrinolytic drugs

Epsilon-amino-caproic acid (EACA, Amicar®) and tranexamic acid (Cyclokapron®) are inhibitors of plasminogen activator. They help preserve clots in the mouth and nose, and help control menorrhagia. They are contraindicated in the presence of bleeding from the renal tubules (because clots in the tubules may not resorb and the tubules may not recanalize.) The dose of EACA is 10 g/day in divided doses; tranexamic acid is about 3 g/day in divided doses. Intravenous formulations are available.

Estrogen-progesterone

Estrogen-progesterone "birth-control" pills, or those hormones released from vaginal rings or intrauterine devices, reduce endometrial proliferation and are used in women with menorrhagia. High doses of intravenous estrogen can be used for extreme menorrhagia.

Anti-inflammatory agents

Oral or intravenous corticosteroids are used occasionally for brief periods of time to reduce edematous swelling around acute hemorrhages. Injections of corticosteroids into joints with synovitis may help subdue it. Non-steroidal anti-inflammatory agents are used to help relieve hemophilic arthritis.

Analgesics

Acetaminophen (paracetamol) with or without codeine is used commonly for the chronic pain of advanced arthritis. Meperidine (Demerol®) or hydromorphone (Dilaudid®) may be used to relieve the severe pain of acute joint hemorrhages, especially in adults who require analgesics often. Aspirin® is contraindicated because it irreversibly inhibits platelet cyclo-oxygenase. The resulting platelet dysfunction adds to the bleeding tendency. Ibuprofen may also increase bleeding, slightly.

Dosage and Choice of Therapy

Hemophilia A without inhibitor

The initial half-life of infused FVIII, during equilibration, is about 4 hours and the biologic half-life is about 12 hours. For primary prophylaxis, that is, prevention of bleeding in young children who do not have joint damage, a dose of about 20 U/kg every other day, sufficient to keep the trough plasma FVIII level above 1%, is used. In essence, such treatment converts a person with severe hemophilia into one with moderate hemophilia. If prophylaxis is initiated after joint damage has occurred, higher or more frequent doses may be needed to prevent bleeding.

The dose given to stop an acute hemorrhage depends on the size of the bleed and its location. Generally, the higher the FVIII level attained, the greater the likelihood of stopping a hemorrhage immediately. The doses commonly used in the developed world ensure rapid hemostasis in nearly all instances. In less affluent countries, lower doses may be used which will provide immediate hemostasis in a large majority of instances. If bleeding is not controlled, repeated doses are given. In the U.S.A., most clinicians raise the FVIII level to about 50% for definite hemorrhages, especially those in "target" joints (joints with chronic

inflammation that bleed frequently). Early bleeding often halts with lower doses. Hemorrhages into dangerous areas, e.g. the central nervous system or retropharyngeal area, may be treated with higher initial doses to achieve a 100% plasma FVIII level. Hemorrhages should be treated when the patient first feels symptoms of bleeding (tingling in the joint, a lessened range of motion). One should not wait until swelling or warmth can be felt.

If bleeding is in a dangerous area, FVIII can be given intermittently (for example, half the loading dose every 8-12 hours) or by continuous infusion to maintain a minimum plasma FVIII level of about 50%.

For surgical operations in the U.S.A., the FVIII level is maintained near 100% during the procedure and at a minimum level of about 50% for the healing period (about 10 days for major procedures). FVIII usually is raised to about 50% for dental procedures (see page 15).
Physiotherapy in persons with synovitis or marked muscle weakness sometimes provokes bleeding. FVIII can be given prior to physiotherapy to raise plasma levels to 20-40%. As strength is gained, the prophylactic dose is lowered.

In some developed countries, prophylaxis from a very early age (around one year), is the standard of care to prevent joint damage in severe hemophilia. Concentrate is given every other day for hemophilia A and twice a week for hemophilia B. The goal is to keep the plasma level of the deficient factor over 1%, that is, to convert the severe hemophilia to moderate hemophilia.

For hemophilia A, 1 U/kg of FVIII is infused for every increase of 2 U/dL of plasma (2%) desired. The dose of cryoprecipitate or concentrate is rounded off to the nearest number of entire bags or vials. Minor over-dosage is not dangerous.
In mild hemophilia A, DDAVP is the treatment of choice if adequate FVIII levels can be attained, to avoid exposure to biological products. In severe hemophilia A, FVIII concentrates are used.

Hemophilia A with inhibitor
In some patients with low inhibitor levels (under 5 Bethesda units [BU]), FVIII infusion does not provoke an increase in antibody. Hemorrhages in these "low-responders" can be treated with FVIII concentrate in a dose sufficient to neutralize the circulating inhibitor and achieve the desired therapeutic plasma level of FVIII. A dose 2-3 times that used in a non-inhibitor patient may be tried initially.

In patients with higher inhibitor levels ("high-responders"), infusions of FVIII stimulate increased production of inhibitor antibodies (anamnesis). Minor hemorrhages usually are treated with a bypassing agent, a PCC or FEIBA® in a dose of 75-100 U/kg, repeated once or twice at 8-12 hour intervals. More frequent dosing is avoided if possible, for fear of thrombotic complications. These products contain very little FVIII antigen and only occasionally provoke anamnesis. Alternatively, rVIIa (NovoSeven®) can be given in a dose of 90 μg/kg, repeated every 2-3 hours.

For very serious, life-threatening hemorrhages, FVIII is given if possible. The probability of controlling a hemorrhage with the initial treatment is much higher if a therapeutic level of FVIII can be attained than if a bypassing agent is used. A high-responder who currently has a fairly low inhibitor level can be given large bolus doses of FVIII, sufficient to neutralize his inhibitor and provide additional FVIII to help form a clot. Some clinicians use a standard large bolus dose, e.g. 10,000 U FVIII in an adult, to try to achieve hemostasis in the short period of time before the FVIII is inactivated. (The interaction of FVIII and its inhibitor is time-dependent.) If direct infusion of FVIII concentrate is inadequate, as is likely with inhibitor levels over 10 BU, an exchange plasmapheresis can be performed, if time permits, to deplete the plasma of its inhibitor, after which a massive infusion of FVIII is given. If plasmapheresis is unavailable or would cause too much delay, then a serious hemorrhage may be treated with a bypassing agent.
Many clinicians attempt surgery in a high-responder only as a life-saving effort. Some high-responders have undergone elective surgery under cover of NovoSeven®.

Immunosuppressive drugs alone have little or no effect on inhibitors in persons with hemophilia (in contrast to their beneficial effect in non-hemophilic persons with autoimmune inhibitors.) Immune tolerance to FVIII can be induced in about 75% of inhibitor patients with daily infusions of FVIII over several months. Doses used in the U.S.A. range from 50-100 U/kg/day. A wider dose range has been used in Europe. Inhibitor levels tend to peak in the first month of treatment, then fall. The process may be hastened a little by the concomitant use of immunosuppressive drugs. Immune tolerance usually must be maintained with low doses of FVIII given every few days. Some patients who were high-responders and who have undergone induction of immune tolerance retain low inhibitor levels, which then behave like low-responding inhibitors.

Hemophilia B

The initial half-life of infused FIX, during equilibration, is about 4 hours and the biologic half-life is about 26 hours. For primary prophylaxis, doses of about 40 U/kg may be given twice weekly to maintain a minimum trough level of 1% or more. Larger doses may be needed in patients with pre-existing joint damage.

The plasma levels of FIX needed to stop bleeding are similar to those sought in FVIII deficiency; 1 U/kg of FIX is infused for every increase of 1 U/dL of plasma (1%) desired (dosages of FIX are twice as high as those of FVIII. FIX is the only plasma clotting factor that requires "double" dosage. No one knows where the "extra" FIX goes.)

Coagulation FIX (purified FIX concentrate, as opposed to PCC), is the treatment of choice in patients requiring surgery or intensive therapy for massive injuries, or in patients with immature or diseased livers, or a history of thrombosis. For intermittent therapy or prophylaxis, some patients who tolerate PCC prefer to use it because it is cheaper than coagulation FIX.

Inhibitors to FIX arise much less frequently than do inhibitors to FVIII. Some inhibitors to FIX precipitate with FIX from exogenous concentrate, causing severe allergic reactions including anaphylaxis. The first such reaction may occur with the first dose of FIX-containing concentrate given after the inhibitor develops, before the inhibitor is diagnosed. Young children with severe hemophilia B usually are treated in the clinic where resuscitation drugs are handy, rather than at home, until they are past the stage of likely inhibitor development (that is, past 20-30 treatments.)

NovoSeven®, which does not contain any FIX, is the treatment of choice for patients with hemophilia B and inhibitors. Induction of immune tolerance has been successful in only a small minority of cases; in many instances, a nephritic syndrome has resulted from the attempt.

von Willebrand disease

In Type 1 VWD there is a decreased circulating level of normal VWF. DDAVP is the drug of choice because it mediates the release of additional normal VWF from storage in endothelial cells. Some patients have an inherently greater ability to respond to DDAVP than others. A test-dose after initial diagnosis of VWD is advocated, with measurement of levels of FVIII and of VWF:RCo at 30 minutes post-infusion, to establish the patient's responsiveness.

Mild to moderate acute hemorrhages in patients with Type 2A VWD may respond to DDAVP. Its use in Type 2B VWD is debated. DDAVP is not used in Type 3 VWD.

For serious hemorrhages in patients who are unresponsive to DDAVP or in whom it is inappropriate, concentrates containing VWF are used. They are now labeled in VWF:RCo international units, as well as FVIII international units. Those with good retention of large multimers are preferred, but any product containing VWF may be effective. LFB, in France, makes a concentrate (Wiloctin®) containing ten times as much VWF as FVIII meant specifically for use in VWD. Acute hemorrhages may be treated with about 20 VWF:RCo U/kg to achieve a plasma level of normal VWF of about 50%.

Concentrate is given for surgical operations in patients who are not adequately managed with DDAVP. In developed counties, sufficient VWF:RCo units are given to raise the plasma VWF:RCo level during the procedure to about 100% and to maintain it at about 50% during the

healing period. (This dosage may be overly generous). One unit of VWF:RCo per kg raises the plasma VWF:RCo level 2 U/dL (2%). The half-life of ristocetin cofactor is about 10 hours. Patients with Type 2 VWD have abnormal VWF molecules, and, for major operations and major hemorrhages, their baseline levels of VWF may be considered to be nil, as in patients with Type 3 VWD. Concentrates typically are given for childbirth in women with type 2 or 3 VWD.

Antifibrinolytic drugs are especially useful for mucosal and menstrual bleeding. They should be given, in addition to concentrate, for surgery in the nose and mouth area and for dental extractions.

Other clotting factor deficiencies

Viral-inactivated concentrates are preferred to untreated cryoprecipitate or plasma, if such a concentrate exists for the factor deficiency in question.

Management of Specific Bleeding Problems

Bleeding in hemophilia is slow but persistent. Small cuts often stop bleeding if firm pressure is applied for a few minutes. Large lacerations or internal bleeding usually require infusions of concentrate or, where appropriate, DDAVP. Early joint or soft tissue hemorrhages may respond to one infusion that raises the plasma clotting factor level to 15-30%. For serious hemorrhages, the level should be raised to 50%. If bleeding is in a dangerous area or has failed to respond to outpatient treatment, hospitalization and maintenance of minimum factor levels at 50% is indicated. Delay in treatment should be minimized. Patients on supervised self-infusion programs may give themselves concentrate immediately if serious bleeding occurs and then report to the emergency room or clinic. Ambulance personnel should be directed to take an injured person with hemophilia to the nearest emergency room that stocks concentrates.

Central nervous system (CNS)

CNS bleeding is the most common cause of death from bleeding in hemophilia. An injury that is trivial in a normal person, such as bumping the head against a cabinet while standing up, or falling on the buttocks and jolting the spinal column, may cause prolonged bleeding from a small CNS vessel. The slowly accumulating blood eventually causes symptoms after a few hours or days. Many persons with CNS bleeding cannot recall an injury. Any patient with symptoms referable to the spinal cord or brain, including unusual headache or lethargy, should be hospitalized, treated with the appropriate clotting factor replacement therapy to maintain normal factor levels, and observed closely. CT and MRI scans are helpful in determining whether a hemorrhage has occurred.

Mouth, throat and nose

Bleeding in the mouth from a laceration or bitten tongue often is persistent. Blood loss in a small child may be so great that red cell replacement is required. A large friable clot resembling a raspberry may protrude from the wound, holding the edges apart. At the time that concentrate is given, such loose clots should be wiped off so wound edges may come together with a strong clot. Antifibrinolytic drugs are given to help preserve clots in the mouth.

Bleeding under the tongue, behind the pharyngeal wall, or in the neck is dangerous because it may choke the patient. Hemorrhages in these areas may be caused by tonsillitis, coughing spells, or regional block anesthesia for dental work. Concentrate is given and the patient is observed closely in the hospital. If the patient already has stridor, intravenous corticosteroids may reduce inflammation just enough to avoid a tracheotomy, while concentrate permits hemostasis.

Nosebleeds are especially common in VWD. DDAVP or concentrate can be supplemented by antifibrinolytic drugs. Cautery should be avoided because burned areas later slough, with repeated bleeding. If the nares are packed, a greased material is used to allow atraumatic removal.

Gastrointestinal tract

The first time gastrointestinal bleeding occurs, a search for a causative lesion, such as an ulcer, is justified. If no lesion is found, the search is not repeated if the patient bleeds again. A person with a bleeding disorder is more likely to bleed from very small lesions than is a normal person. Angiodysplasia of the gut may be a disorder of

aging. As patients age, they are increasingly prone to gastrointestinal bleeding, a phenomenon especially obvious in VWD. Hemostasis may be difficult to achieve, and may require use of multiple agents, including antifibrinolytic drugs, clotting factor replacement, and, in very resistant cases, infusions of normal platelets.

Hematuria

Hematuria is fairly common in persons with severe hemophilia A or B. Clots may obstruct renal tubules or the ureter, causing temporary hydronephrosis. Treatment usually consists of bed rest and daily clotting factor replacement. Antifibrinolytic drugs are contraindicated because renal tubules may fail to recanalize in their presence.

Joints

Joint hemorrhages are common in severe hemophilia A or B and are occasionally seen in other severe clotting factor deficiencies. Affected joints are the knees, elbows, ankles, shoulders, and hips, in decreasing order of frequency. A patient with mild hemophilia who happens to injure a joint may thereafter have frequent hemorrhages in that joint. The first symptoms of joint hemorrhage are stiffness and tingling. If the patient receives clotting factor replacement at that point, the bleeding usually subsides and morbidity is minimal. Early hemorrhages should be treated. They often can be controlled with small doses of clotting factor. One should not wait to see whether the hemorrhage progresses. If a patient presents with a joint that already is warm and swollen, vigorous treatment is needed. If the joint is fluctuant, aspiration of the blood under sterile conditions will reduce pain and shorten the period of disability. Clotting factor replacement is given once or twice a day for a serious joint hemorrhage until it returns to its baseline range of motion and circumference. Narcotic analgesics often are required for relief of the pain of acute hemarthroses in adults and in some children.

For knee or elbow bleeding, a posterior splint is used to immobilize the joint until the swelling has subsided. In small children, ankle hemorrhages often are recurrent; therefore, 2-3 days after the swelling has subsided, a short-leg walking cast may be applied and left in place for 2-3 weeks to allow maximum general activity while protecting the affected joint.

A hemorrhage in the hip joint is dangerous because the increased intra-articular pressure on the tenuous arterial support may lead to aspectic necrosis of the femoral head. A suspected hip joint hemorrhage must be distinguished from bleeding in the iliopsoas muscle. In iliopsoas bleeding, extension of the hip is limited and painful, but gentle rotation is not. In intra-articular hip hemorrhage, all motion of the joint, including internal and external rotation, is extremely painful. A patient with intra-articular hip bleeding should rest in bed with Buck's traction (to relieve intra-articular pressure) and should receive sufficient clotting factor replacement to maintain factor levels at or above 50%. Aspiration of the joint is desirable, to relieve pressure.

Hemorrhages in the shoulder often are very painful. Immobilization with a bandage fixing the flexed arm to the anterior chest may be helpful.

After recovery from an acute hemarthrosis, the patient's joint mobility and muscle strength should be evaluated and physiotherapy instituted to restore any losses. Strong muscles support joints and decrease the frequency of recurrence.

Bacterial joint infections are rare in HIV-negative patients, but are fairly common in HIV-positive persons whose HIV infection is not controlled with antiretroviral drugs. If a swollen, painful joint, thought to be hemorrhaging, does not improve quickly after clotting factor replacement, the joint should be aspirated for Gram stain and culture.

Muscles

Hemorrhages in muscle or soft tissue are particularly dangerous when they occur in closed compartments, such as the volar aspect of the wrist and forearm, the deep palmar compartments of the hand, or the anterior or posterior tibial compartments. Treatment includes clotting factor replacement in major doses and elevation of the affected limb. Steroids may help reduce swelling and alleviate pressure. In severe cases, especially when treatment has been delayed, surgical

decompression is considered. Aspiration is NOT recommended. Intramuscular or subcutaneous hemorrhages not confined in fascial boundaries may spread extensively, especially in the quadriceps or hamstrings, causing a notable drop in hematocrit.

Hemorrhages in the iliopsoas muscle may be misinterpreted by an inexperienced clinician. The patient presents with the hip flexed and has pain on extension, but not on gentle rotation, of the hip. Maximum tenderness usually is found in the femoral ring. In large hemorrhages, some tenderness and fullness in the lower quadrant of the abdomen may be felt. The femoral nerve is compressed by the swollen muscle as both pass under the inguinal ligament, causing decreased sensation over the anterior thigh, loss of the knee jerk and, eventually, loss of quadriceps strength. If the clinical picture is confusing, an iliopsoas hemorrhage can be confirmed by CT or ultrasound scan.

Hemorrhages of the iliopsoas, hamstrings, quadriceps or gastrocnemius muscles are treated intensively with clotting factor replacement and bed rest until swelling has disappeared and range of motion is near normal. Mobilization is cautious because recurrence is frequent. Physiotherapy is begun gradually and continued for a long time to regain muscle strength.

Fractures

Fractures managed with closed reduction and casts require clotting factor replacement therapy for 3-4 days, until swelling subsides. If open reduction is necessary, treatment is the same as for other surgical operations.

Dental Management

Regular professional dental care should be encouraged. Dental cleaning and scaling may cause slight oozing, but clotting factor replacement is rarely needed. Orthodontia may be carried out as in persons who are not bleeders. The major problem in the restoration of carious teeth is the choice of analgesic. Local infiltrative anesthesia can be given without prior clotting factor replacement, but the factor level should be raised to 30-50% before regional block anesthesia because of the risk of piercing a blood vessel. A rapidly enlarging hematoma at the angle of the jaw can result from such an accident, with dissection into the neck and compression of the trachea.

For tooth extractions, antifibrinolytic drugs are given on the day of extraction and for about 10 days afterwards. They may suffice for hemostasis in simple extractions. In most patients, the factor level is raised to 20-50%, depending on the difficulty of the extraction. Patients with VWD receive some replacement therapy (DDAVP or FVIII-VWF concentrate), even if the baseline level of VWF already is in that range. A strict diet of cool liquids is followed for several days to avoid dislodging clots. Most extractions are performed as outpatient procedures. Concentrate is seldom needed post-operatively. Multiple extractions, or those on patients with inhibitors, are best managed in the hospital.

Surgical Operations

Surgical operations in persons with bleeding disorders require planning. They should take place in hospitals with laboratories experienced in clotting factor assays. A hematologist well versed in hemophilia management should attend the patient. The surgeon and the anesthesiologist should be aware of the special needs of a patient with a history of bleeding. An ample supply of the appropriate concentrate should be on hand. The patient should have a sensitive test to rule out the presence of an inhibitor.

About an hour before the operation, the patient should be infused with enough concentrate to raise his deficient factor to about 100%. In most hemophilia centres, that level is checked with a factor assay before the incision. The clotting factor level is maintained around 100% during the operation and at about 50% for about 10 days afterwards. (The probability of delayed post-operative bleeding is lower after 10 days.) Clotting factor levels are checked daily with specific assays. Longer hospital stays are planned for patients requiring intensive physiotherapy, for example, after total knee replacement, whereas shorter stays may be possible in some instances, for example after ankle fusion with casting, if the patient or his

relatives are able to continue a course of concentrate infusion at home.

Chronic Orthopedic Problems

Pathogenesis

Bleeding into joints and deposition of iron inflames the synovium (synovitis). With repeated bleeding, the synovium proliferates and forms vascular villus folds that are easily pinched on joint motion, leading to rebleeding—a vicious cycle. Cartilage gradually is destroyed and bone is resorbed. Degenerative arthritis develops with accompanying pain, loss of mobility, and disuse atrophy of adjacent muscles. Joint inflammation during the growing years stimulates excess growth at the ends of long bones, leading to limb-length discrepancies and knobby enlargement at the ends of bones. Hemorrhages into muscles lead to atrophy and contracture.

Chronic synovitis

Chronic synovitis with effusion may be seen in children and adolescents, especially in the knee, which is swollen, boggy and warm, but not very tender and not held in the flexed position characteristic of acute hemorrhage.

Conservative treatment consisting of concentrate prophylaxis may be given for a few weeks, together with a low-dose course of oral corticosteroids, while the adjacent muscles are strengthened with gentle physiotherapy. Posterior splints may be worn at night to help avoid further injury.

Conservative treatment measures often fail to control synovitis. Further intervention should be considered early rather than late to minimize joint damage. The most effective definitive treatment is achieved with radionucleotide synovectomy, that is, injection into the joint space of a short-lived radioisotope emitting beta radiation with low penetrance, contained in large colloid particles that remain inside the joint capsule. The isotope shrinks the hypertrophied synovium. In some countries, when radionucleotide synovectomy is not available, other agents such as rifampicin are injected into the joint to shrink the synovium. Arthroscopic or open synovectomy sometimes is performed if the synovium is very thick.

Flexion contractures

Flexion contractures occur commonly at the elbow and the knee. At the elbow, an enlarged radial head often impedes forearm rotation. Excision of the radial head improves rotation, a motion of great functional importance, but flexion and extension may not be improved. Knee flexion contractures may be encountered in patients who have not had access to modern care. Moderate contractures can be treated with serial wedge casts and physiotherapy. More serious contractures require use of cylinder casts around the thigh and calf-holding extension-desubluxation hinges at both sides of the knee. Daily tightening of the hinges reduces subluxation of the tibia upon the femur and increases extension. Long-standing contractures may require surgical releases of tissues at the back of the knee and lengthening of tendons.

Degenerative arthritis

Severe degenerative arthritis is seen in adults with severe hemophilia who have not had modern treatment as children. Patients often benefit from use of non-steroidal anti-inflammatory agents. Analgesics often are heavily used.

The joints should be protected from stress. Patients are urged to remain slender to reduce the burden on weight-bearing joints. Shoes with resilient soles absorb the shock of impact on hard surfaces while walking. High-top laced-up athletic shoes are appropriate and lend minor support to ankles. Muscles adjacent to weight-bearing joints (and arm muscles needed to transfer weight to canes and crutches) are strengthened to lend support. External rigid supports often are used for arthritic ankles, but elsewhere, rigid supports are not used over prolonged periods because the adjacent muscles tend to atrophy.

If recurrent bleeding or impaired mobility of a joint is due to the presence of bony spurs (e.g. at the distal tibia) with few other manifestations of arthritic deterioration, the joint may be debrided. If chronic disabling pain persists in a shoulder, ankle or subtalar joint with advanced arthritis, joint fusion provides relief. Prosthetic knee, hip, shoulder, or ankle joints are implanted when degeneration is far advanced and painful, with excellent results. Such

implants are vulnerable to late infection, so they are used only in patients who can take suitable precautions.

Pseudotumors are hemorrhagic cysts in, or adjacent to, bone. Enlarging lesions in the mandible, the long bones, or the pelvic girdle require surgical curettage and, in some instances, bone grafts. Risks of delaying surgery include rupture, pathological fracture, or infection. Pseudotumors in the hands or feet tend to be multiple and sometimes may halt after external-beam irradiation.

Complicating Viral Infections

Many persons treated with pooled plasma products before 1986 were infected with HIV. Transmission of hepatitis B and C continued a little longer, depending on plasma screening and the viral inactivation methods used. Many adult patients have some degree of chronic active hepatitis C, and some develop liver failure or hepatic cancer. Heavy alcohol intake may accelerate liver failure. Treatment of HIV infection and of hepatitis C is the same in patients with hemophilia as in other persons. Antiviral therapies should be pursued vigorously. A few hemophilia patients with advanced liver disease have had successful liver transplants. The transplanted liver produces clotting factors normally, so the bleeding disorder also is ameliorated.

Future directions

Concentrate is becoming more plentiful in the 21st century, with expansion, in particular, of production of recombinant FVIII. The number and availability of concentrates for rare clotting factor deficiencies has not yet improved. Experiments on the production of clotting factors in the milk of transgenic animals are encouraging.

Prophylaxis starting at an early age in children with severe hemophilia is becoming commonplace. It prevents most of the joint damage described in this paper. Placement of venous access devices to facilitate prophylaxis in young children brings its own complications of infection and of retrograde thrombosis. Muscle-building programs are a form of prophylaxis, but they are not widely championed.

Prospects for gene therapy for hemophilia are cautiously optimistic.. Dogs with severe hemophilia were successfully treated with gene therapy several years ago, so there is cause for optimism. The same gene therapy format has not yet been adapted successfully for humans, but trials continue. Any gene therapy will appear to be expensive, except in comparison to the cost of treating hemophilia with concentrates.

Good hemophilia care depends on the existence of an adequate network of expert healthcare professionals, diagnostic laboratories, and organized hemophilia care centres, a plentiful supply of affordable concentrates and continuing patient and public education.

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