HEMOPHILIA AND VON WILLEBRAND'S DISEASE: 2. MANAGEMENT

Association of Hemophilia Clinic Directors of Canada

Abstract • Résumé

Objective: To present current strategies for the treatment of hemophilia and von Willebrand's disease.

Options: Prophylactic and corrective therapy with hemostatic and adjunctive agents: DDAVP (1-desamino-8-D-arginine vasopressin [desmopressin acetate]), recombinant coagulation products (human Factor VIII and human Factor VIIa) or virally inactivated plasma-derived products (high- or ultra-high-purity human Factor VIII or human Factor VIII concentrate containing von Willebrand factor activity, porcine Factor VIII, high-purity human Factor IX, human prothrombin-complex concentrate, human activated prothrombin-complex concentrate), adjunctive antifibrinolytic agents, topical thrombin and fibrin sealant. The induction of immune tolerance in patients in whom inhibitors develop should also be considered.

Outcomes: Morbidity and quality of life associated with bleeding and treatment.

Evidence: Relevant clinical studies and reports published from 1974 to 1994 were examined. A search was conducted of our reprint files, MEDLINE, citations in the articles reviewed and references provided by colleagues. In the MEDLINE search the following terms were used singly or in combination: "hemophilia," "von Willebrand's disease," "Factor VIII," "Factor IX," "von Willebrand factor," "diagnosis," "management," "home care," "comprehensive care," "inhibitor," "AIDS," "hepatitis," "life expectancy," "complications," "practice guidelines," "consensus statement" and "controlled trial." The in-depth review included only articles written in English from North America and Europe that were relevant to human disease and pertinent to a predetermined outline. The availability of treatment products in Canada was also considered.

Values: Minimizing morbidity and maximizing functional status and quality of life were given a high value.

Benefits, harms and costs: Proper prophylactic or early treatment with appropriate hemostatic agents minimizes morbidity and functional disability and improves quality of life. Economic gains are realized through the reduction of mortality and morbidity and their associated costs. The patient has a better opportunity to contribute to society through gainful employment and the fulfilment of social roles. Potential harms include HIV infection, hepatitis B, hepatitis C and the development of inhibitor antibodies to clotting-factor concentrates. The risk of viral transmission has been minimized through the development of procedures for the viral inactivation of plasma-derived clotting-factor concentrates and through the use of recombinant coagulation-factor concentrates and other non-plasma-derived hemostatic agents.

Recommendations: DDAVP is the drug of choice for patients with mild hemophilia or type 1 or 2 (except 2B) von Willebrand's disease whose response to DDAVP in previous testing has been found to be adequate. Therapeutic blood components of choice include recombinant products and virally inactivated plasma-derived products. In Canada the recommended products are recombinant Factor VIII for hemophilia A, high-purity plasma-derived Factor IX for hemophilia B and plasma-derived Factor VIII concentrates containing adequate von Willebrand factor (e.g., Haemate P) for von Willebrand's disease. Dosages vary according to specific indications. Adjunctive antifibrinolytic agents, topical thrombin and fibrin sealant are useful for the treatment of oral or dental bleeds and localized bleeds in accessible sites. In patients with inhibitor antibodies, high-dose human or porcine Factor VIII is usually effective when the inhibitor titre is less than 5 Bethesda units/mL. In nonresponsive patients, or in those whose inhibitor titre is higher, "bypassing" agents (e.g., activated prothrombin-complex concentrate and recombinant Factor VIIa) are useful. Long-term management may include immune-tolerance induction.

Validation: These recommendations were reviewed and approved by the Association of Hemophilia

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Clinic Directors of Canada (AHCDC) and the Medical and Scientific Advisory Committee of the Canadian Hemophilia Society. No similar consensus statements or practice guidelines are available for comparison.

Sponsors: These recommendations were developed at the request of the Canadian Blood Agency, which funds the provision of all coagulation-factor concentrates for people with congenital bleeding disorders, and were developed and endorsed by the AHCDC and the Medical and Scientific Advisory Committee of the Canadian Hemophilia Society.

Objectif : Présenter les stratégies actuelles de traitement de l'hémophilie et de la maladie de von Willebrand.

Options : Traitement prophylactique et correctif à l'aide d'agents hémostatiques et d'appoint : DDAVP (1-diamine 8 D-arginine-vasopressine [acétate de desmopressine]), agents de coagulation recombinants (facteur VIII humain et facteur VIIa humain) ou agents tirés du plasma et traités par inactivation virale (facteur VIII humain de grande ou de très grande pureté ou concentré de facteur VIII humain contenant du facteur de von Willebrand actif, facteur VIII porcin, facteur IX humain très pur, concentré de complexe de prothrombine humaine, concentré de complexe de prothrombine humaine activée) agents antifibrinolytiques d'appoint, thrombine topique et agent de scellement à la fibrine. Il faut aussi tenir compte de l'induction de la tolérance immunitaire des patients chez lesquels des inhibiteurs font leur apparition.

Résultats : Morbidité et qualité de vie liées à l'hémorragie et au traitement.

Preuves : On a examiné des études cliniques et des rapports pertinents publiés de 1974 à 1994. Les auteurs ont procédé à une recherche dans leurs dossiers de réimpressions, dans MEDLINE, dans des citations publiées dans les articles examinés et dans des références fournies par des collègues. Pour la recherche dans MEDLINE, on a utilisé les termes suivants seuls ou combinés : «hemophilia», «von Willebrand's disease», «Factor VIII», «Factor IX», «von Willebrand factor», «diagnosis», «management», «home care», «comprehensive care», «inhibitor», «AIDS», «hepatitis», «life expectancy», «complications», «practice guidelines», «consensus statement» et «controlled trial». L'examen détaillé n'a porté que sur les articles rédigés en anglais, provenant d'Amérique du Nord et d'Europe, qui portaient sur la maladie humaine et sur un aperçu pré-déterminé. On a tenu compte aussi de la disponibilité au Canada des produits de traitement.

Valeurs : On a accordé une valeur élevée à la réduction au minimum de la morbidité et à la maximisation de l'état fonctionnel et de la qualité de vie.

Avantages, préjudices et coûts : Le traitement précoce ou prophylactique à l'aide d'agents hémostatiques appropriés réduit au minimum la morbidité et l'incapacité fonctionnelle et améliore la qualité de vie. La réduction de la mortalité et de la morbidité, ainsi que des coûts qui en découlent, entraînent des gains économiques. Le patient a une meilleure chance de contribuer à la société en occupant un emploi rémunéré et en s'acquittant de rôles sociaux. Les préjudices possibles comprennent l'infection au VIH, l'hépatite B, l'hépatite C et l'apparition d'anticorps inhibiteurs de concentrés de facteur de coagulation. Le risque de transmission virale a été réduit au minimum grâce à la mise en place de procédures d'inactivation virale de concentrés de facteurs de coagulation tirés du plasma et à l'utilisation de concentrés de facteurs de coagulation recombinants et d'autres agents hémostatiques non tirés du plasma.

Recommandations : La DDAVP est le médicament de choix dans le cas des patients atteints d'hémophilie légère ou de la maladie de von Willebrand des types 1 ou 2 (sauf 2B) dont la réaction à la DDAVP lors de tests antérieurs a été adéquate. Les composants sanguins thérapeutiques de choix comprennent les produits recombinants et les produits tirés du plasma et traités par inactivation virale. Au Canada, les produits recommandés sont le facteur VIII recombinant dans le cas de l'hémophilie A, le facteur IX très pur tiré du plasma dans celui de l'hémophilie B et des concentrés de facteur VIII tirés du plasma contenant du facteur de von Willebrand (p. ex., Haemate P) dans celui de la maladie de von Willebrand. Les posologies varient selon des indications précises. Les agents antifibrinolytiques d'appoint, la thrombine topique et les agents de scellement à la fibrine servent au traitement des saignements buccaux ou dentaires et des saignements localisés à des endroits accessibles. Chez les patients qui ont des anticorps inhibiteurs, le facteur VIII porcin ou humain à forte dose est habituellement efficace lorsque le titre de l'inhibiteur est inférieur à 5 unités Bethesda/mL. Chez les patients qui ne réagissent pas ou dont le titre de l'inhibiteur est plus élevé, des agents d'«évitement» (p. ex., concentré de complexe de prothrombine activée et facteur VIIa recombinant) sont utiles. Le traitement à long terme peut comprendre l'induction de la tolérance immunitaire.

Validation : Ces recommandations ont été examinées et approuvées par l'Association canadienne des directeurs des cliniques d'hémophilie (ACDCH) et le Comité consultatif médical et scientifique de la Société Canadienne d'hémophilie. Il n'existe pas d'énoncé consensuel ni de guide de pratique semblable à des fins de comparaison.

Commanditaires : Ces recommandations ont été formulées à la demande de l'Agence canadienne du sang qui finance tous les concentrés de facteur de coagulation fournis aux personnes qui ont des troubles sanguins héréditaires. Elles ont été élaborées et appuyées par l'ACDCH et le Comité consultatif médical et scientifique de la Société Canadienne d'hémophilie.

Comprehensive care, including home therapy, is the mainstay of treatment for patients with hemophilia and von Willebrand's disease.[1-6] In part 1 we focused on the organizational aspects of patient care.[6] In this article we will outline the blood products and treatments currently available and recommended for use in Canada.

The development of management recommendations by the Association of Hemophilia Clinic Directors of Canada (AHCDC, formerly the Canadian Hemophilia Clinic Directors Group) was initially requested by the Canadian Blood Agency, which provides funding for the purchase of all coagulation-factor concentrates for the management of congenital coagulation disorders. A writing committee consisting of the three principal coauthors was established. We developed an outline of the topics to be considered and reviewed relevant clinical studies and reports published from January 1974 to April 1994. (This period was extended to September 1994 for the purposes of this article.) We searched our own reprint files, the MEDLINE database, citations in articles reviewed and references provided by colleagues. For the MEDLINE search we used the following terms singly or in combination: "hemophilia," "von Willebrand's disease," "Factor VIII," "Factor IX," "von Willebrand factor," "diagnosis," "management," "home care," "comprehensive care," "inhibitor," "AIDS," "hepatitis," "life expectancy," "complications," "practice guidelines," "consensus statement" and "controlled trial." We reviewed in depth only literature written in English from North America and Europe that was relevant to human disease and to our outline. The availability in Canada of treatment products was also considered. We then wrote an initial draft that was critiqued by the five members of the executive committee of the AHCDC, who provided input and approved a revised draft for circulation to members of the AHCDC and the Medical and Scientific Advisory Committee of the Canadian Hemophilia Society. Each member of the AHCDC and the chair of the advisory committee critiqued the document. Many AHCDC members also relayed critiques made by their clinic nurse coordinators.

These comments and revisions were incorporated into another draft circulated to each member of the AHCDC. This draft was discussed and approved in May 1994 at the AHCDC annual meeting, held in Quebec City. After minor revisions, a final document was circulated to the Canadian Hemophilia Society's Medical and Scientific Advisory Committee, whose members include representatives of hemophilia clinic nurse coordinators, physiotherapists, social workers, dentists and physicians. The advisory committee met in June 1994 and endorsed the document.

Randomized clinical trials that could provide evidence at levels I and II[7] regarding the clinical efficacy of agents for the management of hemophilia and von Willebrand's disease have not been done. Because the efficacy of hemostatic agents correlates closely with the clotting-factor levels (and, in von Willebrand's disease, reduced bleeding time) that they induce, clinical trials are usually preceded by pharmocokinetic studies to determine in-vivo half-life and recovery. All ultra-high-purity and recombinant Factor VIII concentrates used in the treatment of hemophilia A, and all high-purity Factor IX concentrates used in the treatment of hemophilia B, have been evaluated in pharmacokinetic studies according to the study design and data analysis guidelines established by the Scientific and Standardization Committee of the International Society for Thrombosis and Haemostasis.[8] These guidelines take into account sample size, the need for randomized patient crossover with an adequate washout period, the clinical status of the study participants, dosage, methods of potency assessment, and statistical models and methods for half-life and recovery analyses. The efficacy of Haemate P, a product recommended for the correction of bleeding time in von Willebrand's disease, has been compared with that of a number of other Factor VIII concentrates in randomized crossover studies.[9] Crossover comparison of Haemate P with cryoprecipitate was not deemed ethically acceptable because cryoprecipitate, unlike all Factor VIII concentrates, does not undergo a viral inactivation process.[10] The development of inhibitors (alloantibodies that inhibit clotting-factor activity) in patients receiving recombinant Factor VIII concentrates[11,12] has been evaluated prospectively (but without randomization) in studies involving previously untransfused patients.

Management of hemophilia A and B

In general, therapy for hemophilia is given when a bleeding episode arises (demand treatment) or when bleeding is anticipated or likely (prophylactic treatment). Short-term prophylactic treatment is given to patients before they undergo surgical procedures or engage in activities that carry a high risk of provoking a bleed. It may also be given to break the cycle of frequent bleeding into specific joints (target joints). In view of the increasing safety of clotting-factor concentrates, long-term prophylactic therapy in the form of Factor VIII infusion at least three times a week or Factor IX infusion at least twice a week to prevent hemarthrosis in severely affected patients is gaining acceptance, especially in the treatment of infants and children. It has been shown that increasing in-vivo clotting-factor levels to more than 1% activity (usually accomplished by giving 25 to 40 U/kg of Factor VIII three times a week or 25 to 40 U/kg of Factor IX twice a week) is sufficient to prevent most spontaneous joint bleeds and preserve joint function.[13-16]

DDAVP

DDAVP (1-desamino-8-D-arginine vasopressin [desmopressin acetate]), a synthetic analog of the natural antidiuretic hormone, arginine vasopressin, is capable of releasing Factor VIII and von Willebrand factor into the circulation from biosynthetic stores. The intravenous administration of 0.3 μg/kg (up to 20 μg in total) of DDAVP causes a 2- to 10-fold (average 3- to 4-fold) rise in plasma levels of Factor VIII and von Willebrand factor.[17–19] Following DDAVP infusion, clotting-factor levels peak at 30 to 60 minutes and have a half-life similar to that of infused exogenous clotting factors. DDAVP can also be given subcutaneously at the same dosage.[18,20] Intranasal preparations ideal for home care have undergone clinical trial in North America[21] but are not yet licensed for use in Canada. DDAVP currently costs about $55 (Cdn) for a 20-μg intravenous dose.

Therapeutic use

DDAVP is the drug of choice for the treatment of patients with mild hemophilia A (Factor VIII activity more than 5%) or type 1 or type 2 (except type 2B) von Willebrand's disease whose response to DDAVP has been found to be adequate in previous testing.[17,19] Overall, about 80% of patients with von Willebrand's disease will respond to DDAVP. Patients with moderate to severe hemophilia or type 3 von Willebrand's disease will not have an adequate response. Most experts also prefer not to use DDAVP for the treatment of type 2B[22] or platelet-type (pseudo) von Willebrand's disease[23] because of the potential for DDAVP-induced platelet agglutination and thrombocytopenia. Patients with type 2B and platelet-type von Willebrand's disease can be distinguished by their enhanced platelet aggregation response to low-dose ristocetin (0.5 mg/mL),[22,23] and this test can be used to exclude these patients from DDAVP testing and therapy. DDAVP is not effective in the treatment of hemophilia B.

The response of Factor VIII and von Willebrand factor to DDAVP decreases progressively when closely spaced repeated infusions are given; this is particularly the case in patients with hemophilia A.[17,24] Thus, DDAVP is especially useful in situations in which only a single dose is required. During major surgery or episodes of prolonged bleeding it may be necessary to alternate DDAVP with supplemental coagulation products.

Side effects

The side effects of DDAVP are minor, consisting of facial flushing, headache, nausea, abdominal cramps, tachycardia and, uncommonly, hypertension and hypotension. Rarely, water intoxication with extreme hyponatremia occurs, especially in neonates, infants and elderly people following closely spaced repeated infusions. For these patients and for those with hypertension it is particularly important to monitor blood pressure, the serum sodium level and urine output and to avoid giving hyponatremic fluids following infusions. Myocardial infarction and stroke from arterial thrombosis have been reported rarely after DDAVP infusion among elderly patients with atherosclerosis.[25,26] Caution should therefore be exercised in the treatment of elderly people with DDAVP.

Blood components

Currently, all plasma-derived clotting-factor concentrates except cryoprecipitate undergo viral inactivation procedures. Prospective studies involving previously untransfused patients indicated that when these products are subjected to current virucidal treatments the risk of HIV and hepatitis C virus transmission is negligible.[10] These virucidal procedures include: (a) pasteurization at 60°C for 10 hours, (b) vapour heating at 60°C for 10 hours at 1160 mbar pressure, (c) dry heating at 80°C for 72 hours, and (d) solvent–detergent treatment with tri(n-butyl) phosphate and tween 80 or triton X-100 or cholate. Newer virucidal methods that appear to be effective, and which are being studied in trials involving previously untransfused patients, are treatment with sodium thiocyanate plus ultrafiltration, and treatment with solvent/detergent plus dry heating at 80°C for 72 hours or 100°C for 30 minutes. Because hepatitis B virus may escape inactivation, patients who are expected to receive blood products should be vaccinated against hepatitis B. None of the viral inactivation procedures is expected to inactivate every virus in the concentrate. For example, non-lipid-enveloped viruses such as parvovirus and hepatitis A virus are potentially resistant, although the clinical significance of this fact is unclear. We recommend vaccination against hepatitis A for patients who have tested negative for IgG antibodies to hepatitis A virus and who are likely to receive plasma-derived coagulation products.

In Canada coagulation products for the management of inherited bleeding disorders are licensed by the Bureau of Biologics, funded by the Canadian Blood Agency and purchased and distributed by the Canadian Red Cross Society Blood Services. The AHCDC makes requests with regard to the classes of concentrates that are made available for patient care, but the purchase and distribution of specific brands depends on contract negotiations that take several considerations, including cost, into account. Table 1 gives details on coagulation-factor concentrates currently funded by the Canadian Blood

Agency and available through the Canadian Red Cross Society Blood Services. To obtain products not licensed by the Bureau of Biologics, Emergency Drug Release approval by the Bureau of Biologics is required.

Factor VIII concentrates (hemophilia A)

The following types of concentrate are available:

- Recombinant Factor VIII (rFVIII) concentrate. The clotting factor is produced in cultured hamster cells, purified with the use of procedures including immunoaffinity chromatography on murine monoclonal antibodies, and stabilized in human serum albumin.
- Ultra-high-purity plasma-derived Factor VIII concentrate purified by immunoaffinity chromatography and stabilized in human serum albumin.
- High-purity plasma-derived Factor VIII concentrate stabilized in human serum albumin.

Side effects

Concerns about the possibility of viral transmission have already been discussed. Rarely, allergic reactions, and hemolysis caused by contaminating red cell antibodies, occur. Inhibitors may also develop. Recently, there was some concern that previously untransfused patients receiving rFVIII may be at higher risk of inhibitor development than those receiving the plasma-derived product. Clinical trials suggest that the incidence of inhibitors in previously untransfused hemophilia A patients receiving rFVIII was between 19.4% and 28.6%.[11,12] Many of these inhibitors are of low titre, and some are evanescent. Whether the incidence rate of inhibitor development among patients receiving rFVIII is really higher than that among patients receiving the plasma-derived product is uncertain, given that patients receiving rFVIII in the clinical trials were prospectively monitored at more frequent intervals (every 3 months)

Table 1: Coagulation-factor concentrates used in Canada for the management of hemophilia*

Factor concentrate	Manufacturer	Viral inactivation procedure	Purity standard	Maximum specific activity, IU/mg protein	BOB licensed	Funded by CBA and available through CRC	Cost per unit†
Factor VIII							
Factor VIII HP	CRC–Bayer	Solvent–detergent treatment	High	50–60‡	Yes	Yes	0.20
Hemofil M	Baxter	Solvent–detergent treatment	Ultra high	≥ 3000‡	Yes	Yes	0.76
Kogenate	Bayer	No specific step§	Recombinant	≥ 3000‡	Yes	Yes	0.75
Recombinate	Baxter	No specific step§	Recombinant	≥ 3000‡	Yes	No‖	1.06
Haemate P	Behring	Pasteurization	Intermediate	2.3–5	No¶	Yes	1.00
Hyate:C (porcine Factor VIII)	Speywood	No specific step	High	≥ 140	Yes	Yes	1.35
Factor IX (prothrombin complex)							
Bebulin	Immuno	Vapour heating	Intermediate	1–3	Yes	Yes	0.26
FEIBA	Immuno	Vapour heating	Low to intermediate	0.75–2.5	Yes	Yes	1.02
Factor IX (high purity)							
Alphanine SD	Alpha	Solvent–detergent treatment	High	182 ± 34	No¶	Yes	0.58
Immunine	Immuno	Vapour heating	High	100 ± 50	No¶	Yes	0.58
Mononine	Armour	Sodium thiocyanate treatment plus ultrafiltration	High	188 ± 14	No	No‖	0.74
Factor VIIa							
Niastase	Novo Nordisk	No specific step	Recombinant	NA	No	No**	NA

*BOB = Bureau of Biologics, CBA = Canadian Blood Agency, CRC = Canadian Red Cross Society Blood Services, NA = not available.
†In Canadian dollars as of February 1995. Cost will vary according to contracts and availability.
‡Before human albumin is added as a stabilizer. The specific activity in the final formulation containing added human albumin is much less.
§Specific viral inactivation procedures are not used, but some of the manufacturing or purification steps have virus reduction or removal capability.
‖ May be obtained by special application when adverse reactions to equivalent products occur.
¶BOB licensure has been applied for.
**May be obtained for specific patients on compassionate release basis.

than any previous patient population. Indeed, more recent studies suggest that the use of plasma-derived Factor VIII products may also result in a higher incidence rate of inhibitor development than the previously reported figure of 3.6% to 20%.[27,28]

Recommendation

In general, rFVIII concentrate, which carries a negligible risk of viral transmission, is recommended for the management of hemophilia A. The use of ultra-high-purity Factor VIII concentrates has recently been reported to delay the decline of CD4+ cell counts in asymptomatic HIV-infected patients when compared with less pure plasma-derived Factor VIII.[29,30] Whether this preservation of CD4+ cells is associated with a slower progression of HIV-related disease or increased survival in these patients is unknown. Data from prospective randomized trials are available only on ultra-high-purity plasma-derived Factor VIII concentrates purified by immunoaffinity chromatography. This type of Factor VIII concentrate is therefore available for HIV-infected patients who prefer it. Retrospective analysis of trial data suggests that among patients who received rFVIII, the rate of decline in CD4+ cell counts was no greater among those with HIV infection than among those who were not infected with HIV.[31]

Factor IX concentrates (hemophilia B)

Only plasma-derived products are available. These are as follows.

- High-purity plasma-derived Factor IX concentrates containing a negligible amount of other vitamin-K-dependent clotting factors (i.e., Factors II, VII and X).
- Prothrombin-complex concentrate. This product has an intermediate degree of purity and contains a significant amount of other vitamin-K-dependent clotting factors.

Side effects

As with all plasma-derived concentrates, the potential for viral transmission and allergic reactions exists. In a minority (up to 6.3%) of patients receiving Factor IX therapy, inhibitors may also develop.[32] The development of thrombosis and disseminated intravascular coagulation may be associated with the use of prothrombin complex concentrates[33] and may be related to zymogen overload and the presence of small amounts of activated factors (e.g., Factor Xa) or other thrombogenic contaminants (e.g., phospholipids).[34,35] The thrombotic risk is not predictable but is particularly significant when the product is used in large, repeated doses (e.g., more than 75 U/kg for more than three to four doses at intervals of less than 12 hours) or in the treatment of neonates, patients with bone fractures or patients with crush injuries, extensive intramuscular bleeding or hepatocellular dysfunction.

Recommendation

The use of high-purity Factor IX whenever possible is recommended.

Adjunctive hemostatic agents

When used properly the following types of adjunctive agent can promote hemostasis and permit the use of blood products to be reduced.

- Antifibrinolytic agents such as ε-aminocaproic acid (Amicar) and tranexamic acid (Cyklokapron). These products inhibit plasminogen activation and plasmin activity, thus preventing clot lysis. They are best used for the treatment of mucosal, oral and dental bleeds[36–39] (Table 2). A short course (5 days) of antifibrinolytic therapy (Amicar 75 mg/kg [up to 4 g] every 6 hours or Cyklokapron 25 mg/kg every 8 hours) is also effective in the management of epistaxis. These agents should not be used to treat urinary tract hemorrhage, in which an unlysed clot may cause urinary tract obstruction, or bleeding into a closed space where hemostatic monitoring is difficult. Antifibrinolytics can be administered orally, intravenously or topically for oral and dental bleeds.
- Topical thrombin and fibrin sealant. These agents are useful for the control of localized, accessible bleeding from lacerated tissues or after dental extraction, particularly when blood products are not effective (e.g., when inhibitors have developed). Bovine thrombin powder can be applied directly or on a gelatine sponge.

Treatment of bleeding episodes

DDAVP should be used to treat mild bleeding episodes and in preparation for minor surgical procedures among patients with mild hemophilia A (Factor VIII clotting activity more than 5%) who are known through previous testing to have an adequate response to DDAVP. The approach to treatment with clotting-factor concentrates for hemophilia patients is outlined in Table 2, which also indicates the in-vivo levels of clotting-factor activity that should be achieved for various indications. The dosage required to raise the clotting-factor level to a given value depends on the patient's plasma volume (roughly 5% of body weight in kg or 50 mL per kg of body weight), the level to which the clot-

ting factor is to be raised and the in-vivo recovery of the clotting factor in the circulation after infusion (roughly 100% for Factor VIII and 50% for Factor IX). Thus, to raise the Factor VIII level from 10% activity (0.1 U/mL) to 100% activity (1 U/mL), a 70-kg man whose plasma volume is roughly 3500 mL will need 3150 units ($3500 \times [1.0 - 0.1]$) of Factor VIII. A similar patient with hemophilia B will need 6300 units ($3500 \times [1.0 - 0.1] \times 2$) of Factor IX. For practical purposes the clotting-factor dose is based on the knowledge that 1 unit of Factor VIII per kg of body weight will raise the in-vivo activity by 2% (0.02 U/mL) and that 1 unit of Factor IX per kg of body weight will raise the in-vivo activity by 1% (0.01 U/mL). Thus, for these two patients the Factor VIII dosage will be 45 U/kg ($[100 - 10] \div 2$) and Factor IX dosage 90 U/kg ($100 - 10$).

Antiplatelet drugs (e.g., acetylsalicylic acid) and intramuscular injections should be avoided. Major surgery and major bleeding episodes should be managed in institutions with full coagulation-monitoring facilities.

Management of von Willebrand's disease

The fact that approximately 80% of people with von Willebrand's disease respond favourably to DDAVP[17,19] makes this the therapeutic agent of choice for most prophylactic indications and bleeding episodes. In addition, the adjunctive use of tranexamic acid or ε-aminocaproic acid and topical thrombin will, in many instances, obviate the need for blood-component infusion.

Blood components

The blood component traditionally used in the management of von Willebrand's disease, cryoprecipitate, cannot as yet be virally inactivated and therefore should no longer be used for the treatment of bleeding unless other measures have clearly failed. This problem has prompted a randomized crossover study to assess the efficacy of virally inactivated Factor VIII concentrates.[9] The results of this trial indicate that variable success can be expected with Factor VIII concentrates; the most consistent responses, especially with regard to the correction of bleeding time, have so far been documented with Haemate P, a pasteurized concentrate with an intermediate level of purity manufactured by Behring.[9,44,45] The dosage for Factor VIII concentrate is difficult to determine from baseline laboratory results for patients with types 1 and 2 von Willebrand's disease. Following the recommended guidelines for the management of hemophilia A (Table 2) would seem to be a practical approach.[45]

Table 2: Management of bleeding episodes in patients with hemophilia A and B using clotting-factor replacement therapy

Indication	Recommended dosage of replacement factor (and desired level of clotting-factor activity* to be achieved)	
	Factor VIII† (hemophilia A)	Factor IX† (hemophilia B)
Mild hemorrhage Early joint or muscle bleed Severe epistaxis Persistent hematuria Gingival or dental bleed unresponsive to ε-aminocaproic acid or tranexamic acid	10–15 U/kg (20%–30%)	20–30 U/kg (20%–30%)
Major hemorrhage Advanced joint or muscle bleed Hematoma of neck, tongue or pharynx Head injury or severe physical trauma	20–25 U/kg (40%–50%)	40–50 U/kg (40%–50%)
Life-threatening hemorrhage‡ Intracranial bleed Surgery (except dental) Bleeding from major trauma Gastrointestinal bleeding	35–50 U/kg (70%–100%)	70–100 U/kg§ (70%–100%)
Dental extraction‖	20–25 U/kg (40%–50%)	40–50 U/kg (40%–50%)

*1 U/mL (100% activity) is the clotting-factor activity present in 1 mL of average normal plasma.
†Clotting factor recovery and half-life is as follows. Factor VIII: 1 U/kg produces a rise in plasma titre by approximately 0.02 U/mL (2% activity); half-life is 8–12 h. Factor IX: 1 U/kg produces a rise in plasma titre by approximately 0.01 U/mL (1% activity); half-life is 18–24 h.
‡For life-threatening hemorrhage, maintenance treatment with half the initial dose (every 8–12 h for Factor VIII and every 12–24 h for Factor IX) for 5 d to several weeks may be required. Alternatively, recombinant or ultra-high-purity Factor VIII and high-purity Factor IX can be given by continuous infusion (2 U/kg per hour for Factor VIII, 4 U/kg per hour for Factor IX, with subsequent dosages adjusted according to the plasma clotting-factor levels) following the initial bolus.[40-43]
§If prothrombin-complex concentrate is used, 50–60 U/kg (50%–60% activity) at intervals of 12 h or longer should be given.
‖For dental extraction, ε-aminocaproic acid (Amicar), 75 mg/kg (up to 4 g) every 6 h, or tranexamic acid (Cykokapron), 25 mg/kg every 6–8 h for 5–10 d, should be given in addition to the clotting factor.[36-38] For patients with hemophilia B receiving prothrombin-complex concentrates, the systemic use of antifibrinolytic agents may potentiate the thrombogenic effects of prothrombin complex concentrates. Amicar or Cyklokapron mouthwash (e.g., 10 mL of 5% Cyklokapron acid rinse four times daily for 7–10 d) can also be used for oral or dental bleeding.[37,38] More recent studies suggest that dental extraction can be safely performed with the plasma clotting-factor level as low as 10% if both oral and local antifibrinolytic agents are also given for 7–10 d.[38]

In rare instances the use of Factor VIII concentrates fails to stop a bleeding episode. In such cases the use of cryoprecipitate or platelet concentrates, or both, should be considered.[46]

Complications of treatment

Inhibitor development

The most challenging complication that can occur as a result of hemostatic therapy is the development of a neutralizing alloantibody or inhibitor to the infused clotting factor. As noted earlier, this occurs in approximately 20% of patients with hemophilia A receiving Factor VIII concentrate[11,12,27,28] and in a very small number (less than 6%) of patients with hemophilia B.[32] The management of bleeding in these patients depends in large part on the in-vitro potency of the inhibitor, a parameter conventionally expressed in Bethesda units.

Among patients with hemophilia A whose inhibitor titre is below 5 Bethesda units, the infusion of large doses of human Factor VIII concentrate (100 to 200 U/kg) will sometimes be effective.[47] If this approach fails and the patient's Factor VIII antibodies have been shown to have reduced reactivity against porcine Factor VIII, the next option is to use porcine Factor VIII at a dose of 50 to 100 U/kg.[48,49] In either case it must be remembered that most patients will subsequently have a marked increase in the titre of their neutralizing antibodies.

If the initial inhibitor titre is greater than 5 to 10 Bethesda units, high doses of human or porcine Factor VIII can be tried in conjunction with an antibody-removal protocol such as the use of extracorporeal immunoadsorption with a staphylococcal protein A column or plasma exchange.[50,51] More commonly, effective treatment for this patient group will require the infusion of one of several available "bypassing" concentrates. Prothrombin-complex concentrates and activated prothrombin-complex concentrates in doses of 100 U/kg at 12-hour intervals (no more than three to four doses, to minimize the risk of thrombosis)[52,53] and recombinant human Factor VIIa[54,55] have been reported to be effective in the treatment of bleeding in these patients.

In the long-term management of patients who have inhibitors the induction of immune tolerance to their therapeutic concentrate should be considered. Conventional immunosuppressive regimens are not successful in these patients, but about 50% will respond favourably to infusion protocols.[56,57] Nonresponsive patients will require continued management with bypassing concentrates.

Viral disease transmission

With the introduction of rFVIII concentrate and the development of effective virucidal protocols for plasma-derived concentrates, concern about the potential for human viral disease transmission has lessened substantially. Nevertheless, the catastrophic effects of previously unidentified viruses in these products and recent reports of hepatitis A transmission through Factor VIII concentrates[58–60] serve to remind us that we must not be complacent about the risk of viral transmission.

Additional aspects of management

Genetic counselling is an essential component of all comprehensive care programs. The past decade has seen a dramatic improvement in our ability to detect carrier states and perform prenatal testing for hemophilia. The introduction of molecular genetic testing has made it possible to provide carrier-state and prenatal diagnostic results with probabilities of greater than 99% to most families with hemophilia A or B. This testing has used linked polymorphism analysis when there is a documented family history of hemophilia.[61–63] More recently, new techniques for the direct detection of the disease-causing mutations in hemophilia A and B have enhanced the effectiveness of genetic testing.[64–66] In light of the mild clinical manifestations of von Willebrand's disease, genetic testing is not appropriate except for relatives of patients with the rare type 3 form.

Validation

These recommendations were approved by all members of the AHCDC in May 1994. They were then reviewed by the Medical and Scientific Advisory Committee of the Canadian Hemophilia Society. This committee, whose members include representatives of hemophilia clinic nurse coordinators, physiotherapists, social workers, dentists and physicians, met in June 1994 and endorsed the recommendations. No similar consensus statements or practice guidelines were available for comparison.

Priorities for future research

Research efforts should aim at clarifying whether inhibitors develop more commonly in patients treated with rFVIII than in those treated with plasma-derived Factor VIII.[11,12,27,28] Well-designed, randomized studies are needed to identify the best and most cost-effective treatment of bleeding in patients with inhibitors and to improve methods for eliminating inhibitors once they have developed. Whereas immune-tolerance induction is effective in eliminating inhibitors in about 50% of affected patients,[56,57] additional research is required to identify the optimal dosage, timing and method of administration

(e.g., pulse v. continuous) of clotting factors in immune-induction protocols. Research into the basic immunologic and pathogenic features of inhibitors is also critical. Understanding inhibitor formation and its management will have an impact on the development of gene therapy for coagulation disorders, as this will also involve the delivery of rFVIII and therefore has the potential to result in inhibitor formation.

Recent studies suggest that prophylactic infusion to maintain clotting-factor levels above 0.01 U/mL (more than 1% activity) at all times prevents most episodes of spontaneous bleeding into joints and preserves joint function.[13–16] Randomized studies are needed to confirm the efficacy and cost-effectiveness of this mode of management. Studies are also needed to assess the safety, efficacy and cost-effectiveness of continuous versus pulse coagulation-product infusion in prophylactic therapy.

Continued efforts to develop new products that are safe and effective in the management of coagulation disorders is needed. Such products could include recombinant clotting factors from which viral contamination is virtually eliminated. Alternative stabilizing agents for recombinant clotting-factor concentrates should be sought to replace the plasma-derived human albumin currently in use. Research should also look into better and more convenient methods for the administration of these products.

Hemophilia would appear to be well suited to gene therapy because severe disease can be converted to mild disease with only a minor increase in the clotting-factor level (to 0.05 U/mL, or more than 5% activity). Successful gene therapy would eliminate the need for replacement therapy even though the patient would not necessarily be "cured." Considerable research is still required before this goal can be achieved.

Research should be directed toward the development of effective methods and modalities for the prevention and management of HIV infection, hepatitis and other bloodborne diseases. Protective vaccines against HIV and hepatitis C virus should also be developed.

Finally, patient-outcome research to document the efficacy and cost-effectiveness of current treatment modalities is important in the present context of shrinking health care resources.

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Aug. 16–18, 1995: Chronic Disease Congress
Denver
International Business Communications USA Conferences Inc., 225 Turnpike Rd., Southborough MA 01772-1749; tel 508 481-6400, fax 508 481-7911

Aug. 16–19, 1995: Canadian Society for Epidemiology and Biostatistics Conference '95
St. John's
CSEB Conference '95 Office, c/o Health Research Unit, PO Box 23068, St. John's NF A1B 4J6; tel 709 737-6720, fax 709 737-7382

Aug. 17–18, 1995: Discoveries in Heart Failure: Exploiting New Understanding for Novel Therapeutic Development
Philadelphia
International Business Communications USA Conferences Inc., 225 Turnpike Rd., Southborough MA 01772-1749; tel 508 481-6400, fax 508 481-7911

Aug. 24–26, 1995: Canadian Health Economics Research Association 6th Canadian Conference on Health Economics: Change and Resistance in Health Care Systems
Waterloo, Ont.
Dr. Doug McCready, School of Business and Economics, Wilfrid Laurier University, Waterloo ON N2L 3C5; tel 519 884-1970, fax 519 884-0201

Sept. 7–9, 1995: American Association of Critical-Care Nurses Leadership Institute — Innovations in Healthcare: Continuing to Transform the Environment
San Francisco
Study credits available.
American Association of Critical-Care Nurses, 101 Columbia, Aliso Viejo CA 92656-1491, tel 714 362-2000, fax 714 362-2020

Sept. 8–10, 1995: Pri-Med (Primary Medicine Today) Conference and Exhibition for Primary Care Practitioners
Boston
Study credits available.
Hill Holliday Exhibition Services Inc., The John Hancock Tower, 200 Clarendon St., Boston MA 02116; tel 617 859-4476, fax 617 859-4357

Sept. 10–13, 1995: 12th European Conference on Biomaterials
Porto, Portugal
12th European Conference on Biomaterials, Instituto de Engenharia Biomédica, Praça Coronel Pacheco, 1, 4000 Porto, Portugal; tel 011 351 2 208-7131, fax 011 351 2 208-7310

Sept. 13–16, 1995: Canadian Transplantation Society and Canadian Association of Transplantation Annual Meeting
Montreal
Collette Birks, director of communications, Quebec Transplant, 1560 Sherbrooke St. E, Montreal QC H2L 4K8; tel 514 876-6768

Sept. 13–17, 1995: Royal College of Physicians and Surgeons of Canada 64th Annual Meeting (in association with the Canadian Society for Clinical Investigation and 37 national specialty societies)
Montreal
Anna Lee Chabot, head, Meetings and Assemblies Section, Office of Fellowship Affairs, Royal College of Physicians and Surgeons of Canada, 774 Echo Dr., Ottawa ON K1S 5N8; tel 613 730-6201, fax 613 730-8252

Sept. 14, 1995: Biomedical Communication Workshops (presented by the Canada Chapter of the American Medical Writers Association and held in conjunction with the Royal College of Physicians and Surgeons of Canada Annual Meeting)
Montreal
Ann Bolster, Publications Department, Canadian Medical Association, PO Box 8650, Ottawa ON K1G 0G8; tel 613 731-8610 or 800 663-7336, ext. 2117; fax 613 523-0937; abolster@hpb.hwc.ca

Sept. 20, 1995: Symposium on Advances in Reproductive Endocrinology and Infertility (precedes the Canadian Fertility and Andrology Society Annual Meeting Sept. 21–23)
Montebello, Que.
Canadian Fertility and Andrology Society, 409–2065 Alexandre de Sève St., Montreal QC H2L 2W5; tel 514 524-9009, fax 514 524-2163

Sept. 20–25, 1995: 17th IEEE Engineering in Medicine and Biology Society Annual International Conference and 21st Canadian Medical and Biological Engineering Conference
Montreal
Coplanor Congrès inc., 600–511 Place d'Armes, Montreal QC H2Y 2W7; tel 514 848-1133, fax 514 288-6469; embc95@coplanor.qc.ca

Sept. 21–23, 1995: Canadian Fertility and Andrology Society Annual Meeting
Montebello, Que.
Canadian Fertility and Andrology Society, 409–2065 Alexandre de Sève St., Montreal QC H2L 2W5; tel 514 524-9009, fax 514 524-2163

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