

HEMOPHILIA AND VON WILLEBRAND'S DISEASE:

1. DIAGNOSIS, COMPREHENSIVE CARE AND ASSESSMENT

Association of Hemophilia Clinic Directors of Canada

Abstract • Résumé

Objective: To present current strategies for the assessment and comprehensive care of patients with hemophilia and von Willebrand's disease.

Options: Hospital care, home care, single-provider care and multidisciplinary care.

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 own 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 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: The optimal use of treatment procedures and home care offers patients the advantages of minimized disability, improved survival and financial benefit. It is also cost effective. Potential harm, including the risk of hepatitis B, hepatitis C and HIV infection, has now been minimized through viral inactivation of plasma-derived coagulation-factor concentrates and through the use of recombinant clotting factor concentrates and other non-plasma-derived hemostatic agents.

Recommendations: Patients with hemophilia and severe von Willebrand's disease should be followed in comprehensive care centres that offer expertise in the diagnosis, assessment and management of bleeding and complications and that can meet the educational and counselling needs of patients, family members and health care providers. Eligible patients should be enrolled in a home self-infusion program. Patients with hemophilia and von Willebrand's disease should wear or carry Medic Alert identification. They should be vaccinated against hepatitis B and attend for routine follow-up examinations. Laboratory testing should be carried out as required, and dental and surgical care should be undertaken in consultation with a hematologist.

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

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Objectif : Présenter les stratégies actuelles d'évaluation et de traitement complet des patients atteints d'hémophilie et de la maladie de von Willebrand.

Options : Soins à l'hôpital, soins à domicile, soins dispensés par un seul fournisseur et soins multidisciplinaires.

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 : L'utilisation optimale des méthodes de traitement et des soins à domicile offre aux patients les avantages suivants : incapacité réduite au minimum, survie améliorée et avantages financiers. De plus, elle est rentable. On a réussi à réduire au minimum les préjudices possibles, y compris le risque d'hépatite B, d'hépatite C et d'infection au VIH, par l'inactivation virale de concentrés de facteur de coagulation tirés de plasma et l'utilisation de concentrés de facteur de coagulation recombinant et d'autres agents hémostatiques non tirés du plasma.

Recommandations : Les patients atteints d'hémophilie et de maladie de von Willebrand grave devraient être suivis dans des centres de soins complets qui offrent des compétences spécialisées en diagnostic, évaluation et traitement des hémorragies et des complications et qui peuvent répondre aux besoins d'éducation et de counselling des patients, des membres de leur famille et des fournisseurs de soins de santé. Les patients admissibles devraient être inscrits à des programmes d'auto-perfusion à domicile. Les patients hémophiliques et atteints de maladie de von Willebrand devraient porter un bracelet d'identification Medic Alert. Ils devraient être vaccinés contre l'hépatite B et se soumettre à des examens de suivi de routine. Il faudrait procéder à des tests de laboratoire au besoin, et les soins dentaires et chirurgicaux devraient être assurés en consultation avec un hématologue.

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.

Hemophilia and von Willebrand's disease are the most common congenital bleeding disorders. The optimal management of patients with these disorders, especially those with severe disease, requires more than the treatment and prevention of acute bleeding. Patients who have repeated episodes of bleeding will need long-term management of joint damage and other sequelae as well as attention to education, employment and other psychosocial needs. An additional concern is that blood products used in the past in the treatment of bleeding disorders have been associated with devastating viral complications such as hepatitis and AIDS. The aim of management should be to prevent disease and treatment-associated morbidity and mortality and to optimize quality of life. These goals can usually be met through the provision of comprehensive care, including home therapy, with the effective and safer treatments that are now available. Plasma-derived concentrates are

now purer and are treated by means of effective viral attenuation procedures. Recombinant Factor VIII, which is currently thought to provide the greatest degree of safety from viral transmission, is now available. Modern management of these diseases is expensive, but it is cost effective and of considerable benefit.¹⁻⁴

The development of diagnosis, assessment and treatment 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 the members of the AHCDC and to 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 the members 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.

In our review of the literature it became clear that, although the management of hemophilia and von Willebrand's disease has evolved since the 1960s, randomized clinical trials to provide evidence at levels I and II as stipulated by Sackett⁵ are lacking. The present guidelines represent the collective experience and expert consensus opinion of the members of the AHCDC. They should not be considered to encompass the management of every patient in every situation: exceptions may be dictated by specific clinical circumstances.

In this article we focus on the diagnosis, comprehensive care and assessment of hemophilia and von Willebrand's disease. In a second article (to be published in the July 15 issue) we will outline the blood products and treatments currently available and recommended for use in Canada.

DIAGNOSIS

HEMOPHILIA

"Hemophilia" refers to X-linked bleeding disorders in

which there is a deficiency (activity level of 35% or less) of either Factor VIII (hemophilia A, classic hemophilia) or Factor IX (hemophilia B, Christmas disease). The incidence of hemophilia is about 1 in 5000 males; of those affected, roughly 80% to 85% have hemophilia A and the remainder hemophilia B.⁶

Positive results of tests for hemophilia show a prolonged activated partial thromboplastin time, a normal one-stage prothrombin time and a normal bleeding time. In hemophilia A, Factor VIII activity is decreased or absent, whereas the level of von Willebrand factor (antigen and ristocetin cofactor activity) is normal. In hemophilia B, Factor IX activity is decreased or absent.

In both types of hemophilia, there is usually a strong correlation between the level of clotting factor activity and the clinical severity of the disease (Table 1).

VON WILLEBRAND'S DISEASE

Von Willebrand's disease is typically mild and it generally exhibits an autosomal dominant pattern of inheritance. Several reports have documented the prevalence of von Willebrand's disease in the general population as approximately 1%,^{8,9} which makes this the most common inherited coagulopathy.

The clinical manifestations and laboratory diagnosis of the three main subtypes of von Willebrand's disease are indicated in Table 2. Approximately 85% of confirmed cases are of type 1; most of the remainder are type 2 variants (i.e., type 2A, 2B, 2M, 2N).¹¹ The severe type 3 phenotype has a prevalence of one in a million.

The laboratory diagnosis of von Willebrand's disease can be problematic. If a patient's clinical history strongly suggests this disorder, testing for abnormalities of the von Willebrand factor/Factor VIII complex should be performed on at least two separate occasions if the initial study results are inconclusive.¹²

COMPREHENSIVE CARE

The aim of comprehensive care is to help patients

Table 1: Correlation of clotting factor activity with severity of hemophilia^a

Clotting factor activity level,* %	Clinical severity of hemophilia
<1	Severe: spontaneous musculoskeletal and internal bleeding
1-5	Moderate: occasional spontaneous musculoskeletal bleeding
5-35	Mild: delayed-onset bleeding after trauma, surgery and dental extraction

*1 U/mL (100% activity) is the clotting-factor activity present in 1 mL of average normal plasma.

and their families make decisions affecting their physical, psychologic and social health in the light of the most recent medical knowledge. Given the rarity and complexity of inherited bleeding disorders, it is advisable for all patients to be treated or at least followed regularly at a comprehensive care centre that offers expertise in dealing with the wide range of medical problems that these patients may encounter. Smaller centres with few patients cannot develop or maintain this multidisciplinary expertise but can provide routine care in consultation with a comprehensive care centre.¹³ The composition of the comprehensive care team reflects the fact that management involves more than the treatment of acute bleeding episodes.

THE COMPREHENSIVE CARE TEAM

The "primary" team should consist of a nurse coordinator, a medical director (preferably a hematologist with an interest and expertise in hemostasis), a physiotherapist and a social worker.¹³ This group reviews regularly all patients receiving care at the centre and addresses their medical, familial and social concerns. The nurse coordinator, who coordinates the provision of education and care for patients and their families, is usually the first contact for patients with an acute problem or requiring follow-up.

Arrangements for the involvement of other specialists will be made by the primary team as the need arises.¹³ The "referral" team should include specialists in rheumatology, orthopedic surgery, dentistry and clinical genetics. Specialists in infectious disease, hepatology, psychiatry and psychology should also be available.

Specialized services such as blood-banking facilities and an expert coagulation laboratory to provide studies required for diagnosis and management must also be available.

INVOLVEMENT OF THE FAMILY

These lifelong, life-threatening and costly diseases have a significant impact on many aspects of family life.

Parents and spouses may be asked to participate actively in the patient's care. The diagnosis can produce tremendous anxiety in parents about their children's future and the risks of everyday living. Adolescents who feel that their need for independence is in conflict with the need to conform to a care regimen may also suffer anxiety. Some of this anxiety can be alleviated through proper education of the patient and family about the disease and its management.

Given the hereditary nature of these bleeding disorders, family members will be concerned about their carrier status and the risk to future children. These concerns can be addressed through genetic counselling for the extended family and, when appropriate, through carrier testing and antenatal diagnosis.¹⁴ The emotional and psychologic stress of living with a severe bleeding disorder or of caring for someone with such a disorder may necessitate psychologic counselling. As a result of the AIDS epidemic, counselling needs for families have increased drastically.¹⁵ Sexual partners of those infected with HIV through contaminated blood products are at risk of viral transmission. As for all patients with HIV infection and their partners, education about safer sexual practices must be provided.¹⁶

ASSESSMENT

AT DIAGNOSIS

The most important step following diagnosis of an inherited bleeding disorder is the initiation of an education program for the patient and family. Areas that should be addressed include the hemostatic defect, signs and symptoms of early hemorrhage, therapy, safety precautions and appropriate physical activities. In addition, the following items need attention:

- Registration at a comprehensive care centre. Family members should be given an opportunity to meet the team.
- Application for Medic Alert identification naming the disorder and indicating appropriate emergency therapy.

Table 2: Main subtypes of von Willebrand's disease¹⁰

Subtype	Clinical manifestations	Laboratory test results*
Type 1: partial quantitative deficiency	Mild mucocutaneous bleeding	PTT sometimes prolonged; bleeding time prolonged; low Factor VIII, vWF:Ag and vWF:RiCo levels
Type 2: qualitative defects	Mild mucocutaneous bleeding	As for type 1, plus evidence of abnormal plasma vWF multimers†
Type 3: virtually complete quantitative deficiency	Severe mucocutaneous and musculoskeletal bleeding	PTT very prolonged; very low or undetectable vWF:Ag and vWF:RiCo levels; very low Factor VIII level

*PTT = activated partial thromboplastin time, vWF:Ag = von Willebrand factor antigen (measured by an immunoassay), vWF:RiCo = ristocetin cofactor activity (functional assay for von Willebrand factor).

†Multimers are a series of repeating subunits of the vWF protein resolved on gel electrophoresis. In normal plasma these multimers range in size from a molecular weight of approximately 600 000 (2 subunits) to over 20 000 000 in increments of approximately 600 000.

- Education about hepatitis in general and initiation of a hepatitis B vaccination series. Given that, at present, blood-derived factor replacement therapy may still transmit the hepatitis B virus,¹⁷ all seronegative patients should be vaccinated before receiving such products. The standard schedule consists of three injections: the first two are given 1 month apart, followed by a booster dose at 6 months.^{18,19} Mannucci and associates^{18,20} have recommended a more rapid schedule in which the three injections are given at monthly intervals to speed up seroconversion. Subcutaneous or intradermal injection in the deltoid region is preferable to intramuscular injection,²¹ although intramuscular injection with a small-gauge needle (25 or 26) followed by the application of adequate local pressure is also safe.
- If the patient is to receive most care outside of the comprehensive care centre, the local physician and hospital must be well informed so that appropriate care will be provided both routinely and in the case of an emergency. The local physician as well as the family must know how to contact the comprehensive care team when questions and emergencies arise.

HOME THERAPY

Optimal therapy provides the patient with immediate access to treatment for correction of the hemostatic defect at the first sign of hemorrhage. For most patients with severe or moderate hemophilia, this means a home therapy program.²² Education of patients and families and careful supervision by the comprehensive care team have decreased health care costs for hemophilia⁴ and improved quality of life as measured by time lost from school or work and the number of days spent in hospital.¹⁻³ Home therapy can be achieved in most motivated families for children over the age of 4 years, and even for younger children if indwelling venous access devices are used.

Preparation for home therapy includes teaching the patient and family when and how to treat bleeding episodes, including the practical aspects of replacement therapy preparation, sterile technique and venipuncture, and proper storage and disposal of used needles and syringes. Most of the teaching is carried out by the nurse coordinator.

The comprehensive care team must assess the family's ability to undertake home therapy. It should provide ongoing supervision and encouragement and deal with problems or questions as they arise. Reassessment of patient understanding, technique and compliance should be carried out at regular intervals.²³

Patients must keep a log of bleeding episodes, recording the dates and sites of bleeding, the dosage and lot

numbers of blood products used, and any side effects experienced.

Patients must be given guidelines on contacting the comprehensive care centre to report bleeds that do not respond to the standard treatment regimen, allergic reactions, and trauma to critical areas such as the head and neck.

In the case of young children the responsibility for home therapy is assumed by the parents or guardians. By their early teens, however, patients should be encouraged to start taking responsibility for their own treatment and taught how to prepare and administer their own replacement therapy.

Family members who help with home care therapy should be vaccinated against hepatitis B if they are seronegative.

ROUTINE FOLLOW-UP

Comprehensive re-evaluation should be carried out at least once a year for adults and twice a year for children, and more frequently for patients with significant medical problems or frequent bleeding episodes.¹³ During each evaluation the patient should be reviewed by the nurse coordinator, the medical director/hematologist, the orthopedic surgeon/rheumatologist or physiotherapist (or both), and the social worker and other appropriate members of the comprehensive care team. The evaluation should include the following.

- A general examination, with particular attention to the stigmata of liver disease and of viral disease, as well as to weight, growth and development in children.
- A detailed musculoskeletal examination, with attention to chronic arthropathy and target joints (i.e., joints in which repeated episodes of hemorrhage and resulting inflammation lead to a self-perpetuating cycle of bleeding and progressive damage). Assessment by the orthopedic surgeon/rheumatologist or physiotherapist, or both, should address the management of current problems and provide advice regarding appropriate physical activities.^{24,25}
- A review of treatment logs for patients on home therapy to reinforce the recognition and appropriate management of bleeds and to detect manifestations of target joints early so that prophylactic treatment can be introduced. Problems with home management should be discussed and basic management techniques reviewed.
- Laboratory assessment, including (a) a complete blood count and platelet count, (b) liver function tests, (c) screening for clotting factor inhibitors (allo-antibodies against the patient's deficient clotting factor developed following replacement therapy and ca-

pable of inhibiting the clotting factor function), (d) viral serologic testing (e.g., for HIV antibody, hepatitis C virus antibody and hepatitis A virus IgG antibody [if the results were previously negative]), hepatitis B virus surface antibody titre (if this result was previously positive due to vaccination or infection) and hepatitis B virus surface antigen testing (if the result was previously negative and the patient is not yet vaccinated)²⁶⁻²⁸ and (e) radiographs of target joints or those affected by chronic arthropathy²⁹ if this is expected to modify the treatment approach.

- Routine dental evaluation. This is important in promoting preventive dental treatment and encouraging good oral hygiene to avoid dental disease.³⁰ Hemostasis must be assured during invasive dental procedures. If restorative treatment is required, it should be performed by a dentist familiar with techniques for minimizing hemorrhage. The need for factor replacement will depend on the specific treatment and should be determined in consultation with the medical director/hematologist.

DURING A BLEEDING EPISODE

The timing of assessment in the event of an acute bleed will depend on the site involved. Given that early treatment is essential for a good response, it may be most beneficial to initiate therapy during or even before the assessment. This is particularly important when the bleeding occurs at a site such as the head, neck, chest or abdomen and is therefore potentially life threatening. Assessment should include clinical examination of the area in question. If an intracranial bleed is suspected a thorough neurologic investigation must be made. Appropriate radiologic or sonographic evaluation should be carried out as necessary. If a bleeding episode does not appear to be resolving despite reasonable factor replacement therapy, assessment should include screening for an inhibitor (if the clotting factor activity is unexpectedly low) as the cause for the failure.

PREOPERATIVE ASSESSMENT

Major surgical procedures require consultation between the surgeon and the hematologist and should be undertaken only in centres where coagulation studies are readily available. Major surgery can be performed safely in patients without inhibitors when adequate coverage by coagulation factor replacement therapy is provided. The implementation of the following recommendations during planning for major surgery may avert complications.

- A screen for factor inhibitors should be performed shortly before the surgical date.

- The patient should avoid using antiplatelet medication before and after surgery.
- Surgery should be scheduled for early in the week and early in the day to help ensure the availability of laboratory services and consultants.
- Adequate amounts of the coagulation factor replacement product to be used before and after surgery must be immediately available in the hospital blood bank or pharmacy.

In the case of patients with significant levels of coagulation factor inhibitors, preparation for major surgery is more complicated and good hemostasis more difficult to attain. Decisions regarding surgery for these patients must be made after a careful weighing of the risks; surgery should be undertaken only after consultation with a hematologist experienced in managing patients with inhibitors.³¹

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

Since the superiority of comprehensive care and home therapy programs was first established some 15 to 20 years ago,¹⁻⁴ significant advances have been made in all treatment modalities for patients with hemophilia and von Willebrand's disease. These advances include the development of safer hemostatic products. The cost-effectiveness of current methods of patient assessment, comprehensive care, home care and treatment modalities will, however, need further evaluation in patient outcome research. Such research should measure how well current management reduces morbidity, mortality and the need for interventions, and how well it increases productivity and quality of life. Cost factors that should be considered include direct medical costs as well as indirect medical, economic and socioeconomic costs of the management of complications associated with the disease and with interventions. Longitudinal population analyses can be used to monitor the outcome of comprehensive centre and home care since randomized studies are no longer possible or ethical.

References

- Levine P: Efficacy of self-therapy in hemophilia: a study of 72 patients with hemophilia A and B. *N Engl J Med* 1974; 291: 1381-1384
- Ingram GIC, Dykes SR, Creese AL et al: Home treatment in haemophilia: clinical, social and economic advantages. *Clin Lab Haematol* 1979; 1: 13-27
- Smith PS, Keyes NC, Forman EN: Socioeconomic evaluation of a state-funded comprehensive hemophilia-care program. *N Engl J Med* 1982; 306: 575-579
- Smith PS, Levine PH: The benefits of comprehensive care for hemophilia, a 5 year study of outcomes. *Am J Public Health* 1984; 74: 616-617
- Sackett DL: Rules of evidence and clinical recommendations on the use of antithrombotic agents. *Chest* 1986; 89 (suppl): 2S-3S
- Brettler DB, Levine PH: Clinical manifestations and therapy of inherited coagulation factor deficiencies. In Colman RW, Hirsh J, Marder VJ et al (eds): *Hemostasis and Thrombosis: Basic Principles and Clinical Practice*, 3rd ed, JB Lippincott, Philadelphia, 1994: 169-183
- Hoyer LW: Hemophilia A. *N Engl J Med* 1994; 330: 38-47
- Rodeghiero F, Castaman G, Dini E: Epidemiological investigation of the prevalence of von Willebrand's disease. *Blood* 1987; 69: 454-459
- Werner EJ, Broxson EH, Tucker EL et al: Prevalence of von Willebrand disease in children: a multiethnic study. *J Pediatr* 1993; 123: 893-898
- Sadler JE for the Subcommittee on von Willebrand factor of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis: A revised classification of von Willebrand disease. *Thromb Haemost* 1994; 71: 520-525
- Tuddenham EGD: The varieties of von Willebrand's disease. *Clin Lab Haematol* 1984; 6: 307-323
- Abilgaard CF, Suzuki Z, Harrison J et al: Serial studies in von Willebrand's disease: variability versus "variants." *Blood* 1980; 56: 712-716
- Jones P: Comprehensive care in hemophilia. In Seghatchian MJ, Savidge GF (eds): *Factor VIII — von Willebrand Factor*, vol 2, CRC Press, Boca Raton, Fla, 1989: 135-144
- Kazazian HH: The molecular basis of hemophilia A and the present status of carrier and antenatal diagnosis of the disease. *Thromb Haemost* 1993; 70: 60-62
- Levi J, Simon R, Weis H: Family therapy in haemophilia — a chronic disease model. [abstract] *Clin Lab Res* 1986; 16: 125
- Levine SB, Agle DP: *Intimacy, Sexuality, and Hemophilia*, National Hemophilia Foundation, New York, 1989
- Mannucci PM, Colombo M: Virucidal treatment of clotting factor concentrates. *Lancet* 1988; 2: 782-785
- Mannucci PM, Gringeri M, Morfini M et al: Immunogenicity of a recombinant hepatitis B vaccine in hemophiliacs. *Am J Hematol* 1988; 29: 211-214
- Centers for Disease Control: Update on hepatitis B prevention. Recommendation of the Immunization Practices Advisory Committee. *Ann Intern Med* 1987; 107: 353-357
- Zanetti AR, Mannucci PM, Tanzi E et al: Hepatitis vaccination of 113 hemophiliacs: lower antibody response in anti-LAV/HTLV-III-positive patients. *Am J Hematol* 1986; 23: 339-345
- Desmyster J, Colaert J, Verstraete M et al: Hepatitis B vaccination of haemophiliacs. *Scand J Infect Dis* 1983; 38 (suppl): 42-45
- Jones P: Haemophilia home therapy. *Haemostasis* 1992; 22: 247-250
- Gomperts ED, Sergis-Davenport E: Home therapy programs: the role of the nurse, physician, patient, and family in self-directed care. In Hilgartner MW, Pochedly C (eds): *Hemophilia in the Child and Adult*, 3rd ed, Raven Press, New York, 1989: 173-193
- Hill RA, Smith MA: Orthopedic assessment of the hemophilic patient. In Seghatchian MJ, Savidge GF (eds): *Factor VIII — von Willebrand Factor*, vol 2, CRC Press, Boca Raton, Fla, 1989: 65-88
- Holdredge SA, Cotta S: Physical therapy and rehabilitation in the care of the adult and child with hemophilia. In Hilgartner MW, Pochedly C (eds): *Hemophilia in the Child and Adult*, 3rd ed, Raven Press, New York, 1989: 236-262
- Triger DR, Preston FE: Chronic liver disease in haemophiliacs. *Br J Haematol* 1990; 74: 241-245
- Blanchette VS, Vorstman E, Shore A et al: Hepatitis C infection in children with hemophilia A and B. *Blood* 1991; 78: 285-289
- Mannucci PM, Gdovin S, Gringeri A et al: Transmission of hepatitis A to patients with hemophilia by Factor VIII concentrates treated with organic solvent and detergent to inactivate viruses. *Ann Intern Med* 1994; 120: 1-7
- Petterson H, Ahlberg A, Nilsson IM: A radiological classification of hemophilic arthropathy. *Clin Orthop* 1980; 149: 153-159
- Evans B: Dental management. In Hilgartner MW, Pochedly C (eds): *Hemophilia in the Child and Adult*, 3rd ed, Raven Press, New York, 1989: 89-119
- Kasper CK: Treatment of factor VIII inhibitors. [review] *Prog Hemost Thromb* 1989; 9: 57-86