Challenges and successes in the treatment of hemophilia: the story of a patient with severe hemophilia A and high-titer inhibitors

Hussain I Saba
Duc Quang Tran, Jr
Department of Medicine, University of South Florida Medical Center, Tampa, FL, USA

Abstract: In the past, patients with severe hemophilia have suffered a substantially reduced quality of life with frequent bleeding episodes, disabling arthropathy, and shorter life expectancy. In addition, methods of treatment and management have been costly and time-consuming, and have placed a considerable burden on patients' physical and psychological well-being. With the advent of the on-demand therapy and prophylactic treatment paradigm, patients have been able to receive care with less interruption of daily activities. Treatments may be more challenging for hemophiliacs with inhibitors to replacement factor; however, recent advances in the use of bypassing agents and immune tolerance therapy have enabled them to aggressively manage their disease while maintaining their independence. This review focuses on the challenges of treating such a severe hemophilic through examination of the lifetime experience of a young adult male with a severe form of congenital hemophilia A. At this stage of his life, the patient has minimal disabilities and is inhibitor-free through optimal care and strong family support. His aspiration to pursue a productive life has led him to a career in medicine. After receiving his medical degree, he pursued a specialty in the treatment of hemophilia. By assisting other hemophilia patients, he exemplifies both the rewards of persevering through episodes of bleeding and other complications and the fact that disabilities can be minimized when managed meticulously and in a timely fashion to enable a productive and dignified life.

Keywords: hemophilia, quality of life, factor VIII inhibitors, hemophilia treatment center, early treatment, bypassing agent

Introduction
The management and care of patients with hemophilia have evolved greatly over the last 40 years. Historically, children with hemophilia have had a poor quality of life and have rarely survived past the first decade of life.1 Today, children and adults with hemophilia participate daily in school and work activities, and can expect a fairly normal life expectancy. These critical gains can largely be attributed to scientific advances in our understanding of hemophilia that have been translated into vast improvements in disease management and patient care.

This article highlights the case of a 27-year-old Asian male who was diagnosed as having severe hemophilia at the time of his birth. He initially received on-demand factor VIII (FVIII) infusion and a subsequent prophylactic regimen. The patient developed a factor inhibitor before adolescence, successfully underwent immune tolerance therapy (ITT) for his inhibitor, and has since remained inhibitor-free. The supplementation of a relatively routine treatment paradigm with strong familial involvement and prompt, diligent medical support for his bleeding episodes undoubtedly minimized any...
potential disease-related complications, including disabling arthropathy, in this patient.

**Patient history**

The patient is one of 30% to 40% of congenital hemophilia cases without a familial history of hemophilia. His disease was induced by a spontaneous genetic mutation, and was diagnosed at birth when a forceps-assisted delivery resulted in prominent cranial bruising and a soft-tissue hematoma. His parents were actively involved in his care and were protective during infancy and childhood. The patient avoided contact sports during childhood, but still had severe hemarthroses in both ankles. Currently, he has minimal joint arthropathy, as measured by regularly scheduled imaging studies and clinical evaluations. Although fairly active as a child, the patient struggled with weight gain from 10 to 16 years of age.

Prior to the age of 12, the patient developed inhibitors; however, the exact time and highest titer that developed during this period is unknown due to the lack of medical records. Although the therapeutic (such as a cryoprecipitate) used in childhood was unknown, the patient received intensive, episodic treatment with infusions of FVIII concentrates from childhood and into early adulthood. His ankle bleeds were often not treated when he was a child, which may have contributed to his avoidance of human immunodeficiency virus (HIV) and/or hepatitis C virus (HCV) infection from plasma-derived products available at that time; he is currently negative for both HIV and HCV.

This patient has used bypassing agents to treat bleeding episodes in target joints (bilateral ankles and left elbow) and hematomas, including two bleeds in his iliopectas muscle, the first on his right side at age 15 and the second on his left side at age 23. He experienced approximately one bleed per target joint every 2 to 3 months when he was younger and, prior to the age of 18, relied primarily on physical therapy to manage bleeding events. Later, plasma-derived activated prothrombin complex concentrate (pd-aPCC, FEIBA NF [Anti-Inhibitor Coagulant Complex; Baxter Healthcare Corporation, Westlake Village, CA]) was used on demand for treatment of bleeding events. More recently, he has begun self-administration of prophylactic therapy using bypassing agents three times a week and on the mornings of strenuous days. Because the patient lacks a central venous access device, he performs venipuncture on himself at an average rate of three to four times a week. After being treated for bleeds at a hemophilia treatment center (HTC) as a young child, the patient moved with his family to Charlotte, North Carolina, where he received treatment for bleeds by a local hematologist who was not part of an HTC network. While the patient matriculated as an undergraduate at the University of South Carolina in Columbia, he returned to receive treatment at the HTC where he had been treated as a child. The patient currently receives treatment for bleeds at an HTC in Tampa, Florida, and maintains a healthy lifestyle as a medical doctor.

**Epidemiology**

Hemophilia A is an X-linked genetic bleeding disorder caused by a deficiency in or absence of clotting FVIII. In North America and Europe, the incidence of hemophilia A is approximately 1 in 5000 male births. The prevalence is 20.6 cases per 100,000 males, of which 60% have severe disease. In approximately 40% of cases of severe hemophilia, the mutation involves a large inversion that interferes with the FVIII gene, while the remaining cases typically involve point mutations, deletions, and insertions.

A diagnosis of congenital hemophilia in its severe form (less than 1% of circulating FVIII) is most often made during or shortly after birth, particularly during assisted deliveries and circumcisions.

**Inhibitors**

Inhibitors developing in patients with hemophilia A bind to and inactivate FVIII, which is a result of repeated patient exposure to FVIII. Inhibitors are classified as “high titer” when the immune response is robust (ie, a titer is greater than 5 Bethesda units [BU]). Several prospective studies have determined that 20% to 30% (in the child population, up to 50%) of patients with severe hemophilia A will develop inhibitors to FVIII early in life, even with relatively little exposure. Several studies have demonstrated a correlation of the presence of inhibitors with greater morbidity and a poor quality of life. Patients with severe hemophilia are at the greatest risk for developing inhibitors, which generally appear within the first 10 to 20 days of exposure to FVIII concentrate. Once patients with hemophilia develop inhibitors, treatment becomes more challenging and prevention of orthopedic complications more difficult. Inhibitor development has a considerable impact on patient morbidity and up-front treatment costs. However, it has been demonstrated that improvements in both clinical outcomes and quality of life (days gained at work and school, fewer days of hospitalization, fewer hospitalizations, and a reduced need for surgery) result in ultimate economic benefit.

**Arthropathy**

Beyond infancy, hemarthroses account for the majority of bleeds in hemophilic patients (70%–80%).
Consequently, arthropathy is the most common and debilitating long-term sequela in patients with hemophilia, typically occurring during the second or third decade of life.25,26 The chronic arthropathy resulting from uncontrolled bleeding has a debilitating effect on patients with hemophilia, especially young patients whose joints are under continual development. While many hemophilic patients in their twenties and thirties have severe arthropathy and disability, the patient discussed in this review has largely avoided this fate through prompt management of bleeding episodes. Early recognition and treatment of hemarthroses – made possible by the vigilance of the patient and his parents and the subsequent intervention of knowledgeable, experienced healthcare providers – have likely contributed to this outcome, by reducing the amount of and duration of bleeding into affected joints.27 In addition, given the association between repeated episodes of bleeding and joint damage,28 reduction of the number of bleeding episodes through such measures as prophylaxis and activity modification likely played a role in this patient’s avoidance of severe, disabling arthropathy.

**Treatment**

In 1965, FVIII concentrate was first manufactured using a cryoprecipitation procedure that was easily copied by blood banks to be utilized for the routine treatment of joint and muscle bleeds.1,29 Although this procedure provided great clinical benefits to patients with hemophilia, it also brought about an increased risk of blood-borne viral infections. Viral transmission of HIV and HCV occurred in the hemophilia community via infected human plasma products.30 In 2004, it was estimated that at least one third of hemophilic patients were infected with HIV, and 80% with HCV. This tragedy for the hemophilia community led to the implementation of screening and viral inactivation processes through the use of heat treatment or affinity chromatography.31 Although plasma-derived products are safer now than ever before, concerns remain about infectious agents that may be resistant to existing methods for viral, chemical, or even physical inactivation,32,33 such as non-lipid-enveloped viruses like the paroviruses or the prion that causes variant Creutzfeldt-Jakob disease, which has been identified in blood transfusion recipients in the United Kingdom.34 Further, although there have been no reported cases of HIV or HCV transmission via clotting factor since 1986 and 1997, respectively,35 a recent case of HIV transmission from the transfusion of fresh frozen plasma in the USA in 200836 emphasizes the fact that the risk for transmission of enveloped viruses from human-derived blood products is not zero. Though negligible, this potential for transmission of infectious agents from plasma-derived products has driven the preferential use and ongoing development of recombinant products for hemophilia treatment.

Dramatic improvements in patient outcomes have been seen in hemophilic patients without inhibitors who have undergone the combined use of on-demand plasma-derived replacement FVIII and prophylactic therapy beginning at 1 to 2 years of age. Patients with severe hemophilia had a life expectancy of 11 years in the 1960s, compared with a life expectancy of 50 years and older in the 1980s.37,38 Data collected from 1993 to 1995 show that the age-adjusted mortality rates for hemophilic patients were four times those of the general US male population.39 Modern treatment aims to reduce the mortality rate and improve the quality of life of hemophilic patients by preventing bleeds through aggressive on-demand and prophylactic treatment regimens, along with lifestyle modifications.40,41

Hemophilic patients with high-titer inhibitors have more LIMITED treatment options than do patients without inhibitors. The aims of treating hemophilic patients with inhibitors are to stop acute bleeding episodes and maintain hemostasis (both typically through the use of bypassing agents), and to suppress the inhibitor by ITT. Currently, two bypassing agents are available for treating hemophilia A patients with inhibitors: recombinant factor VIIa (rFVIIa; NovoSeven® RT Coagulation Factor VIIa [Recombinant] Room Temperature Stable; Novo Nordisk A/S, Bagsvaerd, Denmark)42 pd-aPCC.43 These agents bypass the FVIII-dependent step in the coagulation cascade and promote hemostasis by enhancing thrombin generation. Recombinant factor VIIa is also recommended to maintain hemostasis in hemophilic patients with high-titer inhibitors prior to the initiation of ITT, in order to allow inhibitor titers to decrease to below 10 BU and thus increase the likelihood for treatment success.44 This regimen is used to avoid possible anamnesis induced by blood products that contain FVIII.

ITT consists of administering repeated high doses of FVIII to a patient over a period of weeks to months to tolerize his immune system, thereby eliminating inhibitors. This procedure later allows replacement FVIII to continue to be used effectively for treatment.44 In the International Immune Tolerance Registry and the North American Immune Tolerance Registry, ITT was successful in 82% of patients with inhibitor peak titers that were less than 50 BU.45 An inhibitor titer of less than 10 BU at the start of ITT was a strong indicator of its success. However, in the International Immune Tolerance Study, a randomized, controlled study comparing high-dose (200 IU/kg/d) versus low-dose
Patients with severe hemophilia can experience spontaneous or trauma-related bleeding into joints, leading to painful and debilitating arthropathy. It is generally accepted today that prophylactic treatment may prevent hemarthroses and musculoskeletal complications in patients with hemophilia who have not developed inhibitors. Several cohort studies and a more recent prospective randomized study demonstrated that primary prophylaxis may delay or prevent the development of hemophilic arthropathy. The efficacy of secondary prophylaxis in an adult patient with hemophilia has also been reported. In patients with inhibitors, prophylactic versus on-demand administration of bypassing agents has likewise been shown to have several important clinical benefits, including a reduced number of hemarthroses and overall bleeding episodes. Prophylaxis is expensive, as is ITT, and the need for frequent venipuncture or an indwelling central venous access device makes prophylactic treatment difficult for caregivers and patients, especially children.

An alternative to prophylaxis is early and aggressive episodic treatment. Recent studies have provided evidence suggesting that prophylactic treatment has important clinical advantages over episodic on-demand treatment, including fewer bleeding episodes, better orthopedic function, and improved overall quality of life. Few episodic studies, however, have adequately controlled for time to treatment, which, when performed within 1 to 2 hours, is associated with fewer bleeding episodes, more rapid bleed control, and a smaller quantity of clotting agent required for control.

The optimal regimen for the dosing and the frequency of factor concentrate infusions used for prophylaxis in children is unknown. The current protocol in the USA is 25 IU/kg to 40 IU/kg of FVIII three times a week for hemophilia A. It has been demonstrated that long-term outcomes are best achieved when prophylactic treatment is started before the age of 3 years. Fewer adults and adolescents than children receive prophylactic treatment, and currently there is no consensus as to when, or whether, prophylactic treatment could be discontinued in these patients. The risk of bleeding is lower in adulthood than in childhood and adolescence, as a result of joint maturity and a reduction in the degree of physical activity. Elderly patients with hemophilia typically also have a low incidence of hemarthrosis because of severe arthropathy.

**Patient’s experience**

Despite beginning prophylactic therapy relatively late in life as an adult and his early development of inhibitors, the functional ability of our patient, as presented in this review, is remarkable. He completed medical school and a residency, both challenging even for the most physically fit of individuals. As an adult with the experience of many years of treating his condition, the patient knows how and when to avoid overexerting himself; for example, by utilizing a wheelchair when necessary. He is also proficient at determining when a joint “feels” as though it may need to be carefully managed with early treatment; in this case, when there is a reduction in range of motion.

**Primary care and hemophilia treatment centers**

The patient and his family have maintained a long-lasting, professional relationship with their primary care physician. This type of relationship is critical for long-term care in hemophilia, especially with respect to prophylaxis. The adolescent-to-adult transition is a particularly difficult time, when many patients are suddenly responsible for their own care. It is at this time that many hemophilic patients who were previously on prophylactic therapy may experience a lapse in their treatment, with worsening arthropathy as a result. A recent retrospective study predicted that an increase of only one primary care physician per 10,000-person population was associated with an average mortality reduction of 49 per 100,000 people per year (or 5.3%). Studies carried out by the Centers for Disease Control and Prevention also showed that hemophilic patients treated at HTCs have a 40% lower mortality rate than patients treated in local hospitals, even though the former population tends to have more severe disease.

**Additional patient experiences**

In addition to receiving proper medical treatment to prevent or treat bleeds, patients with hemophilia should be made...
more aware of the need to minimize trauma, of psychosocial issues, and of the use of nonpharmacologic, alternative treatment and disease-management options. The parents of this patient took great precautions early on to minimize the risk of bleeds in an environment that was not overprotective. For example, as an infant, he slept in a corner of the room with many blankets; padding was attached to furniture to guard against impacts; and it was stressed to friends and family members that he should be treated with extra care. Later, he avoided contact sports, which carry a high risk of trauma. However, other sports such as swimming or golf are recommended by the National Hemophilia Foundation because they improve overall fitness, help to build muscle strength, and ultimately reduce the risk of joint bleeds.

The incidence of obesity in the hemophilic population is twice that of the general population, often a result of patient inactivity and parental overprotection. Excess body weight weakens already unstable joints, increasing both the number of hemarthroses and arthropic progression. Excess body weight also increases the quantity of clotting factor and the time it takes to administer replacement clotting factor. After reaching a maximum weight of 77 kg, this patient succeeded in reducing his weight to 54 kg during his junior and senior years in high school. Today, he is even more physically active than when he was an adolescent; he swims episodically and works out by lifting weights and utilizing an elliptical machine three times a week.

Nonpharmacologic approaches complement drug-based treatment, helping to minimize the risk of uncontrolled bleeding and its sequelae. Because the availability of clotting factor concentrates is limited by cost in many healthcare systems, alternative management methods have been tried to help reduce the amount of drugs needed. Commonly used nonpharmacologic approaches include hydrotherapy and rest, ice, compression, and elevation (RICE). Joint rest can be achieved through the use of splints, casts, a wheelchair, or crutches. For example, as a hospital resident, this patient made liberal use of a wheelchair for the purpose of resting his joints when on-call during strenuous periods.

Surgical and other invasive procedures historically have proved to be extremely difficult or impossible with hemophilic patients, especially those with inhibitors. Today, in addition to pharmacologic options for managing these patients, adjunctive approaches can be employed. For example, this patient underwent tooth extraction as an adolescent, and his parents applied tea bags to the affected area, significantly reducing the amount of bleeding from the procedure. Tea leaves contain tannic acid, which causes constriction of blood vessels; hence, moistened tea bags may provide a simple, localized hemostatic effect.

**Discussion**

The case of the patient discussed in this review is a prime example of successful hemophilia management with early and aggressive on-demand therapy in addition to diligent parental involvement in bleed-preventive measures. This case is also illustrative of what has been achieved in the realm of diagnosis and treatment within a generation, and of what remains to be achieved to further minimize the morbidity resulting from severe hemophilia. Treatment for severe hemophilia has progressed swiftly, even within the lifetime of this patient, and it is promising to consider the long-term prognosis of hemophilic infants today, especially in light of the advances being made in prophylaxis and home infusion. This patient began prophylactic treatment only as an adult, having been treated early, on demand, as a child and an adolescent. As a consequence, over time, his joint morbidity has been kept to a minimum, with few sequelae from acute bleeding. His current degree of arthropathy, as evidenced by regular radiographic and clinical surveillance, is minimal, as is the impact of any arthropathy on his quality of life. He is able to meet the physical demands of his work without difficulty and maintains an active low-impact exercise regimen.

Bypassing agents are the treatment of choice in patients who have developed inhibitors from factor infusion, and have been used successfully for the prophylactic treatment of bleeds. This patient has been successfully treated using these agents in adulthood, and continues to use them as needed. Bypassing agents have greatly contributed to the prevention of arthropathy, and have provided this patient with the opportunity to maintain an independent and demanding lifestyle. His case highlights the importance of aggressive treatment from infancy, whether with prophylaxis or on demand, and of the absolute necessity for hypervigilant parental involvement in the home and school environment. Hemophilia requires the interaction of the whole healthcare team for optimal care of the patient. The ultimate goals for hemophilic patients and their healthcare providers are the prevention of joint bleeds, optimal function, and a superior quality of life.

**Acknowledgments/disclosure**

The authors have no competing interests that might be perceived as posing a conflict or bias. This manuscript was prepared with editorial assistance provided by Jim Loss, PhD, ETHOS Health Communications, Newtown, Pennsylvania, with financial
assistance from Novo Nordisk, Inc., in compliance with international Good Publication Practice guidelines.

References
1. DiMichele D, Neufeld EJ. Hemophilia. A new approach to an old disease. Hematol Oncol Clin North Am. 1998;12(6):1315–1344.
2. Haldane JB. The rate of spontaneous mutation of a human gene. 1935. J Genet. 2004;83(3):235–244.
3. Rosendaal FR, Brocker-Vriends AH, van Houwelingen JC, et al. Sex ratio of the mutation frequencies in haemophilia A: estimation and meta-analysis. Hum Genet. 1990;86(2):139–146.
4. Soucie JM, Evatt B, Jackson D. Occurrence of hemophilia in the United States. The Hemophilia Surveillance System Project Investigators. Am J Humatol. 1998;59(4):288–294.
5. Ghosh K, Shetty S. Immune response to FVIII in hemophilia A: an overview of risk factors. Clin Rev Allergy Immunol. 2009;37(2):58–66.
6. Astermark J, Oldenburg J, Escobar M, White GC 2nd, Bernertop E. The Malmo International Brother Study (MIBS). Genetic defects and inhibitor development in siblings with severe hemophilia A. Haematologica. 2005;90(7):924–931.
7. Tuddenham EG, Schwaab R, Seehafer J, et al. Haemophilia A: database of nucleotide substitutions, deletions, insertions and rearrangements of the factor VIII gene, second edition. Nucleic Acids Res. 1994;22(22):4851–4868.
8. Kulkarni R, Ponder KP, James AH, et al. Unresolved issues in diagnosis and management of inherited bleeding disorders in the perinatal period: a white Paper of the Perinatal Task Force of the Medical and Scientific Advisory Council of the National Hemophilia Foundation, USA. Haemophilia. 2006;12(3):205–211.
9. DiMichele DM. Inhibitors in haemophilia: a primer. Haemophilia. 2000;6 Suppl 1:38–40.
10. Ehrenforth S, Kreuz W, Scharrer I, et al. Incidence of development of factor VIII and factor IX inhibitors in haemophiliacs. Lancet. 1992;339(8793):594–598.
11. Bray GL, Gomperts ED, Courter S, et al. A multicenter study of recombinant factor VIII (recombinate): safety, efficacy, and inhibitor risk in previously untreated patients with hemophilia A. The Recombinase Study Group. Blood. 1994;83(9):2428–2435.
12. UK Haemophilia Centre Doctors’ Organisation. The incidence of factor VIII and factor IX inhibitors in the haemophilia population of the UK and their effect on subsequent mortality, 1977–1999. J Thromb Haemost. 2004;2(7):1047–1054.
13. Bernertop E, Shapiro A, Astermark J, et al. Inhibitor treatment in haemophiliacs A and B: summary statement for the 2006 international consensus conference. Haemophilia. 2006;12 Suppl 1:7–1.
14. Morfini M. Articular status of haemophilia patients with inhibitors. Haemophilia. 2008;14 Suppl 6:20–22.
15. Morfini M, Haya S, Tagariello G, et al. European study on orthopaedic status of haemophilia patients with inhibitors. Haemophilia. 2007;13(5):606–612.
16. Gouw SC, van den Berg HM, le Cessie S, van der Bom JG. Treatment characteristics and the risk of inhibitor development: a multicenter cohort study among previously untreated patients with severe hemophilia A. J Thromb Haemost. 2007;5(7):1383–1390.
17. Rodriguez-Merchan EC. Prevention of haemophiliac arthropathy in haemophilic children with inhibitors. Haemophilia. 2008;14 Suppl 6:1–3.
18. Goudemand J. Pharmacoeconomic aspects of inhibitor treatment. Eur J Haemtol Suppl. 1998;63:24–27.
19. Lusher JM. Early treatment with recombinant factor VIIa results in greater efficacy with less product. Eur J Haemitol Suppl. 1998;63:7–10.
20. Manco-Johnson MJ, Abshire TC, Shapiro AD, et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. N Engl J Med. 2007;357(6):535–544.
21. Aledort LM, Haschmeyer RH, Pettersson H. A longitudinal study of orthopaedic outcomes for severe factor-VIII-deficient haemophiliacs. The Orthopaedic Outcome Study Group. J Intern Med. 1994;236(4):391–399.
22. Hoots WK, Ebbelesen LS, Konkle BA, et al. Secondary prophylaxis with recombinant activated factor VII improves health-related quality of life of haemophilia patients with inhibitors. The NovoSeven (FTHAEM-1505) Investigators. Haemophilia. 2008;14(3):466–475.
23. Parameswaran R, Shapiro AD, Gill JC, Kessler CM. Dose effect and efficacy of fVIIa in the treatment of haemophilia patients with inhibitors: analysis from the Hemophilia and Thrombosis Research Society Registry. Haemophilia. 2005;11(2):100–106.
24. World Federation of Hemophilia. Guidelines for the Management of Hemophilia. Montreal, Quebec, Canada: World Federation of Hemophilia; 2005. Available from: http://www.wfh.org/2/docs/Publications/Diagnosis_and_Treatment/Guidelines_Mng_Hemophilia.pdf. Accessed April 27, 2012.
25. Rodriguez-Merchan EC, Quintana M, Jimenez-Yuste V. Orthopaedic surgery in haemophilia patients with inhibitors as the last resort. Haemophilia. 2008;14 Suppl 6:56–67.
26. Rodriguez-Merchan E. Pathogenesis of Musculoskeletal Complications of Haemophilia. In: Rodriguez-Merchan EC, Lee LC, editors. Inhibitors in Patients with Haemophilia. Oxford, UK: Blackwell; 2002:116.
27. Oyesiku JO. Home treatment of haemophilia patients with inhibitors. Haemophilia. 2011;17(2):173–178.
28. Rosendaal G, Lafeber FP. Pathogenesis of haemophilic arthropathy. Haemophilia. 2006;12 Suppl 3:117–121.
29. Tullis JL, Melin M, Jurigian P. Clinical use of human prothrombin complexes. N Engl J Med. 1965;273(13):667–674.
30. Tencer T, Friedman HS, Li-McLeod J, Johnson K. Medical costs and resource utilization for hemophilia patients with and without HIV or HCV infection. J Manag Care Pharm. 2007;13(9):790–798.
31. Mannucci PM, Colombo M. Revision of the protocol recommended for studies of safety from hepatitis of clotting factor concentrates. International Society for Thrombosis and Hemostasis. Thromb Haemost. 1989;61(3):532–534.
32. Grillberger L, Kreil TR, Nasr S, Reiter M. Emerging trends in plasma-free manufacturing of recombinant protein therapeutics expressed in mammalian cells. Biotechnol J. 2009;4(2):186–201.
33. Ludlam CA, Powderly WG, Bozzette S, et al. Clinical perspectives of emerging pathogens in bleeding disorders. Lancet. 2006;367(9506):252–261.
34. Hewitt PE, Llewelyn CA, Mackenzie J, Will RG. Creutzfeldt-Jakob disease and blood transfusion: results of the UK Transfusion Medicine Epidemiological Review study. Vox Sang. 2009;91(3):221–230.
35. National Hemophilia Foundation [website]. Blood and product safety. Available from: http://www.hemophilia.org. Accessed February 29, 2012.
36. Centers for Disease Control and Prevention (CDC). HIV transmission through transfusion – Missouri and Colorado, 2008. MMWR Morb Mortal Wkly Rep. 2010;59(41):1335–1339.
37. Chorba TL, Holman RC, Clarke MJ, Evatt BL. Effects of HIV infection on age and cause of death for persons with hemophilia A in the United States. Am J Hematol. 2001;66(4):229–240.
38. Chorba TL, Holman RC, Strine TW, Clarke MJ, Evatt BL. Changes in longevity and causes of death among persons with hemophilia A. Am J Hematol. 1994;45(2):112–121.
39. Soucie JM, Nuss R, Evatt B, et al. Mortality among males with hemophilia: relations with source of medical care. The Hemophilia Surveillance System Project Investigators. Blood. 2000;96(2):437–442.
40. Geraghty S, Dunkley T, Harrington C, Lindvall K, Maahs J, Sek J. Practice patterns in haemophilia A therapy – global progress towards optimal care. Haemophilia. 2006;12(1):75–81.
41. Centers for Disease Control and Prevention. Report on the Universal Data Collection Program. 2005.
42. NovoSeven RT [package insert]. Bagsvaerd, Denmark: Novo Nordisk A/S; 2010.
43. FEIBA NF [package insert]. Westlake Village, CA: Baxter Healthcare Corporation; 2011.
44. DiMichele DM, Hoots WK, Pipe SW, Rivard GE, Santagostino E. International workshop on immune tolerance induction: consensus recommendations. Haemophilia. 2007;13 Suppl 1:1–22.
45. Hay CR, Dimichele DM, on behalf of the International Immune Tolerance Study. The principal results of the International Immune Tolerance Study: a randomized dose comparison. Blood. 2012;119(6):1335–1344.
46. Nilsson IM, Berntorp E, Lofqvist T, Pettersson H. Twenty-five years’ experience of prophylactic treatment in severe haemophilia A and B. J Intern Med. 1992;232(1):25–32.
47. Fischer K, van der Bom JG, Molho P, et al. Prophylactic versus on-demand treatment strategies for severe haemophilia: a comparison of costs and long-term outcome. Haemophilia. 2002;8(6):745–752.
48. Saba HI, Tannenbaum B, Morelli G, Azam R, Atanes I, Nichols C. Prophylaxis in adult hemophiliacs. Blood. 1998;10 Suppl S1:109b.
49. Konkle BA, Ebbesen LS, Erhardt E, et al. Randomized, prospective clinical trial of recombinant factor VIIIa for secondary prophylaxis in hemophilia patients with inhibitors. J Thromb Haemost. 2007;5(9):1904–1913.
50. Leissinger C, Gringeri A, Antmen B, et al. Anti-inhibitor coagulant complex prophylaxis in hemophilia with inhibitors. N Engl J Med. 2011;365(18):1684–1692.
51. Young G, Auerswald G, Jimenez-Yuste V, et al. When should prophylaxis therapy in inhibitor patients be considered? Haemophilia. 2011;17(5):e849–e857.
52. Hacker MR, Geraghty S, Mance-Johnson M. Barriers to compliance with prophylaxis therapy in haemophilia. Haemophilia. 2001;7(4):392–396.
53. Hay CR. Prophylaxis in adults with haemophilia. Haemophilia. 2007;13 Suppl 2:10–15.
54. Richards M, Altisent C, Batorova A, et al. Should prophylaxis be used in adolescent and adult patients with severe haemophilia? An European survey of practice and outcome data. Haemophilia. 2007;13(5):473–479.
55. Fischer K. Can we consider discontinuing primary prophylaxis in adults with severe haemophilia? Haemophilia. 2008;14 Suppl 4:10.
56. Macinko I, Starfield B, Shi L. Quantifying the health benefits of primary care physician supply in the United States. Int J Health Serv. 2007;37(1):111–126.
57. Hebestreit H, Bar-Or O. Differences between children and adults for exercise testing and exercise prescription. In: Skinner J, editor. Exercise Testing and Exercise Prescription for Special Cases: Theoretical Basis and Clinical Application, 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2005.
58. Cassis FRMY. Psychosocial Care for People with Hemophilia. Montreal, Quebec, Canada: World Federation of Hemophilia, 2007. Treatment of Hemophilia series.
59. Hofstede FG, Fijnvandraat K, Plug I, Kamphuisen PW, Rosendaal FR, Peters M. Obesity: a new disaster for haemophilic patients? A nationwide survey. Haemophilia. 2008;14(5):1035–1038.
60. Bleeding Disorder Dental Care [page on the Internet]. Indiana Hemophilia and Thrombosis Center Web site. Available from: http://www.ihtc.org/medical-professionals/blood-disorders/bleeding-disorders/dental-care/. Accessed January 26, 2012.
61. Key NS, Aldorit LM, Beardsley D, et al. Home treatment of mild to moderate bleeding episodes using recombinant factor VIIIa (Novoseven) in haemophilics with inhibitors. Thromb Haemost. 1998;80(6):912–918.