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REVIEW
Blood Safety and the Choice of Anti-Hemophilic Factor Concentrate

Leonard A. Valentino, MD* and Veeral M. Oza

Hemophilia is a congenital disorder due to the deficiency of the activity of factor VIII (classical hemophilia A) or IX (Christmas disease or hemophilia B). Bleeding is common and may result in long-term complications or even death. Bleeding may be treated or prevented by infusion of factor concentrates however these drugs are not without risk. Clinicians often feel ill prepared to provide accurate and impartial information regarding these drugs. This review will provide the reader with an historical yet up to date perspective on blood safety as it relates to the choice of concentrates to treat hemophilia. Pediatr Blood Cancer 2006;47:245–254.
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Key words: blood safety; hemophilia; infection; inhibitor; treatment

INTRODUCTION

Hemophilia is a genetic disorder that is due to the deficiency or absence of a protein necessary for normal blood clotting. Treatment consists of regular injections of anti-hemophilic factor concentrates given on an ''as needed basis'' (episode-based treatment) or according to a regular schedule of prophylactic infusions (prophylaxis) to prevent bleeding and the debilitating complications that ensue from bleeding into joints, muscles, or vital organs and structures. The National Hemophilia Foundation's MASAC [1] and the Canadian Hemophilia Treatment Center Directors [2] both advise that physicians exercise their best judgment in advising patients about their options in terms of product for treatment of bleeding episodes. The choice of which factor concentrate to use is a difficult decision for parents of young children, adult patients, and their physicians. Factors that impact on this decision (Table I) include availability of individual products, their cost, clinical effectiveness, ''ease of administration,'' and the safety of each product [3]. In 2000, more than three billion international units of recombinant anti-hemophilic factor concentrate were produced [4]. This amount is capable of meeting the needs of only 30% of the world hemophilia population. The issues of cost and cost-benefit of individual anti-hemophilic factor concentrates are beyond the scope of this review. The reader is referred to an excellent review by Giagrande [5] on this topic. Similarly, data on the effectiveness of individual anti-hemophilic factor concentrates is present in the literature [6,7]. Prospective trials, retrospective analyses and case reports examining the effectiveness of individual products can be found in the literature and will not be discussed here.

The safety of anti-hemophilic factor concentrates is a major concern for patients with hemophilia and parents of young children with hemophilia [8–10]. Any discussion of product safety should include consideration that the product could potentially transmit a serious, life-threatening infection, induce the formation of a neo-antigen or inhibitor, or cause allergic or other adverse effects [3,11]. Physicians treating hemophilia patients often lack answers to the same questions that patients or their parents have. The discussion here will focus on blood safety as it relates to the choice of a factor concentrate to treat patients with hemophilia.

CASE PRESENTATIONS

To illustrate key points in the decision making process, three clinical scenarios will be presented. Each case illustrates different issues facing the clinician providing care for patients with hemophilia.

Case 1 (Viral infection) is that of a 34-year-old male with severe hemophilia A and chronic degenerative joint disease involving both ankles and elbows and his right knee. The patient receives episodic infusions of 2000 International Units (IU) of factor VIII concentrate as needed. Annually, he infuses approximately 160,000 IU. Over his lifetime he has received more than 2,000 infusions without the development of an inhibitor, an antibody that precludes the function of the infused factor concentrate. During early adolescence, he was treated with a factor concentrate that was contaminated with the virus that causes AIDS—human immunodeficiency virus 1 (HIV-1). Despite almost 20 years of infection, his viral load is minimal (less than 100 viral genome copies per ml) and his CD4 T-lymphocyte cell counts are moderately reduced despite not ever receiving anti-retroviral therapy. He was also infected with hepatitis C virus (HCV) from contaminated factor concentrate and currently has evidence of moderately severe liver dysfunction with prolongation in the Prothrombin time and elevated liver transaminases, for which no therapy has been given.

RUSH Hemophilia and Thrombophilia Center, Department of Pediatrics and Department of Internal Medicine, Rush University Medical Center, Chicago, Illinois

*Correspondence to: Leonard A. Valentino, Rush University Medical Center, 1653 West Congress Parkway, Chicago, Illinois 60612.
E-mail: lvalentino@rush.edu

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TABLE I. Issues to be Considered When Evaluating Options for Anti-Hemophilic Factor Concentrate

Efficacy
Safety
Antibody provacation
Microbiological
Ease of reconstitution
Ease of administration
Cost and affordability
Availability/accessibility

Case 2 (Prophylaxis) is that of a 9-year-old boy who has severe hemophilia A. He has had 12 acute hemarthroses affecting the right knee, both ankles and both elbows but none is a target joint. Since 2 years of age, he has been treated with regular prophylactic infusions of factor VIII concentrate three times weekly utilizing approximately 160,000 IU yearly. There has been neither clinical nor laboratory evidence to suggest the presence of an inhibitor. He received vaccines against hepatitis A and B virus infections and has protective adaptive immunity against these viruses. He has not been exposed to hepatitis C or HIV-1 viruses.

Case 3 (previously untreated patient) is that of 1½ year old previously untreated boy with severe hemophilia A who presents with his first significant bleeding episode characterized by a warm, tender, swollen right knee. This boy is immune to hepatitis B following vaccination but is at risk for hepatitis A, having not yet initiated the vaccination series, and is at risk for HCV infection as well as for HIV-1 and for other microbes that might be transmitted in anti-hemophilic factor concentrates. These three cases illustrate some of the issues that patients, parents and physicians face when choosing a factor concentrate for the treatment of hemophilia.

BLOOD TRANSFUSION THERAPY

Over the past century since first successfully performed in 1818 by James Blundell, a British Obstetrician, transfusion therapy has improved in terms of safety and efficacy. Advances to prevent transmission of microorganisms include donor screening and testing and methods to remove and inactivate microorganisms.

Although each of these steps has lead to an improvement in the safety profile of the blood components available to treat patients with hemophilia, the safety of plasma-derived anti-hemophilic factor concentrates remains an issue. It is more than 30 years since the first cases of infection with hepatitis B virus (HBV) were reported in patients with hemophilia treated with concentrates made from plasma [12]. From 1971 to 1975 and 1975 to 1979, the annual incidence of HBV infection was estimated to be 7% and 9.5% [13]. Currently, 90% of HBV seroconversions in patients with hemophilia are attributed to vaccination programs [14]. According to the most recent data from the Centers for Disease Control and Prevention, the prevalence of natural or acquired immunity to HBV among the 15,682 people with bleeding disorders participating in the Universal Data Collection (UDC) project [15] appears to be decreasing despite the availability and widespread usage of hepatitis B vaccine in childhood. This suggests that patients may once again be susceptible to HBV infection. The signs and symptoms of hepatitis following infection with HBV are present in about 70% of cases, of which about 5% develop chronic infection and 15%–25% of these individuals die from chronic liver disease [16].

Infection with HCV (formerly called non-A, non-B (NANB) Hepatitis) was described phenotypically as being distinct from Hepatitis A and B in the 1970's and the virus was isolated and genome sequenced in 1989. The prevalence of HCV infection among persons with hemophilia is approximately 60% [17]. Data from the UDC report [15] indicates that the prevalence of HCV infection is about 40%, but among 41–60 year old people with hemophilia is approximately 80%. The higher infection rates in adults reflect exposure to the disease prior to viral inactivation of factor products. HCV infection is the leading indication for liver transplantation. Up to 80% of persons infected with HCV have no signs or symptoms. Chronic infection and liver disease develops in 55%–85% and 70%, respectively and 1%–5% die from chronic liver disease [16].

In 1982–1983, the first cases of hemophilia patients with an unusual immunodeficiency syndrome appeared which were eventually shown to be due to infection with HTLV-III, later renamed human immunodeficiency virus (HIV) [18]. Approximately one-third of people with hemophilia between the ages of 21 and 60 years are HIV-infected [15]. Recently, the possibility of other 'emerging' infections has gained the attention of parents, patients, and providers. In the next section these concerns will be addressed.

IS PURITY EQUIVALENT TO SAFETY?

As the new millennium came, so did new and improved anti-hemophilic factor concentrates. The current generation of plasma-derived and recombinant anti-hemophilic factor concentrates are purer than their predecessors [19]. A question that we must answer however ''Does the enhanced purity of the anti-hemophilic factor concentrate translate to enhanced safety?'' To explore this issue, the risks from plasma-derived and recombinant coagulation proteins must be considered by four distinct time eras. The first era was prior to 1970 when plasma and cryoprecipitate were used to treat patients with hemophilia. The second era was during the 1970's and 1980's when low and intermediate purity products derived from human blood were used to control acute bleeding and prevent bleeding with surgery. The third era began in the late 1980's and extends to current time with the use of high purity, monoclonal anti-hemophilic factor concentrate and recombinant products. The fourth era began

in 2000 with the licensure of the current sucrose-formulated products [9,14,20–23]. Each era was marked by the development of purer anti-hemophilic factor concentrates.

MICROBIOLOGICAL RISKS

The microbiological threats or risks to the three patients described above include: bacteria, protozoa, viruses, and prions. Prior to choosing an anti-hemophilic factor concentrate, several questions should be considered. First, ''Is it possible that one of these agents might be present in blood or a blood product?'' Second, ''If a microbe is present in blood or a blood product, is it capable of infecting me or my child?'' Third, ''Is the infectious agent likely to cause significant human disease?'' Finally, ''If present, is the infectious agent removed by currently employed procedures?'' After considering the answers to these questions (Tables II and III), a patient or parent will be better able to make an informed choice regarding the use of an anti-hemophilic factor concentrate for themselves or their child.

Modern blood banking technology and plasma fractionation procedures have essentially eliminated bacteria and protozoan agents from anti-hemophilic factor concentrates [20,24–27]. The major pathogens including HBV, HCV, and HIV have been virtually eliminated from the blood supply [28,29], leaving other viruses including hepatitis A, parvovirus B19 and the ''so-called'' emerging agents [30] including prions as the main potential threats to the patients who use blood and blood derivatives [14,23,31]. Vaccination programs directed against HAV [32] and HBV [33,34] result in persistent immunity and recent advances suggest that a vaccine against hepatitis C may be forthcoming [35].

TABLE II. Microbiological Threats to the Blood and Factor Concentrate Supply

Agent	Present in blood?[a]	Infectious?	Disease causing?
HIV	Yes	Yes	Yes
HCV	Yes	Yes	Yes
HBV	Yes	Yes	Yes
HAV	Yes	Yes	Uncertain[b]
PB19	Yes	Yes	Uncertain[c]
TTV	Yes	Yes	Uncertain
HGV	Yes	Yes	Uncertain
WNV	Yes	Yes	Yes
SENV	Yes	Yes	Uncertain
VCJG	Yes	Yes	Yes
SARS	Uncertain	Yes	Yes
AFV	Uncertain	Yes	Yes

[a]The risk with recombinant products is minimal or absent.
[b]The consequences of long-term infection are not well understood nor is the interaction with other hepatis viruses.
[c]Certain people such as pregnant women, newborns and people with hemolytic anemia are at risk for red cell aplasia. The long-term consequences of infection at an early age are not known.

TABLE III. Characteristics of Microbial Pathogens Threatening the Blood and Factor Concentrate Supply and Resistance to Inactivation

Virus	Genome	Lipid enveloped	Size (nm)	S/D resistant	Heat resistant
PB19	DNA	No	20–25	Yes	Yes
TTV	DNA	No	30–50	Yes	Yes
HAV	RNA	No	27	Yes	No
HBV	DNA	Yes	42	No	No
AFV	RNA	Yes	100–120	No	No
HCV	RNA	Yes	36–65	No	No
HGV (GBV-C)	RNA	Yes	40–60	No	No
HIV1	RNA	Yes	80–100	No	No
SARS-CoV	RNA	Yes	80–160	No	No
SEN	RNA	Yes	150–350	No	No
WNV	RNA	Yes	50	No	No
Prions	Neither	No	—	Yes	Yes

Hepatitis A, Parvovirus B19 and Transfusion-Transmitted Virus

The key properties of the common blood-borne viruses (Table III) include resistance to solvent-detergent and heat inactivation and are important determinants of the likelihood of the presence of each agent in blood and blood derivatives. Sentinel virus is a term that is applied to both HAV and parvovirus B 19, because these viruses may reflect the behavior of other potential, unknown pathogens that could be present in the blood supply. HAV is a solvent-detergent resistant RNA virus, and parvovirus B 19 is a DNA virus that is heat resistant. The current viral inactivation techniques are not very effective against these agents and filtration techniques are used to remove these infectious microorganisms. HAV and parvovirus B 19 are potentially very difficult to eliminate from factor concentrates once present in source plasma [36]. Therefore, donor screening to eliminate HAV and PB19 from source plasma is critical [36–38].

Recent vaccine development studies for PB19 have yielded promising results [39–41]. In 2004, Ito and coworkers successfully treated a patient with a persistent PB19 infection with a mixture of cyclosporine A and high-dose gamma-immunoglobulin [42]. The reader is referred to an excellent review on the subject by Heegard and Brown [43].

First-generation recombinant human factor VIII concentrates, stabilized with human-plasma-derived albumin before lyophilization are widely used by hemophilia patients, primarily because of the perceived safety in regards to viral infection. However, Schneider et al., and coworkers found that PB19 was frequently present in recombinant coagulation factor VIII products [44]. Moreover, another study indicated the presence of PB19 in young patients with hemophilia A [45]. Similarly, circoviruses are also very resistant to treatment with heat, detergents, and disinfectants. Recent studies have linked novel circoviruses to serious post-transfusion conditions. For example, transfusion transmitted virus (TTV) was discovered in 1998 [46] and linked to

post-transfusion hepatitis [46–48]. For this reason TTV has been of great interest to the hemophilia community. Azzi et al. [49] showed that TTV viral genome was present in first-generation recombinant factor VIII and IX concentrates. On the other hand, the second-generation factor VIII product Refacto and recombinant factor IX (Benefix) did not contain TTV. Recently, the most common factor IX products, Mononine and Benefix, used to treat hemophilia B were shown not to contain TTV [50].

Hepatitis G Virus

In 1996, two groups independently discovered a novel RNA virus and called it GB virus C (GBV-C) and hepatitis G virus (HGV), respectively [51,52]. From this point on HGV will be used to refer to GBV-C. HGV is a member of the *Flaviviridae* family and its genome is similar to that of HCV. HGV has been found in FVIII concentrates and has been associated with acute and persistent hepatitis in humans. The long-term clinical significance of such an infection remains uncertain. In general, human HGV infection appears to be mild or clinically silent [31]. There have, however, been a few cases of fulminate hepatitis associated with HGV infection reported [51]. In addition, a recent study questions the cause or effect relationship between HGV and HIV progression. The detection of HGV RNA in blood products and in plasma-derived products further raises questions regarding blood safety [53]. Additionally, HGV's prevalence is well established. For instance, 1.72% of US blood donors are infected with this virus [54], whereas in Japan the prevalence is 0.9% [55]. In hemophilia patients the prevalence rate rises to 18% [54]. If blood products are not treated with specific virucidal methods, it is likely that HGV will be present in factor concentrates.

West Nile Virus

Among the other potential transfusion threats is the re-emerging agent, West Nile Virus (WNV) [31]. It is considered re-emerging because of the cycle of outbreak and dormancy. In 1999, an outbreak of WNV in New York City deeply worried the scientific community in regards to contaminated blood supply used for transfusions. In 2000, WNV went dormant in the USA; only to re-appear in 2001. The infection quickly spread. In 2002, 4 patients received organ donations from the same person. All 4 developed WNV infection. The incident sparked the need to test the blood supply for WNV. That year, a minimum of 21 cases of transfusion-borne WNV infections were identified. The American Red Cross confirmed that 0.01% of blood donations tested positive for WNV (415 of 4.1 million donors). In some states the rate of infection is much higher, as in Kansas where it was 1:243 [31]. Nucleic acid testing (NAT) for WNV was licensed by the FDA in 2000. Importantly, virus inactivation steps commonly used during the manufacture of plasma derivatives, such as pasteurization for human albumin, solvent/detergent treatment for IVIG and FVIII, and vapor heating for FVIII inhibitor-bypassing activity, readily inactivate WNV essentially eliminating this virus from the source plasma [56].

Although the number of WNV infections continues to decrease each summer, epidemiological surveillance and donor screening will have to continue, as vector population carrying the WNV have increasingly adapted, allowing the virus to breed in any volume of liquid. The ability of WNV and other agents to adapt or mutate, especially with new capabilities to infect humans, remains a concern [57].

SEN Virus

Another potential threat is the SEN virus (SENV), a distant cousin of TTV. Five SENV strains (A, B, H [formerly C], D, E) have been identified, from which SENV-H and SENV-D strains have been found in the highest proportion in cases with non-A to E hepatitis [58,59]. Umemura and co-workers showed the presence of SENV DNA (strains D or H) in 86/286 patients who received blood transfusions during surgery [59]. This rate is 10 times higher than in cases where no transfusions were performed. Moreover, it was observed during post-transfusion follow-up, that newly acquired SENV infections were present in 92% of patients with non-A to E hepatitis and only 24% of patients who did not develop post-transfusion hepatitis; hence suggesting a link between non-A to E hepatitis and SENV [59]. Additionally, SENV infection was observed in 41% of patients who developed HCV. This rate is significantly lower than that of non-A to E hepatitis (92%) [58].

Prions

In recent years, there has been a growing concern in regards to variant Creutzfeldt–Jakob disease (vCJD) and the risks associated with its transmission [60]. In 1996, a new human form of CJD was identified in the UK [61]. At the time, infected patients had eaten meat during the severe outbreak of Bovine Spongiform Encephalopathy (BSE). Further studies linked the occurrence of vCJD to cross-species transmission [62,63].

In 2000, studies in mice [64] and sheep [65] showed the transmission of vCJD through blood transfusions, making vCJD a possible blood borne agent [66]. Epidemiological studies up to 2002 in humans had shown that transmission through the blood supply had not yet occurred [37,67]. Unfortunately, two subsequent studies have provided evidence for the transfusion transmission of vCJD in humans [63,68,69]. Moreover, in 2003, UK announced death of a man who had received a blood transfusion from an infected individual [70]. It is believed that, to date, as many as 150 people in the UK may be infected as a result of blood transfusions

TABLE IV. Comparison of Plasma-Derived Monoclonal-Antibody Purified and Recombinant Anti-Factor VIII Products

	Plasma-derived	Recombinant	Comparison[a]
Efficacy	Excellent	Excellent	Equivalent
Safety			
Antibody provocation[b]	37% [31]	36% [31]	Equivalent
Microbiological	Possible	Unlikely	Recombinant
Ease of reconstitution	Very good	Very good	Equivalent
Ease of administration	Very good	Excellent	Recombinant[c]
Cost and affordability	Excellent	Very good	Plasma-derived
Availability/accessibility[d]	Good	Good	Equivalent

[a]The comparison refers to the differential evaluation of plasma-derived and recombinant anti-factor VIII products. The favored product is indicated after considering the risks, benefits, cost and alternatives of plasma-derived and recombinant anti-factor VIII products for each characteristic.
[b]High-titer inhibitor (>5 BU)
[c]Recombinant anti-factor VIII products are considered superior over plasma-derived concentrates in terms of ease of administration due to the lower reconstitution volumes and therefore smaller volume for infusion and the recommended rate of infusion.
[d]Over 2 billion units of plasma-derived factor VIII concentrate and more than 3 billion units of recombinant products are available world-wide yet over 80% of the world's hemophilia patients receive inadequate or no replacement therapy.

[68]. At this time, no reliable test has been developed to determine vCJD contamination of blood or blood components [71] or for the diagnosis of infection in humans.

The risk of transmission of CJD via clotting factor concentrates manufactured from plasma appears to be relatively low. Exclusion of potentially infected donors based on travel history and low prevalence of vCJD in the donor population are key factors. As more information is learned about the disease, it is advisable for health officials to take a proactive and aggressive approach toward minimizing risk. Rigorous decontamination protocols may be used on surgical instruments that have been exposed to tissue possibly contaminated with CJD [72]; however, these harsh measures are not likely to be useful with blood and blood components including plasma. Manufacturing steps, with the potential for the removal of TSE agents, are under evaluation [73]

Several safety measures are in place to prevent transmission of vCJD through the blood supply [14,23,67]. Presently, the only risk factor that can be associated with vCJD is the country of residence [74]. Regulatory agencies in several countries, including the FDA in the USA have policies in place to defer blood donors depending on their travel histories to endemic areas such as the UK.

Although TSE agents (abnormal prion proteins) are known to be resistant to common inactivation techniques [75], animal studies have shown that processes used for protein purification, such as those used to make factor concentrates, can contribute to remove abnormal prion proteins and reducing or eliminating infectivity [76,77]. Similar results have been observed for human TSE strains, vCJD for instance [77]. Therefore the transmission risk of vCJD and other human TSE strains through concentrate products at disease-causing levels appears to be minimal [37,74]. Despite this apparently low risk of infection, experts have therefore recommended that only therapies with the lowest level of risk should be used for care of patients with hemophilia [78].

Severe Acute Respiratory Syndrome Corona Virus and Avian Influenza Virus

Severe Acute Respiratory Syndrome corona virus (SARS-CoV) is a lipid-enveloped single stranded RNA virus. The SARS outbreak came into the media limelight in February 2003, after Chinese officials reported 305 cases to the World Health Organization. After 6 months the outbreak was contained but involved 8,000 cases in 29 countries including 800 deaths. During the outbreak, no known person-to-person blood transmission occurred [79,80].

The incubation period for SARS is 4–6 days [80], and most patients become ill within 2–10 days of exposure. The risk of blood transmission of SARS-CoV is a concern. The American Red Cross and others have in place a screening process to defer donors based on travel history, or recent health conditions, such as dry cough, or shortness of breath. Moreover, the donated blood undergoes several tests and inactivation procedures for HIV, HBV, HCV, and SARS, among other pathogens, which aim to ensure the safety of the nations' blood supply since the viral inactivation procedures are highly successful in elimination of lipid-enveloped single-stranded RNA viruses.

Among other emerging threats is the Avian influenza virus (AFV) that causes Avian flu (Bird flu). The AFV is genetically different from the influenza virus that affects humans. AVF commonly infects birds, which is the natural host. Although, it is rare for AFV to infect humans, several outbreaks have been reported since 1997 [81]. None of these cases are known to have been transmitted through a

TABLE V. Clotting Factor Concentrates Available in the USA

Brand	Manufacturer	Source	Fractionation	Viral inactivation	Comments on production and final formulation	Diluent and volume[a]	Shelf-life[b] and storage[c]	Dosages[d] and infusion rate[e]
Recombinant factor VIII concentrates								
Advate	Baxter	CHO[f]	IAC[g], IEC[h]	TNBP[i]/PS80[j]	No added animal or human proteins in any step, no vWF[k], trehalose as a stabilizer	Water; 5	24; R or RT 6 mos	A; 5–10
Helixate FS	ZLB Behring	BHK[l]	IEC, IAC	TNBP/ PS80,TX100[m]	HSA[n] as a cell nutrient; formulated with sucrose, no vWF	Water; 2.5	23; R	B; 5–10
Kogenate FS	Bayer	BHK	IE, IAC	TNBP/PS80,TX100	HSA as a cell nutrient; formulated with sucrose, no vWF	Water; 2.5	24; R RT (3 mos)	B; 5–10
Recombinate	Baxter	CHO	IEC, IAC	IAC, IEC	BSA[o] as a cell nutrient; HSA added, no vWF	Water; 10	36; R or RT	B; 10
ReFacto	Wyeth	CHO	IE	TNBP/TX100, nanofiltration	HSA as a cell nutrient; formulated with sucrose, no vWF	Saline; 4	24; R or RT (3 mos)	C; several minutes
Plasma derived factor VIII concentrates								
Alphanate	Grifols	US plasma	HLC[p]	TNBP/PS80, dry heat	Albumin added, contains vWF	5 (500 IU) 10 (others)	24; R or RT (2 mos)	A; 10
Hemofil M	Baxter	US plasma	MAC[q], IEC	TNBP/Octoxynol 9	Albumin added, no functional vWF	10	30; R RT (3 mos)	C; 10
Humate P	ZLB Behring	plasma	Multiple precipitation	Pasteurization[r]	Human albumin added, contains vWF	10 (250 IU) 20 (500IU) 30 (1000 IU); R or RT (6 mos)	24; 4 ml per min	A; 10
Koate DVI	Bayer	US plasma	Multiple precipitation, SEC[s]	TNBP/PS80, dry heat	Albumin added, contains vWF	5 (250, 500 IU) 10 (1000 IU)	24; R or RT (6 mos)	A; 5–10
Monoclate P	ZLB Behring	US plasma	MAC, IEC	Pasteurization	Albumin added, no functional vWF	10 (250, 500) 20 (1000, 1500)	24; R or RT 6 mos	A; 2
Recombinant factor IX concentrate								
BeneFIX	Wyeth	CHO	AC, nanofiltration	None	No albumin added	5 (250, 500 IU) 10 (1000 IU)	24; R or RT (6 mos)	A; several minutes
Highly purified plasma derived factor IX concentrates								
Alphanine	Grifols	US plasma	IEC, CLC[t]	TNBP/PS80, nanofiltration	No albumin added	10 (500, 1000, 1500)	24; R or RT 1 month	D; 10
Mononine	ZLB Behring	US plasma	IAC	Sodium thiocyanate, dual ultrafiltration	Histidine and mannitol added	2.5 (250 IU) 5 (500) 10 (1000 IU)	24; R or RT (1 month)	A; 2
Prothrombin complex concentrates								
Bebulin	Baxter	US plasma	IEC	Vapor heat[u]	Heparin added	20	24	500–700

Profilnine SD	Grifols	US plasma	DEAE[v] cellulose adsorption	TNBP/PS80	No albumin or heparin added	5 (500) 10 (1000, 1500 IU	24	D
Proplex T	Baxter	US plasma	Tri-calcium phosphate and PEG adsorption	20% ethanol, dry heat (60°C for 144 hr)	Heparin added	30	24	700–3900
Inhibitor bypassing agents								
FEIBA VH	Baxter	US plasma	IEC	Vapor heat	No heparin added	20	24	400–2500
NovoSeven	NovoNordisk	BHK	AC[w]	Solvent detergent	No albumin	2.2, 4.3, 8.5	36	1.2, 2.4, 4.8[x]

[a]Diluent volume (ml) for injection.
[b]Shelf-life in months, do not use beyond the expiration date printed on the bottle.
[c]R, refrigeration; RT, room temperature (duration in months).
[d]Dosages available in International Units (IU): A, 250, 500, 1000, 1500; B, 250, 500, 1000; C, 250, 500, 1000, 2000; D, 500, 1000, 1500.
[e]Infusion rate not to be exceeded as recommended by the manufacturer in ml per minute.
[f]CHO, Chinese hamster ovary cells.
[g]IAC, immunoaffinity chromatography.
[h]IEC, Ion exchange chromatography.
[i]TNBP, tri(n-butyl)phosphate.
[j]Polysorbate 80.
[k]vWF, von willebrand factor.
[l]BHK, baby hamster kidney cells.
[m]TX-100, Triton X-100.
[n]HAS, human serum albumin.
[o]BSA, bovine serum albumin.
[p]HLC, heparin ligand chromatography.
[q]MAC, monoclonal antibody affinity chromatography.
[r]60°C, 10 hr.
[s]SEC, size exclusion chromatography.
[t]CLC, carbohydrate ligand chromatography.
[u]60°C, 10 hr at 190 mbar then 80°C for 1 hr at 375 mbar.
[v]DEAE, diethylaminoethyl-.
[w]AC, affinity chromatography.
[x]Recombinant activated factor VII dosage in mg.

human-to-human transmission route although this has been suggested indicating that the AFV may be mutating [82]. It should be noted that to date, most of the reported cases seem to have arisen from human contact with infected poultry [81]. Unfortunately, influenza viruses mutate often and can easily spread from birds to people and create an epidemic. Hence, it is crucial to aggressively monitor for new infections and any possible human–human transmissions.

INHIBITOR FORMATION AND ALLERGIC REACTIONS

The presence of an inhibitor represents one of the most important complications of exposure to factor concentrate in hemophilia [83]. Anti-FVIII allo-antibodies develop in 20%–30% of individuals with congenital hemophilia A who are treated for bleeding with factor VIII concentrates. The rate of inhibitor formation in patients with severe hemophilia A treated with the first generation recombinant products Kogenate (Bayer) [5,84–86] or Recombinate (Baxter) [25,87–89] is similar to that observed in patients treated with plasma-derived products [90]. Therefore, these data lead to speculation that the purer recombinant product is not necessarily a safer product from an inhibitor standpoint. Similarly, the incidence of allergic reactions although relatively rare, remains a potential problem with high-purity products [6,91].

CONCLUSIONS AND RECOMMENDATIONS

The decision of which factor concentrate to use is one that generates considerable debate among patients, their parents and the physicians and nurses who care for these patients. The advantages of recombinant factor concentrates include theoretical improvements in microbiological safety. However, this improvement is not without increased cost of therapy. There is no evidence to suspect that recombinant products are more prone to induce the development of neutralizing antibodies against factor VIII or to be associated with allergic or other adverse events. For newly diagnosed and infection-naive patients, similar to those described in cases 2 and 3 respectively, recombinant factor concentrates offer the benefits of reduced microbiological exposures. With respect to the different recombinant products, those formulated without animal or human proteins should be preferred as the microbiological risk, however small or theoretical, is likely to be further reduced, virtually eliminating the possibility of blood-borne infectious disease. At times in the past, shortages of factor concentrates due to manufacturing regulatory issues have led to ''rationing'' of products. If in the future, recombinant products are again scarce, the youngest and previously un-exposed should preferentially receive priority for any available product.

The patient who has existing infection, including HIV, HBV, or HCV, should consider the same issues when deciding on a factor concentrate as there may be interacting effects of co-infection or the introduction of a novel agent upon the progression of existing infectious disease. For example, the diminished hepatocellular disease in HIV-infected individuals co-infected with HCV when compared to those with HCV alone is due to the lack of an immune response against the HCV [53]. Unfortunately, co-infection with another agent, including emerging infections is likely to result in a less favorable clinical course, increasing the virulence of the pre-existing infection. The patient described in case 1 is such an individual who already is infected with HIV and HCV. The introduction of another infection may result in progression of one or both of the pre-existing infections. Therefore, irrespective of the infectious disease status of the patient with hemophilia, all should be afforded the opportunity to receive the safest factor concentrate, a recombinant product formulated without the addition of animal or human proteins and at a reasonable cost.

Table IV summarizes the quintessential issues in choosing between a plasma-derived, monoclonal antibody purified factor concentrate and a recombinant factor VIII product. In Table V, the products available in the USA to treat hemophilia are reviewed. All are treated to inactive viruses, demonstrate similar clinical efficacy to treat and prevent bleeding as well as show no difference in the induction of inhibitors. The single distinguishing feature is the possibility of exposure to an unanticipated infectious agent that causes human disease. It is this difference, whether real or potential, that currently plays most heavily in the decision making process of physicians who prescribe anti-hemophilic factor concentrates and the patients and parents who use these life-saving drugs.

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