The Physician's Role in Selecting a Factor Replacement Therapy

The principle of evidence-based medicine promotes the judicious and conscientious use of the current best evidence when making healthcare decisions for individual patients. While this strategy, popularized in the early 1990s, is frequently useful, it is clearly of limited benefit in the context of emerging infectious diseases. By the time concrete evidence of an emerging infectious agent is available, it is often too late to prevent infection in the most susceptible populations.

Today we have an opportunity for proactive decision-making. We cannot make decisions regarding the safety of our blood supply solely using an evidenced-based approach, but we can take the lessons of the past and, using our current knowledge of disease-causing agents, extrapolate potential risks in order to better formulate effective healthcare policies.

Learning from the Past

In the years immediately preceding the HIV epidemic, medical and scientific communities, government agencies, and the blood therapies industry operated in an essentially reactive mode with respect to infectious diseases. At this time, circa 1980, the risk of patients with hemophilia becoming infected with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) was perceived as theoretical; this lack of forethought led to a delay

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In defense of these stakeholders, there was little or no reliable evidence of HIV or HCV transmission from with plasma-based therapies. As the 1980s proceeded, however, the evidence that these diseases were, in fact, transmitted through blood products began to increase and come to the attention of all involved with the haemophilia community. ¶
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Limitations of Evidence-Based Medicine¶

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in implementing measures that would have protected patients with hemophilia from exposure to these infectious agents.

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While the transmission pathways and disease processes for HIV and HCV are now well understood, uncertainty remains about variant Creutzfeldt-Jakob disease (vCJD) and other emerging pathogens. The clear message is that it is our obligation as healthcare providers to help make proactive decisions for our patients, and that often these must be made in an environment of scientific uncertainty. Threats from infectious agents that were once deemed theoretical can, and often do, ultimately become real, with serious implications for morbidity and mortality.

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Safety Considerations: Pathogen Risks and Inactivation Efforts

The safety of hemophilia therapies can largely be attributed to the use of effective screening and testing technologies available for HIV, HBV, or HCV. For nearly 20 years, since 1987, there has been no transmission of HIV, HBV, or HCV from any plasma-derived or recombinant therapy in the United States.(NHF 2003) The real challenge, however, is presented by the likely emergence of a

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new, blood-borne infectious agent.

For the purposes of discussing inactivation measures, infectious agents can be classified in three categories:

- Lipid-enveloped viruses, eg, hepatitis B virus (HBV), HCV, and HIV
- Non-lipid enveloped viruses, eg, parvovirus B19 (PVB19) and hepatitis A virus (HAV)
- Disease-causing prions, eg, CJD and vCJD

Lipid-Enveloped Viruses

Lipid-enveloped viruses have a protective fatty membrane, or envelope; if this membrane is destroyed the enclosed virus is also destroyed. There is very good evidence that the lipid-enveloped viruses are effectively inactivated with current technologies.(Chandra 2002) All licensed processors of plasma therapies and recombinant therapies made with human and animal protein-additives use validated methods to both detect and eliminate HBV, HCV, HIV, and the other lipid-enveloped viruses for which screening and inactivation methods have been developed.(CDC 2002) West Nile virus is another lipid-enveloped virus for which effective screening methods exist; in the period January-September 20, 2005, 268 cases of viremic blood donors were reported in the US to the US Centers for Disease Control and Prevention. (CDC 2005)

Non-Lipid-Enveloped Viruses

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As the term would indicate, non-lipid-enveloped viruses lack a protective enclosure. Its lack of an envelope makes it difficult to target these viruses. In addition, the physical and chemical conditions created by vapor/heat, solvent/detergent, and gamma irradiation technologies adequate for inactivation may denature the factor VIII protein.(Chandra 2002, Knight 2004, Abe 2000, Farrugia 2004, Hoots 2001, Fischer 2001)

Parvovirus B19

Human parvovirus B19 (PVB19) is a widespread non-lipid-enveloped virus that causes the common childhood illness called fifth disease. Community-acquired exposure and seroconversion to this virus is common and occurs quite early in the lives of most people. Parvovirus B19 shares the hallmark of other non-lipid-enveloped viruses: resistance to inactivation technologies. Parvovirus is of particular concern to the hemophilia community because of reports that parvovirus has been found in factor concentrates. A prospective study published in 1997 by Santagostino et al indicated that very high temperatures applied to lyophilized factor concentrates did not prevent the transmission of PVB19 to patients with hemophilia. (Santagostino 1997)

Soucie et al evaluated the risk of parvovirus B19 transmission as a result of treatment with recombinant antihemophilic factor. To compare the seroprevalence of PVB19 antibodies in two- to seven-year-old males with hemophilia, 798 subjects were grouped by

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their exposure to types of factor VIII or IX concentrates: those who had received only plasma-derived therapies, only recombinant therapies, both recombinant and plasma-derived therapies, or no antihemophilic factor at all (control group). The study found that the prevalence of seropositivity was higher in both the plasma-derived only and recombinant and plasma-derived therapies groups than in the control and recombinant only groups.(Soucie 2004).

The results of this study illustrate the potential for non-lipid-enveloped viruses to persist in blood and blood-based therapies. In 2001 processors of plasma-derived factor therapies instituted the use of nucleic acid amplification technology to screen plasma and adopted a voluntary industry standard for the management of PVB19. Nonetheless, Soucie and colleagues recommend the development of effective virus inactivation techniques for parvovirus and other non-enveloped viruses that might emerge.(Soucie 2004)

Disease-Causing Prions

As with PVB19 and other non-lipid-enveloped viruses, current inactivation methods are ineffective against prions. Prions are soluble cellular protein particles (PrP^{c}) that lack nucleic acid and do not depend on genes or other factors for transmission of their traits. As discussed elsewhere in this supplement, transmissible spongiform encephalopathies (TSEs) such as the sporadic and variant forms of Creutzfeldt-Jakob disease are

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characterized by the accumulation of an abnormal form of this protein particle (PrP^{Sc}) in the brain.

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Because prions lack nucleic acid, standard nucleic acid amplification technology cannot be used to detect vJCD and other TSEs. Also, the presence of abnormal prions does not trigger a measurable host immune response, making standard enzyme-linked diagnostic tests that measure antibodies, such as those used for AIDS, useless. New screening methods are in currently development.

During the disease's incubation period, estimated to be upwards of 40 years, infected individuals appear clinically healthy. Without a screening method for vCJD, donations by infected individuals will continue to pose a threat to patients using blood-derived therapies.

Opportunities for Discussions

Most patients become aware of the worldwide emergence of air- and blood-borne pathogens through articles and news broadcasts in the popular press. Without the benefit of broad-based medical knowledge for context, patients may become unduly alarmed about the risks these infectious agents pose. Hemophilia treaters have an opportunity to be proactive in addressing their patients' fears about these diseases and the particular health threats that blood-borne infectious agents might pose. To be effective, practitioners must themselves be informed about these new

infectious agents and the relative safety of the available therapeutic options.

The point of these discussions is to reduce patient fear and anxiety with regard to these new infectious diseases and to enhance patient trust in both hemophilia treaters and their therapeutic options. Fear is unavoidable if the potential threats of emerging pathogens are not met with an informed and appropriate response.

Discussing the Safety of Factor Replacement Therapies

Hemophilia treaters must be cognizant of and acknowledge the risk that emerging pathogens present their especially vulnerable patients. The majority of hemophilia treaters are cautiously optimistic about the safety of current plasma-derived clotting factors and recombinant therapies. Their optimism is the result of more than 20 years of access to blood therapies free of HIV and more than 10 years of access to therapies free of HCV.

Pediatric hemophilia treaters, for example, today see few, if any, HIV- or HCV-infected patients. (Reference?) As a result, it is unlikely that these hemophilia treaters engage in regular conversations with their patients regarding emerging pathogens or the safety of the blood supply. Some clinicians believe that the responsibility for holding those discussions now resides with hemophilia consumer or advocacy groups. However, in order to offer their patients the best possible care, hemophilia treaters

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Current Treatment Guidelines

In recent years, patient advocacy groups and hemophilia treaters' organizations have provided information, recommendations, and guidelines to help educate practitioners and others in the hemophilia community about the issue of the safety of the blood supply. For example, in November 2003, the Medical and Scientific Advisory Council (MASAC) of the US-based National Hemophilia Foundation (NHF) published Recommendation 151, advising manufacturers that "all efforts should be made to remove human albumin from recombinant factor VIII products." (NHF 2003)

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Similarly, in their 1999 update of the 1995 clinical practice guidelines for patients with hemophilia and von Willebrand disease, the Association of Hemophilia Care Directors of Canada stated that, "until methods for total viral removal or inactivation are available, alternative methods of cell culture and stabilization of recombinant clotting factor concentrates should be sought to avoid the need for plasma-derived human albumin that's currently in use." (AHCDC 1999)

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Additionally, the National Haemophilia Foundation Medical and Scientific Advisory Council Recommendation 151 published in November of 2003 advises that, "All effort should be made to remove human albumin from recombinant factor VIII products." (NHF 2003) ¶
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These guidelines, along with others published by groups such as the United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO 2003), indicate the proactive measures some organizations are taking to protecting their communities from blood-borne

infectious agents.

Three Countries, Three Approaches to Safety

Despite the fact that the recommendations of hemophilia groups in first-world nations are quite consistent, there is no uniform approach for protecting the blood supply; governments' approaches range from proactive to cautious. Three examples are immediately evident: the UK, the US, and Australia.

The most proactive of the three, the UK Department of Health, began a rolling phase-out of plasma-derived factor replacement therapies (UKHCDO 2004) and promoted the use of recombinant therapies that do not contain human or animal protein additives as the first-line choice for both children and adults with hemophilia A and B. These expanded measures were taken as a precaution against possible vCJD infection transmission through blood and blood products.

In the United States, the Food and Drug Administration (FDA) regulates the safety of plasma-derived and recombinant therapies. (IOM 1995) The US blood supply is perceived as safe and is considered preferable source for plasma for factor replacement. A number of therapies, both recombinant and plasma-derived, are available in the US; some of these recombinant therapies include plasma protein additives.

Australia, the most cautious of these three countries, only

provided access to recombinant factor VIII for all hemophilia patients in 2004 (Haemophilia Foundation Australia 2004). The result of these varying approaches to the safety of the blood supply is that many patients with hemophilia remain at risk for infection by blood-borne pathogens. These patients must rely on clotting factor replacement therapies, many of which still include the addition of human or animal plasma proteins that can carry infectious pathogens.

Developing a Safe Blood Factor Replacement Therapy

To completely eliminate the risk for blood-borne transmission of any *new* infectious pathogen, eg, vCJD, a recombinant factor therapy would likely need to include all of following features. It should be:

- Grown in a cell line without any animal- or human-derived plasma proteins
- Processed with effective dedicated identification, exclusion, and inactivation steps for viruses and other pathogens
- Rigorously tested for both lipid- and non-lipid-enveloped viruses
- Packaged and/or stabilized in the absence of any human- or animal-derived plasma proteins.

The goal is clear: reduce the risks for infection through clotting factors while maintaining the high levels of efficacy and low levels of immunogenicity evident in currently available

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Additional Factor Replacement Considerations

The primary goal of any hemophilia practitioner is to enable one's patients to live as actively and productively as possible; selecting the appropriate factor replacement therapy for each patient can be very complex. Safety and efficacy are first and foremost considerations in choosing an antihemophilia therapy; inhibitor risk is an important but secondary concern.

Other considerations include patient convenience,, and issues related to the consistency and reliability of supply for any particular therapy. The relative cost/benefit ratio can occasionally play a role, depending on what therapy is chosen. In the United States, policies regarding reimbursement for therapies can differ from state to state, which can cause confusion and consternation for patients and providers alike. Last, but not least, it is important to take patient preference and brand loyalty under consideration when choosing the appropriate factor therapy.

Conclusion

Underestimating what were seen as merely theoretical risks in the late 1970s and early 1980s ultimately resulted in the tragedy of HIV and HCV infection in patients with hemophilia worldwide. With the benefit of hindsight and the commitment of a proactive approach to emerging pathogens even in the face of scientific

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Most patients are informed and aware of emerging worldwide pathogens through articles and news broadcasts in the popular press. As a result, haemophilia treaters have an opportunity to be proactive in addressing patients' fears surrounding these potential threats to their safety. To be effective, practitioners must themselves be informed about the issues regarding these new infectious agents and the relative safety of the range of therapeutic options currently available. ¶
The point of these discussions is to reduce patient fear and anxiety with regards to these new infectious diseases and to enhance patient trust in both haemophilia treaters and the pharmacologic options from which they can choose. Fear is unavoid ... [1]

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uncertainty, patients with hemophilia should never have to endure such a crisis again.

The most fundamental lesson learned in the past 25 years is that government, patient advocacy groups, medical and scientific communities, and the manufacturers of clotting therapies all have an opportunity, and perhaps even an obligation, to approach potential threats from emerging pathogens in a proactive and productive manner.

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Table 1. Percent of Hemophilia A Patients With Parvovirus B19 Antibodies, By Age and Clotting Factor Exposure (N = 798)*

	Clotting Therapy Type†			
Age (years)	Recombinant Only	Plasma-Derived Only	Both	None
2	11.4	52.4	40.4	0
3	16.3	76.5	47.2	5.6
4	23.2	62.5	49.1	17.6
5	33.6	85.7	55.2	26.3
6	35.6	86.7	58.8	36.8
7	40.4	100	57.9	45.4

*Data are from a study in young males in the US, 1998-2001, by Soucie JM, et al.

†Data are reported as a percent.