Current and Emerging Infectious Risks of Blood Transfusions

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THE BLOOD SUPPLY IN THE UNITED States and other developed countries has never been as safe as it is now. During the past several decades, there have been dramatic progressive reductions in the risk of transfusion-transmitted clinically significant blood-borne infections. This has been accomplished as a result of extensive research to characterize transfusion-transmitted pathogens, development of strategies to measure infection rates in blood donor and recipient populations, characterization of the dynamics of early viremia, and implementation of progressively more restrictive donor eligibility criteria and increasingly sensitive laboratory screening methods.

In addition, regulatory oversight by the US Food and Drug Administration (FDA) has been strengthened, resulting in enhanced quality assurance programs in blood collection and transfusion facilities. Pathogen reduction methods, already successfully applied to pooled plasma derivatives (eg, albumin, clotting factor concentrates, immunoglobulin preparations) are now in development for cellular blood components and fresh-frozen plasma. If these methods are approved by the FDA and widely implemented, they could virtually eliminate the risk of transmission by transfusions of both known and emerging infectious agents in technologically advanced countries. This progress needs to be balanced against the continued emergence of potential new transfusion-transmissible pathogens and the disparity in blood safety in developing countries where resources are insufficient to enable basic infectious disease donor screening.

Major Viral Infections and Impact of Nucleic Acid Testing

The FIGURE summarizes progress during the past 2 decades resulting in virtual elimination of transfusion-transmitted major viral infections.[1] Blood is now so safe that classic approaches to measure transfusion risk (eg, prospective follow-up and retrospective look-back studies of recipients, or studies that determine the frequency of missed infections in screened donors using culture or molecular methods) are now virtually unable to document transmission events or even quantitate risk.[1] Risk estimates for human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) are now based on mathematical models that integrate data from 4 potential sources of risk: marker-negative window-phase donations, immunovariant viral strains not reliably detected by current serological assays, persistent antibody-negative (immunosilent) carriers, or procedural testing errors.[2] These model-based estimates (2000-2001) indicate current per unit risks of 1 in 1 800 000 for HIV and 1 in 1 600 000 for HCV following recent introduction of nucleic acid technology (NAT) screening. The risk of HBV, for which NAT screening is not currently performed, is approximately 1 in 220 000 per unit.[1-3]

Nucleic acid technology was introduced in the United States in 1998 to screen all volunteer blood donors for HCV and HIV type 1 (HIV-1) RNA.[4,5] Nucleic acid technology detects these agents earlier in the window period (period of time between infection and the first appearance of a detectable viral or antibody marker) than currently used HCV antibody, HIV-1 antibody, and antigen assays. The window period for HIV-1, using antibody assays, is approximately 22 days. The HIV-1 p24 antigen assay, which was introduced into donor screening in 1995, reduced the window period to approximately 16 days. Current HIV-1 RNA minipool NAT assays (for logistical and cost reasons NAT testing is currently performed on minipools of plasma from 16-24 donations) reduce the window period even further to 11 days. The reduction of the window period for HCV RNA is even more dramatic. The window period for HCV, which was approximately 70 days using the HCV antibody assay, has been reduced to 8 to 10 days using HCV NAT assays.[2]

In the 3 years since minipool NAT screening was implemented, more than 30 million blood donations have been screened in the United States with detection of more than 120 HCV-infected, antibody-negative donations (rate of detection of 1 in 260 000 units) and 9 seronegative HIV-viremic donations (1 in 3 million units).[5] Follow-up studies of these cases have confirmed that the primary reason these donations were missed by serologic methods was that the donations occurred during the preseroconversion window period, with a small number of cases due to serological test errors and immunosilent carriers.[5]

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Emerging Infections

Despite this dramatic progress, there continues to be pressure from legislators, regulatory authorities, and the public to further enhance transfusion safety.[6] A single recent case of HIV transmission involving a unit of red blood cells that had screened negative for HIV RNA by current minipool NAT screening has led to renewed pressure to implement even more sensitive individual donation NAT screening methods.[7] It is likely that NAT testing for HBV, hepatitis A virus, and Parvovirus B19 nucleic acids will be added to blood donor screening requirements during the next several years.[8,9] The 2002 epidemic of West Nile virus transmission, which included the first documented cases of transfusion and transplant transmission, has led to a major effort to develop and implement West Nile virus NAT assays by the summer of 2003.[10]

Nonviral complications that were previously considered relatively minor, such as bacterial contamination of blood components, transfusion-associated acute lung injury, and transfusion-induced immunomodulation, have received increasing attention as the risks of HIV and HCV transmission have diminished.[11-14] Nonviral issues are now the focus of intense efforts toward development of donor screening and prevention strategies (eg, implementation of universal leukocyte reduction of all blood components and bacterial cultures of all platelet components).

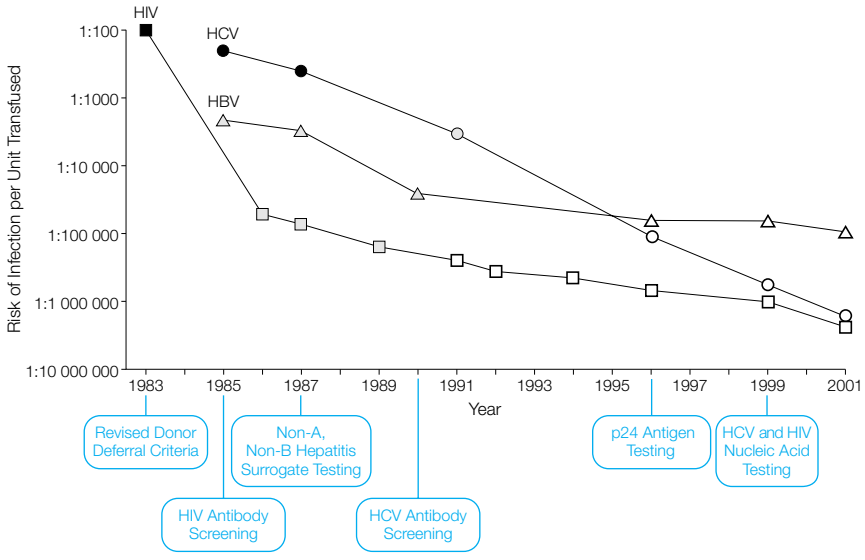
The concept of a global village has also emerged, reflecting the fact that a potential blood-borne infectious agent present in any region of the world could travel to the United States overnight. This has led to increased concern with transfusion risk of parasitic agents such as malaria, *Trypanosoma cruzi* (agent of Chagas disease), and other tick-borne agents.[15,16] There have been an average of 2 to 3 cases per year of transfusion-transmitted malaria in the United States during the past 40 years, a rate of 0.25 cases per million donated units. Policies for preventing malaria transmission by blood transfusion rely on donor questioning regarding travel. Since 1982, all evaluable transfusion-transmitted cases have resulted from donors who were emigrants from or residents of endemic areas; in the majority of cases, the donor did not reveal the proper information during the donor interview.[17] There are currently no FDA-approved assays for screening blood donors for malaria.

From the mid-1980s, 6 cases of fulminant transfusion-transmitted Chagas disease have been reported in North America.[15] However, increased immigration to the United States from countries where *T cruzi* is endemic has led to the concern that transfusion-transmitted Chagas disease may become more common in the United States. Estimates of *T cruzi* seroprevalence in US blood donors range from 0.01% to 0.20% and are higher in geographic regions with higher rates of Hispanic donors.[15,16] As with malaria, there are no currently approved screening assays. These and other parasitic agents are susceptible to inactivation by pathogen reduction methods now under development.

Variant Creutzfeldt-Jakob disease (vCJD) is a fatal degenerative neurological disease first discovered in England in 1996. As of December 2002, 129 definite or probable cases had been reported in England, with 3 reported cases elsewhere but assumed to be acquired in England, and an additional 6 cases originating in France and 1 in Italy.[18] The etiologic agent of vCJD (probably a prion) is the same agent that causes bovine spongiform encephalopathy, which has become a major global animal health problem during the last decade, although no cases have been reported in the United States to date.

The spread of the bovine spongiform encephalopathy agent from cattle to humans and the detection of the vCJD prion in human lymphoid tissue have established a biological basis for the possibility that vCJD may be transmitted by blood transfusion.[19] Transmission of related prion diseases by blood transfusions has been reported

Figure. Decline in Human Immunodeficiency Virus (HIV) and Hepatitis B (HBV) and Hepatitis C (HCV) Risks of Transmission Through Transfusion



Data were derived from studies sponsored by the National Heart, Lung, and Blood Institute. Specific references are available from the authors upon request. Estimates before 1991 are based on donor prevalence measurements (black data markers) or recipient follow-up studies (gray data markers); estimates after 1991 represent projections based on mathematical modeling (open data markers). Estimated risk of infection per unit transfused in 2000-2001 was 1:220 000 for HBV; 1:1 600 000 for HCV; and 1:1 800 000 for HIV.

in several animal models.[20] No cases of transfusion-transmitted vCJD in humans have been reported anywhere in the world to date. Because vCJD is a new disease and other transmissible spongiform encephalopathies are known to have long incubation periods, the 6-year observation period from the discovery of the disease is too short to draw any firm conclusions about transfusion-related transmission.

Although the risk of transfusion-transmitted vCJD is theoretical, increasingly stringent donor deferral policies (based on length of stay in England or Europe) have been implemented and are undergoing revision in the United States. These revised donor policies are expected to lead to the deferral of a significant number of blood donors (3%-5%) and will therefore have an adverse impact on the availability of blood for transfusion. No tests have as yet been developed that are capable of detecting abnormal prions in the blood of asymptomatic carriers. Pathogen reduction methods under development, which target the nucleic acids and envelopes of viruses and cells, are not effective against prions.

Variant CJD represents an example of transspecies (zoonotic) transmission of an infectious agent, with the potential for adaptation in humans and subsequent spread to blood donors and recipients. Salient other examples include the origins of HIV-1 and HIV type 2 from chimpanzee and simian immunodeficiency viruses, and of human T-lymphotropic virus type 1 and type 2 from primate T-lymphotropic viruses. Proactive surveillance for such events is important.[21,22] There is research to identify new blood-borne agents using novel molecular discovery strategies. Although recent examples of putative agents of concern have proven to be nonpathogenic (eg, hepatitis G [also known as GBV-C] virus and TT-virus) or not transmitted by transfusions (eg, human herpesvirus type 8),[21,23,24] every newly discovered agent requires serious investigation to assess its relevance to transfusion safety. To meet this challenge, investigations of putative transfusion-transmissible agents must be accomplished in a rapid and rigorous fashion.[22]

Impact of Safety Measures

Every discovery of a new infectious agent in humans leads to consideration of potential blood safety implications, often resulting in expanded deferral or screening recommendations. On the other hand, the continued exclusion of donors is threatening the adequacy of the blood supply. The recent increase in potential donors after September 11, 2001, was unfortunately short-lived, and blood shortages are again occurring on a regular basis. There is particular concern in New York City and other major metropolitan areas where the European travel deferrals for vCJD risk first implemented in 2002 have had a major impact on the blood supply.

There is also growing pressure to control the escalating costs of medical care in general and of blood transfusions in particular. The ability to close the infectious window periods through new assays has resulted in enhanced safety at a very high cost. Although serological screening of donors for HBV, HIV, and HCV was essentially cost-neutral (ie, the cost of testing was offset by the savings in prevented infections or disease), the costs for NAT testing exceeds $1 million per infection prevented or per quality-adjusted life-year saved.[2,3,25] Although blood safety has had a relatively high level of political and financial support during the past decade, there are signs that limits on additional funding for blood safety initiatives are under consideration.[6,25,26] This reinforces the need to accurately define the value of new safety initiatives and to reassess the use of old procedures as new measures are introduced. Decisions regarding blood screening policies must be based on accurate estimates of the incremental safety benefit balanced against cost, both monetary and the loss of potential donors.[26]

Conclusions

The virtual elimination of serious infectious consequences of transfusions reflects an effective partnership between medical scientists, test manufacturers, and government regulators. However, chasing ultimate safety (a zero-risk blood supply) has consequences. The regulatory and medical-legal environment in the United States and other developed countries has resulted in implementation of very expensive measures that offer little incremental safety benefit, such as minipool NAT, NAT for other pathogens, and donor deferral of persons who have spent time in Europe. Further high-cost safety initiatives are under consideration, such as individual donation NAT and pathogen reduction treatment of cellular blood components. Stringent donor deferral policies are also being implemented to reduce risks of sometimes theoretical emerging infectious agents. These measures may be necessary to regain the trust of the public in the safety and stewardship of the blood supply. However, it is important to balance safety with the need to maintain an adequate and affordable blood supply.

Finally, it is critical that resources be directed to assist developing countries to establish sustainable blood collection, processing, and transfusion systems.[27,28] This will safeguard recipients who require transfusions in these countries, and in the long term enhance transfusion safety in the developed world. In light of global travel, new and emerging infectious agents can spread from any region of the world. Proactive surveillance through collaborations with blood collection programs in developing countries is a critical barrier to such events.

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