

INFECTIOUS RISKS OF BLOOD TRANSFUSION

This is a perspective on the infectious risks associated with transfusion from volunteer whole blood donors (red cells, platelets, fresh frozen plasma and cryoprecipitate). While risk estimates for many important complications of hemotherapy are imprecise, the risks of traditional transfusion-transmitted viral infections are negligible, and no longer should dominate decisions about transfusion safety. Table I shows estimated risks.

Table I. Estimated risk of viral transmission from allogeneic blood components

Virus	Estimated risk pre-NAT/ component*	Estimated risk post- NAT/component
Hepatitis C Virus	1:237,000	<1:1,000,000
Hepatitis B Virus	1:137,000	
HTLV I and II	1:641,000	
HIV	1:1,326,300	1:1,930,000

See Stramer, Blood Safety in the New Millennium

*NAT is Nucleic Acid Amplification Technology (e.g. PCR and transcription-mediated amplification). Individual blood donations are pooled in groups of 16-24 donations and tested for HCV and HIV nucleic acid sequences.

Donor screening for HCV and HIV by NAT (under IND) was implemented in March 1999. The rates of clinical diseases are low following HCV, HBV or HTLV infections because these viruses have intrinsically modest pathogenicity. They cause illness in only a few patients since many recipients (around 50% at 5 years) die of their primary disease before transfusion-associated infections are manifested. Similarly, negligible transmission rates, the long incubation period, and high mortality following transfusion have made transfusion-associated AIDS rare. Thus, the crude transmission rates above are "worst case" estimates.

Bacterial Contamination. Table II shows that the estimated rates of bacterial contamination of components are 50 to >250 times higher than those of viral infection. While many bacterially contaminated components produce no clinical morbidity, consensus is developing that it is under-recognized and the most important infectious complication of transfusion. Bacterial contamination has been found in autologous units, and may be more common in that setting because donors are less well, and their blood may be stored for longer periods prior to transfusion. Pathogen reduction technologies currently in clinical trials appear to have excellent activity against the bacteria most often implicated in clinical bacterial contamination.

Several other real or theoretical infectious risks of transfusion are being studied; the most frequently mentioned are discussed below. Transfusion transmission of all but vCJD has been seen.

Malaria. Ninety-three US transfusion malaria cases were reported in 1963-99. From 1993-98, the incidence was 0-0.18 cases per million units transfused. Donors are screened using travel and residence history and deferred for risk of exposure or infection. Sixty-two percent of the implicated donors should have been excluded by criteria in place at the time of the donation. Malaria deferrals total around 50,000 donations annually (2.9 percent of all deferrals). In the last decade, 83% of transmissions were from immigrants from endemic areas, and only 16% from US travelers to or US immigrants returning to endemic countries. Although *Plasmodium vivax* and *P. malariae* historically have been associ-

ated with transfusion, *P. falciparum* now is the most frequent species, reflecting increased immigration from areas where it predominates, especially sub-Saharan Africa.

Screening for malaria is problematic. Blood smear examination is insensitive for asymptomatic donors who might transmit. Antibody assays are less so but would exclude many uninfected donors who have recovered from old infection. European experience with serology applied to travelers and immigrants from endemic areas suggests such testing can decrease the donor deferral rate, but not eliminate rare transmissions. NAT assays, applied selectively to donors at potential risk are being investigated.

Babesiosis. *Babesia microti* and related tick-borne species cause malaria-like illness, most severe in asplenic, immunodeficient or elderly blood recipients. Approximately 30 cases of transmission have been reported from parasitemic blood donors since 1979. They are concentrated in the Northeast US where the vector ticks are prevalent, with isolated cases in the Midwest and Northwest. A history of Babesiosis results in permanent donor deferral. While recent data using investigational NAT suggest as many as 1:1800 Connecticut blood donors may be infectious for *B. microti*, clinical infection is a rare observation.

Table II. Estimates of bacterial contamination of allogeneic components from prospective microbiological surveillance studies

Random donor platelets from whole blood	Apheresis platelets	Red blood cells
≤1:3254 components, or ≤1:542 six-unit pools	≤1:777 components	1:38,565 units

See Blajchman

Herpesviruses. Cytomegalovirus (CMV) can be transmitted by transfusion of cellular products and may cause serious disease in immunocompromised recipients who are seronegative. Seroprevalence among blood donors ranges from 40-80%. Herpesviruses cause primary infection, then life-long latency with a potential for reactivation. All are highly cell-associated in latency. CMV transmission can be reduced by serological screening and/or leukocyte reduction of cellular products transfused into patients when their risk is recognized by clinicians.

"New" members of the herpesvirus family include HHV-6, 7, and 8. Human herpesvirus-6 (HHV-6) and -7 (HHV-7) are ubiquitous and lymphotropic. Seroprevalence in older children, adults and blood donors are >95 and >85% respectively. Primary infections are silent or manifest as mild febrile illnesses including roseola infantum (exanthem subitum). Case reports and epidemiologic data support the rare occurrence of HHV-6 encephalitis in both immunocompromised and immunocompetent subjects.

In transplant patients, HHV-6 infection or reactivation may result in marrow suppression, pneumonitis, encephalitis, hepatitis, fever, rash or delayed engraftment. Other diseases have been putatively associated with HHV-6 or HHV-7, but the associations are poorly documented. Tests for diagnosing active HHV-6 and HHV-7 infections include virus culture, antigen detection, and NAT. Infection and disease due to HHV-6 and 7 associated with transfusion of blood components are not de-

scribed, but are theoretically possible because of the viruses' white blood cell tropism; surveillance in appropriate populations should continue.

HHV-8 causes Kaposi's sarcoma, body cavity based lymphomas, and multicentric Castleman's disease. Disease from HHV-8 requires severe immunosuppression as in AIDS, transplantation and senescence—and is highly associated with B-cells. Seroprevalence in the developed world varies, but is high (>80%) in HIV infected patients with Kaposi's sarcoma, and much lower among blood donors (0-11%). Its tropism and recent data suggest potential infectivity in blood. While sexual transmission predominates, seroprevalence data (e.g. up to 8% in children) suggest other routes, including injecting drug use. Infectious virus has been detected in a healthy blood donor, but 32 recipients of cellular components from seropositive donors were not infected. Hemophiliacs are not infected more than the general population, suggesting that plasma derivatives are safe. The apparent lack of transfusion transmission may reflect the impact of processing (e.g. leukoreduction) and/or storage of blood products on infectivity or effective immune control of the virus by healthy blood donors. More data are needed to assess transfusion transmissibility of HHV-8.

Chagas' disease, a vector-borne parasitosis caused by *Trypanosoma cruzi*, is endemic in Latin America. Chronic infection causes cardiomyopathy and/or gastrointestinal motility disturbances in about 20% of infected individuals. Infection is lifelong and treatment of chronic infection is ineffective. Donors can transmit infection. Five cases of transmission from transfusions have been reported in the US and Canada. However, increased immigration of millions from endemic areas raises the potential for transfusion-transmitted Chagas' disease in the US.

Screening for residence or origin in endemic areas is non-specific for excluding infectious donors. About 0.1-1.0% of Mexican blood donors have antibodies to *T. cruzi*. Rates in US donors vary from 0-0.48%. Extrapolation suggests that transmission here should be a fairly frequent event in the US, but look-back studies of 11 recipients of seropositive units found no evidence of transmission, and a study of more than 11,000 heart surgery patients transfused with 120,000 components found no transfusion transmission. There are no FDA-licensed tests.

B19 Parvovirus causes erythema infectiosum (Fifth Disease) in children, arthritis in adults, and red cell aplasia in patients with chronic hemolytic anemias or severe cellular immune deficiency. Levels of viremia during infection may exceed 10^{10} viral particles/ml. Studies have shown that between 1:3300 and 1:40000 blood donors are viremic. However, transmission by blood components is rare, and only 3 cases have been reported, probably because of the high incidence of immunity in transfused populations. NAT screening of plasma for further manufacture (recovered and source) is being implemented—to limit the input of infectious virus in large manufacturing pools, and allow abrogation of infectivity by neutralizing antibodies present in the pool.

Hepatitis A (HAV) has rarely been associated with transfusion, and the infection is clinically mild; screening whole blood donors is not anticipated. Donors of source and recovered plasma will likely be screened using NAT assays with the rationale similar to that for B19.

"New" Viruses represent a diverse group of agents isolated from donors, transmitted to recipients, but without confirmed disease associations. They include the SEN family, TT Virus, and HGV (GBV-C) and were discovered using NAT-based techniques in the search for agents of non A-E hepatitis. Absent significant morbidity, their importance in transfused patients is limited—they are examples of the ability of these detection systems to identify organisms in search of diseases. They certainly are not the last potential pathogens to be discovered during the search for cause in a variety of syndromes. As new "agents" are found, they will be considered for their importance in transfusion medicine.

Variante Creutzfeldt-Jakob Disease (vCJD) is the human form of Bovine Spongiform Encephalopathy (BSE or "mad cow" disease). It is a transmissible spongiform encephalopathy (TSE) or prion disease. As of December 2001, there have been 113 cases in the UK, 4 in France and one each in the Republic of Ireland and Hong Kong, acquired by eating products from infected cattle. Transfusion transmission has not been seen. Studies of recipients of blood donated by classic CJD patients and a small number of vCJD patients do not reveal disease in recipients. Likewise, surveillance for TSEs in heavily-transfused populations like hemophiliacs, as well as animal experiments, do not yet confirm transfusion transmission.

Because the vCJD prion is present in peripheral lymphatic tissue to a greater extent than that of classical CJD, there is heightened concern that blood might theoretically be infectious. Accordingly, potential blood donors with residence in the UK during the height of the BSE epidemic (1980-96), and in other countries with endemic BSE, are or soon will be deferred from donation. Ongoing reevaluation of the BSE incidence in other countries will be used to modify these deferrals as our knowledge expands. In the meantime, epidemiological and animal studies to refute or establish transmission by blood continue.

Conclusion. The foregoing demonstrates that safety of transfusions from infection is historically high—so high, in fact, that common precautions like autologous and directed donation no longer approach traditional thresholds of risk or cost-benefit. Leukoreduction of cellular blood components, evaluation of additional targets for NAT, and donor historical screening for various theoretical risks to transfusion recipients (e.g. potential exposure to BSE) are being performed. Their ultimate impact is speculative. Several companies have begun advanced clinical trials of methods to inactivate pathogens in donated blood via their nucleic acids. These would have the advantage of inactivating not only those organisms of which we are aware, but also future unknown threats. These technologies should be available for licensure in the next several years. The impact of these technologies in transfusion medicine remains speculative. More attention is needed to non-infectious risks of transfusion.

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