Emerging Infectious Agents: Do They Pose a Risk to the Safety of Transfused Blood and Blood Products?

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The blood supply is safer than it has been at any other time in recent history, and, in the context of other health care–related adverse events, the risks associated with blood transfusion are extremely small. The current high level of safety is the result of successive refinements and improvements in how blood is collected, tested, processed, and transfused; nonetheless, blood and plasma products remain vulnerable to newly identified or reemerging infections. In recent years, numerous infectious agents—including several newly discovered hepatitis viruses, the agents of transmissible spongiform encephalopathies, and tickborne pathogens—have been identified as potential threats to the safety of blood and plasma. Continued vigilance is critical to protect the blood supply from known pathogens and to monitor for the emergence of new infectious agents. Recent terrorist activities in the United States add new considerations to maintaining the safety and supply of blood. Education of clinicians and patients regarding the benefits and risks associated with the judicious use of blood and blood products can assist in informed decision making.

Transfusion of blood and blood products is a common and often lifesaving procedure. Each year in the United States, ~4 million patients receive transfusions of >20 million units of whole blood and blood components. In addition, an estimated 1 million persons receive products manufactured from human plasma, such as clotting factor concentrates, intravenous immunoglobulin, and albumin. Despite its common occurrence, blood transfusion often raises concerns among patients and clinicians about potential infectious complications.

Concerns about the high rate of posttransfusion hepatitis led to the development of the National Blood Policy in 1973 and the move from paid donors to an all-volunteer system of whole-blood donation [1]. This change, along with the implementation of serologic testing for hepatitis B virus (HBV) surface antigen, was temporally associated with a marked decrease in the incidence of viral hepatitis among transfusion recipients [2]. In contrast, most of the plasma obtained in the United States is obtained directly from plasmapheresis at specialized collection centers from paid donors. The high demand for plasma products and the lengthy and sometimes uncomfortable procedure led to the justification and legalization of compensation for plasma donors in the United States [1]. The plasma industry has taken new steps in recent years to bolster the safety of its donors and products [3]. Furthermore, plasma derivatives can undergo treatment and inactivation procedures, unlike RBCs and platelets.

The safety of the blood supply is a shared responsibility of government and industry. The US Food and Drug Administration (FDA) is charged with regulation of blood and blood products, including donor screening and testing requirements and inspection of blood and plasma collection, testing, manufacturing, and processing centers [4]. Improvements in donor screening and testing and viral inactivation of plasma derivatives have combined to result in substantial decreases in transfusion-transmitted infections during the 1980s and 1990s [5]. Today, the blood supply is safer than it has been at any other time in recent history, and, in the context of other health care–related adverse events, the risks associated with blood transfusion are extremely small. None-
theless, the blood supply remains vulnerable to newly identified or emerging infections. Overlapping factors that contribute to disease emergence and that are of particular interest to transfusion medicine include global travel (Trypanosoma cruzi), microbial adaption and change (variant Creutzfeldt-Jakob disease [CJD] and simian foamy virus [6]), human demographic characteristics and behaviors (HIV and human herpesvirus 8 [7]), and economic and land development that alter the habitats of disease-carrying insects and animals (Babesia microti and the agents of the human ehrlichioses) [8, 9]. The identification of newly recognized or emerging bloodborne infectious agents often quickly leads to questions about the potential threat they may pose to the blood supply.

This paper will discuss HIV, HBV, and hepatitis C virus (HCV) and the role of nucleic acid testing (NAT) in reducing transmission of these agents by transfusion, review selected emerging pathogens for which blood safety concerns have been a focus of ongoing research, and conclude with a brief overview of safety and supply considerations in light of recent terrorist actions in the United States.

HIV, HCV, and HBV

The decrease in risk over time for HIV, HCV, and HBV has been truly dramatic. For example, in San Francisco, the risk of HIV transmission increased exponentially from 1978 through late 1982 before the implementation of antibody testing of donations, peaking at 1.1% per unit transfused [10]. In the subsequent 20 years, there has been a 4-log reduction in the risk of HIV infection through transfusion. The successive introduction of increasingly sensitive and specific serologic tests and donor history questions for behavioral risks associated with HIV and other bloodborne pathogens have resulted in similar decreases for posttransfusion HBV and HVC in the United States (figure 1) [5, 12, 13].

Today, the risk of transfusion-transmitted viral infections exists primarily because serologic screening tests fail to detect recently infected donors in the window phase of infection before seroconversion. Since 1999, there has been a rapidly evolving revolution in the way blood and plasma donations are tested that attacks the heart of this issue—namely, the use of NAT to reduce the window period during which viral infection can go undetected. To facilitate its timely introduction, NAT has been implemented using a novel strategy—namely, creating and testing mini-pools of 16–24 donations instead of testing individual donations [14]. Testing is being done under FDA-approved investigational new-drug applications. Although it is not mandatory at this time, NAT is performed on essentially all blood and plasma donations in the United States [14].

Various estimates suggest that pooled NAT can reduce the window period before antibody seroconversion from 22 to 13–15 days for HIV and from 70 to 10–29 days for HCV [12, 15, 16]. Mathematical models have been developed to estimate the current risks of transfusion-related transmission of the major viral agents (table 1), because transmission now occurs so infrequently that direct measurement of these infections in transfusion recipients is not practical. These testing advances are associated with substantial costs; for example, mini-pool NAT for HIV and HCV has been estimated to cost $1.27 million per quality-adjusted life year [16].

NEW HEPATITIS AGENTS: ARE THEY THE CAUSE OF NON-A–E POSTTRANSFUSION HEPATITIS?

A small proportion of persons with acute posttransfusion hepatitis [19], as well as community-acquired hepatitis [20], test negative for all known hepatitis agents, which suggests that there may be 1 or more as-yet-unidentified hepatitis virus. Advances in molecular virology have identified several “candidate” viruses. Although 2 of these viruses, hepatitis G virus/GB virus type C (strain variants of a member of the Flaviviridae family) and TT virus (named for the patient from whom it was first isolated in Japan), can be found in blood donors and be transmitted by transfusion, neither agent has been found to be associated with the development of posttransfusion hepatitis [21–23].

Recent work has focused on SEN virus (SENV), which was discovered in the serum of an injection drug user also infected with HIV. Subsequent phylogenetic analysis has shown that SENV is not 1 virus but rather 8 diverse strains; 2 of these strains (SENV-D and SENV-H) have been evaluated as potential causes of transfusion-associated non-A–E hepatitis [24]. Testing stored serum samples obtained from donors and patients undergoing cardiac surgery who were enrolled in prospective studies of transfusion-associated hepatitis at the National Institutes of Health from October 1972 to December 1997 found that the proportion of patients undergoing cardiac surgery who had evidence of new infection with SENV was 10 times higher among those who received transfusions (86 [30%] of 286 persons) than it was among those who did not (3 [3%] of 97 persons). In the National Institutes of Health’s prospective study [24], 13 patients with transfusion-associated non-A–E hepatitis were observed; 1 of these patients was infected with SENV prior to transfusion. Of the remaining 12 recipients with non-A–E hepatitis, 11 (92%) became SENV positive after transfusion, generally in temporal association with the onset of elevated alanine aminotransferase levels. New SENV infections were observed in a significantly smaller proportion of patients (55 [24%] of 225) who received transfusions but did not develop hepatitis. Investigators also detected SENV RNA in liver-tissue samples obtained from 2 patients with hepatocellular
carcinoma, which suggests the presence of an RNA replicative intermediate for this DNA virus.

Although SENV is clearly transmitted by transfusion, these data are insufficient to establish that SENV is one of the primary agents of non-A–E hepatitis [24]. First, the number of evaluable persons with non-A–E hepatitis was small. Second, the estimated frequency (5%) of biochemical/clinical hepatitis in SENV-infected patients was low, although it is not uncommon for immunocompetent persons to have mild or absent clinical signs or symptoms in response to a viral infection. Third, it will be essential to prove that SENV replicates inside hepatocytes. Finally, there are no data showing that SENV is a cause of fulminant liver failure, and its role in chronic cryptogenic hepatitis and cirrhosis is uncertain [25].

TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES

CJD is an invariably fatal human transmissible spongiform encephalopathy (TSE) believed to be caused by an unusual agent—a prion protein—that is an altered form of a normal protein found in many tissues of the body [26, 27]. Most cases of CJD are classified as sporadic and result from spontaneous generation of the abnormal prion protein that then continues to replicate and accumulate in the brain. An inherited form of the disease accounts for 10%–15% of cases of CJD. In addition, ~200 persons have been reported to have acquired CJD after receiving contaminated human pituitary–derived growth hormone, dura mater, or corneas; incubation periods in some of these persons have been as long as 20 years [26, 27]. Despite active research, at present there is no sensitive and specific noninvasive test for CJD. Various procedures, such as immunohistochemical staining, histoblot, or Western blotting, can be used to detect the prion protein in brain tissue, either before or after death [27–29].

Concerns regarding the transmissibility of the agent of CJD

Table 1. Estimated risks of collecting and transfusing a unit of blood donated during the window period for infection with HIV, hepatitis C virus (HCV), and hepatitis B virus (HBV), per number of tested donations, on the basis of data through the year 2000, United States.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Risk</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV(^a)</td>
<td>1/725,000 to 1/835,000</td>
<td>[12]</td>
</tr>
<tr>
<td>HCV(^a)</td>
<td>1/250,000 to 1/500,000</td>
<td>[12]</td>
</tr>
<tr>
<td>HBV</td>
<td>1/63,000 to 1/500,000</td>
<td>[17, 18]</td>
</tr>
</tbody>
</table>

\(^a\) When mini-pool nucleic acid testing is used.
Table 2. Epidemiologic and clinical characteristics of sporadic and variant Creutzfeldt-Jakob disease (CJD).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sporadic CJD</th>
<th>Variant CJD</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of reported cases</td>
<td>0.5–1.5 cases per million population per year</td>
<td>119a</td>
</tr>
<tr>
<td>Geographic distribution</td>
<td>Worldwide</td>
<td>Majority from United Kingdom</td>
</tr>
<tr>
<td>Age at death, median years</td>
<td>68</td>
<td>28</td>
</tr>
<tr>
<td>Duration of illness, median</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical features</td>
<td>Rapidly progressive dementia and motor symptoms</td>
<td>Behavioral, psychiatric, and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>sensory symptoms</td>
</tr>
<tr>
<td>Diagnostic EEG pattern, % of</td>
<td>75–85</td>
<td>0</td>
</tr>
<tr>
<td>patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropathology</td>
<td>Spongiform changes; amyloid plaques rare</td>
<td>Florid amyloid plaques with</td>
</tr>
<tr>
<td></td>
<td></td>
<td>vacuoles</td>
</tr>
</tbody>
</table>

NOTE. EEG, electroencephalogram. Data are from [26, 27, 36–40].

by blood have resulted primarily from laboratory and experimental studies [28, 29]. By use of a mouse-adapted strain of a TSE agent, these studies have demonstrated that the agent can be transmitted from rodent to rodent during the incubation period through intracerebral and intravenous inoculation of blood [27, 28, 30, 31]. In addition, transmission of hamster-adapted scrapie through transfusion has been demonstrated, albeit rarely, when blood that was known to be infected was administered intravenously [28]. Studies on the distribution of infectivity in blood components and plasma derivatives in various experimental models of TSE consistently have shown that the highest concentrations of infectivity are associated with the WBC-rich buffy coat, with lower levels in plasma, and very low to undetectable levels in the Cohn plasma fractions [28, 30, 31].

In contrast, data from long-term surveillance programs and various epidemiologic studies suggest that the risk, if any, for transmission of sporadic CJD by transfusion of blood and blood products is extremely small and theoretical at present [27]. First, there are no confirmed reports of sporadic CJD transmission by blood or blood products. Second, several case-control studies have not found blood transfusion to be a risk factor for sporadic CJD [27, 32–34]. Third, CJD was not reported as a cause of death for 212 deceased recipients of blood from 23 donors who developed sporadic CJD months to years after donating blood, when they were presumably incubating CJD (M. T. Sullivan, National Blood Data Resource Center, written communication). This long-term follow-up study, begun in 1995, has a total survival rate after transfusion of nearly 1000 person-years as of September 2001. Finally, active surveillance in 144 hemophilia centers in the United States since 1995 has not identified any patients with CJD; as part of this effort, brain tissue samples obtained from 24 deceased patients were examined [35].

In 1996, a new variant form of CJD was first recognized in the United Kingdom. The cause of this new human TSE is believed to be the same agent responsible for an outbreak of bovine spongiform encephalopathy (BSE) among cattle in the United Kingdom, which was diagnosed initially in 1986 [36]. The BSE epizootic is thought to have resulted from the inclusion of carcasses of scrapie-infected sheep in the meat-and-bone meal fed to cattle in the early 1980s and the subsequent use of bovine offal, derived from BSE-infected cows, in cattle meal. Features of variant CJD are distinctly different from those of sporadic CJD (table 2).

Transmission of variant CJD by blood and blood products has not been observed to date. However, variant CJD differs from sporadic CJD in ways that have raised concern about its potential transmissibility by blood and plasma. First, the route of transmission of variant CJD in humans is hypothesized to be oral ingestion of neural tissue–contaminated meat—that is, direct intracerebral inoculation is not required. Second, the prion protein has been detected in WBC-rich organs, such as human spleens and tonsils, from persons with variant CJD but not from persons with sporadic CJD [41]. Limited early evidence has suggested that blood from experimentally infected animals may be infectious. In one study, intravenous administration of blood from an asymptomatic donor sheep (at the halfway point in its incubation period after being fed BSE-infected cattle brain) resulted in transmission of BSE to a single recipient sheep [42]. Furthermore, intravenous administration of BSE-infected tissue can transmit infection in macaque monkeys [43]. Answers to questions about the transmissibility of variant CJD by blood may ultimately come from follow-up studies of persons (currently ~20 in the United Kingdom) who received blood or fresh frozen plasma from asymptomatic donors who later died of the disease.

In the interim, health officials in the United Kingdom have instituted several blood safety–related precautions, including withdrawal of products obtained from blood donors subsequently identified with variant CJD, importation of all plasma
for production of plasma-derived products, and universal leukoreduction of blood components. In the United States, beginning in August 1999, persons who resided in or traveled to the United Kingdom for a total of 6 months from 1980 through 1996 have been deferred from donation, as have persons who received bovine insulin derived from cattle in the United Kingdom. Recently, both the American Red Cross [44] and the FDA [45] announced new, expanded geographic deferrals for travel and residence in the United Kingdom and other European countries.

PARASITES AND THE ROLE OF TRAVEL AND IMMIGRATION

Transfusion-transmitted malaria is a well-recognized, albeit uncommon, occurrence in the United States that is linked to travel and immigration of infected donors [46]. Less well known is Chagas’ disease—a vectorborne disease caused by the parasite T. cruzi that is endemic in Latin America and Mexico, where infected persons can transmit the disease by transfusion [47]. The immigration of several million persons from T. cruzi–endemic areas and increased international travel have raised concerns about the increased potential for transfusion-transmitted Chagas’ disease. To date in North America, 5 cases of Chagas’ disease from transfusions have been reported [48]. Recent seroprevalence studies of blood donors who were likely to have been born in or to have traveled to endemic countries have found that between 0% and 0.48% of donors were seropositive for T. cruzi [49]. Although transfusion transmission of T. cruzi in the United States appears to be very limited, the lack of sensitive and specific donor history questions and/or licensed tests has limited efforts to identify donors who may be at increased risk of infection.

TICKBORNE INFECTIOUS AGENTS

More than 30 cases of transfusion-transmitted babesiosis have been documented in the United States (R. Cable, American Red Cross, and B. Herwaldt, Centers for Disease Control and Prevention, written communication); most were attributed to B. microti, but the more recently recognized WA1-type Babesia parasite also has been implicated [50]. Other reports of transfusion-transmitted tickborne agents have been limited to 1 case of Rocky Mountain spotted fever (RMSF) [51] and 1 possible case of human granulocytic ehrlichiosis [52]. Curiously, Borrelia burgdorferi has yet to be reported as being transmitted by blood transfusion, despite Lyme disease being the most commonly reported tickborne disease in the United States and despite efforts to evaluate recipients of blood from donors who are known to be infected [53, 54]. Factors that probably influence the risk of transfusion-transmitted tickborne agents and the development of clinical disease include the prevalence and incidence of the agent among donors; the survival and infectivity of the pathogen in blood bank storage conditions (unlike plasma-derived products, RBCs and platelets are not subjected to inactivation procedures); the type and number of components that are transfused, reflecting the different cell tropisms of tickborne agents; and the immunocompetence of the recipient (table 3) [53].

Relatively few seroprevalence surveys have been conducted among blood donors for the various tickborne agents. However, in highly endemic areas of Connecticut and New York, recent surveys that used immunofluorescence assays have found seropositivity rates for B. microti of 0.9% [55] and 4.3% [56], respectively. Individuals who become infected with these agents through the bites of infected ticks are often asymptomatic or experience only mild and nonspecific clinical symptoms (e.g., fever, headache, myalgia). In addition, Babesia can persist for years as a chronic asymptomatic infection in otherwise healthy persons [57]. Therefore, blood donors may feel healthy yet have circulating organisms that can be transmitted by transfusion. Of note, an ongoing study of blood donors in Connecticut found that 19 (56%) of 34 seropositive donors were positive for nucleic acid of B. microti by PCR. Blood obtained from 3 (33%) of 9 PCR-positive donors was infectious when inoculated into hamsters; 5 (26%) of 19 PCR-positive donors transmitted infection to recipients of their blood [55].

Strategies to prevent transfusion-transmitted tickborne infections are limited at present to questioning donors about a history of babesiosis and deferring of persons with acute illness or fever. No licensed test is available to screen donors for any of these agents. Questioning donors about recent tick bites has been shown to be ineffective, because donors who are seropositive for antibody to tickborne agents are often no more likely than seronegative donors to recall tick bites [49, 53]. Furthermore, in some areas, as many as 9% of donors reported that they had recently sustained a tick bite [53]. One proposed approach is to provide immunocompromised persons who are at increased risk for severe disease with blood that has been selectively tested and is negative for B. microti; selective testing and designation of blood that is negative for cytomegalovirus is available for high-risk recipients (e.g., infants and seronegative allogeneic bone marrow transplant patients) [49].

TRANSFUSION-TRANSMITTED BACTERIA: A PERSISTENT PROBLEM

Against the backdrop of the dramatic decreases in transfusion-transmitted viral infections during the past 30 years, transfusion-associated bacterial infections, a long-standing and poorly quantified complication of transfusion, are “emerging” as a significant, unresolved problem. One hospital-based surveil-
Table 3. Factors related to transfusion-related transmission of tickborne infections in the United States.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Babesiosis</th>
<th>Lyme disease</th>
<th>Human ehrlichioses</th>
<th>Rocky Mountain spotted fever</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agent</td>
<td>Babesia microti, WA1 type</td>
<td>Borrelia burgdorferi</td>
<td>Ehrlichia chaffeensis</td>
<td>HGE agent</td>
<td>Rickettsia rickettsii</td>
</tr>
<tr>
<td>Seroprevalence rates for blood donors/ community residents, %</td>
<td>0.3–6.9</td>
<td>1.4–8.9</td>
<td>4.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.0–4.2</td>
</tr>
<tr>
<td>Duration of presymptomatic period</td>
<td>Days to months&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Days</td>
<td>Days</td>
<td>Days</td>
<td>Days</td>
</tr>
<tr>
<td>Survival in blood components</td>
<td>35 days in RBCs</td>
<td>6 weeks in RBCs</td>
<td>11 days in RBCs</td>
<td>2 weeks in whole blood</td>
<td>9 days in whole blood</td>
</tr>
<tr>
<td>Cell tropism</td>
<td>RBC&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Extracellular</td>
<td>Monocytes</td>
<td>Granulocytes</td>
<td>Endothelial cells</td>
</tr>
<tr>
<td>Reported transfusion cases</td>
<td>&gt;30&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0</td>
<td>0</td>
<td>1 possible</td>
<td>1</td>
</tr>
<tr>
<td>Recipient health status, reference</td>
<td>Many immunocompromised patients [49]</td>
<td>75-year-old with rheumatoid arthritis and GI bleeding [52]</td>
<td>67-year-old with congestive heart failure and anemia [51]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


<sup>a</sup> In addition, seroprevalence rates of 0.5–3.6 have been reported for Ehrlichia species.

<sup>b</sup> Babesia infections may be asymptomatic for years.

<sup>c</sup> At least 4 cases have been associated with receipt of platelets, which usually contain a small no. of contaminating RBCs.

<sup>d</sup> Ritchard Cable, American Red Cross, Connecticut Region, and Barbara Herwaldt, Centers for Disease Control and Prevention, written communication.
lance study found that 1 in ~13,500 transfusions of single-donor platelets resulted in clinical septic reactions; this rate increased >5-fold for pools of platelet concentrates, which are maintained at room temperature [58]. In the present study and according to others’ experience, Staphylococcus epidermidis is the organism most commonly recovered; however, gram-negative pathogens have also been implicated [5, 58, 59]. The risk for RBC-associated sepsis has been estimated to be 1 case per 500,000 units transfused [60]; one-half of clinically recognized erythrocyte-associated sepsis is caused by Yersinia enterocolitica [5, 59].

Adverse transfusion reactions due to bacterial contamination are often underrecognized, underdiagnosed, and underreported. Increased awareness of the signs and symptoms typical of a transfusion reaction, coupled with increased awareness that bacterial contamination may be the cause, can significantly increase the number of such cases reported by clinical personnel [61]. A prospective, multiorganizational effort (the Assessment of the Frequency of Blood Component Bacterial Contamination Associated with Transfusion Reaction [BaCon] Study), which used educational materials about adverse transfusion reactions for health care professionals, recently reported the first national rates of transfusion-transmitted bacteremia in the United States [62].

Bacterial contamination can occur at ≥1 point during the collection, processing, pooling, and transfusion of blood components. Approaches to reduce the frequency of transfusion-associated bacterial infections include minimizing skin contaminants during donation by use of alternative skin disinfection procedures [63] or diversion and removal of a small volume of the initial blood that is obtained [64]; bacterial monitoring of components; and inactivation procedures, including compounds that target the nucleic acids of bacteria, viruses, and protozoa [65].

THE CHALLENGE OF TERRORISM: BLOOD SAFETY AND SUPPLY CONSIDERATIONS

Recent terrorist events in the United States have brought new challenges in maintaining a safe blood supply. The 11 September 2001 attacks on the World Trade Center and the Pentagon were immediately followed by an overwhelming and unrelenting outpouring of blood donations that regrettably few victims survived to use [66]. Although similar responses, particularly by persons who donate blood for the first time, have occurred after other major natural and man-made disasters [67], the events surrounding 11 September presented some unique circumstances. For example, the shutdown of all air travel in the United States required that blood collection centers seek alternative methods of transporting blood to centralized laboratories where infectious disease testing could be performed; another concern was ensuring the availability of testing reagents and supplies used for blood collection and processing [66]. By the afternoon of 11 September, the FDA had released an interim policy statement on procedures for urgent collection, shipment, and use of blood to meet immediate needs [68]. Three days later, after it been determined that blood supplies in the affected areas were more than adequate, the FDA rescinded its emergency guidance and directed blood collection facilities to complete quality-assurance reviews to ensure that blood collected under urgent conditions met established requirements [69].

Data regarding infectious disease-marker rates for donations made after 11 September have not yet been analyzed. However, previous experience with other disasters suggests that such donations are similar to routine donations, especially when adjustments are made for the increased representation by first-time donors, who have higher rates of infectious disease markers than are seen among persons who have made multiple donations [67].

Beginning in October 2001, cases of bioterrorism-related inhalation and cutaneous anthrax began to be reported in several cities of the United States [70]. Shortly thereafter, the FDA issued recommendations to address concerns about the possible risk of transmission of anthrax from blood and blood products [71]. Because the likelihood of bacteremia occurring in an asymptomatic person infected with Bacillus anthracis is considered to be extremely remote, the FDA recommended no changes to routine donor questioning and testing procedures. However, if a donor has anthrax diagnosed or develops an illness highly suspected of being anthrax after donation, blood establishments are required to retrieve unused blood or plasma units.

Acknowledgments

I thank Drs. Ermias Belay, Barbara Herwaldt, Matthew Kuehnert, and Jennifer McQuiston, for their careful review and comments, and John O’Connor, for his editorial assistance.

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