Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

CHAPTER 8

Infectious Complications of Transfusion of Blood Components

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HISTORY

Early in transfusion compatibility, hemolysis, whether delayed or immediate, was the most life-threatening condition/risk. As blood groups were discovered and avoidance of stimulation of alloantibodies became the norm, transfusion transmissible infections became a greater risk. The risk for acute hemolytic transfusion reaction is reported as 1 in 76,000 and that of bacterial contamination of platelets is 1 in 3000.[1] Most infections were not usually immediately evident, but some came to be recognized as equally fatal as the immediate death from septic transfusions. In the 1940s, testing for syphilis was initiated.[2,3] Syphilis is a disease of direct transfusion.[3] The causal organism is not stable at colder temperatures: after 72 h at 1–6 °C it is not viable and it becomes nonviable immediately at freezing temperatures. During the 1950s, blood was no longer collected from paid donors or inmates to decrease the incidence of transmission of hepatitis.[2] With the development of health questionnaires, which eventually became the universal health questionnaire, the risk for transmission began to decline. In the 1990s, tests were developed to detect antibodies and eventually antigens of hepatitis viruses to further decrease the risk of transfusion transmission.[2] Eventually, nucleic acid testing (NAT) was developed to detect exposure to pathogens by detecting their genetic material in the donor, which has resulted in lower risks for transmission of infection and has created the safest blood products in history. Infection rates for most viruses are very low secondary to screening. Only higher incidence rates can be measured directly; when the rate is less than $1:10^5$, mathematical modeling is required to predict the residual risk. This is a testament to the benefit of the screening questionnaire and serologic testing and NAT in producing the safest transfused blood components to date.[4]

In this chapter, we will explore viruses, bacteria, parasites, and, briefly, prions with some specific examples, mode of detection, risks, and risk mitigation. Finally, what may be done in the future to further reduce the current and potential risks/dangers of these pathogens is discussed.

VIRUSES

Even though the agent of transmission for hepatitis was not known to be viruses, the risk of transfusion transmission of hepatitis has been recognized since the 1940s.[5] Regulations have been in place since the 1950s to decrease the risk of transmission of hepatitis, long before the causative agents were identified.[6] All individuals with hepatitis are screened via the health donor questionnaire with the exception of those who have had hepatitis after the age of 11. In 1998, approximately 13,000 donors were deferred based solely on this questionnaire.[6] Those who are not aware of having this illness have been further screened with an enzymatic immunoassay test to detect the presence of hepatitis B surface antigen, hepatitis B surface antibody, or hepatitis B core antibody and alanine transferase in the 1980's and using NAT since 2012.[7] Historically, hepatitis not caused by hepatitis A or B viruses was called hepatitis non-A non-B. The majority of these was found to be hepatitis C. After screening for hepatitis B, the posttransfusion hepatitis risk was 1 in 400 with 90% of these being due to hepatitis C.[5] Like the hepatitis B virus, the viruses causing hepatitis C typically have an indolent course, which may lead to severe morbidity and eventually mortality through liver failure or hepatitis carcinoma. These viruses are detected in the donor with enzymatic immunoassay (EIA) testing, recombinant immunoblot assay for confirmation, and NAT. The transmission of this infection has decreased from 1:100 to $1:1.9 \times 10^6$.[6,8]

Other viruses that cause hepatitis are not routinely tested. Some of these include transfusion transmitted virus/torque teno virus (TTV); cytomegalovirus (CMV); Epstein-Barr virus (EBV); hepatitis E virus; hepatitis A virus; hepatitis D virus; adenovirus; Lassa fever virus; Rift Valley fever virus; parvovirus B19; Ebola virus; dengue virus; human herpesvirus 6, 7, and 8; influenza virus; echovirus; and Colorado tick virus. Some of these viruses are of unknown clinical significance, even if associated with transfusion transmission. More significant pathogens in this group are discussed later in this chapter.

Other viruses routinely screened for are human T-lymphotrophic virus (HTLV) and human immunodeficiency virus (HIV). HTLV has two copies of single-stranded RNA (ssRNA). HTLV-1 and HTLV-2 were discovered in the 1980s. HTLV can cause lymphoproliferative or demyelinating diseases in those infected, leading to T-cell leukemia or HTLV-associated myelopathy. To prevent the transmission of this virus, serologic testing for antibody against HTLV has been performed since 1988. For this, EIA has a sensitivity and specificity of 99.4% and 98% and Western blot has a sensitivity and specificity of 97% and 65%, respectively. Those receiving seropositive blood products had a 25%–63% conversion rate.[9] Products stored longer were less likely to be infectious. If stored less than 5 days, contaminated units had 75% transmission rate, and if stored longer than 11 days, the risk decreased to 0%. Multiple case reports from around the world demonstrate the transfusion transmissibility of this virus. One case was from a walking donor pool acquired during treatment at military combat operations.[10,11] At present, no NAT is performed for HTLV and none are under development. The prevalence of this infection is 5–10,000,000 worldwide. There is low prevalence in the United States with $1{:}5.1 \times 10^5$ positive results in first-time tested donors. After screening, there is a $1{:}2.9 \times 10^6$ chance of transmission of this infection.[10]

HIV has a storied history in the blood community. HIV is a positive-sense ssRNA enveloped virus. Initially, infection and transmission via blood transfusion were thought to be rare events. As time progressed and the seriousness of acquired immunodeficiency syndrome prognosis and ease of transmission via blood transfusion became more appreciated, health questionnaire screening was developed because high-risk populations were identified. In the early 1980's, transfusion transmission of HIV was more recognized and further work on screening testing came to the forefront because screening for history of high risk was not sufficient to protect transfusion recipients. By early 1985, serologic testing for HIV was developed and donor testing was initiated.[2] The questionnaire decreased the risk from 1:100 to $1{:}5 \times 10^4$; screening with EIA, antigen testing, and Western blot confirmation decreased the risk to $1{:}5 \times 10^5$; finally, NAT decreased the risk to $1{:}1.9 \times 10^6$. Only four cases of transfusion transmission have been reported from 1999–2009. In the United States, the last case of transmission of HIV in via blood transfusion occurred in 2008.[12] Continued formation of new clades will require updating the questionnaires and testing, as was done most recently with clade O, the most recent to arrive, this one from Africa.

Two additional viruses recently included in donor screening testing are the West Nile virus [WNV] and the Zika virus (investigational new drug (IND) testing Phase III at present). WNV is associated with the potentially fatal neurologic disease, meningoencephalitis. This Flavivirus is an ssRNA virus. The natural reservoir is birds, and it is transmitted to incidental hosts, humans, horses, and other mammals, via mosquitoes. It was first seen in New York in 1999, with transfusion transmitted cases noted in 2002 in the United States. Symptoms can be mild to severe (meningoencephalitis), and 80% of those infected are asymptomatic.[13,14] The development of NAT for this virus was rapid. IND research testing went smoothly, and permanent testing was put in place by 2002.[10] Now, the risk from this viral transmission is 1:350,000.[3,15]

Zika infection is a newly documented transfusion transmissible infection. Zika virus is a positive-sense ssRNA enveloped virus first evident in Africa in 1947. From this time to the 1980s it has spread in Africa and Asia. In 2015, it was found to cause microcephaly in in vivo–infected fetuses of mothers infected with this virus in Brazil. There are at least 56 countries in the world with active Zika infections. Zika viremia may last 1–2 weeks in the primary infection. Since Nov. 2016, NAT is in Phase III testing in the United States. Food and Drug Administration (FDA) approval as a licensed screening test is pending.[16] As with previous NAT risk of transmission should decrease the risk of transfusion transmission to $<1{:}1 \times 10^6$ as was seen with hepatitis C virus and HIV testing.

CMV is a double-stranded DNA (dsDNA) enveloped virus also called human herpesvirus-5 (HHV-5). Humans are the sole host of this virus, and it is transmitted by person-to-person contact or iatrogenically via blood transfusion or tissue/organ transplantation. After primary infection there is a lifelong viral persistence likely within mononuclear white cells and hematopoietic progenitor cells in the bone marrow.[17] CMV infection during pregnancy can affect the neurodevelopment of the fetus with a 40% vertical transmission rate. In immunocompromised patients, such as those receiving bone marrow/stem cell transplants, infection can cause severe disease in the pulmonary, gastrointestinal, and central nervous systems. Immunocompetent individuals typically have mild flulike symptoms. After primary infection this virus remains in the white cells. Repeat infections can also be seen. Seronegative and prestorage leukocyte-reduced blood products both decrease the risk for CMV transmission.[18,19] There may be additional benefit to having leukodepletion and negative serology together.[17]

There are more recent studies that conclude that CMV-seronegative blood products are safer than leukoreduced blood products.[19] The debate continues. Residual risk after leukocyte reduction for CMV transfusion transmission is 1: 1.3×10^7.[20]

There are other viruses causing viremia with potential for transfusion transmission that are not screened by history or test in the blood donor setting. These viruses may be geographically isolated, produce mild clinical symptoms, and are yet to be identified in transfusion transmission cases. EBV/HHV-4 is a dsDNA enveloped virus with a human reservoir. Blood transfusion transmission is reported rarely. Primary infection can lead to mononucleosis, Burkitt lymphoma, nasopharyngeal carcinoma, and postviral lymphoproliferation. After primary infection this virus remains latent in the lymphocytes. Infection prevalence is 95% by the age of 40 years. Only screening at the time of donation can defer those with hepatitis after the age of 11, no serologic test or NAT is available.[21]

Parvovirus B_{19} is a positive- or negative-sense single-stranded DNA nonenveloped virus. This virus is resistant to pathogen reduction techniques with heat or cold treatment and solvent detergent treatment. This virus was discovered in 1974 and has three genotypes. Parvovirus B_{19} is trophic to red cells and demonstrates a high viremia rate 7–12 days postinfection. There is a 70%–80% prevalence of previous infection by adulthood, and it has been associated with transfusion-associated transmission. Infections can lead to fifth disease in children and fetal hydrops in the unborn. Patients with high red cell turnover rates are susceptible to aplastic anemia following infection with this virus. There are currently no screening tests at blood donor centers. NAT is performed for pooled blood component products produced commercially (albumin, intravenous immunoglobulin (IVIG) anti-D immune globulin, etc.).[22]

Chikungunya is an ssRNA enveloped virus with two genotypes. The vectors for this virus are multiple mosquito species. Birds, humans, mammals, and reptiles are reservoirs for this virus. A high concentration of viremia occurs within the first week of infection. At-risk populations for more severe disease include the elderly, pregnant, and immunocompromised patients. There is at present only theoretical risk of associated transfusion transmission. At present no screening tests are available.[23]

Dengue virus is a positive ssRNA enveloped virus with four serotypes. There are at least two mosquito vectors for this virus. Humans are the main hosts. Viremia may be present 2–12 days postinfection. Infection can lead to dengue or severe dengue fever (also known as dengue hemorrhagic fever). The incidence of infection has increased 30-fold over the last 50 years. This virus is mainly present in the tropics and subtropics of Asia and the Americas. Associated transfusion transmission has been seen in cellular and acellular blood components. Transmission has also been seen with needle sticks and organ transplants. A dengue vaccine has been developed for individuals aged 9–45 years in endemic areas. Blood screening tests are under development and are used in some parts of the world. [22,24,25]

Other emerging viral infections that are transmissible via transfusions include but are not limited to human poxvirus; monkeypox virus; Whitewater Arroyo virus; hantavirus causing hantavirus pulmonary syndrome; viruses causing yellow fever, Marburg hemorrhagic fever, and Ebola hemorrhagic fever; enterovirus 71; Hendra virus; Nipah virus; avian influenza virus (H5N1); viruses causing severe acute respiratory syndrome, Lassa fever, and Rift Valley fever; Hepatitis-G virus (GBV-C); TTV; SEN virus; and HHV-8.[26–28] The risks of transmission for these infections remain relatively low or seasonal. The donor health questionnaire (DHQ) "Are you healthy today," travel history, and temperature measurement ensure that approximately 99.5% potentially infectious donors are screened out. In the future, pathogen reduction technologies should protect against these infectious agents.

BACTERIA

Historically the risks of transfusion transmission of bacteria has been underappreciated. Because we have gained control of the screening out of viruses, the potential clinical sequela of bacteremic/septic transfusion reactions has received more attention. Transmission of these organisms is much more frequent than that of viruses. DHQ and mini-physical examination, puncture site preparation, diversion pouch, and subculturing platelet units have decreased the risks somewhat. Septic reactions occur from bacterial/pathogen-contaminated blood components, usually originating from the blood donor at venipuncture site or during unsuspected bacteremia. Less commonly, it may also result from donor unit processing. Bacterial contamination is more likely to occur in components stored at room temperature than in components stored refrigerated. The risk of transfusion transmission remains relatively high at 1:30,000 for red cells and 1:3000 for platelets as opposed to the residual risk after viral screening.

At the time of collection, bacterial contamination of components is about 10 colony forming units (CFU)/mL, and initially no sepsis occurs when the components are stored for short periods. At the end of the storage time, however, these same components can have 10^7–10^9 CFU/mL. This level of contamination can much more easily lead to sepsis especially in the most at-risk immunocompromised patients. *Staphylococcus* and *Pseudomonas* at optimal conditions can double every 4–8 h without a lag phase.[29]

Even with cold storage bacteremia/sepsis has been associated with transfusion of these components. Red cell components stored longer than 14 days are implicated in bacteremic transfusion. More often still are the red blood cell components stored longer than 25 days. *Yersinia enterocolitica* and *Pseudomonas fluorescens* are the most common agents associated with bacteremic transfusion reactions involving red blood cell components. *Y. enterocolitica* has a 7- to 14-day lag time with an 18- to 20-h doubling time for the remainder of the storage period. Contamination levels can reach 10^9 CFU/mL after 38 days of storage. Prestorage leukoreduction may prevent/inhibit *Yersinia* proliferation. Red cells stored for very short time continue to be associated with *Treponema pallidum* transmissions. Other less common red cell component bacterial contaminants are *Pseudomonas* sp., *Flavobacterium* sp., *Campylobacter jejuni*, *Enterobacter* sp., *Klebsiella* sp., *Escherichia coli*, *Serratia* sp., *Proteus* sp., *Staphylococcus aureus*, and coagulase-negative *Staphylococcus*.[29–31]

Since the 1970's bacterial contamination of platelet components was recognized. Bacteria is the leading cause of death in transfusion transmitted infections. Single-donor platelets (apheresis) and platelet concentrates (3–6 donor pools) are stored at higher temperatures than red cell units. Platelets are stored at 20–24 °C with agitation for up to 5 days. These storage conditions favor aerobic bacterial growth. Organisms typically causing bacterial septicemia more often are skin flora including *Staphylococcus* and *Streptococcus*; however, *Serratia*, *Bacillus*, and *Salmonella* are also among the most common bacterial contaminants in platelet products. *Acinetobacter*, *Proteus*, *Klebsiella*, and *Serratia* have also been implicated in fatal septic transfusion reactions. *Propionibacterium acnes* has been found as a common contaminant of blood products but is usually associated with minimal morbidity and mortality; nonetheless, one fatal reaction with transfusion has been reported. Bacteremic/septic reactions are usually seen at the end of storage of the platelet unit at day 4–5. Higher bacterial septic reactions secondary to longer stored platelet units in 1985 led the FDA to reverse the 7-day storage to 5 days. In the 2005–08 period 7-day storage was again attempted after subculturing platelets 24 h after collection to try to screen out contaminated units. This reduced the risk slightly but not significantly, and storage was again set for 5 days. Storage is limited to 5 days because longer storage continues to be associated with unacceptable rates of bacterial transmission. When *S. aureus* contaminates platelets, there is a 2-day lag, whereas with *Enterococcus faecalis*, there is no lag in the growth period. The doubling time for these organisms is ≤3 h. By day 3–5 there are 10^8–10^9 CFU/mL of component. Efficacy for removal of bacteria with leukocyte depletion is less clear for platelet products. Risk for bacteremia from platelet transfusion is $1{:}10^3$–3×10^3. Transfusion-related sepsis risk ranges from $1{:}1$–5×10^4 and $1{:}4.7 \times 10^3$, depending on the study; with subculturing, the risk of immediate death from septic transfusion is $1{:}5 \times 10^5$. [29,31–34]

Potential sources of contamination of blood products are improper preparation of the phlebotomy site at donation, donor bacteremia, blood containers used for processing and storage, or equipment used for processing. The risk of transmission from the donor is decreased with the mini-physical examination and clinical, medical, and travel histories. Phlebotomy site risk is reduced by ruling out intravenous drug use, evaluating for skin lesions, and preparing the site with iodine or chlorhexidine and alcohol. Donor bacteremia risk is evaluated with a history of dental procedures, gastrointestinal tract symptoms, and current osteomyelitis. Contamination of blood collection containers is a very rare event with better sterility of the plastics used. When processing (thawing) products, water baths may be a source of contamination and should be cleaned regularly. At the time of issue further steps can be taken. A visual inspection of the unit for color changes, hemolysis, or turbidity is performed. Red cell units tend to be much darker in color because the bacteria use the oxygen stored in the red cells; platelets have lower pH and loose "swirling" when potential contamination is present. These units should be quarantined and not issued to patients. Blood components should be transfused within 4 h of being issued from the blood bank. Proper storage temperature during transport is also recommended. Transfusion administration tubing sets should be changed between blood transfusions per policy: approximately every 4 h. At the time of issue products can be examined to evaluate for contamination. Septic reaction is the fourth leading cause of death as a complication of

transfusion. While receiving a transfusion, signs of a septic reaction include temperature greater than 102° F (or higher than 2°F or 3° C above baseline temperature), chills, rigors, tachycardia (heart rate greater than 40 beats over baseline) and shock/falling systolic blood pressure (30 mm Hg below systolic), backache, nausea/vomiting, and unexplained bleeding from mucous membranes or the infusion site. Renal failure may follow later. Once suspected, transfusion is immediately halted and the patient given supportive treatment. Maintain respiratory status, and use mechanical ventilation if indicated. Maintain cardiovascular support with vasopressors as indicated. With the patient stabilized, initiate transfusion reaction workup; send blood (pink or purple tube) and first posttransfusion urine (not from Foley collection bag) to the laboratory. Also send the unit with attached administration set to the laboratory. Perform a gram stain and culture from the implicated blood component and administration set. Draw blood culture from the patient, preferably from two sites. Prompt initiation of intravenous antibiotics as indicated by the gram stain results. Again, future use of pathogen reduction agents will greatly decrease the risk of bacterial transmission of blood products.[29,35]

PARASITES

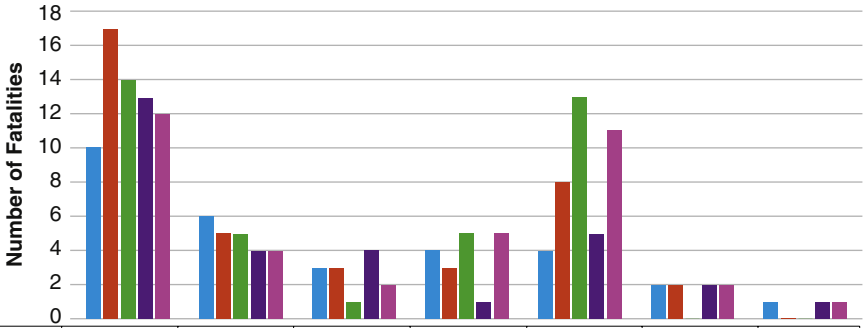
Leishmania species is an intracellular macrophage/monocyte protozoan that causes leishmaniasis. Sandfly is the vector of this pathogen. A few cases of transmission from blood products have been reported in the United States. Likely leukocyte reduction greatly reduces transfusion transmission because these pathogens are within white blood cells. This protozoan is able to survive for 15 days at erythrocyte storage conditions. Deferral of potential donors with travel history to countries with endemic pathogens likely aids in the prevention of transmission in the United States. There is a 1-year travel history deferral because the incubation for this infection may be weeks to months. Pathogen reduction technology can decrease the viability by a factor of 10^4–10^5.[36]

Plasmodium species is an intracellular erythrocyte protozoan pathogen spending part of its life cycle in hepatocytes. Malaria is a very common disease worldwide caused by this pathogen. *Anopheles* mosquito is the vector for *Plasmodium*. In the universal health donor questionnaire, extensive travel history and questions on exposure/prophylaxis use are included to decrease the risk. There is a 1-year deferral for travel to endemic areas, 3-year deferral for those living in endemic areas, and deferral of 5 or more years for those who had malaria and now are asymptomatic. The Centers for Disease Control and Prevention frequently updates travel exposure risks. These are used by blood donor centers to ensure decreased risk of exposure. There are no FDA-approved screening tests for malaria. Historically, this protozoan can survive 7–10 days in blood containers; there are no new studies on the effect of modern additive solutions on the survival of this organism. Leukocyte reduction is unlikely to decrease the risk of transmission. Ongoing pathogen reduction studies are very promising in reducing transmission via blood transfusion in endemic regions.[36]

Babesia is an intracellular erythrocyte protozoa that causes babesiosis. It is associated with transfusion transmission as shown in at least 162 transfusion events, all red cell components. Freezing red cells did not prevent the transmission of infection. This organism is closely related to *Plasmodium*. The vector of *Babesia* is the ixodid tick with the primary species in the United States being *Babesia microti*. It is most commonly seen in the United States in the New England region and the North Midwest states (e.g., Wisconsin, Minnesota). Humans are an accidental host. Risk of transmission is at $1:10^5$. Patients infected with this organism have a long incubation period, 1–6 weeks after a tick bite and 1–9 weeks after contaminated transfusion, as well as prolonged infectivity. Many are asymptomatic with mild fevers at most. If immunocompromised, the patient may develop hemolysis, disseminated intravascular coagulation, or multiple organ dysfunction syndrome. Travel history is remote to the incidence of inoculation and is a poor screening tool. At present, there are serologic and polymerase chain reaction studies being performed with immunofluorescence assay (IFA)/enzyme-linked immunosorbent assay (ELISA)/NAT; Phase III clinical trials are ongoing to test for this pathogen and screen out potentially infected donors.[2,3,37]

PRIONS

Prions are not infections agents in the classic sense but are proteins that act as infectious particles by recruiting normal cellular isoforms to form disease-causing isoforms. Creutzfeldt-Jakob disease (CJD) may be sporadic, infectious, or inheritable. Even though there is potential for transfusion transmission of this disease, to date there have been no documented human cases of transfusion transmission of this classic form of CJD. There is no donor testing for this, and deferral is permanent to all those with a history of this illness.



	TRALI	HTR (non-ABO)	HTR (ABO)	Microbial Infection	TACO	Anaphlaxis	Other
FY11	10	6	3	4	4	2	1
FY12	17	5	3	3	8	2	0
FY13	14	5	1	2	13	0	0
FY14	13	4	4	1	5	2	1
FY15	12	4	2	2	11	2	1

Complications

FIG. 8.1 Transfusion-related fatalities by complication, FY 2010 through FY 2014. *FY*, financial year. (From Food and Drug Administration. *Fatalities Reported to FDA Following Blood Collection and Transfusion Annual Summary for Fiscal Year 2014*. Available at: https://www.fda.gov/downloads/biologicsbloodvaccines/safetyavailability/reportaproblem/transfusiondonationfatalities/ucm459461.pdf.)

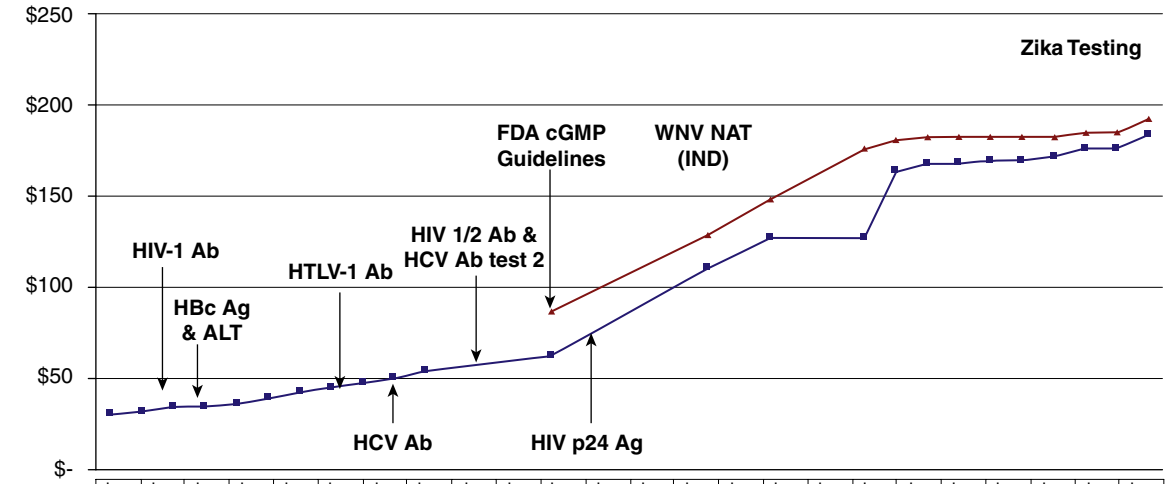
For variant CJD the story is different. This disease first occurred in the United Kingdom in 1994 and was recognized as a distinct disease in 1996 as bovine spongiform encephalopathy (mad cow disease). There is no known vector; cattle and humans serve as reservoirs. Experimentally, in animals a intravascular phase is present before symptoms and there is widespread deposition and replication in the lymphoreticular tissues. Transfusion transmission has been documented. This prion is likely to survive any storage conditions of blood products secondary to the physiochemical characteristics noted in other prions. Incubation of infection is 5–15 years. With transfusion incubation is quicker at 5–8 years. Leukocyte reduction may offer some protection; nanofiltration is effective in experimental model systems. Affinity-based prion removal filters are under development. Pathogen reduction has unknown effect on prions.[38,39]

REDUCING RISK IN THE FUTURE

In the past, the rate of transfusion transmission of infection was over 1% of all transfusions. Now with better screening questions, travel/medical history and screening tests we have decreased the risk of transfusion transmission of infection to many-fold lower levels. Where once the primary cause of death was infection from transfusion, now transfusion transmitted infections may cause only 10% of the transfusion-associated deaths (Fig. 8.1). We have become very good at discovering transfusion transmitted agents and screening for their presence (Fig. 8.2). This, however, takes time and a new virulent pathogen may still await us and we will not be protected by geography. Pathogen reduction technology will soon become routine in the United States as it is in Europe. As this technology becomes easier to use it will become more accepted and utilized first in our most high-risk immunocompromised populations and then universally, as it happened with leukocyte reduction. Commercially developed tests are performed to screen pathogen, but nanofiltration, solvent detergent, and pasteurization reduce the risks of pathogen transmission not detected with screening tests. These processes cannot be used on cellular products. There are processes in place for pathogen reduction in platelets and plasma. For whole blood or red cell components, Phase III studies are ongoing, and in the near future these can be added to our pathogen reduction repertoire.[40]

DISCLOSURE STATEMENT

Research project with Terumo.



	Jun-84	Jun-85	Jun-86	Jun-87	Jun-88	Jun-89	Jun-90	Jun-91	Jun-92	Jun-93	Jun-94	Jun-98	Jun-03	Jun-05	Jun-08	Jun-09	Jun-10	Jun-11	Jun-12	Jun-13	Jun-14	Jun-15	Jun-16	Jun-17
RBC	$30	$32	$34	$34	$36	$39	$42	$45	$47	$50	$54	$62	$111	$127	$127	$164	$168	$168	$170	$170	$172	$176	$176	$184
RBC-LR												$87	$129	$148	$176	$181	$183	$183	$183	$183	$183	$185	$185	$193

FIG. 8.2 Blood donor center costs from 1994 to 2017. *Ab*, antibody; *Ag*, antigen; *ALT*, alanine transferase; *cGMP*, cyclic guanosine monophosphate; *FDA*, Food and Drug Administration; *HBcAg*, hepatitis B core antigen; *HCV*, hepatitis C virus; *HIV*, human immunodeficiency virus; *HTLV*, human T-lymphotrophic virus; *IND*, investigational new drug; *NAT*, nucleic acid testing; *WNV*, West Nile virus.

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