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The Potential Threat to Blood Transfusion Safety of Emerging Infectious Disease Agents

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H&O How safe is the US blood supply at this time?

SS The blood supply with respect to known infectious disease agents—such as HIV, hepatitis B virus (HBV), and hepatitis C virus (HCV)—is very safe because of donor selection, donor screening, and blood donation testing. The per unit risk of contamination with HIV is approximately 1 in 1,000,000 units, which is also true for both HBV and HCV (see the table). People who receive multiple units are therefore at higher risk.

The risk of receiving a bacteria-contaminated unit that causes a septic transfusion event is higher—approximately 1 in 109,000. Although we use strategies to mitigate the risk of contamination, most contaminating bacteria are common because they are present on the donor's skin.

H&O Are there agents that we currently do not test for that pose a potential risk?

SS We do not usually test for *Babesia*, which is an infection caused by a parasite that lives in red blood cells. *Babesia* causes the disease babesiosis, which varies from being asymptomatic to causing fatal malaria-like disease. The fatality rate in transfusion recipients is approximately 18%. The parasite is transmitted to humans by the same ticks that transmit Lyme disease, and commonly occurs in the Upper Midwest and the New England area. Infection and clinical disease caused by the parasite may also occur via blood transfusion. Although investigational blood donation screening tools are available, they are not in common use. Such testing is not required by the US Food and Drug Administration (FDA), and many hospitals do not wish to pay for the additional screening.

H&O Do you think that Babesia screening should become a requirement?

SS I definitely do, because patients are at risk. In our studies in New England and the Upper Midwest, we have found *Babesia*-positive blood donors to be very prevalent, at a rate of approximately 4 per every 1000 donations tested. We also have seen cases of transfusion-transmitted babesiosis in recipients in endemic areas from unscreened blood. Something needs to be done regionally to prevent transfusion transmission of *Babesia* because this parasite, along with bacterial infections, represents the 2 greatest infectious disease threats to the blood supply. The statistics from the FDA bear this out.

People who live in *Babesia*-endemic areas, which include Minnesota, Wisconsin, Connecticut, Rhode Island, New York, New Jersey, Massachusetts, Maine, and New Hampshire, should know that they are at risk for babesiosis if they receive blood at a hospital that does not screen for *Babesia*.

H&O Which emerging pathogens present a threat to the blood supply?

SS Right now, there are potential emerging threats from mosquito-borne viruses including dengue viruses, chikungunya virus, Zika virus, and Ross River virus. The first 3 agents are now present worldwide, and the last agent is present in Australia and the Pacific Islands. All may be

Table. Comparative Rates of Transfusion Residual Risks in the United States

Infection or Complication	Period	Intervention	Risk Per Unit	Source
Babesia	2009-2012	Untested; no intervention Testing for Ab + PCR	1/18,000 0/75,000[b]	ARC, investigational screening in endemic states
Bacteria	2004-2012	Apheresis platelets; no intervention 4 mL + 39% diversion 8 mL + 100% diversion	1/36,000 1/66,000[b] 1/109,000[b]	ARC HV
TRALI[a]	2006-2012	AB plasma; no intervention Apheresis platelets; no intervention Male-predominant plasma (contains some AB plasma) ABO plasma (contains no AB plasma) RBCs baseline; no intervention deemed necessary	1/37,000 1/149,000 1/263,000[b] 1/550,000[b] 1/500,000	ARC HV
HBV, HCV, HIV	2009-2011	FDA-licenced screening tests	~1/1,000,000[b]	ARC, published

Ab, antibody; ARC, American Red Cross; FDA, US Food and Drug Administration; HBV, hepatitis B virus; HCV, hepatitis C virus; HV, hemovigilance program; RBCs, red blood cells; PCR, polymerase chain reaction; TRALI, transfusion-related acute lung injury.

[a] Transfusion-related lung injury (TRALI) is a transfusion reaction characterized by shortness of breath and pulmonary edema that occurs within 6 hours of transfusion. TRALI is a rare complication, thought to occur in approximately 1 in 5000 transfusions. Approximately 5% to 10% of TRALI reactions are fatal.

[b] Mitigated.

spread by the same daytime-biting mosquitoes and can present with similar symptoms. Humans are the amplifying host, which means that we can transmit the virus back to mosquitoes. These viruses result in explosive outbreaks. Dengue is the most important arthropod-borne virus, affecting more than 100 countries globally. The World Health Organization estimates that there are 100,000,000 cases per year worldwide. In the calendar year 2010, when there was a worldwide pandemic, there were an estimated 400,000,000 cases. However, despite the huge number of estimated cases each year, transfusion transmission of dengue virus has only been demonstrated in 7 case clusters.

A Ross River virus outbreak is ongoing in Australia, and this virus was recently shown to likely be transmissible by transfusion. Chikungunya virus has never been demonstrated to be transfusion-transmitted, but we have high suspicion that it is because it is very closely related to the Ross River virus.

The Transfusion Transmitted Diseases Committee of the AABB (formerly the American Association of Blood Banks) put together a list in 2009 of agents that are known or have the potential to be transfusion-transmitted. The initial list included 68 agents; since then, the number has grown to 77 agents.

H&O Which of these agents are the most concerning?

SS The agents that are considered to be of greatest concern at the time of the 2009 publication were dengue viruses, Babesia, and variant Creutzfeldt-Jakob disease (vCJD), which is caused by a prion. Although CJD, which is a spontaneously occurring disease with a frequency of about 1 per 1,000,000 individuals, has never been shown to be transfusion-transmitted, vCJD, which is closely related to bovine spongiform encephalopathy (BSE) in cattle, has been. vCJD is a highly dreaded, fatal disease that was designated as a high-priority pathogen, and more needs to be done. Fortunately, we have seen only 3 transfusion transmissions since BSE was first identified in the United Kingdom in 1980.

H&O What other infectious agents are of concern in transfusions?

SS We continue to be concerned about hepatitis E virus (HEV), which has not been much of a problem in the United States but continues to be a problem worldwide. This virus is composed of 4 different genotypes that have different epidemiologic characteristics. Genotypes 1 and 2 are primarily food- and waterborne, and cause the most common form of acute hepatitis worldwide. These have been responsible for explosive disease outbreaks that are similar to hepatitis A in many parts of the developing world. Genotypes 3 and 4 produce zoonotic infections; the reservoir is animals, and humans get infected incidentally or accidentally. These infections usually occur when people eat infected animal meats or organs that have not been thoroughly cooked. For example, in parts of the world such as Northern Japan and the South of France, pig livers are considered a delicacy when consumed in lightly cooked sausages or raw, on their own. The liver can transmit infections to donors, who may be asymptomatic when they donate blood. Blood donors in

Northern Japan are screened for HEV nucleic acid. Studies are underway to determine whether blood donation screening should be extended to other parts of Japan. The virus is resistant to inactivation methods because its nucleic acid is surrounded by a tightly wound outer protein capsid without an envelope coat. HEV transmission has been documented throughout Europe but most notably in the Netherlands, where there is a large amount of pig farming, and in Southwestern France, where HEV is linked to the consumption of raw or undercooked pork. A study conducted in the United Kingdom documented a frequency of 1 HEV-infected donor per every 3000 donations screened. Of the positives identified, 42% (18/43) of recipients who received their blood became infected. Long-term infection occurred in recipients who were immunosuppressed because there was no or only a delayed antibody response. Units were more likely to cause infection if the donor was antibody negative and had a high viral titer. There may be a need to institute screening for HEV in parts of the world where the virus is demonstrated to exist, especially if blood is given to solid organ transplant recipients or immunosuppressed populations. These patients have a very high risk of developing hepatitis chronicity, liver failure, and death, especially if the disease is not promptly treated.

H&O How do we keep the blood supply safe in this country?

SS The first step is selecting appropriate donors, followed by screening the donors at the time of presentation to ensure that they feel well and are healthy. Registries are kept of people who should not be donating blood owing to either behavioral or health-related deferrals or prior positive test results for infectious diseases. Once donors are selected, a sample of their donation is tested. Testing involves both serologic (antibody or antigen) tests as well as nucleic acid testing. Of course, it is possible that infections in donors may be missed if the pathogens in the donor's blood are below the threshold for which we can detect them.

We also now have the ability to use pathogen inactivation technology, which reduces the concentrations of pathogens in blood. The technology is robust and effective against most viruses, bacteria, and protozoan parasites, but some agents are resistant, such as HEV and prions.

H&O What steps should be taken to increase the safety of the blood supply?

SS I believe that pathogen inactivation should be an FDA requirement. This is especially true for plasma, in which much larger volumes are transfused than red blood cells or platelets. There are currently 2 pathogen inactivation methods that are FDA-approved for plasma: Octaplas from Octapharma, which involves the use of a solvent and detergent, and the Intercept Blood System from Cerus, which employs amotosalen and ultraviolet A light exposure. Both are FDA-approved, and in my opinion there is little reason not to use them. Of course, treated plasma is more expensive than conventional plasma. Additionally, because of the high residual risk of bacterial septic transfusion reactions from platelets, and the fact that testing interventions to successfully eliminate bacterial platelet contamination are inadequate and complex, pathogen inactivation of platelets should also be an FDA requirement. Although no technologies are available for use in red blood cells at this time, the Cerus system is in phase 3 clinical trials for red blood cells.

Suggested Readings

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