EDUCATIONAL COMMENTARY – EMERGING INFECTIOUS DISEASE AGENTS

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LEARNING OUTCOMES

On completion of this exercise, the participant should be able to

- understand the importance of early detection of emerging infectious agents.
- appreciate the challenges in identifying donors at risk for threatening the blood supply.
- identify the routes of transmission of the infectious agents discussed.

Introduction

Early detection of infectious agents that pose a risk to the safety of the blood supply is crucial for protecting transfusion recipients. Continued surveillance of these emerging infectious agents is necessary. In 2009, the AABB’s Transfusion Transmitted Diseases (TTD) Committee categorized 68 infectious diseases. Each infectious agent was assigned a priority level based on scientific/epidemiologic evidence regarding blood safety, as well as public perception and/or regulatory concern. Four categories were created: red, orange, yellow, and white. The red category includes agents with low to high evidence of risk to the blood supply, especially in the United States and Canada. Orange agents show evidence of risk that might support their elevation to a higher category in the future, and yellow agents have absent to low evidence of risk to the blood supply. The final category, white, includes agents that the committee deems to pose no risk at this time. The emerging infectious diseases that appear to pose the biggest risk to the blood supply are found in the red and orange categories. Human variant Creutzfeldt-Jakob disease prion, dengue virus, and Babesia species are categorized as red agents; the orange category consists of chikungunya virus, Trypanosoma cruzi, Plasmodium species, Leishmania species, and St. Louis encephalitis virus. Selected emerging infectious diseases will be discussed.

Infectious Agents

Babesia species

Babesia species are protozoan parasites that cause babesiosis and are transmitted by ticks through bites. Babesia microti and Babesia duncani are the most common species found in the United States and are endemic to the northeastern and midwestern regions. Babesiosis infection causes symptoms ranging from a mild, influenzalike illness to a potentially fatal malarialike disease that occur 1 to 6 weeks following the tick bite. Immunocompromised persons have a higher risk for severe disease. Babesia species have been shown to remain viable in blood storage conditions for longer than 3 weeks. Since 1979, the
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Centers for Disease Control and Prevention (CDC) has identified 162 cases of transfusion-transmitted babesiosis, mostly due to *B microti*; however, some were due to *B duncani*, which is on a rise on the west coast of the United States. The donor question “Have you ever had babesiosis?” is currently the only strategy for protecting the blood supply from this agent. Although the Food and Drug Administration (FDA) offers no guidance for deferral, AABB standards require indefinite deferral for those identified as having had babesiosis. Attempts to identify at-risk donors by asking tick-bite related questions have been shown ineffective. Because of the long incubation period, it may be difficult to identify donors based on clinical signs. There is no FDA-licensed donor screening laboratory test. Some states, such as Rhode Island, perform limited donor screening. The AABB has identified *Babesia* species as showing high scientific/epidemiologic evidence as well as high public perception of risk to the blood supply. Many laboratory professionals believe this infectious agent is currently the leading risk to the U.S. blood supply.

**Dengue Virus**

The dengue virus (DENV) is a vector-borne virus that is transmitted to humans via mosquitoes. More than one-third of the world population lives in endemic areas and incidence of dengue fever has increased 30-fold in the past 50 years. It is not endemic to the United States, but it is the leading cause of illness and death in the tropics and subtropics. DENV can cause dengue fever, which can manifest mild influenza-like symptoms or potentially life-threatening dengue hemorrhagic fever. There are no vaccines or specific treatments for DENV. There have been several outbreaks in the United States over the past few centuries. The latest outbreak occurred in Florida in 2009, and through 2012, Florida reported 103 autochthonous dengue cases. The first reported case of transfusion transmission was in Hong Kong, a nonendemic area, in 2002. There is no FDA or AABB recommended deferral period. The donor questionnaire identifies those with a history of travel to areas endemic for malaria, which are similar to those areas endemic for dengue. There is no FDA-licensed screening test for donors. According to the CDC, the risk to blood safety in the United States is low although most infected persons remain asymptomatic.

**Variant Creutzfeldt-Jakob Disease Prion (vCJD prion)**

Variant Creutzfeldt-Jakob disease (vCJD) is a prion disease that is contracted by ingesting infected beef. It can be confirmed only at autopsy, through brain tissue. This disease differs from chronic CJD in that it affects younger people, has atypical features such as psychiatric symptoms, and has a delayed onset of neurologic abnormalities. According to the CDC there have been more than 220 cases worldwide, four of which have been identified in the United States. Most cases have occurred in the United Kingdom; three of these were transmitted through blood transfusions from asymptomatic donors. Because no FDA-licensed donor screening test exists, donor questions required by the FDA and AABB are the current strategy to protect the blood supply. FDA guidance and AABB standards recommend permanent deferral.
for those identified as having a potential exposure to vCJD infection. The FDA estimates that approximately 3% of the donor base in the United States is deferred based on residence in the UK for 3 months between 1980 and 1996 or residence in Europe for 5 years since 1980. The AABB considers this agent to pose a low threat to the blood supply, owing to the absence of human infection in North America; however, it is placed in the red category because of public perception and concern.

**Chikungunya Virus (CHIKV)**

The chikungunya virus (CHIKV) is an arbovirus that is transmitted to humans by mosquitoes. It is epidemiologically and clinically similar to the dengue virus. It is endemic to Africa, India, Southeast Asia, and the Philippines and has been known to cause explosive outbreaks. CHIKV causes severe disease with headaches, fever, severe joint pain, and rash. Although transmission of CHIKV through blood transfusion has not been documented, AABB's TTD committee has determined that it is a theoretical risk to the blood supply and should be monitored owing to its high viremic levels, rapid replication rate, and because approximately 25% of infected persons are asymptomatic. From 1995 to 2009, the CDC reported 109 cases of CHIKV disease in the United States, all in individuals who had traveled to endemic areas. To date, there is no FDA guidance or AABB standard in place to screen donors. As with other emerging infectious agents, potentially infected donors are identified through travel history and health evaluation; malaria-endemic areas are similar to those endemic to CHIKV.

**Trypanosoma cruzi**

*Trypanosoma cruzi* is a parasite endemic to Latin America that causes Chagas disease. It can be transmitted by the reduviid bug, transfusion/transplant, congenitally and through breastfeeding, and through oral ingestion of contaminated food or drink. The acute disease caused by this agent is mild; however, infection is usually lifelong and can cause a chronic, life-threatening disease. The CDC has placed this parasite on its Neglected Parasitic Infections (NPI) list owing to the lack of surveillance, prevention, and testing in the community. Transfusion-transmitted cases are believed to be underreported: in total, seven cases of transfusion transmission have been reported in the United States and Canada in 2007. *Trypanosoma cruzi* has been shown to survive in whole blood at 4°C for up to 18 days. The Donor History Questionnaire asks “Have you ever had Chagas' disease?” and a positive answer requires a permanent deferral. There is no FDA guidance for *T cruzi* donor testing, but AABB does require one-time donor testing. Although there is no criterion standard, some screening methods include nucleic acid testing, Western blot, and chemiluminescence and immunofluorescence assays. The FDA-licensed test is an enzyme immunoassay. Since the implementation of donor screening tests, the risk to the blood supply has been reduced.
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Ebola

The Ebola virus has recently become a public concern with the outbreak in Africa. According to the CDC website, as of December 8, 2014 there have been four cases of Ebola diagnosed in the United States. Two of those patients had traveled from Africa and the other two patients contracted the virus while providing medical support in the United States. No cases of transfusion-transmitted Ebola have been documented. Current malaria deferral criteria and donor health assessment screening will identify and defer donors at risk for Ebola. The AABB is currently requesting donors who have been exposed to a patient with Ebola to refrain from donating for at least 21 days following last contact.

Strategies to Reduce Risk

Unfortunately, there is no established protocol for when infectious agents threaten the safety of the blood supply. Often, the initial response to protect the blood supply is to add a question to the Donor History Questionnaire, which has disadvantages, including the potential to defer many healthy donors. For example, the strategy for protecting the blood supply from malaria is to ask questions about travel to malaria-endemic areas. One study estimated that more than 500,000 donors were lost because of this strategy, which can have a negative financial impact. Another possible strategy to handle threats to the blood supply is to implement laboratory testing. This approach can also have a big financial influence. Donor testing is expensive, and if the risk to the blood supply is low or not prevalent in the United States, it may not justify the additional cost. Another possible strategy to manage the threat of emerging infectious agents is to use pathogen inactivation.

Pathogen inactivation is a technology that has the potential to reduce the risk for transfusion transmission of these infectious agents, especially for babesiosis, Chagas disease, and malaria. Although not approved in the United States, there are several pathogen-inactivation systems that have been used successfully in other countries to reduce the pathogens in plasma, platelet concentrates, and red blood cells. There are three different methods used in pathogen inactivation: photochemical, photodynamic, and UV-C illumination methods. Photochemical methods can be used on platelet concentrates, plasma, and red blood cells. The chemical connects with DNA, inactivating the pathogen. One photochemical system, Intercept (Cerus Corporation) has submitted a clinical protocol to the FDA to use for inactivating CHIKV and dengue in platelets. The UV-C light illumination method may be effective for parasites and bacteria. Although these systems are promising, limitations remain. Some agents with a high titer may not be inactivated, along with some nonenveloped viruses. A new challenge in pathogen inactivation is to develop systems that would efficiently inactivate even unknown pathogens.
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Conclusion

There are constant threats to the safety of the blood supply and it is important to remain vigilant for emerging infectious agents. AABB’s TTD committee maintains and updates fact sheets for emerging infectious diseases. To date, there is no method that protects the blood supply from all infectious diseases. Pathogen inactivation is a strategy that has much potential and has been shown to be effective outside of the United States.

References


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