Babesia Species

Disease Agent:

- In the US: *Babesia microti*, *B. duncani* (collective term for WA1-type and CA-type isolates), *Babesia* variant CA1, *B. divergens*-like variant MO1
- In Europe: *B. divergens*, *B. microti*, *B. venatorum* (EU1)
- In Asia: *B. microti*-like (Japan), KO1 (Korea), TW1 (Taiwan)
- In Australia: *B. microti*

Disease Agent Characteristics:

- Protozoan, 1-2.5 µm (small *Babesia* species generally infect humans; large *Babesia* species of 2.5-5 µm occur primarily in animals with the exception of the human variant KO1 that is classified as a large *Babesia* organism)
- Order: Piroplasmorida; Family: Babesiidae
- All are intraerythrocytic parasites with characteristic microscopic appearance similar to *Plasmodium* species. *B. microti* apical membrane antigen-1 (AMA1) is 31% homologous to *P. falciparum* AMA1.

Disease Name:

- Babesiosis

Priority Level:

- Scientific/Epidemiologic evidence regarding blood safety: High
- Public perception and/or regulatory concern regarding blood safety: High
- Public concern regarding disease agent: Low/high in focal endemic areas

Background:

- Approximately 100 *Babesia* species that infect mammals have been described, some of which may be synonymous; traditionally, species have been defined based primarily on morphology and host specificity. Worldwide distribution including Australia, Egypt, Europe, Japan, Korea, Mexico, North/South America, South Africa and Taiwan
- WA1 and some CA-type isolates are now classified as the new species, *B. duncani*.
- Emergent in the US, probably due in part to the expanding range of ticks and their mammalian hosts, increased intrusion of humans into tick-infested habitats, and increased awareness and testing.
- *B. microti* is highly endemic in the US in Connecticut, Massachusetts, New Jersey, New York, Rhode Island, Minnesota and Wisconsin; geographic expansion reported in other states.
- *B. divergens* is primarily a bovine parasite; > 30 human infections have been documented in Europe, but only in immunocompromised patients.
- Worldwide; cases caused by various species are increasingly being recognized.

Common Human Exposure Routes:

- Tick-borne zoonese: humans are accidental/incidental hosts
- For *B. microti*, in the US, sporozoites of the parasite are present in the saliva of ticks and the agent is transmitted during the acquisition of a blood meal by an infected nymphal stage of the hard tick, *Ixodes scapularis*, commonly known as the black-legged or deer tick. Other tick species and adult ticks also may transmit *B. microti*.
- Tick species vary with *Babesia* species, but usually of genus *Ixodes*.
- Transmission occurs after a period of tick attachment that is generally at least 48 hours; ticks may remain attached to the host for longer periods (3-6 days).
- Blood transfusion

Likelihood of Secondary Transmission:

- Transmission by organ/tissue transplantation is theoretically possible but not demonstrated to date.
- Transplacental/perinatal transmissions documented for *B. microti*

At-Risk Populations:

- Asplenic, elderly, and immunocompromised adults (including those with sickle cell disease who are functionally asplenic) and infants at risk for infection which might be severe
- People exposed to tick vectors during hiking, gardening, and other outdoor activities in endemic states
- *B. microti, Borrelia burgdorferi* and *Anaplasma phagocytophilum* are all transmitted by the same tick vector *(I. scapularis)*. Co-infection with *B. microti* and *B. burgdorferi* (the agent of Lyme disease) can occur and is associated with more severe babesiosis. Co-infection with *B. microti* and *A. phagocytophilum* (the agent of human granulocytic anaplasmosis) also is possible.

Vector and Reservoir Involved:

- *Ixodes* ticks for *B. microti*; *I. scapularis* in the eastern US is the most common; however, other tick species may be involved.
- White-footed mice (*Peromyscus leucopus*) serve as the natural reservoir for *B. microti*.
- Although white-tailed deer (*Odocoileus virginianus*) are not infected with *B. microti*, they serve as the transport hosts for adult ticks.
- *I. ricinus* is one tick species identified as a vector for *B. divergens* in Europe.
- Roe deer serve as a reservoir host for *B. venatorum* (EU1) in Europe.
- For some of the *Babesia* species, the tick vector and reservoir hosts have not been identified.

Blood Phase:

- Intermittent parasitemia can be detectable for months to more than two years during asymptomatic infection.

Survival/Persistence in Blood Products:

- At least 42 days in red cells based on transfusion-transmission data

Transmission by Blood Transfusion:

- *Babesia* is the most frequently reported transfusion-transmitted infectious agent in the US.
- The CDC summarized 162 US cases of transfusion-associated babesiosis diagnosed from 1979 to 2009 primarily from blood centers in the Northeast US. Among the 162 US transfusion-associated cases, 159 were attributable to *B. microti*, while 3 involved *B. duncani*. The median age of the cases was 65 years (range, < 1 to 94 years). All but 4 cases were associated with red cell components, with the others attributed to whole blood-derived platelets which are generally contaminated with RBCs. Cases were linked to donations made in all 12 months, with peak periods of transmission occurring from July to October. A predominant number of cases (87%) were observed in the seven primary *B. microti*-endemic states. Seventy-seven percent of the cases were reported in the last 10 years, suggesting a rapid increase in the frequency and/or better surveillance/monitoring for transfusion-transmitted *Babesia* cases in the US. To date, no transfusion-transmitted *Babesia* cases have been observed from apheresis platelets.
- *B. duncani* has emerged as a blood safety threat on the US West Coast. Three transfusion cases involving this agent were described above; the most recent case occurred in Northern California and the prior two occurred in Washington and in California. All were from healthy donors with presumptive tick-borne infections that involved RBC units negative for *B. microti*.
- Donors from nonendemic areas infected while traveling to endemic areas, donors from *Babesia*-endemic areas who donate elsewhere, and export of blood components from infected donors in endemic areas are increasingly implicated in transfusion cases recognized outside endemic regions.
- Another study defined the infectivity of blood products following IFA and PCR screening of donors from highly endemic regions of Connecticut from 1999 to 2005. Recipient tracing and subsequent testing demonstrated that 12.7% of recipients who received a seropositive index or prior donation from a seropositive donor were *Babesia* IFA and/or PCR positive. More recipients were positive following transfusion of a positive index component (50%) than from a prior untested donation from an infected donor (7.3%), and if the donor was DNA positive (33.3%) versus negative (2.9%). Seven of eight positive recipients received RBCs while one received whole blood-derived platelets; RBC age at the time of transfusion ranged from 7 to 42 days, and the platelets at transfusion were 5 days old.
- One transfusion-transmitted case of *B. microti* was reported in Canada (donor was exposed in the US), one case in Japan that implicated an autochthonous *B. microti*-like parasite, and potentially one case in Europe involving *B. microti*.
- The infectious dose to transmit *Babesia* through a blood transfusion is not known. The median infectious dose for *B. microti* in the DBA/2 strain of mice, however, is 10 parasites.
- Frozen and deglycerolized RBCs also have been associated with *B. microti* transmission.

Cases/Frequency in Population:

- *B. microti* is endemic in the Northeast as far south as New Jersey and the Upper Midwest, areas which include approximately 16% of the US population. Seroprevalence in healthy blood donors in endemic areas ranges up to 2%. Areas of hyperendemicity (up to 10%) in the general population have been reported in areas of Rhode Island and Connecticut, particularly on offshore islands (e.g., Nantucket Island, MA, Martha's Vineyard, MA and Shelter Island, NY).
    - A recent study of blood donors in Minnesota reported 42 of 2150 (2%) positive for *B. microti* by IFA; one also positive by PCR. Study focused on donors residing in areas considered endemic for *B. microti*. All positive donors reported extensive outdoor activities, many with tick exposure.
    - A limited study in the highly endemic areas of Connecticut tested 1002 donors during the tick season by IFA and real-time PCR. Twenty-five (2.5%) donors were positive by IFA and 3 (0.3%) positive by real-time PCR. Among the PCR positive donors, two were IFA positive, while one was IFA negative and suggestive of a window period infection.
    - A recent study of 13,269 linked repository donation samples tested by real-time PCR and next generation IFA (automated, arrayed fluorometric immunoassay, AFIA) found rates of positivity of 0.025% in low-risk areas (AZ, OK), 0.12% in moderate-risk areas (MN, WI) with 2/4167 antibody and DNA positive, and 0.75% in high-risk areas (CT-highest endemic counties, MA) with 5/5080 antibody and DNA positive.
- *B. duncani* is found in several western states.
- MO1 and other *B. divergens*-like organisms have been identified in Missouri and several other states.
- *B. divergens*, *B. venatorum* (EU1), and *B. microti* are found in Europe; a *B. microti*-like parasite has been reported in Japan where it was implicated in a transfusion case; other *Babesia* variants are found in Korea (KO1) and in Taiwan (TW1).

Incubation Period:

- 1-6 weeks following tick bite
- 1-9 weeks following transfusion but may be longer depending in part on the immune status of the individual

Likelihood of Clinical Disease:

- Generally produces mild and transient infection in immunocompetent hosts; however, intermittent parasitemia may be detected for months to more than two years
- Higher likelihood of more severe clinical disease in at-risk populations, especially in patients who are asplenic

Primary Disease Symptoms:

- Clinical infection ranges from mild, flu-like illness to fulminant, malaria-like disease that can be fatal.
- Severe babesiosis can manifest with hemolysis, disseminated intravascular coagulation, hemodynamic instability and multiorgan dysfunction (e.g., renal failure, respiratory distress).

Severity of Clinical Disease:

- Absent/Low: Healthy, immunocompetent persons
- High: Asplenic, elderly, and/or immunocompromised adults; infants and neonates

Mortality:

- For clinically apparent *B. microti* infections, estimated at 5% in population-based study
- Rates may be higher among splenectomized patients.

Chronic Carriage:

- Months to more than two years in some people
- Self-limiting infection in most people

Treatment Available/Efficacious:

- Clindamycin and quinine remain the standard of care for severe babesiosis, but side effects are very frequent.
- The combination of atovaquone and azithromycin is equally efficacious with significantly fewer side effects than clindamycin and quinine and is first line therapy for uncomplicated infection.
- Exchange transfusion may be indicated in severe cases (i.e., high-level parasitemia) although a recent review has cast doubt on the effectiveness of this approach in clinically similar infection with malaria.

Agent-Specific Screening Question(s):

- Currently in use as part of Donor History Questionnaire: "Have you ever had babesiosis?" Donors responding "yes" are indefinitely deferred.
- In endemic areas, a question on exposure to tick bites has been shown to be ineffective in distinguishing *Babesia*-infected from uninfected donors. The question lacks sensitivity and specificity.

Laboratory Test(s) Available:

- Currently no FDA-licensed blood donor screening assay or FDA-approved or cleared diagnostic test exists.
- Commercial options for diagnostic testing are limited. Only a restricted number of *B. microti* antigens are available for studies. Diagnosis is currently based on blood smear microscopy, automated and standard IFA (cut-off titers vary with assay and lab), ELISA, western blot, and animal inoculation. Pan-*Babesia* and species-specific PCR tests are being developed using primers from conserved regions such as the *Babesia* 18S rRNA gene.
- Limited donor screening is being conducted or considered using investigational tests (i.e., IFA, ELISA, PCR) in some endemic areas. Rhode Island Blood Center is currently using a selective testing algorithm under IND employing both IFA and real-time PCR for donor testing to maintain an inventory of test-negative blood components for transfusion to high-risk patients (i.e., neonates, pediatric patients with hemoglobinopathies). A preliminary report from this IND study revealed that 2113 units were tested with 26 (1.23%) antibody positive; one donor had an indeterminate PCR result (0.05%). No reported cases of transmission occurred with any *B. microti*–screened unit transfused to the targeted patients (0/787 units) or to any patient who received the screened units (0/2086 units). Another IND study from the American Red Cross tested 30,435 donations as part of product release during 2012-2013 in hyperendemic counties of CT and MA using next generation versions of the same tests (AFIA) and real-time PCR. Preliminary data include 155 (0.51%) reactive donations including 14 reactive by both tests, 133 with antibody reactivity only and 5 that were DNA-positive only, window-period donations (from 5 donors): 3 were PCR and/or Ab indeterminate. PCR-positive donations had parasite loads of 13-870,000 piroplasms/mL with 12/17 (70%) infectious in hamsters. Since the initiation of screening, no transfusion-associated babesiosis from screened donations occurred versus 6 in recipients receiving units from the same/adjacent locations but not included in screening.

Currently Recommended Donor Deferral Period:

- Indefinite deferral for history of babesiosis per AABB Standard. No FDA Guidance exists.
- Although not required by FDA or AABB, most blood centers defer donors implicated in suspect transfusion-transmitted *Babesia* cases or those testing positive by research/investigational tests.

Impact on Blood Availability:

- Agent-specific screening question(s): Current question has no impact in some regions and may have minimal impact in others.
- Laboratory test(s) available: Infections are regional, and seroprevalence rates will vary. Impact of antibody screening could be significant in high seroprevalence areas should serologic tests be introduced due to the detection of donors with prior exposure who are not necessarily infectious. The impact of NAT on donor deferral would be negligible since only rare, incident infections would be detected according to available data.

Impact on Blood Safety:

- Agent-specific screening question(s): Minimal/none as current screening question, as well as potential question about tick-bite exposure, are insensitive
- Laboratory test(s) available: Serologic testing, whether universal or selective, would likely have a high impact on blood safety, and NAT may reduce rarer window period transmissions.

Leukoreduction Efficacy:

- Unlikely to be effective because the parasite is intraerythrocytic and documented transfusion cases associated with leukoreduced products have been reported. Parasites do not survive freezing in the absence of a cryoprotective agent.

Pathogen Reduction Efficacy for Plasma Derivatives:

- Not applicable. Viable parasites do not survive in frozen plasma.

Other Prevention Measures:

- Personal practices to avoid ticks (e.g., insect/tick repellants, long pants and sleeves)
- Removal of ticks within 48 hours of attachment
- Tick control measures in the environment
- Pathogen inactivation/reduction in platelets, plasma and red cell products has been demonstrated to be effective using *B. divergens* and *B. microti* as target agents.
- Education/Awareness

Other Comments:

- Clinical recognition and early treatment are important.
- Because of the parasite's regional distribution, transfusion cases outside the endemic area may not be recognized or accurately diagnosed; however, under-recognition is a problem even in areas where babesiosis is endemic.

Suggested Reading:

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