Babesia Infection through Blood Transfusions: Reports Received by the US Food and Drug Administration, 1997–2007

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Background. Human babesiosis is an illness with clinical manifestations that range from asymptomatic to fatal. Although babesiosis is not nationally notifiable, the US incidence appears to be increasing. Babesia infection is a transfusion-transmissible disease. An estimated 70 cases were reported during 1979–2007; most of these cases were reported during the past decade.

Methods. We queried the 3 following US Food and Drug Administration safety surveillance systems to assess trends in babesiosis reporting since 1997: fatality reports for blood donors and transfusion recipients, the Adverse Event Reporting System (which includes MedWatch), and the Biological Product Deviations Reporting system. We analyzed fatality reports for time frames, clinical presentations, and patient and donor demographic characteristics.

Results. Eight of 9 deaths due to transfusion-transmitted babesiosis that were reported since 1997 occurred within the past 3 years (2005–2007). Four implicated donors and 5 patients lived in areas where Babesia infection is not endemic. Increasing numbers of Biological Product Deviations Reports were submitted to the US Food and Drug Administration over the past decade; the Adverse Event Reporting System received no reports.

Conclusions. After nearly a decade with no reported death due to transfusion-transmitted babesiosis, the US Food and Drug Administration received 8 reports from November 2005 onward. The increased numbers of deaths reported and Biological Product Deviations Reports suggest an increasing incidence of transfusion-transmitted babesiosis. Physicians should consider babesiosis in the differential diagnosis in immunocompromised, febrile patients with a history of recent transfusion, even in areas where Babesia infection is not endemic. Accurate and timely reporting of babesiosis-related donor and transfusion events assists the US Food and Drug Administration in developing appropriate public health–control measures.

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Clinical manifestations range from mild, self-limited flu-like symptoms to severe malaise, fatigue, fever, anorexia, arthralgia, myalgia, depression, vomiting, and anemia. Complications can include acute respiratory failure, congestive heart failure, and renal failure [2, 3]. Patients who are immunocompromised, asplenic, coinfected with other tick-transmitted infectious pathogens, and/or elderly are at risk of increased disease severity [1, 4, 5].

After acquiring Babesia parasites from a tick bite, infected individuals may develop symptoms within 1–4 weeks. Most cases are probably not reported, because many infections are asymptomatic, symptoms are mild, or a patient may be coinfected with Borrelia burgdorferi (with Babesia infection remaining undiagnosed) [6–8]. In addition to a probable lack of clinical awareness, especially in areas of nonendemicity, many states have...
no reporting requirement [6, 9, 10], and babesiosis, unlike Lyme disease, is not nationally notifiable. Infected patients can harbor circulating parasites for months or years without symptoms; patients with chronic low-level parasitemia may unknowingly transmit the organisms through donating blood [7, 8]. There is no licensed test for Babesia screening of donated blood products.

The majority of an estimated 70 transfusion-transmitted Babesia infections since 1979 involved B. microti; most of these infections were reported in the past decade (D. Leiby, personal communication) [7]. The national standard blood donor questionnaire includes questions about prior babesiosis infection and general donor health [11]. Individuals with previously diagnosed babesiosis are indefinitely deferred (ineligible to donate blood). However, mild Babesia infections may remain unrecognized, and infected individuals may not recall recent tick bites [12].

The purpose of this article is to alert clinicians and the public health community of reported deaths related to transfusion-transmitted babesiosis; to describe the US Food and Drug Administration’s (FDA’s) surveillance systems for adverse events and product manufacturing deviations related to donor blood collection, distribution, and transfusion; and to encourage the reporting of suspected cases of transfusion-transmitted babesiosis.

METHODS

The FDA’s surveillance systems. The FDA receives information about suspected complications of blood collection and transfusion via the 3 following systems: fatality reports for blood donors and transfusion recipients, the Adverse Event Reporting System (AERS; which includes the FDA MedWatch program), and the Biological Product Deviations Reporting (BPDR) system (table 1).

Blood establishments are required to notify the FDA “when a complication of blood collection or transfusion is confirmed to be fatal” [13, p. 58]. Center for Biologics Evaluation and Research medical officers review documentation from the reporting facility and reports from FDA investigators to assess the relationship, if any, to the blood donation or transfusion.

Biologics manufacturers are required to submit reports of adverse experiences to the AERS, the FDA’s computerized database for postmarketing safety surveillance. The voluntary MedWatch program allows health care professionals and consumers to report adverse events to the AERS.

The FDA’s BPDR system receives reports of “any event...associated with the manufacturing, to include testing, processing, packing, labeling, or storage, or with the holding or distribution of a licensed biological product or blood or blood components...in which the safety, purity, or potency of a distributed product may be affected” [14].

Data query. We queried these systems for babesiosis-related blood donation or transfusion events reported from 1 October 1996 (FDA fiscal year 1997) through 31 December 2007 (first quarter of fiscal year 2008). We analyzed fatality reports for time frames, clinical presentations, and patient and donor demographic characteristics. Babesiosis-related reports to the BPDR system typically describe either possible transfusion-transmitted disease or postdonation illness, with potential implications for the safety of the donated blood units. We categorized cases reported to the BPDR system as postdonation illness and potential transfusion transmission–related events. To avoid distortion of BPDR trends, we excluded reports of infected donors identified prospectively through antibody assay research [7].

RESULTS

Reported deaths of blood donors and recipients. Before 2005, the FDA received the last fatality report of transfusion-transmitted babesiosis in 1998; there were 2 reports in 2005, 3 in 2006, and 3 in 2007. Clinical presentations (table 2) were consistent with natural tick-borne Babesia infection in asplenic, immunocompromised, or other patients with serious comorbid chronic disease [12]. All were infected with B. microti and had received RBCs; 1 death was attributable to a unit of frozen deglycerolized RBCs. Recipients developed symptoms in 2.5–7 weeks and died within 2 months after transfusion of the implicated blood units (table 3). FDA medical review verified that transfusion-transmitted babesiosis contributed to each death.

BPDR. Figure 1 summarizes 10 years of BPDRs for potential transfusion-transmitted Babesia infection and postdonation babesiosis. The numbers that were received range from 0 in fiscal year 1999 to 25 in fiscal year 2007.

AERS. Since 1997, the AERS has not received any report of transfusion-transmitted babesiosis.

Laboratory and blood establishment investigations. All fatal cases (in blood recipients) reported here were initially diagnosed with use of a thin peripheral blood smear. For each fatality, subsequent donor testing by immunofluorescence antibody assay revealed elevated B. microti antibody titers (≥1:128). All implicated donors were indefinitely deferred from donating blood.

DISCUSSION

Babesiosis has gained attention as an emerging zoonotic disease with an expanding known geographical range [6, 9, 15, 16]. Since November 2005, the FDA learned of 8 deaths involving transfusion-transmitted babesiosis and has received increasing reports of nonfatal cases and postdonation illness. Because of the likelihood of underreporting to the FDA’s surveillance systems, these data suggest that the incidence of transfusion-transmitted babesiosis may be increasing.
Table 1. US Food and Drug Administration (FDA) surveillance systems for biologics.

<table>
<thead>
<tr>
<th>Surveillance system</th>
<th>Regulatory authority</th>
<th>Products covered</th>
<th>Reporting entity</th>
<th>Additional information</th>
<th>Publicly accessible data</th>
</tr>
</thead>
<tbody>
<tr>
<td>AERS</td>
<td>Required per 21 CFR 600.80</td>
<td>Drugs and therapeutic biologics</td>
<td>Manufacturer</td>
<td><a href="http://www.fda.gov/cder/aers/default.htm">http://www.fda.gov/cder/aers/default.htm</a></td>
<td>Quarterly data files (<a href="http://www.fda.gov/cder/aers/extract.htm">http://www.fda.gov/cder/aers/extract.htm</a>)</td>
</tr>
</tbody>
</table>

NOTE. AERS, Adverse Reporting System; BPDR, Biological Product Deviations Reports; CFR, Code of Federal Regulations.
Table 2. Summary of deaths attributed to transfusion-transmitted *Babesia* infection that were reported to the US Food and Drug Administration.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>State of residence</th>
<th>Medical history</th>
<th>Presenting complaint</th>
<th>Clinical course</th>
<th>Donor information</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>81</td>
<td>Female</td>
<td>Maryland</td>
<td>Hypercholesterolemia, hypertension, severe nosebleeds requiring transfusion but otherwise in good health</td>
<td>Severe fatigue and lethargy</td>
<td>CBC showing a hemocrit of 21%, a platelet level of 21,000 platelets/mL, BUN level of 80 mg/dL, and a creatinine level of 2.5 mg/dL (indicating renal failure); examination for anemia and fatigue identified Babesia species on PB smear (positive PCR result); treated with quinine and dapsone; developed signs of adult respiratory distress syndrome; experienced thrombotic cerebrovascular accident on day 5 of treatment with high fever</td>
<td>Resident of Maryland; traveled to New York (Long Island); positive PB smear result; B. microti IFA titer of 1:512</td>
</tr>
<tr>
<td>2</td>
<td>88</td>
<td>Male</td>
<td>Rhode Island</td>
<td>Chronic myelomonocytic leukemia with chronic anemia (transfusion-dependent) and GI bleed</td>
<td>4-Day history of progressive weakness, fatigue, and anorexia with low-grade fever</td>
<td>Babesia species identified by PB smear; treated with atovaquone and azithromycin; died on hospital day 12 with persistent parasitemia, progressive renal failure, anemia, and altered mental status</td>
<td>Resident of Rhode Island; B. microti IFA titer of 1:1024</td>
</tr>
<tr>
<td>3</td>
<td>57</td>
<td>Male</td>
<td>Texas</td>
<td>Recent history of melena and previous hepatitis B and C virus infection, cirrhosis, coronary artery disease, congestive heart failure, receipt of coronary artery bypass grafts, and GI bleed requiring transfusion</td>
<td>10–12-Day history of fever, night sweats, chills, and other complaints of melena, weakness, dizziness, anorexia, and increasing ascites</td>
<td>Babesia species identified by PB smear; treated; developed altered mental status; respiratory distress and GI bleed</td>
<td>Resident of Texas; history of travel to Massachusetts; B. microti IFA titer of 1:256</td>
</tr>
<tr>
<td>4</td>
<td>76</td>
<td>Male</td>
<td>Minnesota</td>
<td>Transfusion-dependent acute myeloblastic leukemia, rheumatoid arthritis, steroid-induced immunosuppression, and history of splenectomy, coronary artery disease, idiopathic thrombocytopenia, and multiple other medical problems</td>
<td>Several-day history of fever, cough, weakness, and dyspnea</td>
<td>Sepsis examination and broad-spectrum antibiotics started at hospital admission, with Babesia infection diagnosed (by PB smear) and treated on hospital day 2; death due to multiple medical problems</td>
<td>Resident of Minnesota; B. microti IFA titer of 1:256; negative PCR result</td>
</tr>
<tr>
<td>5</td>
<td>71</td>
<td>Female</td>
<td>Connecticut</td>
<td>Chronic liver disease (portal hypertension with gastroesophageal varices and hepatic encephalopathy), chronic transfusion-dependent anemia and diabetes, splenectomy, and cholecystectomy</td>
<td>Low-grade fever, complaints of chills and weakness for several days, with hemocrit decreasing from 29% to 23% at routine outpatient CBC monitoring</td>
<td>Babesia species identified by PB smear; treated; developed acute tubular necrosis, altered mental status, and progressive hypotension</td>
<td>Resident of Connecticut; B. microti IFA titer of 1:256; positive Western Blot result; negative PCR result</td>
</tr>
<tr>
<td>6</td>
<td>82</td>
<td>Female</td>
<td>Ohio</td>
<td>Receipt of coronary artery bypass grafts and aortic valve replacement with transfusion, asial fibrillation, cerebrovascular accident, and hyperlipidemia</td>
<td>Several-day history of fever and chills, with anemia and thrombocytopenia diagnosed at hospital admission</td>
<td>Babesia species identified by PB smear; treated with clindamycin and quinine plus automated RBC exchange by apheresis, which reduced parasitemia from 26% to 5%; developed altered mental status; the patient died of multiple-organ failure, Staphylococcus aureus pneumonia, and acute myocardial infarction</td>
<td>Resident of Ohio; traveled to Connecticut 2 months before donating blood; B. microti IFA titer of 1:256</td>
</tr>
<tr>
<td>7</td>
<td>74</td>
<td>Female</td>
<td>New Jersey</td>
<td>Insulin-dependent diabetes, end-stage renal disease (receiving dialysis), coronary artery disease (receipt of coronary artery bypass graft), GI bleeding, and polyph removal with transfusion</td>
<td>Nausea, cough, vomiting, weakness, and fever</td>
<td>Low platelet count on CBC with 8% Babesia species found by manual PB smear; confirmed by PCR as B. microti atovaquone, dapsone, and quinine failed to prevent respiratory failure, hypotension, cardiac complications, and progressive shock</td>
<td>Resident of New Jersey; B. microti IFA titer of 1:128</td>
</tr>
<tr>
<td>8</td>
<td>61</td>
<td>Female</td>
<td>Indiana</td>
<td>End-stage renal disease (receipt of hemodialysis), congestive heart failure, GI bleed requiring transfusion at previous hospital admission</td>
<td>Nausea with fever while receiving hemodialysis</td>
<td>Initially treated for bacterial sepsis (vancomycin and cefazidime); then parasite was treated with Exchange transfusion; originally received a misdiagnosis of malaria; treated with clindamycin and quinine; developed altered mental status and disseminated intravascular coagulation and died; positive PCR results and an IgG titer of 1:2048 for B. microti</td>
<td>Resident of Indiana; traveled to wooded areas of Wisconsin 2 months before donating blood; no known tick bite; IgG titer of &gt;1:256 and IgM titer of 1:20 for B. microti; negative PCR result after donation</td>
</tr>
<tr>
<td>9</td>
<td>43</td>
<td>Female</td>
<td>Delaware</td>
<td>Congenital hypoplastic anemia (Diamond-Blackfan syndrome), splenomegaly, hepatitis C virus infection, pulmonary hypertension, iron overload, and multiple transfusions</td>
<td>Fatigue, &quot;shakes&quot; for 4 days without fever, decreased appetite and loose bowel movements for 1 week, chronic dry cough with infiltrates on chest radiograph</td>
<td>Treated for pneumonia with levofloxacin, vancomycin, and oseltamivir; previous PB smear reexamined as positive for Babesia species; treated with clindamycin and quinine and transferred to ICU because of respiratory distress</td>
<td>Resident of New Jersey; traveled to Rhode Island but no known tick bite; B. microti IFA titer of 1:1024; negative PCR result; donated RBC unit was frozen and deglycerolated before transfusion</td>
</tr>
</tbody>
</table>

**NOTE.** The information in this table was reported through a passive surveillance system; we report here the information provided. BUN, blood urea nitrogen; CBC, complete blood count; GI, gastrointestinal; ICU, intensive care unit; IFA, indirect immunofluorescence antibody assay; PB, peripheral blood.
Babesia infection should be considered among potential etiologies for otherwise unexplained fever in patients who have recently received blood products. Because of the mobility of donors and transportation of blood products, babesiosis should be considered even beyond geographical regions with naturally occurring disease. As noted in table 2, several donors did not live in areas of endemicity but had traveled to these regions before donating blood.

Patients presented with symptoms (table 2) that were typical of natural infections. Most developed altered mental status, renal failure, or respiratory distress. The interval from blood transfusion to symptom onset was 2.5–7 weeks (table 3). An earlier article reported a 1–9-week time frame for transfusion-transmitted babesiosis [17]. These ranges of latency periods contrast with the natural infection incubation time of 2–4 weeks.

With 1 exception, all patients received transfusions from August through December, consistent with the seasonality of Babesia infection. Chronic parasitemia in the donor may have accounted for the 1 case involving a blood transfusion in April.

Implicated donations were identified in all cases; the donors tested positive by peripheral blood smear or immunofluorescence antibody assay. Four donors’ samples also tested by PCR had negative results. They may have been convalescent and no longer parasitemic or were PCR negative because of the small sampling volume. All donors were asymptomatic at donation and remembered no tick bite.

Because many babesiosis cases may escape recognition, questioning donors has limited preventive value [17]. Babesia species can survive blood banking procedures, including refrigeration, leukoreduction, and filtration; pathogen transmission through transfusion of RBCs, deglycerolized RBCs, or platelets can occur [1, 18–21]. Babesia parasites can survive in frozen RBCs, because the glycerol treatment prevents lysis.

In view of the short periods between symptom onset and death (5–17 days) (table 3), examination of a peripheral blood smear (or other testing, depending on availability and the level of clinical suspicion) for possible Babesia species should be considered early in the evaluation of unexplained fever during the first few weeks after transfusions, particularly in asplenic or otherwise immunocompromised patients. Infectious disease consultation may be required to microscopically distinguish Babesia species from Plasmodium organisms.

Although babesiosis is not nationally notifiable, reporting transfusion-transmitted Babesia infections to public health authorities can allow investigators to identify infected donors and interdict remaining units. Investigation of prior donations also allows testing of associated recipients.

Similarly, blood collectors should immediately report post-donation babesiosis to the transfusion facilities to expedite investigations.

**Table 3. Timing of clinical events in fatal cases involving transfusion-transmitted Babesia infection reported to the US Food and Drug Administration.**

<table>
<thead>
<tr>
<th>Timing</th>
<th>Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of implicated blood unit transfusion</td>
<td>1</td>
</tr>
<tr>
<td>9 April 1998</td>
<td>35</td>
</tr>
<tr>
<td>16 November 2005</td>
<td>43</td>
</tr>
<tr>
<td>6 December 2005</td>
<td>49</td>
</tr>
<tr>
<td>24 August 2006</td>
<td>49</td>
</tr>
<tr>
<td>20 September 2006</td>
<td>49</td>
</tr>
<tr>
<td>6 September 2007</td>
<td>43</td>
</tr>
<tr>
<td>17 September 2007</td>
<td>49</td>
</tr>
<tr>
<td>20 September 2007</td>
<td>49</td>
</tr>
<tr>
<td>26 November 2007</td>
<td>49</td>
</tr>
</tbody>
</table>

* a Periods from the date of implicated transfusion to the onset of symptoms are approximate (based on available estimated dates of symptom onset).

* b Posttransfusion diagnosis of Babesia infection.

* c The patient died prior to diagnosis of Babesia infection.

**Figure 1.** Summary of babesiosis-related Biological Product Deviation Reports (BPDRs) received by the US Food and Drug Administration (FDA) during fiscal years 1997–2007 (the FDA fiscal year is from 1 October through 31 September). These data do not include reports of infected donors identified prospectively through antibody assay research trials. BPDRs may include >1 recipient, unit, or donation. Potential implication in transfusion-transmitted disease refers to reports that indicate the safety of a blood component unit that may have been affected (e.g., instances when a blood transfusion recipient received a diagnosis of babesiosis, but the donor could not be contacted for confirmation). Postdonation illness refers to illness in donors who notified the blood collection establishment after donation that they had received a diagnosis of babesiosis. Whether these donors were infected at the time of donation was unknown; all units (not yet transfused) from these donors were withdrawn, and the donors were indefinitely deferred.
prompt withdrawal of potentially infected unexpired blood components. We remind blood establishments of the requirement to submit fatality and BPDRs to the FDA.

Our data cannot distinguish whether the increase in the numbers of deaths and reports to the BPDR system reflect an increasing incidence of babesiosis and/or improved diagnosis and reporting. State Health Departments (e.g., in New York and Connecticut) have also seen an increase in the number of babesiosis case reports over the past 10 years [22–25].

Each year, >5 million recipients receive >14 million transfusions of whole blood or RBCs [26]. Transfusion-transmitted babesiosis appears to be rare, but increased clinician awareness of the possibility of babesiosis in febrile transfusion recipients may facilitate earlier diagnosis and more successful treatment. It will also trigger timely public health investigations to interdict extant infected units and alert other associated recipients, protecting others from this potentially fatal blood-borne pathogen. 

**Addendum.** During final revisions of this article in late September 2008, the FDA received a report of another death associated with transfusion-transmitted babesiosis. An elderly woman in Minnesota died ∼3 weeks after receipt of 2 units of RBCs. One of the donated units’ retention segments was positive for *Babesia* species by serologic testing and PCR.

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**References**