Original Research

Transfusion-Associated Babesiosis in the United States: A Description of Cases

Barbara L. Herwaldt, MD, MPH;
Jeanne V. Linden, MD, MPH;
Elizabeth Bosserman, MPH;
Carolyn Young, MD;
Danuta Olkowska, MD; and
Marianna Wilson, MS

+ Author Affiliations
From the Centers for Disease Control and Prevention, Atlanta, Georgia; New York State Department of Health, Wadsworth Center, Albany, New York; and Rhode Island Blood Center, Providence, Rhode Island.

Abstract

Background: Babesiosis is a potentially life-threatening disease caused by intraerythrocytic parasites, which usually are tickborne but also are transmissible by transfusion. Tickborne transmission of Babesia microti mainly occurs in 7 states in the Northeast and the upper Midwest of the United States. No Babesia test for screening blood donors has been licensed.

Objective: To ascertain and summarize data on U.S. transfusion-associated Babesia cases identified since the first described case in 1979.

Design: Case series.

Setting: United States.

Patients: Case-patients were transfused during 1979–2009 and had posttransfusion Babesia infection diagnosed by 2010, without reported evidence that another transmission route was more likely than transfusion. Implicated donors had laboratory evidence of infection. Potential cases were excluded if all pertinent donors tested negative.

Measurements: Distributions of ascertained cases according to Babesia species and period and state of transfusion.

Results: 159 B. microti transfusion-associated cases were included; donors were implicated for 136 (86%). The case-patients' median age was 65 years (range, <1 to 94 years). Most cases were associated with red blood cell components; 4 were linked to whole blood–derived platelets. Cases occurred in all 4 seasons and in 22 (of 31) years, but 77% (122 cases) occurred during 2000–2009. Cases occurred in 19

states, but 87% (138 cases) were in the 7 main B. microti–endemic states. In addition, 3 B. duncani cases were documented in western states.

Limitation: The extent to which cases were not diagnosed, investigated, reported, or ascertained is unknown.

Conclusion: Donor-screening strategies that mitigate the risk for transfusion transmission are needed. Babesiosis should be included in the differential diagnosis of unexplained posttransfusion hemolytic anemia or fever, regardless of the season or U.S. region.

Primary Funding Source: None.

Editors' Notes

Context
Babesiosis, a parasitic infection transmitted through tick bites, can also be acquired via blood transfusion and may result in life-threatening disease. There is no U.S. Food and Drug Administration–licensed test to screen blood donors for Babesia infection.

Contribution
The risk for transfusion-associated Babesia infection may be increasing. Cases have occurred year-round and have been seen in states where Babesia species are not endemic.

Caution
Although the cases ascribed to transfusion undoubtedly represent a fraction of those that occurred, some tickborne cases inadvertently might have been included.

Implication
Improvements in the prevention and detection of transfusion-associated babesiosis are urgently needed. —The Editors

Babesiosis is caused by intraerythrocytic parasites, which usually are tickborne but also are transmissible by transfusion (1–9). In the United States, 2 species—Babesia microti and B. duncani (formerly, the WA1-type parasite [10, 11])—have been associated with both transmission routes. The predominant zoonotic agent is the rodent parasite B. microti, which is transmitted by Ixodes scapularis ticks in expanding foci in the Northeast and upper Midwest United States, particularly during spring and summer (1–3, 12). The first described tickborne and transfusion-associated B. microti cases occurred in Massachusetts in 1969 and 1979, respectively (13–15); the first such B. duncani cases were in Washington State in 1991 and 1994 (10, 16).

Regardless of the transmission route, Babesia infection can range from asymptomatic to severe, in part depending on host factors (for example, asplenia and advanced age). Clinical infection is characterized by hemolytic anemia and nonspecific flu-like symptoms (such as fever, chills, and myalgia). Complications can include multiorgan dysfunction, disseminated intravascular coagulation, and death (1–3, 6, 7). Although a history of babesiosis is an exclusion criterion for blood donation (1), persons who meet all eligibility criteria (for example, they feel well, are afebrile, and are not anemic) can have low-level

parasitemia and remain infective for months, even longer than a year (1–6, 16, 17). No Babesia assay for screening donors has been approved by the U.S. Food and Drug Administration (FDA) (1).

Posttransfusion babesiosis has been increasingly recognized (5–9, 18–29). However, national data and perspective about the U.S. burden of cases have been lacking. The Centers for Disease Control and Prevention (CDC) led a collaborative endeavor to ascertain and compile data on U.S. posttransfusion cases identified during the 3 decades since the first described case in 1979 (14). Here we summarize the transfusion-associated Babesia cases that we ascertained, including their distributions by species, time, and place.

Methods

Data Sources

Since the 1960s, the CDC's Parasitic Diseases Laboratory has been a national reference laboratory for Babesia testing. The CDC is often contacted regarding diagnostic, clinical, and epidemiologic aspects of transfusion-associated and other Babesia cases. In addition to CDC records (such as records of test results, consultations, and case investigations), data sources for this endeavor included health departments, blood collection and transfusion services, other health professionals, and published materials and abstracts. The data available via health departments varied by jurisdiction and period; babesiosis was not a reportable disease in all states and was not nationally notifiable until January 2011. Although data were not systematically collected, some health departments, including those in babesiosis-endemic states, have routinely notified the CDC of potential transfusion cases and have submitted Babesia surveillance data to the CDC. Despite the inherent limitations of passive surveillance, collaborative relationships with public health and other pertinent agencies facilitated case ascertainment and data collection. We compiled and compared information obtained from multiple sources to maximize the quantity and quality of data and to minimize double counting.

Case Criteria and Classification

For these analyses, we established selection and classification criteria for transfusion-associated Babesia cases. Our minimal case criteria included receipt of 1 or more cellular blood components during 1979–2009, posttransfusion laboratory evidence of Babesia infection detected by 2010, and no reported evidence that another route of transmission (for example, tickborne or perinatal) was more likely than transfusion. We also required that linked (implicated) donors have laboratory evidence of infection. We excluded potential transfusion cases if all pertinent donors tested negative. If multiple cases were linked to the same donor, we defined the interrelated cases as a cluster, the first identified case as the index case (1 per donor), and the other cases in the cluster as nonindex cases (Figure 1; Table 1). To facilitate bookkeeping, we defined all cases that were not cluster-associated as index cases (1 per donor).

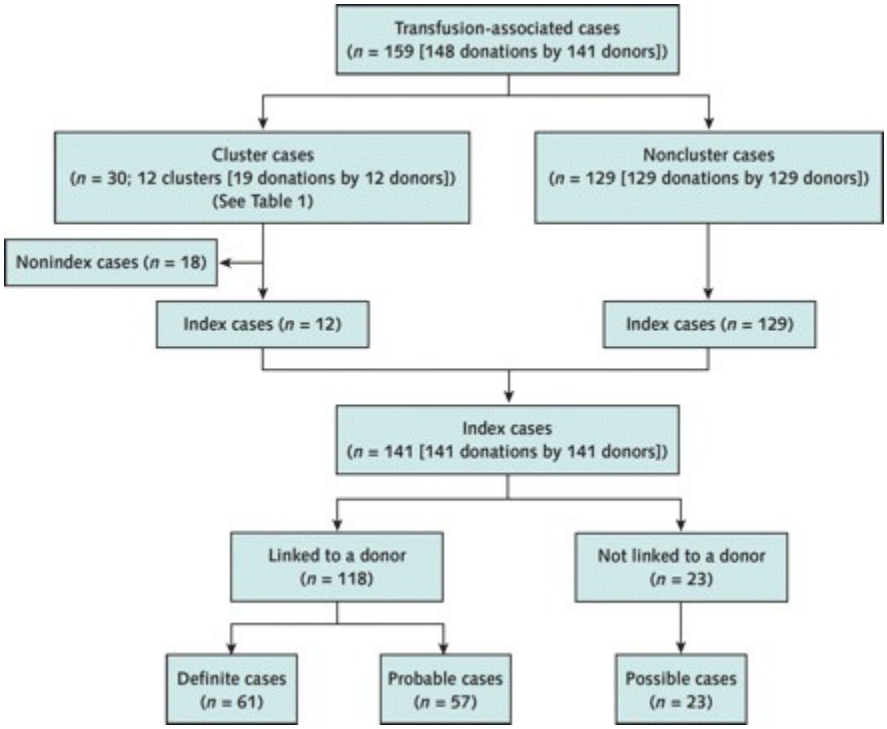


Figure 1. *Stratification of 159 U.S. transfusion-associatedBabesia microti cases, 1979–2009.*

By type of case (cluster vs. not; index vs. not) and by class of index case (definite, probable, or possible). The Figure, in conjunction with Table 1, provides perspective about the criteria for and the tallies of cases, donors, and donations. The 159 B. microti cases include 141 index cases and 18 nonindex, cluster cases. Each index case was associated with a different donor, whether implicated (n = 118) or virtual (n = 23; see Methods section). The 61 index cases classified as definite by definition include the index cases for the 12 multicase clusters (Table 1), which encompass 18 additional cases, for a total of 79 cases. The 3 B. duncani cases are not included in the Figure.

Table 1. *Twelve Clusters of U.S. Transfusion-Associated Babesia microti Cases, 1979–2009**

In general, index cases were parasitologically confirmed (Table 2) (30, 31); their detection prompted a transfusion investigation; and the linked donors and nonindex cases, if any, that were identified had parasitologic or serologic evidence of infection. We defined parasitologic evidence as detection of Babesia parasites (on blood smear or by animal inoculation) or Babesia DNA (by a molecular method). Serologic evidence of B. microti infection required positive results either by indirect fluorescent antibody (IFA) testing for total immunoglobulin or IgG or by immunoblot for IgG.

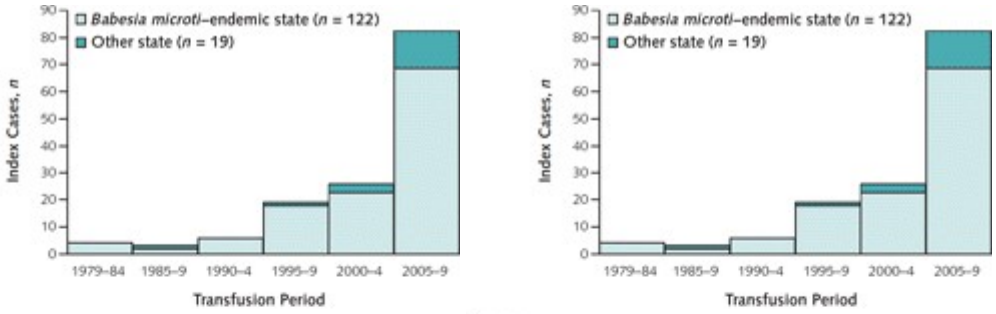
Table 2. *Characteristics of U.S. Transfusion-Associated Babesia microti Cases, Stratified by Type and Class (n= 159 Total Cases, Including 141 Index Cases), 1979–2009**

Index Babesia cases that fulfilled the selection criteria were classified as definite, probable, or possible transfusion-associated cases (Figure 1). If no donor was implicated among the subset of pertinent donors who could be tested, an index case was defined as a possible case, even if transfusion was the only known risk factor for infection. All index cases that were linked to a donor were classified as definite or probable cases. An index case was defined as a definite (vs. probable) transfusion case if at least 1 of the following additional criteria was fulfilled: 1) Transfusion was the only known or plausible risk factor for infection (for example, there was no history of residence or travel in babesiosis-endemic areas); 2) a multicase cluster was identified, with at least 1 nonindex case besides the index case (Table 1); 3) the linked donor's infection was parasitologically confirmed by testing an extant segment from the original blood unit; or 4) other donor evidence indicated active infection at the time of donation (for example, a polymerase chain reaction [PCR]–positive specimen that reflected the donor's status at donation).

Data Analysis

We conducted univariate analyses for descriptive purposes by using Epi Info, version 3.5.1 (CDC, Atlanta, Georgia), and SAS software, version 9.2 (SAS Institute Inc., Cary, North Carolina). Proportions were compared by using the chi-square test, or if expected cell counts were less than 5, the Fisher exact test. The Wilcoxon 2-sample test was used to compare the ranked distributions of ordinal variables. Statistical significance was defined as a 2-sided P value less than 0.05.

Unless otherwise specified, we stratified cases by period and state of transfusion (Table 2; Figure 2) (32). We refer to 7 states with well-established foci of zoonotic transmission as B. microti–endemic states: 5 states in the Northeast (Connecticut, Massachusetts, New Jersey, New York, and Rhode Island) and 2 in the upper Midwest (Minnesota and Wisconsin) (1, 12). The distinction between these and other states (for example, in Figure 2) is not meant to imply that tickborne transmission occurs throughout these 7 states, that it occurred in all 7 states throughout 1979–2009, or that these are the only states in which it did or does occur. Of note, during case selection and classification, we considered the evolving focality of tickborne transmission within and among states.



Babesia microti–endemic state (n = 122)
Other state (n = 19)
Index Cases, n
Transfusion Period

Cases, *n*						
Endemic states*						
Massachusetts	2				2	12
New York	2			7	10	26
Connecticut		1	4	7	1	6
Minnesota		1	1	1		8
Rhode Island			1	1	8	11
New Jersey				2	1	4
Wisconsin					1	2
Other states†						
New Hampshire‡		1				
Maryland§				1		2
Pennsylvania					1	2
Texas					1	1
Washington					1	
Ohio‖						2
Indiana‖						1
Delaware						1
North Carolina						1
California						1
Florida						2
Virginia§						1
Total index cases per period	4	3	6	19	26	83

Cases, *n*						
Endemic states*						
Massachusetts	2				2	12
New York	2			7	10	26
Connecticut		1	4	7	1	6
Minnesota		1	1	1		8
Rhode Island			1	1	8	11
New Jersey				2	1	4
Wisconsin					1	2
Other states†						
New Hampshire‡		1				
Maryland§				1		2
Pennsylvania					1	2
Texas					1	1
Washington					1	
Ohio‖						2
Indiana‖						1
Delaware						1
North Carolina						1
California						1
Florida						2
Virginia§						1
Total index cases per period	4	3	6	19	26	83

Figure 2. *Distribution of U.S. transfusion-associatedBabesia microti index cases, 1979–2009.*

By period and state of transfusion (n = 141 cases). The data are limited to the 141 B. microti index cases, 12 of which were associated with multicase clusters (Table 1). Data for the 3 B. duncani cases, which occurred in Washington (in 1994) and California (in 2000 and 2008), are not included. The x-axis includes one 6-year period (1979–1984), followed by five 5-year periods. See the Methods section for the distinction between the 7 main B. microti–endemic states and “other states”; within each category, for the tallies by state (by period), the states generally are listed in the order of their first identified case.

* Local and intraregional movements of donors and blood components were common both in the Northeast and in the upper Midwest (data not shown).

† Among the 19 index cases in 12 “other states,” the North Carolina case and 1 Florida case were not linked to donors, the other Florida case was linked to a Wisconsin resident who donated blood while wintering in Florida (cluster K; Table 1), and 1 of 3 Pennsylvania cases was linked to a Pennsylvania donor who reportedly had not traveled to a known B. microti–endemic area in another state (8). Information on the donors linked to the other 15 index cases is provided in the text or the footnotes below for 7 and 8 cases, respectively.

‡ The donor was exposed in Massachusetts (32).

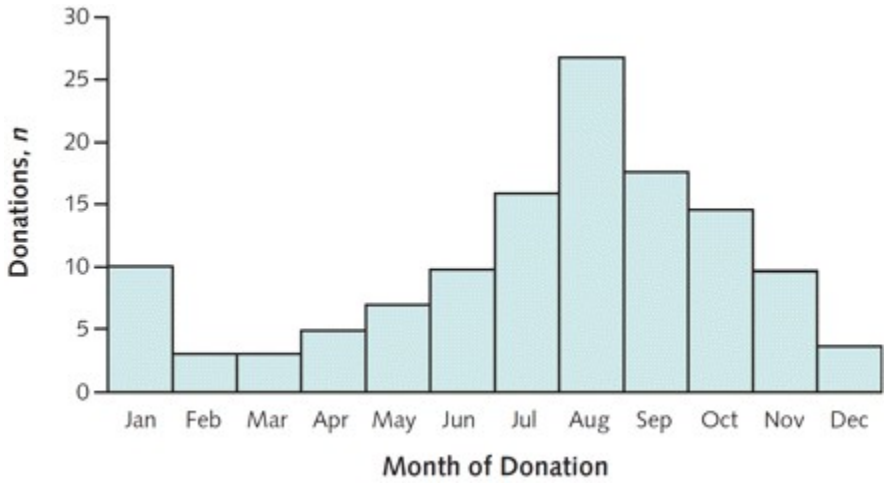
§ The 4 index cases in Maryland and Virginia were linked to donations in these states. The linked donors either were or could have been exposed in the Northeast.

The cases in Ohio (n = 2) and Indiana (n = 1) were linked to donations in Indiana (n = 2) and Ohio (n = 1) by donors exposed in B. microti–endemic states.

Results

General Perspective and Summary

For the period of 1979–2009, we included 162 transfusion-associated cases: 159 B. microti cases and 3 B. duncani cases, which are described separately. The 159 B. microti cases include 12 multicase clusters encompassing 30 cases: 12 index cases (1 per cluster) and 18 nonindex cases (5, 8, 9, 20–25) (Figure 1; Table 1). In total, 141 B. microti cases were defined as index cases: the 12 cluster-associated index cases and 129 additional cases (Table 2). Figure 2 shows their distribution by period and state of transfusion. During the initial 11 years (1979–1989), 7 index cases occurred in 5 states (14, 17, 32–36). In contrast, during the third decade (2000–2009), 109 index cases (77% of 141) and 122 total cases (77% of 159) occurred in 18 states (5–9, 18–21, 24–29, 37–42). The associated blood donations occurred in all 12 months (Appendix Figure); 59% were during July–October.



Appendix Figure. *Distribution by month of the blood donations associated with U.S. Babesia microti transfusion cases (n = 128 of 148 total donations), 1979–2009.*

The month of donation was known or estimable for 128 of 148 donations (by 141 donors) associated with transmission (Figure 1). The 19 donations by the 12 donors linked to multicase clusters occurred in 10 different months. If applicable, the month of donation was approximated by subtracting 16 days (the

median age of liquid-stored red blood cells at the time of transfusion; see text) from the transfusion date. The donations linked to the 3 B. duncani cases occurred in April (n = 2) and August (n = 1); these data are not included.

Overall, 122 (87%) of the index cases (138 total cases [87%]) were associated with transfusions in the 7 main B. microti–endemic states (Figure 2; Table 2), although not necessarily in areas of endemicity. The other 19 index cases (13%) generally were attributable to interstate movements of donors or blood components (Figure 2). Various scenarios are exemplified by the 4 cases not in eastern states (Table 2), 2 of which were attributable to donor travels: A Rhode Island resident donated while training in Washington (26), and a Texas resident donated in that state after spending the summer in Massachusetts (6). In contrast, the other case in Texas and the case in California were linked to donations in New Jersey and Maine (27), respectively. Local distributions of components collected in New Jersey also accounted for 2 cases in Pennsylvania (8, 37) and 1 in Delaware (18).

Case Characteristics

Table 2 summarizes selected characteristics of the cases, stratified by type of case (index vs. nonindex) and by class of index case (definite, probable, or possible). Table 1 provides additional perspective on the cluster-associated cases, which necessitated distinguishing between index and nonindex cases. Overall, the case-patients had a median age of 65 years; 32% were either very old (33 were in the ninth or tenth decade of life) or very young (18 were infants, 13 of whom were cluster-associated). The 19 patients with hereditary blood disorders account for the bulk (73%) of the 26 patients in the age range of 4 to 43 years. These 19 patients include 11 with sickle cell disease (8, 9, 28), 7 with thalassemia major (35, 43), and 1 with Diamond–Blackfan anemia (18); they account for at least 9 of the 32 patients known to have undergone surgical splenectomy. Three elderly patients with hematologic disorders underwent posttransfusion splenectomy (32, 134, or 215 days later), and their Babesia cases were diagnosed thereafter (Figure 3; Table 2). For 2 of these patients, parasites were noted during retrospective review of presplenectomy blood smears, a finding that refocused the investigations on earlier transfusions and donors than on those initially targeted.

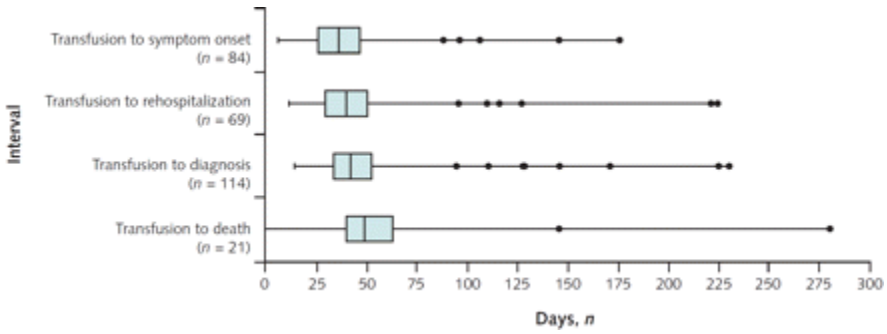


Figure 3. *Box-and-whisker plots of the distributions of time from transfusion to various events for U.S. transfusion-associated Babesia microti index cases, 1979–2009*.

The data are limited to the subsets of the 141 index patients for whom particular intervals were relevant and were known or estimable (for example, the incubation period was unclear for some patients who

had comorbid conditions or altered mental status). Each box represents the interquartile range (IQR), the internal vertical line indicates the median, the whiskers show the minimum and maximum, and the dots indicate the outliers with the longest intervals (≥75% quartile plus 1.5 × IQR). The 21 total dots—5 (6%), 6 (9%), 8 (7%), and 2 (10%) for the first, second, third, and fourth intervals from the top, respectively—are accounted for by 8 case-patients, all of whom were linked to a donor. The farthest outliers include a patient with sickle cell disease who received hematopoietic progenitor cells from a sibling with sickle trait and became symptomatic approximately 6 months after the implicated peritransplantation transfusion (28) and 2 of 3 patients who underwent posttransfusion splenectomy (see text). The second interval from the top reflects the posttransfusion hospitalization during which babesiosis was explicitly diagnosed, for patients who had been discharged at least once in the interim or had been transfused as outpatients but were hospitalized thereafter. The fourth interval includes data for 21 of 27 index patients known to have died, including the kidney donor who died the day he was transfused (see text). This interval was greater than 90 days for 2 immunocompromised patients whose intervals from diagnosis to death were less than 60 days. The patient who underwent splenectomy 215 days after transfusion died 280 days after transfusion; the patient's lymphoma also relapsed. For patients with available data, the median interval from symptom onset to death was 10 days (range, 2 to 51 days; n = 18) and the median interval from diagnosis to death was 7 days (range, 0 to 55 days; n = 22).

Five patients with transfusion cases had been transplanted with solid organs within the previous 3 months (Table 2). In addition, indirect evidence suggests that a kidney donor who received multiple transfusions the day he died served as a conduit of Babesia parasites from 1 of his blood donors to both of his kidney recipients, who developed parasitologically confirmed infection (40). No B. microti antibodies were detected by IFA testing of archived pretransplantation serum from the kidney recipients or of pretransfusion serum from the kidney donor (Table 2). However, postdonation specimens from 1 of his blood donors were seropositive (24).

The median interval from transfusion to onset of clinical manifestations was 37 days (range, 11 to 176 days) among 84 index patients with available data (Figure 3). Although babesiosis generally is considered a febrile illness, 13 (of 105) index patients were afebrile (9, 26, 32), including at least 4 adults who had cancer or were receiving immunosuppressive therapy. The median interval from symptom onset to diagnosis of index cases was 6 days (range, 0 to 54 days; n = 84). Babesiosis often was diagnosed incidentally, in some instances during routine outpatient evaluations (6), during hospitalizations for unrelated reasons, or after the patient had recovered (30) or died (data not shown). Typically, Babesia parasites were an unexpected finding when a blood smear was examined, usually in the context of a complete blood count with a manual differential (9). When intraerythrocytic ring forms were noted, malaria was the first diagnostic consideration for more than 20 index patients, at least 14 of whom were initially treated for malaria.

The minimum all-cause mortality rate among index patients was 19% (6–9, 18, 19, 32–34, 40, 44) (Table 2); Figure 3 provides various intervals to death. Some patients had a bleak prognosis even without the potential compounding effects of babesiosis. The 27 index patients known to have died include the kidney donor described earlier, whose posttrauma death on the day of transfusion clearly was unrelated to babesiosis. For other patients with available data, there was a spectrum of likelihood that babesiosis

had a causal or contributory role (6, 7); causes of death often were presumptive or unclear (data not shown).

Blood Donors and Components

A linked donor with laboratory evidence of B. microti infection was identified for 118 index cases (84%), which encompass 136 total cases (86%) (Figure 1). Among the 117 linked donors whose B. microti IFA test results were known, the median reciprocal antibody titer was 256 (range, 64 to 4096; interquartile range, 256 to 1024). Twenty-four donors (20%) had parasitologically confirmed infection (Table 2). The 20 donors with positive PCR results include 12 (71%) of 17 for whom blood retained from the original donation was tested compared with 8 (14%) of 56 for whom only postdonation specimens were available ($P < 0.001$). The median age of the 80 donors with available data was 49 years (range, 17 to 72 years); 18 donors (23%) were at least 60 years of age. Although clinical information typically was anecdotal or unspecified, some donors had pre- or postdonation symptoms or anemia of potential relevance (5, 24–27). For example, the donor who had 4 consecutive donations linked to transmission (cluster H; Table 1) had been temporarily deferred because he was anemic when he first attempted to donate after exposure (5).

Among the 151 cases for which the type of blood component was determined, 4 cases were linked to whole blood–derived platelets (4, 5, 14) and 147 were associated with red blood cells (RBCs). The median age of liquid-stored RBCs at the time of transfusion was 16 days (range, 4 to 40 days; n = 106); 4 case-patients received RBCs that were 35 to 40 days old. At least 4 patients received frozen-deglycerolized (vs. liquid-stored) RBCs (18, 35, 43). Many patients received leukoreduced RBCs (data not shown); at least 10 received irradiated RBCs.

Babesia duncani Cases

The 3 documented B. duncani cases were linked to RBC transfusions in Washington (in 1994 [16]) and California (in 2000 [45] and 2008). In each instance, the case-patient and implicated donor lived in the same state and had parasitologically confirmed infection. The case-patients include a preterm infant (45), a 59-year-old man with hemoglobinopathy (Bloch EM, Herwaldt BL, Leiby DA, et al. Unpublished data), and a 76-year-old man with a myelodysplastic syndrome who underwent cardiac surgery (16).

Discussion

Babesiosis is an uncommon but potentially life-threatening complication of transfusion that has been increasingly recognized since the first described U.S. case in 1979. Donor-screening practices do not yet include routine testing for evidence of Babesia infection. In this context, prompt detection, treatment, investigation, and reporting of Babesia cases are essential. Babesiosis should be included in the

differential diagnosis of unexplained posttransfusion hemolytic anemia, with or without fever, regardless of the season or U.S. region. To enhance the ability of public health authorities to detect, monitor, and prevent transfusion and tickborne cases, babesiosis has been designated a nationally notifiable condition, effective January 2011; as such, cases reported to health departments are notifiable to the CDC.

For the 31-year period of 1979–2009, we included 159 B. microti transfusion-associated cases, which were dispersed in time (all 4 seasons and 22 years) and place (19 states). Protracted parasitemia in some infected donors (5, 6, 16, 17), donor travels to and from areas of endemicity (6, 26), and distributions or shipments of blood components account for the potential for year-round transmission anywhere in the country. Donor travel also accounted for the 1 reported transfusion-associated case of babesiosis in Canada, which was linked to a Canadian donor infected during a camping trip in Massachusetts (46). The majority (87%) of the 159 identified U.S. cases occurred in the 7 main B. microti–endemic states, which probably reflects higher risk and greater awareness. The annual case counts fluctuated, both overall and by locale (data not shown); the limited available risk estimates for transfusion transmission also have varied in time and place (2, 3, 8, 9, 30, 39). Even so, that the majority (77%) of these 159 cases occurred during 2000–2009 is noteworthy, regardless of whether some of the aggregate increase reflects improved recognition and reporting. In comparison, for the period of 1979–2009, the CDC's National Malaria Surveillance System tallied 49 cases of transfusion-associated malaria, only 5 of which occurred during 2000–2009 (Arguin P. Personal communication). Babesia microti has become the most frequently reported transfusion-transmitted parasite in the United States (2, 3). In general, public health reports of tickborne Babesia cases also have increased in aggregate, with temporal and spatial fluctuations (CDC. Unpublished data); a national surveillance definition was first implemented in January 2011.

In addition to the 159 B. microti cases, we included 3 B. duncani cases in western states (16, 45) for a total of 162 transfusion-associated cases. The B. duncani cases, like those caused by B. microti, were in patients who ranged from preterm to elderly and who had comorbid conditions. That infection with B. duncani—and with other U.S. zoonotic Babesia agents described since the 1990s (47, 48)—is not detected by serologic or molecular assays for B. microti has implications for diagnostic testing, transfusion investigations, and potential future donor screening.

As expected, almost all cases for which the type of component was determined were associated with RBC transfusions. Red blood cell components of all storage ages, including greater than 5 weeks, were associated with transmission, as were components that had been leukoreduced, irradiated, or frozen. Although we did not conduct risk analyses, our findings underscore that Babesia parasites can survive blood bank procedures and storage conditions for RBC components. The 4 identified cases linked to whole blood–derived platelets span from 1979 (the first described transfusion case) to 2000 and presumably were attributable to residual RBCs or to extracellular parasites in the platelet units (4, 5, 14, 49). These 4 cases—and the cases in infants transfused with small RBC aliquots—underscore that small inocula can suffice to cause infection. However, even a segment from an implicated unit may test negative by PCR: The small volumes tested do not approximate the volumes transfused (1, 2).

Some of the demographic and other characteristics of the case-patients reflect those of transfused patients in general (2, 4) but may have particular importance in the context of babesiosis. For example, advanced age is a risk factor for severe babesiosis, even in otherwise healthy persons; transfusion recipients often have comorbid conditions that can increase their vulnerability to the compounding effects of babesiosis and interrelated complications (such as multiorgan dysfunction and death) (6, 7, 18, 19, 33, 34). On the other hand, even some of the adult index patients were afebrile, including several patients receiving immunosuppressive therapies that may affect the host response to infection. Although most index cases with available data were diagnosed within 2 months of transfusion, a noteworthy minority was diagnosed months later, such as in the context of posttransfusion splenectomy (Figure 3). These points not only have clinical relevance but also may affect transfusion investigations and case counts: The likelihood that transfusion transmission is considered and is investigated successfully may be lower for cases with longer intervals from the pertinent transfusion to symptom onset or diagnosis.

The 162 transfusion-associated cases we enumerated undoubtedly represent a fraction of those that occurred. The extent to which cases were not detected, investigated, or reported (to the CDC, to other public health authorities, or in publications) is unknown, both in general and with respect to periods, regions, and various case characteristics and outcomes. As underscored by the incidental diagnosis of Babesia infection, even severe cases in babesiosis-endemic regions can be missed or misdiagnosed, not just cases that are asymptomatic or mild or that occur in other U.S. regions. Even if a case is diagnosed, a transfusion investigation might not be considered, conducted, completed, or conclusive. The cases we included that were not linked to a donor (Figure 1; Table 2) highlight the challenges associated with contacting all pertinent donors and obtaining posttransfusion specimens for testing; segments from the original donations typically are not still available. Our tallies probably constitute undercounts even of documented transfusion cases (for example, those that did not come to our attention or did not meet our selection criteria) but inadvertently might include some tickborne cases. As with all surveillance, case ascertainment, selection, and classification depended on the completeness and accuracy of the available data.

Our findings underscore the year-round vulnerability of the U.S. blood supply—especially, but not only, in and near babesiosis-endemic areas. They also highlight the importance of multiagency collaborative efforts to detect, investigate, and document transfusion cases; to assess the risks for transfusion transmission; and, thereby, to inform the scope of prevention measures. In 2009, the Transfusion-Transmitted Diseases Committee of AABB (formerly, the American Association of Blood Banks) categorized babesiosis in the highest risk level for blood safety to be prioritized for intervention (50). Donors with subclinical infection are not identified by existing measures (such as temporary deferral of persons with systemic symptoms, fever, or anemia), no Babesia assay for screening donors has been approved by the FDA, and pathogen reduction techniques for RBCs or platelets are not available in the United States (1, 2, 50). The FDA's Blood Products Advisory Committee that was convened on 26 July 2010 supported the concept of regional donor testing for Babesia (51). The increasing recognition of transfusion cases strengthens the impetus for screening strategies that mitigate the transmission risk (1–3, 50, 51), including testing approaches implemented under FDA-approved protocols (1, 3, 51) and longer-term strategies with development of a high-throughput Babesia screening assay.

Article and Author Information

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC). CDC Human Subjects staff determined that the activity described here did not constitute research, as defined under 45 CRF 46.102(d).

Acknowledgment: The authors thank the many persons who contributed to this collaborative endeavor, including colleagues at CDC and in public health departments; Kathleen Grima, MD, and Debra Kessler, RN, MS, at New York Blood Center; Joanne Cote and Laurie Parent at Rhode Island Blood Center; staff of the American Red Cross, other blood collection agencies, and hospital transfusion services; and other health professionals.

Potential Conflicts of Interest: None disclosed. Forms can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M11-1169.

Requests for Single Reprints: Barbara L. Herwaldt, MD, MPH, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, 1600 Clifton Road NE, Mailstop A06, Atlanta, GA 30333; e-mail, bherwaldt@cdc.gov.

Reproducible Research Statement: The study protocol, statistical code, and dataset are not available.

Current Author Addresses: Dr. Herwaldt, Ms. Bosserman, and Ms. Wilson: Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, 1600 Clifton Road NE, Mailstop A06, Atlanta, GA 30333.

Drs. Linden and Olkowska: Wadsworth Center, New York State Department of Health, Empire State Plaza, Albany, NY 12201-0509.

Dr. Young: Rhode Island Blood Center, 405 Promenade Street, Providence, RI 02908.

Author Contributions: Conception and design: B.L. Herwaldt.

Analysis and interpretation of the data: B.L. Herwaldt, J.V. Linden, E. Bosserman, C. Young, D. Olkowska, M. Wilson.

Drafting of the article: B.L. Herwaldt.

Critical revision of the article for important intellectual content: B.L. Herwaldt, J.V. Linden, E. Bosserman, C. Young, D. Olkowska, M. Wilson.

Final approval of the article: B.L. Herwaldt, J.V. Linden, E. Bosserman, C. Young, D. Olkowska, M. Wilson.

Provision of study materials or patients: C. Young.

Administrative, technical, or logistic support: E. Bosserman.

Collection and assembly of data: B.L. Herwaldt, J.V. Linden, C. Young, D. Olkowska, M. Wilson.

Previous Section

References

1. Gubernot DM, Nakhasi HL, Mied PA, Asher DM, Epstein JS, Kumar S. Transfusion-transmitted babesiosis in the United States: summary of a workshop. Transfusion. 2009;49:2759-71. [PMID: 19821952]

2. Leiby DA. Transfusion-transmitted Babesia spp.: bull's-eye on Babesia microti. Clin Microbiol Rev. 2011;24:14-28. [PMID: 21233506]

3. Young C, Krause PJ. The problem of transfusion-transmitted babesiosis [Editorial]. Transfusion. 2009;49:2548-50. [PMID: 20163687]

4. Cable RG, Trouern-Trend J. Tickborne infections. In: Linden JV, Bianco C, eds. Blood Safety and Surveillance. New York: Marcel Dekker, Inc.; 2001:399-422.

5. Herwaldt BL, Neitzel DF, Gorlin JB, Jensen KA, Perry EH, Peglow WR, et al. Transmission of Babesia microti in Minnesota through four blood donations from the same donor over a 6-month period. Transfusion. 2002;42:1154-8. [PMID: 12430672]

6. Cangelosi JJ, Sarvat B, Sarria JC, Herwaldt BL, Indrikovs AJ. Transmission of Babesia microti by blood transfusion in Texas. Vox Sang. 2008;95:331-4. [PMID: 19138264]

7. Gubernot DM, Lucey CT, Lee KC, Conley GB, Holness LG, Wise RP. Babesia infection through blood transfusions: reports received by the US Food and Drug Administration, 1997–2007. Clin Infect Dis. 2009;48:25-30. [PMID: 19035776]

8. Tonnetti L, Eder AF, Dy B, Kennedy J, Pisciotto P, Benjamin RJ, et al. Transfusion-transmitted Babesia microti identified through hemovigilance. Transfusion. 2009;49:2557-63. [PMID: 19624607]

9. Asad S, Sweeney J, Mermel LA. Transfusion-transmitted babesiosis in Rhode Island. Transfusion. 2009;49:2564-73. [PMID: 19761547]

10. Quick RE, Herwaldt BL, Thomford JW, Garnett ME, Eberhard ML, Wilson M, et al. Babesiosis in Washington State: a new species of Babesia? Ann Intern Med. 1993;119:284-90. [PMID: 8328736]

11. Conrad PA, Kjemtrup AM, Carreno RA, Thomford J, Wainwright K, Eberhard M, et al. Description of Babesia duncani n.sp. (Apicomplexa: Babesiidae) from humans and its differentiation from other piroplasms. Int J Parasitol. 2006;36:779-89. [PMID: 16725142]

12. Herwaldt BL, McGovern PC, Gerwel MP, Easton RM, MacGregor RR. Endemic babesiosis in another eastern state: New Jersey. Emerg Infect Dis. 2003;9:184-8. [PMID: 12603988]

13. Western KA, Benson GD, Gleason NN, Healy GR, Schultz MG. Babesiosis in a Massachusetts resident. N Engl J Med. 1970;283:854-6. [PMID: 4989787]

14. Jacoby GA, Hunt JV, Kosinski KS, Demirjian ZN, Huggins C, Etkind P, et al. Treatment of transfusion-transmitted babesiosis by exchange transfusion. N Engl J Med. 1980;303:1098-100. [PMID: 7191475]

15. Jacoby GA. Was babesiosis transmitted by transfusion? [Letter]. N Engl J Med. 1981;304:733.

16. Herwaldt BL, Kjemtrup AM, Conrad PA, Barnes RC, Wilson M, McCarthy MG, et al. Transfusion-transmitted babesiosis in Washington State: first reported case caused by a WA1-type parasite. J Infect Dis. 1997;175:1259-62. [PMID: 9129100]

17. Wittner M, Rowin KS, Tanowitz HB, Hobbs JF, Saltzman S, Wenz B, et al. Successful chemotherapy of transfusion babesiosis. Ann Intern Med. 1982;96:601-4. [PMID: 7200341]

18. Zhao Y, Love KR, Hall SW, Beardell FV. A fatal case of transfusion-transmitted babesiosis in the State of Delaware. Transfusion. 2009;49:2583-7. [PMID: 19906041]

19. Blue D, Graves V, McCarthy L, Cruz J, Gregurek S, Smith D. Fatal transfusion-transmitted Babesia microti in the Midwest. Transfusion. 2009;49:8. [PMID: 18694463]

20. Fox LM, Wingerter S, Ahmed A, Arnold A, Chou J, Rhein L, et al. Neonatal babesiosis: case report and review of the literature. Pediatr Infect Dis J. 2006;25:169-73. [PMID: 16462298]

21. Kurkjian K, Marshall BC, Kumar P, Koch W, Mismas M, Garrett J, et al. Transfusion-associated babesiosis among three neonates—Virginia, 2009 [Abstract]. In: Annual Conference of the Council of State and Territorial Epidemiologists (CSTE). Portland, OR: CSTE; 2010.

22. Dobroszycki J, Herwaldt BL, Boctor F, Miller JR, Linden J, Eberhard ML, et al. A cluster of transfusion-associated babesiosis cases traced to a single asymptomatic donor. JAMA. 1999;281:927-30. [PMID: 10078490]

23. Linden JV, Kolakoski MH, Wong SJ, Carpenter JH, Kessler DA, Bianco C. Transfusion-associated babesiosis in two recipients [Abstract]. Transfusion. 2000;40 Suppl:96S.

24. Bachowski G, Kemperman MM, Skeate RC, Mair DC. Transfusion-related Babesia: outbreak and investigations in the St. Paul, Minnesota Red Cross Region in 2008 [Abstract]. Transfusion. 2009;49 Suppl:35A.

25. Wudhikarn K, Perry EH, Kemperman M, Jensen KA, Kline SE. Severe transfusion-transmitted babesiosis in an immunocompromised patient: a case report and review of literature. Am J Med. 2011 Jun 15. [Epub ahead of print] [PMID: 21683324]

26. Della-Giustina D, Laird TW Jr, Smith T. Transfusion-acquired babesiosis in a nonendemic area. Mil Med. 2005;170:295-6. [PMID: 15916297]

27. Ngo V, Civen R. Babesiosis acquired through blood transfusion, California, USA. Emerg Infect Dis. 2009;15:785-7. [PMID: 19402969]

28. Cirino CM, Leitman SF, Williams E, Fedorko D, Palmore TN, Klion A, et al. Transfusion-associated babesiosis with an atypical time course after nonmyeloablative transplantation for sickle cell disease [Letter]. Ann Intern Med. 2008;148:794-5. [PMID: 18490697]

29. Lux JZ, Weiss D, Linden JV, Kessler D, Herwaldt BL, Wong SJ, et al. Transfusion-associated babesiosis after heart transplant. Emerg Infect Dis. 2003;9:116-9. [PMID: 12533293]

30. Gerber MA, Shapiro ED, Krause PJ, Cable RG, Badon SJ, Ryan RW. The risk of acquiring Lyme disease or babesiosis from a blood transfusion. J Infect Dis. 1994;170:231-4. [PMID: 8014507]

31. Perdrizet GA, Olson NH, Krause PJ, Banever GT, Spielman A, Cable RG. Babesiosis in a renal transplant recipient acquired through blood transfusion. Transplantation. 2000;70:205-8. [PMID: 10919602]

32. Smith RP, Evans AT, Popovsky M, Mills L, Spielman A. Transfusion-acquired babesiosis and failure of antibiotic treatment. JAMA. 1986;256:2726-7. [PMID: 3773183]

33. Marcus LC, Valigorsky JM, Fanning WL, Joseph T, Glick B. A case report of transfusion-induced babesiosis. JAMA. 1982;248:465-7. [PMID: 7201036]

34. Gordon S, Cordon RA, Mazdzer EJ, Valigorsky JM, Blagg NA, Barnes SJ. Adult respiratory distress syndrome in babesiosis. Chest. 1984;86:633-4. [PMID: 6541117]

35. Grabowski EF, Giardina PJ, Goldberg D, Masur H, Read SE, Hirsch RL, et al. Babesiosis transmitted by a transfusion of frozen-thawed blood. Ann Intern Med. 1982;96:466-7. [PMID: 7199884]

36. Mintz ED, Anderson JF, Cable RG, Hadler JL. Transfusion-transmitted babesiosis: a case report from a new endemic area. Transfusion. 1991;31:365-8. [PMID: 2021001]

37. Herman JH, Ayache S, Olkowska D. Autoimmunity in transfusion babesiosis: a spectrum of clinical presentations. J Clin Apher. 2010;25:358-61. [PMID: 20824620]

38. Nicholson GT, Walsh CA, Madan RP. Transfusion-associated babesiosis in a 7-month-old infant after bidirectional Glenn procedure. Congenit Heart Dis. 2010;5:607-13. [PMID: 21106022]

39. Linden JV, Olkowska D, Grima KM, Kessler D. Incidence of babesiosis and anaplasmosis in New York State, 2004-2009 [Abstract]. Transfusion. 2010;50 Suppl:35A-40A.

40. Brennan MB, Klein CL, Thompson DM, Kazmierczack JJ, He R, Leith C, et al. Babesia microti infection in renal transplant recipients [Abstract]. In: Fifth Decennial International Conference on Healthcare Associated Infections 2010. Atlanta: Society of Healthcare Epidemiology of America; March 2010.

41. Raju M, Salazar JC, Leopold H, Krause PJ. Atovaquone and azithromycin treatment for babesiosis in an infant. Pediatr Infect Dis J. 2007;26:181-3. [PMID: 17259886]

42. Wormser GP, Lombardo G, Silverblatt F, El Khoury MY, Prasad A, Yelon JA, et al. Babesiosis as a cause of fever in patients undergoing a splenectomy. Am Surg. 2011;77:345-7. [PMID: 21375849]

43. Linden JV, Wong SJ, Chu FK, Schmidt GB, Bianco C. Transfusion-associated transmission of babesiosis in New York State. Transfusion. 2000;40:285-9. [PMID: 10738027]

44. Evenson DA, Perry E, Kloster B, Hurley R, Stroncek DF. Therapeutic apheresis for babesiosis. J Clin Apher. 1998;13:32-6. [PMID: 9590496]

45. Kjemtrup AM, Lee B, Fritz CL, Evans C, Chervenak M, Conrad PA. Investigation of transfusion transmission of a WA1-type babesial parasite to a premature infant in California. Transfusion. 2002;42:1482-7. [PMID: 12421222]

46. Kain KC, Jassoum SB, Fong IW, Hannach B. Transfusion-transmitted babesiosis in Ontario: first reported case in Canada. CMAJ. 2001;164:1721-3. [PMID: 11450217]

47. Herwaldt BL, de Bruyn G, Pieniazek NJ, Homer M, Lofy KH, Slemenda SB, et al. Babesia divergens–like infection, Washington State. Emerg Infect Dis. 2004;10:622-9. [PMID: 15200851]

48. Herwaldt B, Persing DH, Précigout EA, Goff WL, Mathiesen DA, Taylor PW, et al. A fatal case of babesiosis in Missouri: identification of another piroplasm that infects humans. Ann Intern Med. 1996;124:643-50. [PMID: 8607592]

49. Pantanowitz L, Telford SR 3rd, Cannon ME. The impact of babesiosis on transfusion medicine. Transfus Med Rev. 2002;16:131-43. [PMID: 11941575]

50. Stramer SL, Hollinger FB, Katz LM, Kleinman S, Metzel PS, Gregory KR, et al. Emerging infectious disease agents and their potential threat to transfusion safety. Transfusion. 2009;49 Suppl 2:1S-29S. [PMID: 19686562]

51. Food and Drug Administration. Meeting of the Blood Products Advisory Committee. Risk of Babesia infection by blood transfusion and potential strategies for donor testing. 26 July 2010. Accessed at www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/BloodProductsAdvisoryCommittee/ucm205013.htm on 1 July 2011.