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Parasite burden and red blood cell exchange transfusion for babesiosis

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Abstract

Background: The association between parasite burden and end-organ dysfunction in subjects with *Babesia microti* infection has not been extensively studied, nor has the optimal role of red blood cell exchange (RCE) transfusion in babesiosis treatment. This retrospective chart review evaluates the associations between parasitemia, end-organ dysfunction, and outcomes in babesiosis patients treated with antimicrobial agents and RCE compared to those treated with antimicrobial agents alone.

Materials and Methods: We evaluated adults (≥18 years of age) with laboratory-confirmed babesiosis who were admitted between 2011 and 2017 to Yale New Haven Hospital, located in a *Babesia*-endemic region of the Northeastern United States. Patient demographics, parasitemia levels, clinical and laboratory indicators of end-organ dysfunction, and outcomes were examined.

Results: Ninety-one subjects (mean age 65.1 years, 69.2% male) were studied. Subjects were stratified according to peak parasitemia: <1% (n = 34), 1-5% (n = 24), 5-10% (n = 15), and >10% (n = 18). Laboratory measures indicating degrees of hemolysis, coagulopathy, and pulmonary, renal and hepatic dysfunction differed significantly across peak parasitemia levels. Median length of hospital stay increased with each successive peak parasitemia level ($P < .001$). These results indicate a strong association between peak parasitemia level and disease severity. Nineteen subjects underwent RCE, all with peak parasitemia ≥9% and some degree of end-organ dysfunction.

Conclusions: *Babesia microti* parasitemia is closely associated with disease severity, though not all subjects with end-organ dysfunction had high-grade parasitemia. Our data suggest that the use of parasitemia >10%, coupled with clinical status, is a reasonable indicator for RCE in babesiosis patients.

KEYWORDS
babesiosis, exchange transfusion, organ dysfunction, parasite burden

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1 | INTRODUCTION

Babesiosis is an emerging tick-borne infection caused primarily by the parasite *Babesia microti*.[1] Disease transmission may also occur through blood transfusion,[2,3] organ transplantation,[4,5] and perinatally.[6,7] Symptoms and complications are often severe in immunocompromised hosts, including those with asplenia, malignancy, HIV/AIDS, or receiving immunosuppressive drug therapy.[8] Individuals with cardiac, hematologic, liver, or renal comorbidities are also susceptible to severe disease, as are those at the extremes of age.[9] For mild to moderate disease, most patients are given a 7-10-day course of atovaquone and azithromycin or alternatively, clindamycin and quinine. Red blood cell exchange (RCE) transfusion is reserved for severe infection. The first reported case of severe babesiosis treated with RCE was in 1978.[10] Since that time a number of case reports and case series have been published that have examined the use of RCE for babesiosis.[2,11-13]

Clinical practice guidelines from the American Society for Apheresis (ASFA, 2019) recommend RCE for subjects with severe babesiosis due to *Babesia microti*, as indicated by high-grade parasitemia (>10%) or who have any one or more of the following: significant hemolysis, disseminated intravascular coagulation (DIC), and/or pulmonary, renal, or hepatic compromise.[14] The Infectious Diseases Society of America lists similar indications for RCE.[15] Although RCE has been shown to effectively reduce parasite burden and improve anemia in subjects with babesiosis, it is uncertain whether RCE is more effective than medical management alone.[12] European investigators have attributed a decrease in *Babesia divergens* infection mortality over the past four decades to better diagnostic and therapeutic support, especially the early use of exchange transfusion.[16,17] The use of RCE as an adjunctive treatment for malaria is similarly uncertain but is no longer recommended by the Centers for Disease Control and Prevention (CDC) or the World Health Organization (WHO).[14,18] It also remains unclear whether the recommended indicators for RCE for severe babesiosis are optimal for identifying those who might benefit most from this procedure.

Over the past decade, high-grade *Babesia microti* parasitemia (>10%) has typically been used as an indicator for RCE at hospitals with apheresis capability. We carried out a retrospective analysis of babesiosis subjects admitted to Yale New Haven Hospital (YNHH) from 2011 to 2017 in order to: (a) assess the association between parasitemia and end-organ dysfunction, (b) determine the clinical utility of using high-grade parasitemia (>10%) compared with other parameters as an indicator for RCE, and (c) compare the outcomes of babesiosis patients who underwent RCE with those who did not.

2 | MATERIALS AND METHODS

The subject population of this retrospective medical record review consisted of adult patients (≥18 years of age) admitted for babesiosis to YNHH between 2011 and 2017. YNHH is located in a *Babesia*-endemic region of the Northeastern United States. Eligible subjects were identified in collaboration with Yale Center for Clinical Investigation Joint Data Analytics Team (JDAT). Babesiosis diagnosis was confirmed by identification of *Babesia* parasites on thin blood smear and/or amplification of *Babesia microti* DNA by PCR. Patients treated for babesiosis in an outpatient setting were excluded. The apheresis service followed the ASFA/IDSA guidelines, including consideration of automated RCE for subjects with babesiosis and heavy parasitemia (>10%), or those with significant comorbidities. The fraction of cells remaining was generally set at 0.3, the post-procedure target hematocrit (Hct) was generally 28% to 30%, and procedures were completed using a Spectra Optia or Cobe Spectra (Terumo BCT, Lakewood, Colorado). Two authors (JO and AG) performed comprehensive chart reviews and systematically abstracted the relevant demographic, clinical, and laboratory parameters for the study using a standardized template. Study procedures were approved by the Yale University Human Investigation Committee.

All statistical analyses were performed using SAS Studio 3.8. Demographic characteristics of the sample were summarized using appropriate descriptive statistics. Subjects were categorized according to peak parasitemia level (group 1: <1.0%; group 2: 1.0-5.0%; group 3: 5.0-10.0%; and group 4: >10.0%). Differences in patient demographic characteristics by treatment group (RCE vs non-RCE) were tested for significance using t tests for continuous variables or chi-squared (χ^2) tests for categorical variables. Fisher's exact test was used where the sample count in a given category was less than five.

Median laboratory values and interquartile ranges for each of the groups were computed based on either the recorded minimum or maximum laboratory value (as appropriate) relative to the reference range for each individual subject. Differences in laboratory values among the four groups were tested for significance using the Kruskal-Wallis test. Pairwise comparisons with Bonferroni correction ($\alpha = 0.0083$) were performed following a significant result for a Kruskal-Wallis test. Chi-squared (or Fisher's exact) tests were used to assess the prevalence of complications and end-organ dysfunction (ie, hemolytic anemia, pulmonary, renal, and hepatic compromise, coagulopathy, and death) across groups.

3 | RESULTS

3.1 | Study population and anti-*Babesia microti* treatment

A total of 105 babesiosis subjects were initially identified through the JDAT search. Twelve subjects were excluded because they were treated in an outpatient setting and two subjects were excluded due to lack of laboratory confirmation of babesiosis. The remaining 91 subjects admitted for babesiosis treatment from 2011 to 2017 constituted our analytic sample. Babesiosis diagnosis was confirmed by peripheral blood smear and/or *Babesia microti* PCR.

Demographic characteristics of the study group are shown in Table 1. The mean age of study subjects was 65.1 years (range: 31-93 years) and the majority were male (69.2%), white or Caucasian (77.5%), and non-Hispanic (87.6%). All study subjects received atovaquone and azithromycin with or without quinine or doxycycline as initial therapy. Nineteen subjects were treated with antimicrobial agents and RCE while 72 were treated with antimicrobial agents alone. Twelve of the 19 subjects who received RCE were given a subsequent course of clindamycin and quinine. The RCE and non-RCE groups differed in terms of race ($P = .008$), but not with respect to age at diagnosis, sex or ethnicity. None of the non-white patients had a peak parasitemia greater than 9.0% and none received RCE. Over half of subjects in the RCE group were immunocompromised (57.9%) compared to 23.6% in the non-RCE group ($P = .004$). Overall, twelve patients (13.2%) were asplenic. Asplenia differed significantly between the RCE (n = 7; 36.8%) and non-RCE (n = 5; 6.9%) groups ($P = .003$). Twenty-two subjects (24%) were co-infected with Lyme disease, 15.8% in the RCE group and 26.4% in the non-RCE group ($P = .337$).

3.2 | Association between peak parasitemia and disease severity

Subjects were categorized according to peak parasitemia level (group 1: <1.0% (n = 34; 37.3%); group 2: 1.0-5.0% (n = 24; 26.4%); group 3: 5.0-10.0% (n = 15; 16.5%); and group 4: >10.0% (n = 18; 19.8%). These groups of subjects were then assessed for disease severity. We found a strong association between parasite burden and disease severity as indicated by clinical and laboratory parameters of end-organ dysfunction (Table 2).

Hematocrit levels differed significantly across parasitemia groups ($P = .002$), with the lowest levels seen among subjects with the highest parasite burdens. Pairwise comparisons with Bonferroni correction revealed a significant difference in hematocrit level between groups 1 and 4 ($P < .001$). Lactate dehydrogenase levels also differed significantly across groups ($P < .001$), and pairwise comparison revealed differences between the following groups: 1 vs 3 ($P = .008$), 1 vs 4 ($P < .001$), 2 vs 4 ($P < .0001$), and 3 vs 4 ($P = .0003$). Indirect bilirubin levels similarly differed across groups ($P = .003$), with a significant difference between groups 1 and 4 ($P < .001$) in pairwise comparison.

The proportion of subjects requiring any oxygen supplementation differed significantly by group ($P < .001$). No subjects in group 1 (peak parasitemia <1.0%) required oxygen supplementation, compared to nearly half of subjects in group 4. Severe pulmonary compromise (requiring intubation and mechanical ventilation) was noted in

TABLE 1 Demographic characteristics of the sample population

Characteristic, n (%)[a]	Total sample (n = 91)	RCE (n = 19)	Non-RCE (n = 72)
Age at diagnosis (years), mean ± SD	65.1 ± 14.4	68.8 ± 16.1	66.3 ± 13.9
Sex			
Male	63 (69.2)	12 (63.2)	51 (70.8)
Female	28 (30.8)	7 (36.8)	21 (29.2)
Race*			
White or Caucasian	69 (77.5)	19 (100.0)	50 (71.4)
Non-White	20 (22.5)	0 (0.0)	20 (28.6)
Ethnicity			
Hispanic or Latino	11 (12.4)	0 (0.0)	11 (15.7)
Non-Hispanic or Latino	78 (87.6)	19 (100.0)	59 (84.3)

*Denotes a statistically significant difference between the RCE and non-RCE groups ($P < .05$); analysis of variance was assessed using F-test (continuous variable) or χ^2 test (categorical variable); Fisher's exact test was utilized where the sample count in a given category was <5.

[a]Numbers may not sum to totals due to missing data, and column percentages may not sum to 100% due to rounding.

TABLE 2 Association between peak parasitemia level and disease severity

Laboratory value, median (IQR)[a]	Reference range (normal)	Total sample (N = 91) Group 1 < 1.0% (n = 34)	Group 2 1.0-5.0% (n = 24)	Group 3 5.0-10.0% (n = 15)	Group 4 > 10.0% (n = 18)	P^b
Hemolysis/anemia						
Hematocrit	40-52% (male) 37-52% (female)	31.0 (7.6)	27.5 (7.4)	26.5 (8.8)	23.7 (7.6)	**.002**
Lactate dehydrogenase (LD)	122-241 U/L	435.0 (239.0)	504.0 (179.0)	670.5 (290.0)	915.0 (616.0)	**<.001**
Indirect bilirubin	—	0.7 (0.4)	0.8 (0.8)	1.0 (0.3)	1.4 (0.7)	**.003**
Pulmonary function, n (column %)[c]						
Mild–moderate compromise[d]	—	0 (0.0)	2 (8.3)	4 (26.7)	7 (38.9)	**<.001**
Severe compromise[e]	—	0 (0.0)	2 (8.3)	2 (13.3)	1 (5.6)	.120
Any O_2 supplementation	—	0 (0.0)	4 (16.7)	6 (40.0)	8 (44.4)	**<.001**
Renal function						
Blood urea nitrogen (BUN)	7-20 mg/dL	20.5 (14.0)	21.0 (15.5)	24.0 (13.0)	40.0 (30.0)	**.001**
Creatinine	0.5-1.2 mg/dL	1.0 (0.4)	1.1 (0.6)	0.9 (0.2)	1.5 (0.9)	**.003**
Hepatic function						
Total bilirubin	<1.20 mg/dL	1.0 (0.7)	1.3 (1.4)	1.6 (1.0)	2.4 (3.7)	**<.001**
Direct bilirubin	<0.20 mg/dL	0.3 (0.3)	0.4 (0.5)	0.5 (0.7)	0.9 (3.2)	**<.001**
Aspartate aminotransferase (AST)	0-34 U/L	52.0 (68.0)	83.0 (82.0)	109.0 (115.0)	143.0 (80.0)	**.002**
Alanine aminotransferase (ALT)	0–34 U/L	43.5 (83.0)	64.5 (88.0)	88.0 (37.0)	114.5 (73.0)	.092
Coagulopathy						
Platelet count	150-350 × 1000/μL	64.0 (37.0)	73.5 (58.0)	58.0 (53.0)	38.5 (21.0)	**<.001**
Fibrinogen	139-456 mg/dL	496.0 (328.0)	488.0 (113.0)	284.0 (275.0)	309.0 (103.0)	**.038**
International normalized Ratio (INR)	0.9-1.11	1.1 (0.2)	1.2 (0.7)	1.1 (0.2)	1.1 (0.4)	.832
Partial thromboplastin time (PTT)	22.4-28.9	28.7 (7.3)	29.7 (9.5)	29.2 (7.1)	30.4 (8.1)	.979

P-values were bolded to denote statistical significance ($p < .05$).

[a]Median laboratory values for the comparison groups are based on each subject's recorded maximum or minimum value outside of the reference range.

[b]*P*-values are for Kruskal-Wallis test; pairwise comparisons with Bonferroni correction ($P = .083$) tested differences between groups.

[c]For pulmonary compromise, variables are described using n (column %) and *P*-values are for χ^2 test; Fisher's exact test was utilized where the sample count in a given category was <5.

[d]Mild to moderate pulmonary compromise was defined as requiring O_2 supplementation via aerosol mask, nasal canula, Bilevel Positive Airway Pressure (BIPAP) machine or Continuous Positive Airway Pressure (CPAP) machine.

[e]Severe pulmonary compromise was defined as requiring intubation and mechanical ventilation to support oxygenation.

five total subjects (n = 2 in group 2; n = 2 in group 3; n = 1 in group 4).

Renal function differed across groups, as evident by variable levels of blood urea nitrogen (BUN) ($P = .001$) and creatinine ($P = .003$) that worsened as parasitemia increased. In pairwise comparison, BUN levels differed significantly between group 1 vs 4 ($P < .001$) and group 2 vs 4 ($P = .006$), while creatinine levels differed between group 1 vs 4 ($P = .002$) and group 3 vs 4 ($P = .001$). Hepatic function differed across groups according to levels of total bilirubin ($P < .001$), direct bilirubin ($P < .001$), and aspartate aminotransferase (AST) ($P = .002$), but not alanine aminotransferase (ALT). Significant differences in total bilirubin levels were found between group 1 vs 4 ($P = .002$) and group 3 vs 4 ($P = .001$), while direct bilirubin differed in three pairwise comparisons: group 1 vs 3 ($P = .004$), 1 vs 4 ($P < .001$), and 2 vs 4 ($P = .006$). AST levels only differed significantly between group 1 vs 4 ($P < .001$).

Coagulopathy parameters including platelet count ($P < .001$) also differed across groups. There were significant differences in platelet counts between group 1 vs 4 ($P < .001$) and 2 vs 4 ($P = .002$). International Normalized Ratio (INR) and Partial Thromboplastin Time (PTT) showed no association with parasite burden.

3.3 | Association between peak parasitemia and hospital length of stay

The overall median length of hospital stay for the study population was 5 days (IQR: 3.0; range: 1-21 days). The median length of stay was significantly longer for patients in the RCE group (7 days; IQR: 6.0) vs the non RCE group (5 days; IQR: 8.0) ($P < .001$). With each successive peak parasitemia level (from group 1 up to group 4), the median length of hospital stay increased by 1 day (Figure 1). Subjects with a peak parasitemia of <1.0% (group 1) had a median length of stay of 4 days (IQR: 2.0), while subjects in the highest peak parasitemia category (group 4; >10%) had the longest median stay at 7 days (IQR: 3.0).

3.4 | Study subject outcome

There was a marked decrease in parasitemia (Figure 2) and improvement in anemia following RCE in all subjects. In 7 subjects, a second RCE was carried out due to a residual parasite burden of higher than 5.0% (Figure S1). Transient adverse events associated with RCE were noted in six (31.6%) subjects. The most common adverse effect was a transient exacerbation of hypotension. The overall mortality rate was low at 3.3% (n = 3). Two of the three deceased patients were in the RCE group. The first had a peak parasitemia of 9.4%, cirrhosis and hypotension, was on vasopressors prior to exchange, and ultimately succumbed to septic shock. The second had a peak parasitemia of 15.6% (decreased post-RCE to 3.0%, then 2.0% and finally 1.1%), had cirrhosis and a subarachnoid hemorrhage, and died of multisystem organ failure. The patient in the non-RCE group who died had a peak parasitemia of 4.6% (decreased to 2.8% then <1.0% with antimicrobial treatment), and developed acute respiratory distress syndrome (ARDS) and shock.

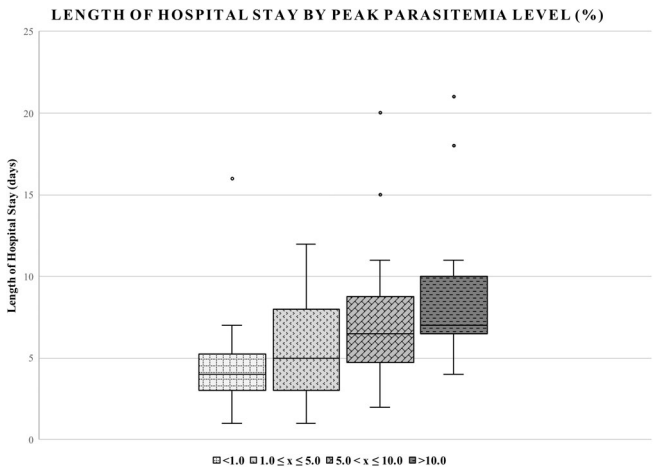

FIGURE 1 Length of hospital stay by peak parasitemia level (%)

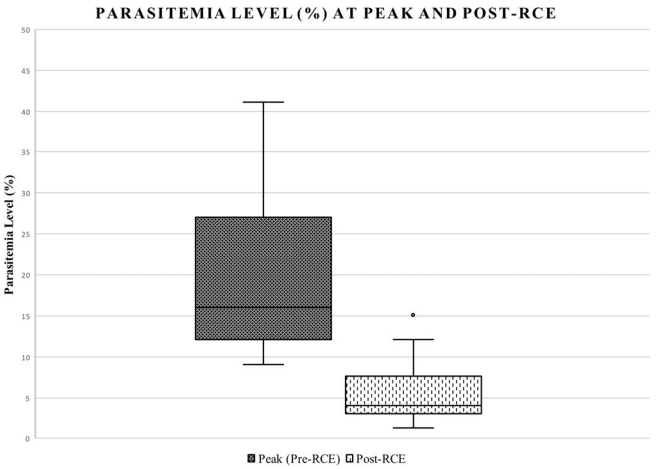

FIGURE 2 Parasitemia level (%) at peak and post-red cell exchange (RCE) transfusion

TABLE 3 ASFA/IDSA recommendations for RCE, evaluated for the study subjects

ASFA/ISDA recommendations for RCE for babesiosis treatment	Assigned clinical and laboratory indicators for RCE	Study subjects n (column %) RCE (n = 19)	non-RCE (n = 72)	P[a]
High grade parasitemia (parasitemia >10%)	Parasitemia >10%	17 (89.5%)	1 (1.4%)	**<.001**[b]
OR any one or more of the following[c]				
Severe hemolytic anemia	Hematocrit <20% and/or indirect bilirubin >1.0 mg/dL and/or lactate dehydrogenase >900 U/L	16 (84.2%)	24 (33.3%)	**<.001**
Pulmonary compromise	Mild-moderate[d]	7 (36.8)	6 (8.3)	**.002**
	Severe[e]	2 (10.5)	3 (4.2)	.279[b]
	Any O_2 supplementation required	9 (47.4)	9 (12.5)	**<.001**
Renal compromise	Creatinine >1.2 mg/dL	12 (63.2)	21 (39.6)	**.007**
Hepatic compromise	Total bilirubin >5.0 mg/dL and/or INR ≥1.5	7 (36.8)	12 (16.7)	.054[b]

P-values were bolded to denote statistical significance ($p < .05$).
[a]*P*-value for χ^2 test; Fisher's exact test was utilized where the sample count in a given category was <5.
[b]Denotes where Fisher's exact test was used.
[c]Severe hemolytic anemia and pulmonary, renal and hepatic compromise are not explicitly defined by ASFA/IDSA Guidelines.
[d]Mild to moderate pulmonary compromise was defined as requiring O_2 supplementation via aerosol mask, nasal canula, Bilevel Positive Airway Pressure (BIPAP) machine or Continuous Positive Airway Pressure (CPAP) machine.
[e]Severe pulmonary compromise was defined as requiring intubation and mechanical ventilation to support respiration.

3.5 | Indicators for RCE

Seventeen of the nineteen exchanged patients met the ASFA/IDSA clinical indicator criteria of parasitemia >10%; two additional patients with a peak parasitemia of >9% also underwent RCE. Clinical indicators for severe end-organ dysfunction (ie, severe hemolytic anemia, and pulmonary renal, and hepatic compromise) have not been well defined by existing guidelines. We therefore evaluated hypothetical criteria for end-organ dysfunction. The criteria for hemolytic anemia and pulmonary dysfunction were based on clinical criteria that would elicit a treatment response; specifically, red cell transfusion or supplemental oxygen (Table 3).

Nineteen of 91 patients (20.9%) received RCE in our study cohort. A greater number of subjects (n = 40, or 44.0%) would have undergone RCE if the assigned laboratory threshold values for severe hemolytic anemia (hematocrit <20% and/or indirect bilirubin >1.0 mg/dL and/or lactate dehydrogenase >900 U/L) were used in isolation to make an RCE decision. Eighteen subjects (19.8%) would have undergone RCE if the need for supplemental oxygen was selected as the decision point. Half of patients requiring supplemental oxygen had a parasite burden <10% and were not treated with RCE. Additional subjects (n = 33, or 36.3%) also would have undergone RCE if the assigned laboratory threshold for renal compromise (creatinine >1.2 mg/dL) was used to make an RCE decision. Nineteen subjects (20.9%) would have undergone RCE if the assigned laboratory thresholds for hepatic compromise (total bilirubin >5.0 mg/dL and/or INR ≥1.5) were used to make an RCE decision—the majority with a parasite burden <10%. We present these hypothetical end-organ RCE criteria primarily to provoke discussion and to demonstrate the need for more concrete definitions of babesiosis-associated complications and end-organ dysfunction in future iterations of RCE guidelines.

4 | DISCUSSION

In this case series of patients hospitalized for babesiosis during the past decade, we sought to address two primary questions regarding RCE: (a) is it useful? and (b) what are appropriate clinical criteria for its use? We focused on parasitemia >10% as a clinical indicator for RCE based on its association with babesiosis severity and its historical and current use as a criterion for RCE. Limited data from this study and others suggest that RCE is useful, although a definitive answer to the latter question remains elusive. RCE is beneficial in the treatment of babesiosis because it is a relatively safe procedure, markedly decreases parasite load, corrects anemia, and may help to decrease potentially harmful biological factors in blood, such as excessive pro-inflammatory cytokines.[11-14,16,19] A decrease in *Babesia divergens* infection mortality over the past four decades has been attributed in part to the early use of exchange transfusion.[16,17]

Although there is some evidence for decreased mortality due to *Babesia microti* infection in the United States over the past three decades, the contribution of RCE to this decrease has not been established. We found a strong association between parasitemia level and disease severity, which strengthens the case for parasitemia as the primary indicator for RCE. Impairment of hematologic, pulmonary, renal, and/or hepatic function are additional factors that should be considered for use of RCE in severely ill babesiosis patients.

We found that increasing parasitemia is associated with increased severity of the most common complications of babesiosis; complications that are the basis of the other parameters recommended as indicators for RCE. These include severe hemolytic anemia and pulmonary, renal, and hepatic impairment. Previous studies have found that severe outcome or complications of babesiosis are associated with parasitemias of >4%[20] or >10%.[21,22] A few exceptions include reports of death in babesiosis patients with parasitemia <3%.[12,13,23] In some of these cases, higher parasitemia may have existed earlier in the disease course, which may have caused irreversible tissue damage followed by a decrease in parasitemia in the terminal phase of illness. The mechanism of death in these patients is unclear but possibilities include worsening of a preexisting comorbid condition such as congestive heart failure or triggering of a hyperreactive immune response to *B. microti* infection with excessive production of proinflammatory cytokines.

Several recent studies have questioned the use of parasitemia >10% as a sole indication for RCE.[12,13,24] The study authors have advocated for a more holistic approach that takes into greater consideration the overall clinical status of the patient, especially with regard to renal compromise or failure. The authors emphasized that use of RCE based on a >10% parasitemia (or the other criteria presented in the guidelines) has not been validated in a randomized controlled trial and that the association between disease severity and parasitemia does not necessarily mean that this parameter is a useful indicator for exchange or that RCE is effective. Cervera-Hernandez et al (2019) described three patients with >10% parasitemia who were successfully treated without RCE.[24] We noted one such case in this retrospective series. The patient was treated with antimicrobial therapy alone after the parasitemia level rapidly decreased (from 12.7% at peak to 8.2%) within 12 hours of admission. Our sample also included one patient with a modest parasite load at the time of death, as has been observed by others.[12,13,23] Randomized controlled trials are critically needed to determine whether exchange is effective in severely ill babesiosis patients and to identify optimal indications for exchange.

Limitations of our study are similar to those of other retrospective studies. Babesiosis patients who received RCE were generally more ill than our control group who did not receive RCE and prevented a comparative evaluation of the effectiveness of RCE vs antimicrobial therapy alone. Medical management decisions were made in real time, with charts reviewed retrospectively. The apheresis service utilized the ASFA guidelines for RCE decisions and thus generally recommended RCE for subjects with parasite burdens >10%, independent of end-organ dysfunction. Likewise, the service typically recommended against RCE for ill subjects with low parasite burdens due to the questionable efficacy of such an exchange because minimal change in parasitemia would have been realized using RCE.

5 | CONCLUSIONS

Babesia microti parasitemia is closely associated with disease severity and length of hospital stay. The use of parasitemia >10% seems to be a reasonable indicator for RCE. A randomized controlled trial of RCE for severe babesiosis is needed to determine the effectiveness of this treatment, including in cases with significant end-organ impairment in the setting of low parasitemia.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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