

Case Report: Overwhelming *Babesia* Parasitemia Successfully Treated Promptly With RBC Apheresis and Triple Therapy With Clindamycin, Azithromycin, and Atovaquone

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Babesiosis with high-grade parasitemia is life-threatening, especially in asplenic hosts. We report an asplenic patient with parasitemia >50% who was successfully treated with prompt red blood cell apheresis and triple therapy with clindamycin + azithromycin + atovaquone. This regimen may be an alternative to poorly tolerated clindamycin + quinine in severe cases.

Keywords. apheresis; atovaquone; azithromycin; babesia; quinine.

Babesiosis, a tickborne illness transmitted by the *Ixodes scapularis* tick, has been increasing dramatically in incidence in the past decade, especially in the New England area [1]. As per the Centers for Disease Control and Prevention (CDC), in the state of Massachusetts the incidence of babesiosis nearly tripled, from 3.1 per 100 000 people in 2011 to 8.6 per 100 000 people in 2017 [1]. Babesiosis has a wide range of clinical manifestations and severity, from subclinical infection to severe disease leading to multiorgan failure and death. The treatment regimens for babesiosis, especially for severe babesiosis, however, are largely based on small-scale studies and anecdotal data. The latest Infectious Diseases Society of America (IDSA) guideline recommends clindamycin plus quinine for severe disease in addition to red blood cell (RBC) exchange if parasitemia is $\geq 10\%$ [2]. However, the evidence supporting this regimen is limited [3]. Quinine is associated with multiple adverse effects, which often limits its use. The combination of atovaquone and azithromycin, when compared with clindamycin plus quinine, has been shown to be similarly effective in non-life-threatening babesiosis, with far fewer severe adverse effects, in a small-scale ($n = 58$),

nonblinded randomized trial with participants who had a median parasitemia level of only 0.5% [4]. An optimal quinine-free regimen for severe babesiosis remains to be determined.

In this case report, we describe a case of an asplenic patient who survived severe babesiosis with parasitemia >50% receiving an induction regimen combining clindamycin, azithromycin, and atovaquone, in addition to RBC exchange, followed by azithromycin and atovaquone for maintenance therapy.

CASE

The patient is a 68-year-old gentleman with a history of asplenia due to a motor vehicle accident 5 years earlier and hypertension who was admitted for fever and altered mental status. One month before admission, he experienced right-sided facial droop and received a diagnosis of Bell's palsy. He received a prednisone taper along with valacyclovir, and his symptoms resolved within 1 month. Lyme disease screening returned negative at that time. Six days before admission he started to experience fever, nausea, vomiting, and diarrhea. Nasopharyngeal swab for severe acute respiratory syndrome coronavirus 2 using a reverse transcription polymerase chain reaction (RT-PCR) assay was negative. Symptoms worsened, and he was found unresponsive at home. He was initially transported to an outside hospital; initial laboratory findings are summarized in Table 1 and are notable for white blood cell count (WBC) $21.9 \times 1000/\mu\text{L}$, hemoglobin 11.5 g/dL, platelet count (PLT) $31 \times 1000/\mu\text{L}$, total bilirubin 9.6 mg/dL, and creatinine 4.68 mg/dL (baseline level 0.90 mg/dL). Peripheral blood smear demonstrated 64.2% babesia parasitemia. He was given 1 dose of azithromycin and atovaquone and transferred to our hospital. His medical history was otherwise significant for hereditary spastic paraplegia. He lives in a wooded area in New England and enjoys hiking. He did not recall any tick bites and denied recent travel. He denied any history of recent blood transfusion.

Laboratory findings from our hospital are summarized in Table 1, notable for peripheral blood smear showing 51.6% of babesia parasitemia (Figure 1). This potentially fatal high-grade parasitemia and end-organ involvement prompted immediate red blood cell (RBC) exchange. He was initially given 1 dose

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Table 1. Summary of Laboratory Values

	Reference Range	One Day Before This Admission, Outside Hospital	Day 1 (RBC Exchange Session 1)	Day 2 (RBC Exchange Session 2)	Day 5	Day 7	Day 22 (Day of Discharge)
Hematocrit, %	41.0–53.0	33.4	27.7	23.7	22.5	25.0	28.6
Hemoglobin, g/dL	13.5–17.5	11.5	9.8	8.2	7.5	8.0	8.9
White cell count, ×1000 per μL	4.5–11.0	21.9	22.1	178	12.7	13.5	5.81
Differential, %							
Neutrophils	40–70	38	65.4	75.7	73.0	61.8	35.4
Bands	0–10	21	7.1	0.9	2.0	1.0	0
Lymphocytes	22–44	19	14.2	10.8	14.0	22.1	38.6
Monocytes	4–11	15	12.4	11.7	10.0	12.1	14.6
Eosinophils	0–8	0	0	0	1.0	2.6	8.8
Basophils	0–3	0	0	0	0	0.4	2.4
Platelet count, ×1000 per μL	150–400	31	32	23	42	205	253
Sodium, mmol/L	135–145	131	133	137	138	135	134
Potassium, mmol/L	3.4–5.0	N/A (hemolyzed)	4.4	4.5	4.4	4.9	4.1
Urea nitrogen, mg/dL	8–25	98	94	88	47 (on iHD)	48 (on iHD)	56 (off iHD)
Creatinine, mg/dL	0.60–1.50	4.68	4.43	4.10	2.36 (on iHD)	3.99 (on iHD)	3.36 (off iHD)
Alanine aminotransferase, U/L	10–55	60	52	30	24	22	32
Aspartate aminotransferase, U/L	10–40	N/A (hemolyzed)	316	124	58	35	38
Total bilirubin, mg/dL	0.0–1.0	9.6	10.5	4.9	0.9	0.9	0.7
Direct bilirubin, mg/dL	0–0.4	N/A (hemolyzed)	5.0	2.7	0.5	0.3	0.2
Lactic acid, mmol/L	0.5–2.0	7.1	4.3	2.0	N/A	N/A	N/A
Lactate dehydrogenase, U/L	110–210	N/A	3072	1198	595	500	311
Haptoglobin, mg/dL	30–200	N/A	<10	<10	N/A	N/A	N/A
<i>Babesia</i> , %	0.0	64.2	51.6 (pre-RBC exchange)	9.8 (pre-RBC exchange)	0.35	<0.1	Negative
			10.0 (post-RBC exchange)	1.8 (post-RBC exchange)			
Blood culture	Negative	Negative	Negative	N/A	N/A	N/A	N/A

Abbreviations: iHD, intermittent hemodialysis; N/A, not available; RBC, red blood cells.

of clindamycin and quinine upon arrival. However, based on the experience of our center with severe babesiosis and frequent adverse effects with quinine, the treatment regimen was promptly changed to clindamycin (600 mg intravenously every 8 hours), azithromycin (500 mg intravenously every 24 hours), and atovaquone (750 mg by mouth every 12 hours). The patient underwent 2 RBC exchange sessions, with decline of his babesia percentage to 9.8% after the first session and to 1.8% after the second session. Clindamycin was continued for a total of 5 days and then discontinued. He remained on azithromycin (500 mg by mouth every 24 hours) and atovaquone, and by day 7 of admission his parasitemia burden decreased to <0.1%; other laboratory values are summarized in Table 1. *Babesia* smear was negative on day 14 of his admission. He also received an empiric 14-day course of doxycycline, although his lyme serology and anaplasma PCR were negative. His hospitalization was complicated by renal failure requiring renal replacement therapy for 14 days. His mental status improved, along with hemolysis-related laboratory values. He was discharged on day 22 of admission, remaining on atovaquone and azithromycin, both by

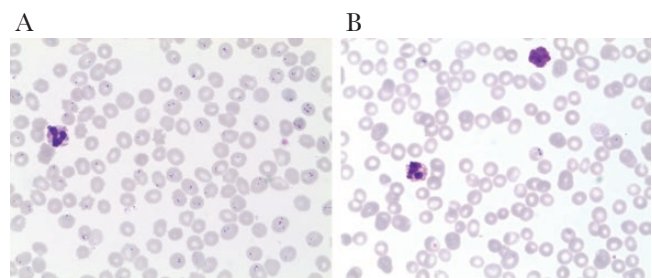


Figure 1. A, Peripheral blood thin smear on the day of admission showing multiple infected red blood cells with intraerythrocytic, nonpigmented, pleomorphic, and pyriform ring-form trophozoites of *Babesia* spp. Vacuolated intraerythrocytic ring-form trophozoites and occasional clusters of clumped extracellular rings are also seen. The estimated parasitemia in 10 high-power fields was 51.6%. Occasional merozoite tetrad-forms can be found (Maltese cross-like tetrad). B, Peripheral blood thin smear on day 5 of this admission. The estimated parasitemia in 10 high-power fields was 0.35%. Scanned peripheral blood smears from day 1 (slide 1 thick smear and slide 2 thin smear) and day 5 can be found at <https://learn.mghpathology.org/index.php/DZ120-180>.

mouth, and finished a course of treatment 14 days after parasitemia clearance.

DISCUSSION

In this case report, we described an asplenic patient who survived life-threatening severe babesiosis with an extraordinarily high-grade babesia parasitemia (>50%), treated with timely RBC exchange and an essentially quinine-free 3-drug regimen.

The role of timely RBC exchange in this case needs to be highlighted, as it promptly decreased the overwhelming parasite burden (reviewed by Radcliffe et al. [5]). However, there is no high-quality evidence to fully evaluate the utility of RBC exchange [2]. Based on a large case series of 34 cases, in which 7 patients underwent RBC exchange, a parasitemia level >10% was associated with the decision to perform RBC exchange, an arbitrary threshold unsupported by high-quality evidence. Clinicians would still need to be vigilant about post-RBC exchange parasitemia rebound [6]. Further clinical trials are warranted to fully evaluate the role of RBC exchange. While clindamycin and quinine are still recommended in the IDSA guideline [2], a growing body of evidence suggests that a quinine-free regimen may work just as well in babesiosis [4], even in severe cases [5, 7]. The rapid clinical improvement with RBC exchange in conjunction with this quinine-free regimen in this extraordinary level of parasitemia extends these observations.

Of note, this patient did receive 1 dose of quinine upon arrival. Quinine has a half-life of 10–12 hours [8], and this 1 dose was unlikely to contribute substantially to his treatment, as his parasitemia level was 10.0% after the first RBC exchange and 9.8% 12 hours before the second RBC exchange.

Based on early animal model studies, we suggest that the efficacy of quinine in babesiosis treatment might be limited. As demonstrated by Rowin et al., quinine alone was not associated with parasitemia clearance in a hamster model. When compared with untreated controls (peak parasitemia levels 53%), the combination of clindamycin + quinine (peak 22%), compared with clindamycin alone (peak 27%), was only slightly better at reducing peak parasitemia levels, while parasitemia clearance after therapy ended in both treatment arms was complete [9]. Similarly, in another animal study comparing quinine, azithromycin, and quinine + azithromycin, quinine yielded the least antiparasitic effect compared with the other treatment group; when comparing the quinine + azithromycin group with the azithromycin only group, the parasitemia level was comparable at the end of the treatment course [10]. In light of this, we believe that the role of quinine in the recommended clindamycin + quinine combination adds considerable potential toxicity for minimal therapeutic gain. Thus, we would argue that atovaquone + azithromycin in place of quinine might be more efficacious against severe parasitemia with babesia, in addition to its superior side effect profile. Accumulating evidence from in vitro and animal models also suggests that agents including tafenoquine and clofazimine are potential candidates

for severe babesiosis treatment [11–13]. Furthermore, we stress the critical importance of prompt RBC exchange in severe babesiosis to promptly decrease the parasitemia burden and halt further end-organ damage in the early phase of fulminant, life-threatening disease.

In summary, our report demonstrates that the combination of clindamycin, azithromycin, and atovaquone together with prompt RBC exchange is efficacious in life-threatening babesiosis. We advocate further clinical trials to compare clindamycin + quinine and clindamycin + azithromycin + atovaquone to provide better evidence supporting this quinine-free regimen in severe babesiosis. In addition, new agents such as tafenoquine and clofazimine could be other alternatives to quinine in babesiosis treatment, and further studies are warranted.

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