

# Babesiosis in Pregnancy: An Imitator of HELLP Syndrome

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Am J Perinatol Rep 2019;9:e147–e152.

## Abstract

### Keywords

- ▶ HELLP imitators
- ▶ tick-borne illness
- ▶ pregnancy
- ▶ infectious disease
- ▶ babesia microti
- ▶ babesiosis

HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets) is a serious pregnancy complication that can cause significant maternal and neonatal morbidity and mortality. There are several conditions that may occur in pregnancy that may imitate the laboratory findings and clinical presentation of HELLP syndrome. Babesiosis is a parasitic imitator of HELLP syndrome that can be spread by the tick, transfusions, or congenitally. Recognition and treatment of this condition is important to optimize maternal and fetal outcomes.

Babesiosis is an infectious disease caused by the tick-borne protozoa, *Babesia*.<sup>1</sup> *Babesia microti*, spread by the *Ixodes scapularis* tick, is the primary infectious agent causing babesiosis in the United States.<sup>2</sup> It is endemic to the Northeast and upper Midwest, especially in parts of New England, New York, New Jersey, Wisconsin, and Minnesota.<sup>2</sup> In 2014, 1,731 cases were reported to the Centers for Disease Control and Prevention (CDC) from 31 states, with sporadic cases reported outside of endemic areas in places, such as California, Alabama, and Washington.<sup>2</sup>

The expansion of the white-tailed deer population, wild-life habitat encroachment and greater awareness of the disease by physicians and the public have all contributed to the increasing numbers of Babesiosis.<sup>3</sup> Clinical manifestations can vary from asymptomatic to life-threatening disease. In pregnancy, babesiosis can imitate HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome.<sup>4,5</sup> A high index of suspicion is needed to appropriately diagnose and treat HELLP imitators, such as Babesiosis, in pregnancy.

## Transmission

### Tick-borne

Although adult ticks can transmit *B. microti*, most cases are result from exposure to *I. scapularis* nymphs (▶ Fig. 1) during late spring through summer.<sup>3</sup> Tick-borne transmission of

*Babesia* primarily peaks during warm months and has been on the rise in the last decade, becoming almost as common as Lyme disease in some areas of southern New England.<sup>2,3</sup> Symptoms usually occur 1 to 4 weeks after an infected tick bite,<sup>3</sup> although many patients infected with babesiosis cannot recall a tick bite.<sup>2</sup>

### Blood Transfusion

Babesiosis is currently the most common red blood cell (RBC) transfusion-transmitted pathogen reported to the U.S. Food and Drug Administration (FDA).<sup>6</sup> Transfusion-transmitted babesiosis has been linked various blood products including RBCs, frozen deglycerolized RBCs, and whole blood-derived platelet concentrates (presumably from residual RBCs).<sup>6</sup> This method of transmission may be one explanation for cases to occur in nonendemic areas because (1) patients with sub-clinical infection may donate blood in nonendemic areas and (2) infected blood may be exported to nonendemic areas in times of shortages.<sup>3,6,7</sup> Patients with transfusion of contaminated blood products usually become symptomatic 1 to 9 weeks after transfusion with a median incubation period of 34 days.<sup>3,6</sup>

In a highly endemic area, some blood collection agencies have implemented investigational testing protocols for blood donor testing which helped in removing infected units from blood supply.<sup>6,8</sup> In March 2018, the FDA approved the

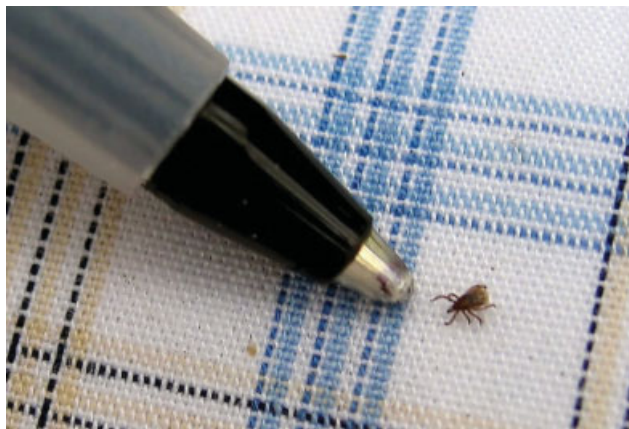
received  
November 29, 2018  
accepted after revision  
December 11, 2018

DOI <https://doi.org/10.1055/s-0039-1687873>.  
ISSN 2157-6998.

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**Fig. 1** *Ixodes scapularis* tick in nymph stage. Image provided by Dr. Graham Hickling, University of Tennessee, Institute of Agriculture.

Imugen *B. microti* arrayed fluorescent immunoassay (AFIA) for detection of antibodies to *B. microti* in human plasma samples and Imugen *B. microti* nucleic acid test (NAT) for detection in human whole blood samples.<sup>8</sup> Approval of both tests was granted to Oxford Immunotec, Inc and are in house tests that can only be formed at the Norwood, Massachusetts facility. Currently, there is no guidance for testing of donor samples; however, the FDA is planning on issuing a draft guidance later this year with recommendations for reducing the risk of transfusion-transmitted babesiosis.<sup>8</sup>

### Transplacental

Transplacental and congenital babesiosis has been documented in the literature.<sup>9</sup> Cases of congenital babesiosis were detected 19 to 41 days after birth and were characterized by asymptomatic maternal infection, maternal fever, neonatal hemolytic anemia, and thrombocytopenia. Infants responded to antibiotic therapy and all infants required blood transfusion.<sup>10</sup>

### Pathogenesis

*Babesia* organisms enter the erythrocyte and mature into merozoites which then invade nearby red cells, ensuring persistence of the infection. Pathogenesis is dependent on the host response to infection and parasite-induced alterations in the erythrocyte membrane.<sup>3,11</sup> In mild cases of babesiosis, inflammatory cytokines, adhesion molecules, and vascular cell adhesion molecules are upregulated.<sup>3</sup> In severe disease, excessive cytokine production may impair host mitochondrial function leading to tissue hypoxia, decreased erythrocyte deformability, and parasite killing causing severe infection and complications.<sup>12</sup> Invasion and destruction of the erythrocytes can manifest as many other complications of babesiosis including fever, anemia, jaundice, hemoglobinemia, hemoglobinuria, and metabolic acidosis. Notably, this understanding of the varied host response in human subjects is limited and based on case studies, natural vertebrate hosts, and animal models.<sup>11</sup> In mouse models, the protection conferred by adoptive transfer of splenic immune cells is age dependent and genetically determined.<sup>11</sup>

### Clinical Presentation

*B. microti* infection can vary in clinical manifestation from asymptomatic to acute and fatal disease.<sup>7</sup> As previously mentioned, presentations vary and depend on the host's immune status.<sup>5</sup> In one cohort study, 20% of adults were asymptomatic.<sup>11</sup> Patients with clinical manifestations can present with mild to moderate disease or severe disease.<sup>3</sup> Asymptomatic and mild infections usually occur in patients who are immunocompetent and have parasitemia < 4%.<sup>1</sup> Symptoms of mild/moderate disease are similar to common viral illnesses with gradual onset of malaise and fatigue.<sup>1,11</sup> Fever usually develops with temperatures as high as 105.6°F. Other common symptoms include chills and sweats and may be accompanied by a headache, myalgia, anorexia, nonproductive cough, arthralgias, and nausea.<sup>11</sup>

Patients affected with severe infection often have nausea, vomiting, diarrhea, and hemoglobinuria.<sup>7</sup> Severe derangements in laboratory values can lead to a variety of complications and require hospitalization. Also, a parasitemia level > 4% is associated with severe disease. Risk factors associated with severe disease are parasitemia > 4%, neonates, age of 50 years old and immunocompromised persons, such as those with cancer, human immunodeficiency virus infection, hemoglobinopathy, functional asplenia, chronic heart, lung, or liver disease.<sup>3</sup> Pregnancy may predispose to increased severity of disease since it is an immunocompromised state; however, maternal risk factors for severe babesiosis are not well understood.<sup>4,13</sup> However, it is important to note that there is not a strict relationship between the level of parasitemia above 4% and the severity of illness.<sup>12</sup>

In both mild and severe disease, fever is the most common sign of babesiosis infection and maybe occasionally accompanied by splenomegaly or hepatomegaly.<sup>3,11</sup> Although less common, mild pharyngeal erythema, jaundice, retinopathy, and retinal infarcts are also sometimes present.<sup>3</sup> A rash is not usually present; however, if noted should raise the concern for coinfection with Lyme disease.<sup>3,11</sup> Physicians should keep babesiosis on their list of differentials for febrile transfusion reaction, especially for the elderly, immunocompromised, and patients who have undergone a splenectomy.<sup>7</sup>

### Complications

About 50% of patients hospitalized with babesiosis develop complications.<sup>11</sup> The most common complications are acute respiratory distress syndrome and disseminated intravascular coagulation.<sup>11,14</sup> Other complications, such as congestive heart failure, coma, liver failure, renal failure or splenic rupture, may also occur.<sup>11</sup> Fatality rates are 6 to 9% amongst hospitalized patients and up to 21% in those patients with immunosuppression.<sup>11</sup>

When comparing nonpregnant patients with complications, severe anemia defined as a hemoglobin level ≤ 10 g/dL, were associated with complicated babesiosis.<sup>14</sup> Parasitemia level > 10% was associated with complicated babesiosis but the association did not reach statistical significance.<sup>14</sup>

## Diagnosis

A high index of suspicion is required to make a diagnosis of babesiosis.<sup>7</sup> A diagnosis should be considered if a patient resides in or has traveled to a *Babesia* endemic area or has received a blood transfusion in the last 6 months and presents with symptoms that might be consistent with babesiosis.<sup>3</sup> Diagnosis of babesiosis is by visualization of intraerythrocytic trophozoites or merozoites on Wright–Giemsa stained blood smears under oil immersion.<sup>7</sup> The level of parasitemia is generally between 1 and 10% but can be as high as 80%.<sup>3</sup>

Polymerase chain reaction (PCR) is a more sensitive blood test compared with a blood smear and provides molecular characterization of *Babesia species*.<sup>3</sup> PCR can be considered of diagnostic benefit when the patient may be early in the phase of the infection and parasites may be difficult to visualize on blood smears.<sup>15</sup> Serology is a useful tool for supporting the diagnosis; however, it may be absent in early disease and thus doesn't replace microscopy or PCR.<sup>15</sup> A 4-fold rise in *Babesia* IgG (immunoglobulin G) titer helps to differentiate between recent or past infection which a single positive antibody titer cannot do.<sup>3</sup> During the acute phase of the illness, IgG titers can exceed 1:1,024 which usually decline to 1:64 or less within 8 to 12 months.<sup>3</sup>

About 1% of patients infected with babesiosis have coinfection with another tick-borne disease, including anaplasmosis, ehrlichiosis, and Lyme disease.<sup>4</sup> Thus, it is important to test for other tick-borne agents when presented with a presumed tick-borne disease.<sup>7</sup>

## Laboratory Abnormalities

Laboratory findings from the invasion and destruction of RBCs can lead to hemolytic anemia and can render laboratory abnormalities including low hemoglobin, low hematocrit, and elevated lactate dehydrogenase. Serum liver enzyme concentrations are often elevated, and thrombocytopenia is common. Severe illness may cause elevated serum levels of blood urea nitrogen and creatinine and are often accompanied by proteinuria.<sup>3</sup>

The laboratory findings of babesiosis are similar to HELLP syndrome and can often lead to a diagnostic dilemma.<sup>4</sup> The clinical course of HELLP syndrome, like babesiosis, is often

characterized by progressive and sometimes with a sudden deterioration. Thus, management of patients with preeclampsia or HELLP syndrome with worsening laboratory findings includes prompt delivery if beyond 34 weeks of gestation or earlier if there is disseminated intravascular coagulation, liver infarction, hemorrhage, renal failure, pulmonary edema, placental abruption, or nonreassuring fetal status.<sup>16</sup>

The differential diagnosis of babesiosis should be considered on the differential of HELLP syndrome imitators to avoid iatrogenic preterm delivery, delay in treatment, and complications of undiagnosed and untreated babesiosis.<sup>17</sup> **Table 1** demonstrates the similar clinical manifestations and laboratory evaluation in HELLP syndrome and babesiosis.

A peripheral blood smear, which is typically done to evaluate for hemolysis in patients with HELLP syndrome, may aid in the diagnostic process by detecting intraerythrocytic parasites.<sup>5</sup>

## Babesiosis in Pregnancy: Case Series

In a review of the literature and our institution's experience with babesiosis, we identified eight cases in pregnancy found in **Table 2**. Two of these patients never had a fever.<sup>5,17</sup> HELLP syndrome was considered in 50% of the cases. All patients had laboratory features found in HELLP syndrome, including transaminitis (not reported by Raucher et al); and thrombocytopenia ranging from 8,000–120,000/ $\mu$ L. One patient had proteinuria (case 2). Two patients had coinfection with other tick-borne diseases, namely Lyme disease (case 2) and anaplasmosis.<sup>17</sup>

Our review in pregnancy reinforced that parasitemia load does not necessarily correlate with severity of illness. One patient that had acute hypoxemic respiratory failure had a parasitemia load of just 1.1% (case 1). Laboratory abnormalities and symptomatic infection were present in a patient with a parasitemia load of just 0.08% (case 2). One patient with a parasitemia load of 19.13% developed severe disseminated intravascular coagulation (DIC), acute kidney infection (AKI), and complications of hemorrhage secondary to DIC (case 3).

Seventy-five percent of the patients were treated with the preferred first line treatment, clindamycin, and quinine. One patient (case 1) had a drug reaction to the regimen; hence, azithromycin and atavoquone were used in her case. Raucher, et al did not utilize antiparasitic agents. One patient with severe babesiosis and parasitemia of 19.13% required

**Table 1** HELLP versus Babesiosis

	HELLP syndrome	Babesiosis
Clinical Manifestations	Nausea, vomiting, diarrhea, malaise, abdominal pain, midepigastic pain, headache, jaundice, visual changes, $\pm$ elevated blood pressure	Fever, myalgias, arthralgias, anorexia, fatigue, chills/sweats, headache, abdominal pain, photophobia
Laboratory findings	Hemolysis, liver enzymes, LDH, BUN/Cr, Thrombocytopenia, $\pm$ proteinuria	Hemolysis, liver enzymes, LDH, BUN/Cr, thrombocytopenia, hematuria, $\pm$ proteinuria
Complications	DIC, liver infarction, renal failure, pulmonary edema	ARDS, DIC, CHF, coma, liver failure, renal failure, splenic rupture.
Treatment	Delivery	Clindamycin/quinine, exchange transfusion for some patients.

Abbreviations: ARDS, acute respiratory distress syndrome; BUN, blood urea nitrogen; CHF, congestive heart failure; Cr, creatinine; DIC, disseminated intravascular coagulation; HELLP, hemolysis, elevated liver enzymes, and low platelets; LDH, lactate dehydrogenase.

**Table 2** Case series of babesiosis in pregnancy

Case age (y)	Gestational age (wk)	Symptoms	Duration of symptoms	Temperature (°Fahrenheit)	Pertinent labs	Parasitemia load (%)	Complications	Management	Concern for HELLP	Vertical transmission	Placenta findings
Case 1, <sup>a</sup> 35	28	Fever, chills, cough, back pain, hematuria	10 d	103.2	Hb: 5.5 g/dL Hct: 24.3% Plts: 55,000 $\mu$ /L	1.1–1.5%	Acute hypoxic respiratory failure, ARDS, shock liver, pancreatitis, vasopressor support, acute renal failure, H1N1	Clindamycin and quinine $\rightarrow$ changed to azithromycin, atovaquone (allergies) Empiric rifampin H1N1: oseltamivir 2 units PRBCs Delivery date unknown	Yes	N/A	N/A
Case 2, <sup>a</sup> 34	27	Fever, chills, rash; on previous treatment for Lyme disease	2 wk	102	Hb: 9 g/dL Hct: 29% Plts: 41,000 $\mu$ /L	0.08	Co infection: Lyme disease	Clindamycin + quinine; amoxicillin Delivery at term	No	No	N/A
Case 3, <sup>a</sup> 44	35 twin gestation	Myalgia, fever, shortness of breath	7 d	101.8	WBC: $1.8 \times 10^3$ cells/ $\text{mm}^3$ Hb: 10.7 g/dL Hct: 31.3% Plts: 8,000 $\mu$ /L	19.13	DIC, drug-induced thrombocytopenia, AKI requiring hemodialysis; complications of hemorrhage secondary to DIC: Sheehan's Syndrome, stress-induced postpartum cardiomyopathy, shock liver, hypoglycemia due to quinine	Clindamycin + quinine Plasma exchange Delivery at 35 4/7 weeks	Yes	Yes	Normal dichorionic diamniotic placenta
Feder et al <sup>13</sup> 31	37	Fever	5 d	103	Plts: 96,000/ $\mu$ L	2	None	Clindamycin + quinine Delivery at 39 wk	No	No	N/A
Gulerson et al <sup>33</sup>	38	Headache, RUQ pain, nausea, malaise	Acute onset	98.2	Hct: 34.4% Plts: 79,000 $\mu$ /L	0.71	Uncomplicated	Clindamycin + quinine Delivery at term	Yes	No	N/A
Luckett et al <sup>4</sup> 31	25	Headache, chills, myalgias, fatigue, fever, neck pain, headache, decreased fetal movement. Treated for Lyme disease	4 wk	103.1	WBC: $8.7 \times 10^3$ cells/ $\text{mm}^3$ Hct: 29.1% Plts: 120,000 $\rightarrow$ 67,000/ $\mu$ L	4	Acute dyspnea, tachypnea, tachycardia, hypoxia on hospital d 2 after starting treatment Pleural effusion Hypoglycemia and cinchonism due to quinine.	Clindamycin + quinine Delivery at 39 6/7 wk	No	No	Mild acute chorioamnionitis
Mupombwa et al <sup>17</sup> 34	38	Malaise, diffuse joint pain, headaches, "painful skin"	1 wk	Afebrile	Hct 32.4% Plts: 40,000/ $\mu$ L	< 0.1	Coinfection with anaplasmosis	Clindamycin + quinine Postpartum: azithromycin+ atovaquone + doxycycline Delivery at term	Yes	No	N/A
Raucher et al <sup>30</sup>	19	Chills	1 wk	104.9	Hb: 7.3 g/dL Hct: 20.8% Plts: 86,000/ $\mu$ L	4.3	Uncomplicated	Transfusion for anemia Term delivery	No	No	N/A

Abbreviations: AKI, acute kidney infection; ALT, alanine aminotransferase; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; Cx, culture; DIC, disseminated intravascular coagulation; H1N1, hemagglutinin type 1 and neuraminidase type 1; Hb, hemoglobin; Hct, hematocrit; LDH, lactate dehydrogenase; N/A, not available; Plts, platelets; PRBC, packed red blood cells; RUQ, right upper quadrant; Ucx, urine culture; WBC, white blood cell count.

<sup>a</sup>Cases from the Maternal–Fetal Medicine division at John Dempsey Hospital.

**Table 3** Antibiotic regimen and side effects

Regimen	Dosage	Common side effects
<sup>a</sup> Clindamycin and quinine		
Clindamycin	Oral: 600 mg every 8 h Intravenous: 300–600 mg every 6 h	Diarrhea, abdominal pain, hypersensitivity reaction
Quinine	650 mg every 6–8 h	Hypoglycemia, skin flushing, vision impairment
Atovaquone and azithromycin		
Atovaquone	750 mg every 12 h	Diarrhea, abdominal pain, rash, headache
Azithromycin	500 mg on d 1 followed by 25 mg on subsequent d	Diarrhea, abdominal pain, nausea

<sup>a</sup>Preferred treatment in pregnancy. Modified from CDC, available at: [www.cdc.gov/parasites/babesiosis/health\\_professionals/index.html](http://www.cdc.gov/parasites/babesiosis/health_professionals/index.html). Modified from (Vannier and Krause<sup>3</sup>).

treatment with plasma exchange in addition to antibiotics (case 3). Two cases required blood transfusion for anemia. Case 1 was lost to follow-up, and all other pregnancies were delivered at term. There was one case of vertical transmission of babesiosis in this series.

## Treatment

### Antimicrobial Therapy

Per CDC guidelines, the standard antibiotic treatment regimen for nonsevere babesiosis in adults is azithromycin plus atovaquone. Clindamycin and quinine is the preferred regimen in pregnant patients and severely ill patients. Drug regimens for both groups are for approximately 7 to 10 days. Clindamycin and quinine provide better placental penetration to prevent vertical transmission; however, atovaquone and azithromycin have also been used to treat malaria in pregnancy without increased risk of congenital birth defects, stillbirth, or anemia.<sup>4,17</sup> An alternative drug therapy option is critical to note because quinine therapy is often interrupted because of drug toxicity; thus, azithromycin plus atovaquone may be considered appropriate for some hospitalized patients with severe babesiosis.<sup>14</sup> Antibiotic dosing and side effects are noted in ►Table 3.

Persistent or relapsing babesiosis infections may be present in profoundly immunocompromised patients, and treatment can be extended for 6 weeks or longer. Negative blood smears are obtained for 2 weeks or longer before discontinuation.<sup>15</sup>

Current guidelines only advocate treating symptomatic babesiosis patients.<sup>15</sup> There are no randomized trials or studies to guide the treatment in pregnancy. However, persons with underlying health conditions may have a significant mortality risk with exposure to babesial infection.<sup>12</sup> As pregnant women are often considered immunocompromised, and evidence also exists in the literature regarding transplacental infection and congenital babesiosis, we would advocate for the treatment of all pregnant women diagnosed with babesiosis, even if asymptomatic. The pediatric team should also be alerted to maternal history of babesiosis so that appropriate blood work and surveillance can be performed after delivery.

### Exchange Transfusion

Exchange transfusion has been recommended by the Infectious Disease Society of America and American Society for Apheresis for patients with high-grade parasitemia > 10% or in the presence of significant comorbidities including hemolysis, renal, hepatic, or pulmonary compromise.<sup>12</sup> Exchange transfusion is used in conjunction with antimicrobial agents.<sup>18</sup> Patients generally tolerate the exchange transfusion well with exposure to multiple red cell transfusions being the most significant risk.<sup>12</sup> The exchange transfusion is believed to have multiple beneficial effects including removing proinflammatory cytokines and reducing the level of parasitemia.<sup>12</sup> Because the severity of disease is not always directly related to parasite load, some have suggested consideration for RBC exchange at lower parasite loads, especially in immunocompromised hosts.<sup>18</sup> There are no data available to determine if partial exchange is preferable to whole blood exchange. Expert consultation with a hematologist and infectious disease experts should be obtained.<sup>19</sup>

### Take Home Points

Babesiosis is a rare tick-borne illness which can be a parasitic imitator of HELLP syndrome. Clinical manifestations and laboratory evaluation may be similar between the two conditions making it difficult to sometimes distinguish between them. Babesiosis should be considered on the differential for patients who live or have traveled to endemic areas of babesiosis or have received a blood transfusion. A blood smear with the presence of intraerythrocytic parasites may help to guide diagnosis in patients with hemolytic anemia.<sup>4</sup> A high index of suspicion is essential to ensure prompt and correct treatment of babesiosis and to avoid iatrogenic preterm delivery potentially.<sup>4</sup>

### Conflict of Interest

None.

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