Clinical Infectious Diseases

IDSA FEATURES

Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA): 2020 Guideline on Diagnosis and Management of Babesiosis

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The purpose of this guideline is to provide evidence-based guidance for the most effective strategies for the diagnosis and management of babesiosis. The diagnosis and treatment of co-infection with babesiosis and Lyme disease will be addressed in a separate Infectious Diseases Society of America (IDSA), American Academy of Neurology (AAN), and American College of Rheumatology (ACR) guideline [1]. Recommendations for the diagnosis and treatment of human granulocytic anaplasmosis can be found in the recent rickettsial disease guideline developed by the Centers for Disease Control and Prevention [2]. The target audience for the babesiosis guideline includes primary care physicians and specialists caring for this condition, such as infectious diseases specialists, emergency physicians, intensivists, internists, pediatricians, hematologists, and transfusion medicine specialists.

EXECUTIVE SUMMARY

Summarized below are the 2020 recommendations for the diagnosis and management of babesiosis. The panel followed a systematic process used in the development of other IDSA clinical practice guidelines, which included a standardized methodology for rating the certainty of the evidence and strength of recommendation using the GRADE approach (Grading of Recommendations Assessment, Development, and Evaluation) (Figure 1). A detailed description of background, methods, evidence summary, and rationale that support each recommendation, and knowledge gaps can be found online in the full text.

I. How Should the Diagnosis of Babesiosis Be Confirmed?

Recommendation:

1. For diagnostic confirmation of acute babesiosis, we recommend peripheral blood smear examination or polymerase chain reaction (PCR) rather than antibody testing *(strong recommendation, moderate-quality evidence)*. **Comment:** The diagnosis of babesiosis should be based on epidemiological risk factors and clinical evidence, and confirmed by blood smear examination or PCR.

II. Can an Active Case of Babesiosis Be Diagnosed Based on a Single Positive Antibody Test or Is a Blood Smear, PCR, or a Four-fold Rise in Antibody Necessary for Confirmation?

Recommendation:

1. For patients with a positive *Babesia* antibody test, we recommend confirmation with blood smear or PCR before treatment is considered *(strong recommendation, moderate-quality evidence)*. **Comment**: A single positive antibody test is not sufficient to establish a diagnosis of babesiosis because *Babesia* antibodies can persist in blood for a year or more following apparent clearance of infection, with or without treatment.

III. What Are the Preferred Treatment Regimens for Babesiosis?

Recommendation:

1. We recommend treating babesiosis with the combination of atovaquone plus azithromycin or the combination of clindamycin plus quinine *(strong recommendation, moderate-quality evidence)*. **Comment:** Atovaquone plus azithromycin is the preferred antimicrobial combination for patients experiencing babesiosis, while clindamycin plus quinine is the alternative choice. The duration of treatment is 7 to 10 days in immunocompetent patients but often is extended when the patient is immunocompromised (Tables 1 and 2).

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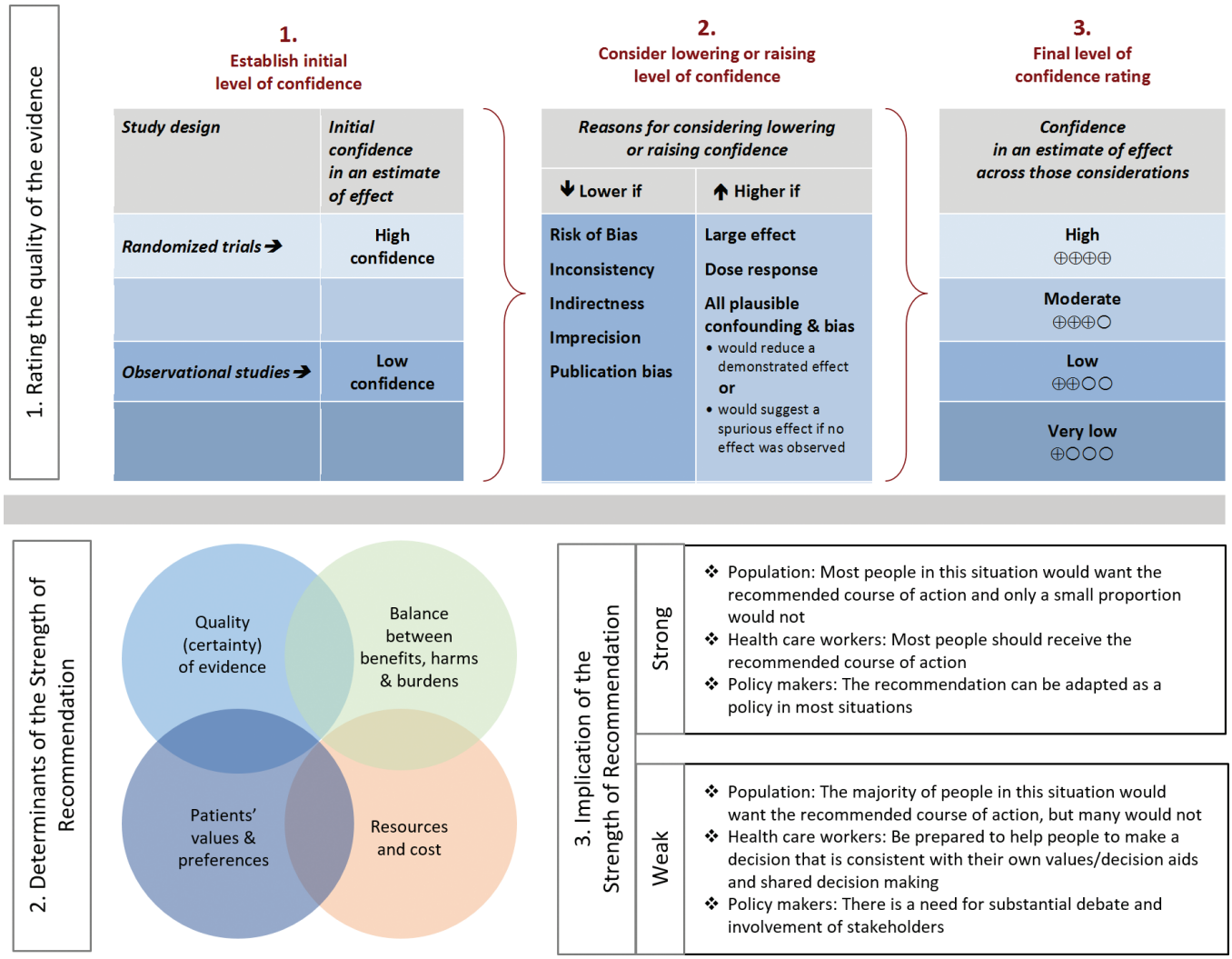

Figure 1. Approach and implications to rating the quality of evidence and strength of recommendations using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology. Unrestricted use of the figure granted by the U.S. GRADE Network (Approach and implications to rating the quality of evidence and strength of recommendations using the GRADE methodology, 2015. url: http://www.gradeworkinggroup.org).

IV. Is Exchange Transfusion Indicated for Severe Babesiosis?

Recommendation:

1. In selected patients with severe babesiosis, we suggest exchange transfusion using red blood cells *(weak recommendation, low-quality evidence)*. **Comment**: Exchange transfusion may be considered for patients with high-grade parasitemia (>10%) or who have any one or more of the following: severe hemolytic anemia and/or severe pulmonary, renal, or hepatic compromise. Expert consultation with a transfusion services physician or hematologist in conjunction with an infectious diseases specialist is strongly advised.

V. How Should Immunocompetent and Immunocompromised Patients Be Monitored After Babesiosis Therapy Is Initiated? How Frequently and for How Long?

Recommendations:

1. For immunocompetent patients, we recommend monitoring *Babesia* parasitemia during treatment of acute illness using peripheral blood smears but recommend against testing for parasitemia once symptoms have resolved *(strong recommendation, moderate-quality evidence)*.
2. For immunocompromised patients, we suggest monitoring *Babesia* parasitemia using peripheral blood smears even after they become asymptomatic and until blood smears are negative. PCR testing should be considered if blood smears have become negative but symptoms persist *(weak recommendation, moderate-quality evidence)*.

INTRODUCTION

Babesiosis is a disease caused by intraerythrocytic protozoa of the genus *Babesia* that are transmitted throughout the world by hard-bodied ticks [3]. More than 100 *Babesia* species infect a

Table 1. Treatment Regimens for Babesiosis Patients

Patient Category	Treatment Regimen	
	Adult doses	Pediatric doses
Ambulatory patients: mild to moderate disease[a]	**Preferred** Atovaquone 750 mg orally (with a fatty meal) Q12h plus azithromycin 500 mg orally on day 1, then 250 mg Q 24h for 7 to 10 days. **Alternative** [c]Clindamycin 600 mg orally Q8h plus quinine sulfate 542 mg base (which equals 650 mg salt) orally Q6h–8h for 7 to 10 days.	**Preferred** Atovaquone 20 mg/kg per dose (up to 750 mg) Q12h orally plus azithromycin 10 mg/kg (up to 500 mg) orally on day 1, then 5 mg/kg (up to 250 mg) Q24h for 7 to 10 days.[b] **Alternative** [c]Clindamycin 7–10 mg/kg (up to 600 mg/dose) orally Q8h plus quinine sulfate 6 mg base/kg (which equals 8 mg salt/kg) (up to 542 mg base or 650 mg salt/ dose) orally Q6–8h for 7 to 10 days.
Hospitalized patients: acute severe disease[d]	**Preferred** Atovaquone 750 mg orally Q12h plus azithromycin 500–1000 mg IV Q24h until symptoms abate, then convert to all oral therapy (see step-down therapy). **Alternative** [c]Clindamycin 600 mg IV Q6h plus quinine sulfate 542 mg base (which equals 650 mg salt) orally Q6h–8h until symptoms abate, then convert to all oral therapy (see step-down therapy). If infection relapses, consider one of the regimens listed in Table 3.	**Preferred** [e]Atovaquone 20 mg/kg per dose (up to 750 mg) Q12h orally plus azithromycin 10 mg/kg (up to 500 mg) Q24h IV until symptoms abate, then convert to all oral therapy (see step-down therapy). **Alternative** [c]Clindamycin 7–10 mg/kg IV (up to 600 mg/dose) IV plus quinine sulfate 6 mg base/kg (which equals 8 mg salt/kg) per dose (up to 542 mg base or 650 mg salt) Q6–8h orally until symptoms abate, then convert to all oral therapy (see step-down therapy). If infection relapses, consider one of the regimens listed in Table 3.
Hospitalized patients: step-down therapy (transition to oral therapy)	**Preferred** Atovaquone 750 mg orally Q12h plus azithromycin 250–500 mg orally Q24h. Treatment of acute disease plus step-down therapy typically lasts 7–10 days in total. A high dose of azithromycin (500–1000 mg) should be considered for immunocompromised patients. **Alternative** [c]Clindamycin 600 mg orally Q8h plus quinine sulfate 542 mg base (which equals 650 mg salt) orally Q6h–8h. Treatment of acute disease plus step-down therapy typically lasts 7–10 days in total.	**Preferred** Atovaquone 20 mg/kg per dose (up to 750 mg) orally Q12h plus azithromycin 10 mg/kg (maximum dose 500 mg) orally Q24h. Treatment of acute disease and step-down therapy typically last 7–10 days in total. **Alternative** [c]Clindamycin 7–10 mg/kg orally (up to 600 mg/dose) orally Q8h plus quinine sulfate 6 mg base/kg (which equals 8 mg salt/kg) (up to 542 mg base or 650 mg salt/ dose) orally Q6–8h. Treatment of acute disease plus step-down therapy typically lasts 7–10 days in total.
Highly immunocompromised patients	Start with one of the regimens recommended for hospitalized patients: acute severe disease and follow with step-down therapies but treat for at least 6 consecutive weeks, including 2 final weeks during which parasites are no longer detected on peripheral blood smear [3]. When oral azithromycin is used, a 500–1000 mg daily dose should be considered. If infection relapses, consider one of the regimens listed in Table 3.	

[a]These patients usually are immunocompetent, experience mild to moderate symptoms, have a parasitemia <4%, and do not require hospital admission.

[b]Azithromycin modestly increases the risk of pyloric stenosis for infants less than 6 weeks old [4].

[c]Clindamycin plus quinine is preferred when parasitemia and symptoms have failed to abate following initiation of atovaquone plus azithromycin. Some physicians have used parenteral quinidine instead of oral quinine; however, quinidine is no longer available in the United States.

[d]Exchange transfusion may be considered for patients with high-grade parasitemia (>10%) or moderate to high-grade parasitemia and any one or more of the following: severe hemolytic anemia or pulmonary, renal, or hepatic compromise. Expert consultation with a transfusion services physician or hematologist is strongly advised.

[e]This regimen has not yet been reported for treatment of children with severe babesiosis.

wide variety of wild and domestic animals. Babesiosis has long been recognized as an important disease of livestock with significant economic impact in many parts of the world. A subset of *Babesia* species infect humans, including *Babesia microti*, *Babesia duncani*, and *Babesia divergens* in the United States; *B. divergens*, *B. microti*, and *Babesia venatorum* in Europe; and *B. venatorum, B. microti,* and *Babesia crassa*-like pathogen in Asia (Figure 2) [3,5–15]. The first human case of babesiosis was described in 1957 in Europe and was attributed to *B. divergens* [16]. A decade later, human babesiosis was described in the United States. Currently, *B. microti* is endemic in the Northeast and upper Midwest and is the most common cause of human babesiosis (Figure 3) [3, 5, 17, 18].

Babesiosis due to *B. microti* imposes a significant health burden in the United States. More than 2000 cases of babesiosis are reported to the CDC annually, but several lines of evidence indicate that the actual number of cases is higher and increasing (Figure 4). The causes for the emergence of babesiosis both in number of cases and geographic range are thought to include an increase in the white-tailed deer/*Ixodes scapularis* tick populations, increased recognition of the disease, and increased human exposure to *B. microti*-infected ticks [3, 6, 20]. *Babesia microti* is transmitted primarily during the bite of an *I. scapularis* tick, but also can be transmitted through blood transfusion, organ transplantation, and perinatally [3, 21–27]. *Babesia microti* is one of the most common transfusion-transmitted pathogens in the US and causes death in about 20% of infected blood recipients, a fatality rate similar to that reported among highly immunocompromised individuals who acquire the infection through tick bite [27, 28]. Furthermore, the incidence of transfusion-transmitted babesiosis has been increasing. These factors have prompted efforts to screen the blood supply in *Babesia*-endemic states [6, 27, 29, 30]. Clinical manifestations of babesiosis include fever, fatigue, chills, sweats, headache, and anorexia [3, 6]. Severe babesiosis requires hospital admission and can be complicated by marked anemia, acute respiratory distress syndrome, disseminated intravascular coagulation, congestive heart failure, renal and liver impairment/failure, shock, splenic infarct or rupture, warm autoimmune hemolytic anemia, and/or fatal outcome [3, 6, 28, 31–36]. Of the cases reported to the CDC between 2011 and 2015 and from whom data were available, about half were hospitalized at least overnight and about one-third experienced one or more complications [6].

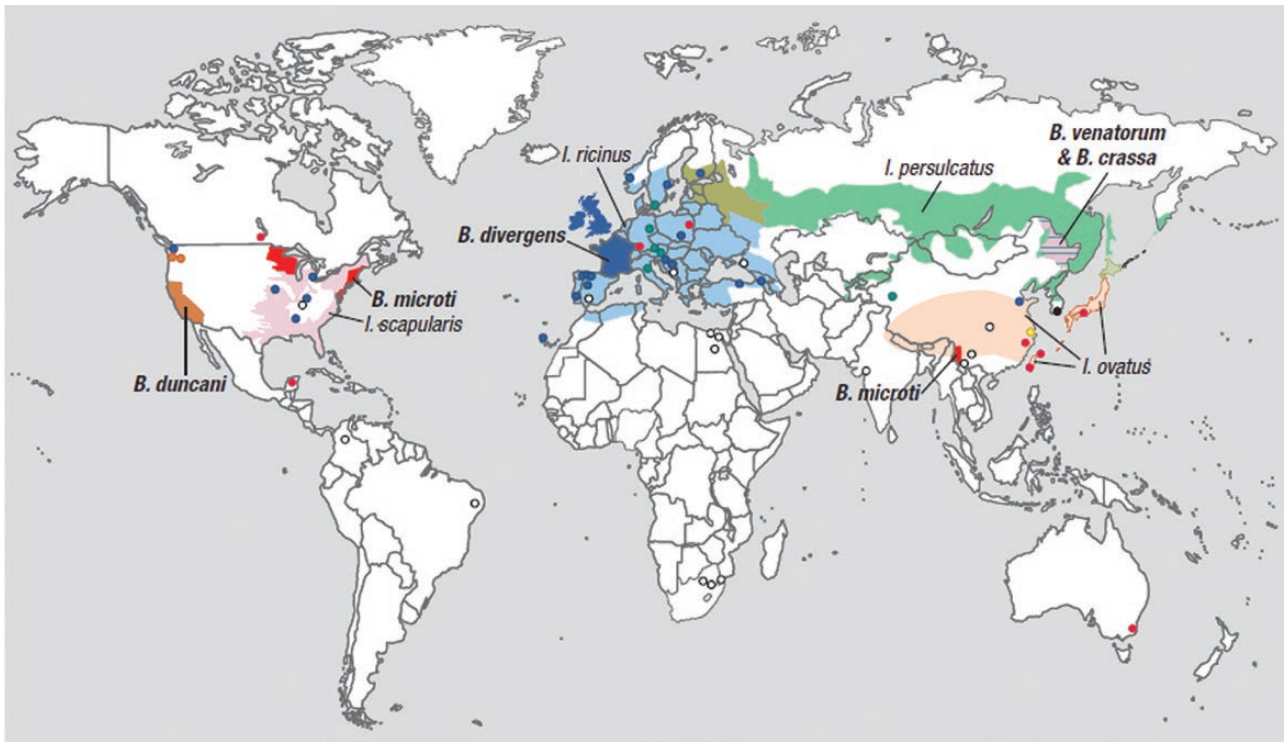

Figure 2. Worldwide distribution of human babesiosis and tick vectors. Dark colors indicate areas where human babesiosis is endemic or sporadic (defined by a total of ≥5 cases). Light colors indicate areas where tick vectors are present but human babesiosis is rare (<5 cases ever reported in an area), undocumented, or absent. Circles depict single cases, except in 3 locations (Mexico, Montenegro, and eastern Poland) where several patients were described but lived in the same area. Colors distinguish the etiologic agents: red for *Babesia microti*, orange for *Babesia duncani*, blue for *Babesia divergens*, green for *Babesia venatorum*, pink for *Babesia crassa*, black for KO1, and yellow for *Babesia* spp. XXB/Hang-Zhou. The vector for *B. duncani* tentatively has been identified as *Dermacentor albipictus* [19]. Cases due to *B. crassa*-like pathogen have been reported in northeastern China, the same region where *B. venatorum* is endemic. White circles depict cases caused by *Babesia* spp. that were not characterized at the molecular level. Asymptomatic infections and cases of travel-associated babesiosis are omitted (adapted from Vannier E. and Krause P.J. 2019. Babesiosis. In: Hunter's Tropical Medicine and Emerging Infectious Diseases pp.799–802).

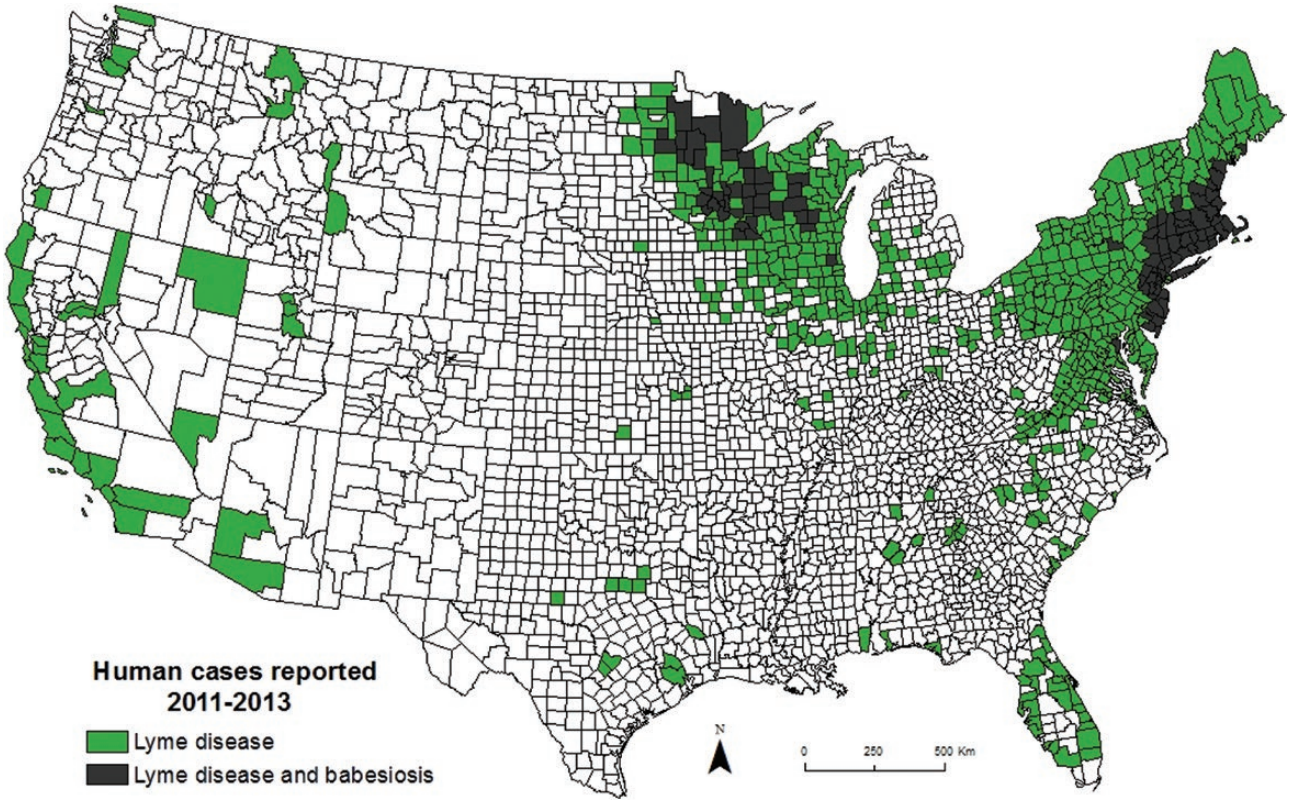

Figure 3. Human babesiosis occurs within Lyme disease endemic areas in the United States. Lyme disease and human babesiosis have been nationally notifiable conditions since 1991 and 2011, respectively. The names of counties that reported cases of Lyme disease and/or babesiosis from 2011 to 2013 were obtained from the Centers for Disease Control and Prevention. Counties with 3 or more cases of Lyme disease but fewer than 3 cases of babesiosis are depicted in green. Counties with 3 or more cases of Lyme disease and 3 or more cases of babesiosis are depicted in gray. No county reported 3 or more cases of babesiosis but fewer than 3 cases of Lyme disease (adapted from [18]).

Babesiosis has no easily recognized clinical features such as the erythema migrans skin lesion of Lyme disease. A diagnosis should be considered in a patient who resides in or has traveled to an endemic area, experiences clinical symptoms that are consistent with babesiosis, and has characteristic laboratory test abnormalities. The diagnosis is confirmed with the identification of *Babesia* parasites by microscopic evaluation of blood smears or amplification of *Babesia* DNA using a polymerase chain reaction (PCR) assay. The diagnosis of acute babesiosis cannot be confirmed solely by the presence of *Babesia* antibody in a serum sample collected at a single time point. Treatment with a combination of atovaquone plus azithromycin for 7 to 10 days achieves cure in most cases [32, 37–39]. Delay in diagnosis and treatment is associated with severe disease [37]. Prolonged antibiotic therapy should be reserved for highly immunocompromised patients [28].

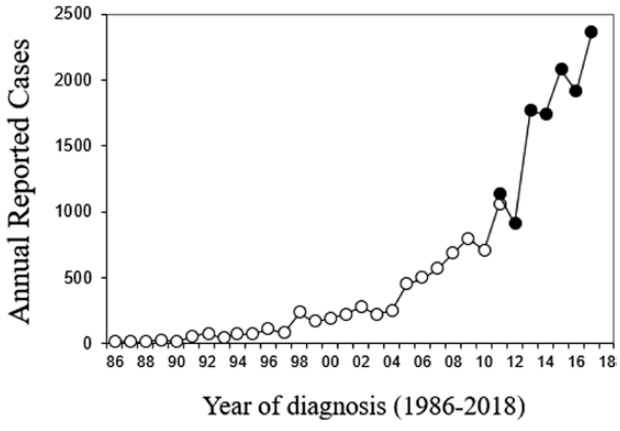

Figure 4. Sharp rise in the incidence of babesiosis in the United States in the past 2 decades. Clear circles represent total babesiosis cases reported from all State Departments of Public Health that mandated reporting between 1986 and 2011. Black circles represent cases reported to the Centers for Disease Control and Prevention from 2011 until the present. Babesiosis became a national reportable disease in 2011. The actual number of cases is likely to be higher based on evidence of asymptomatic infection, the use of passive surveillance, and the problem of misdiagnosis [3, 6].

This guideline provides current standards of diagnosis and management of human babesiosis. It is based on the best available scientific information and the sources of this evidence are provided in the guideline. The use of this guideline is intended to facilitate clinical decision-making and is designed to improve patient outcome.

Scope

This guideline encompasses the diagnosis and management of babesiosis. It is primarily intended for medical practitioners in

North America, although many recommendations apply to babesiosis patients in other geographic areas. In contrast to a prior guideline that also covered Lyme disease and anaplasmosis [40], this guideline only addresses babesiosis. Lyme disease is now comprehensively addressed in a separate guideline sponsored by the Infectious Diseases Society of America (IDSA), American Academy of Neurology, and American College of Rheumatology [1]. Anaplasmosis, along with other North American rickettsial infections, is addressed in the rickettsial disease guideline developed by the Centers for Disease Control and Prevention [2].

METHODOLOGY

Clinical Practice Guidelines

Clinical Practice Guidelines are statements that include recommendations intended to optimize patient care by assisting practitioners and patients in making shared decisions about appropriate health care for specific clinical circumstances. They are informed by a systematic review of evidence and an assessment of the benefits and risks of alternative care options [41].

Guideline Panel Composition

The Chair (P. J. K.) was selected by IDSA to lead the guideline panel. A total of 17 panelists comprised the full panel. The panel included infectious diseases specialists representing IDSA, as well as representatives from the American Academy of Pediatrics—Committee on Infectious Diseases (AAP-COID), Pediatric Infectious Diseases Society (PIDS), and GRADE working group. Finally, the panel included 3 patient representatives and 1 healthcare consumer representative. At the request of the patient representatives, we have not disclosed their names to maintain their confidentiality. Both academic and community practitioners were included, as well as members representing the disciplines of laboratory medicine and pharmacology. Guideline methodologists (Y. F. Y. and V. L.) oversaw all methodological aspects of the guideline development. A technical review team from Tufts Medical Center (R. R. B., M. C. O., and E. E. V.) performed the systematic reviews of the literature and identified and summarized the scientific evidence using the "PICO" question format (Patient/Population[P]; Intervention/Indicator[I]; Comparator/Control[C]; Outcome[O]). An IDSA staff member (G. D.) oversaw all administrative and logistic issues related to the guideline.

Disclosure and Management of Potential Conflict of Interest

All members of the expert panel complied with the IDSA policy on conflict of interest (COI), which requires disclosure of any financial, intellectual, or other interest that might be construed as constituting an actual, potential, or apparent conflict. Evaluation of such relationships as potential conflicts of interest was determined by a review process which included assessment by the Standards and Practice Guideline Committee (SPGC) Chair, the SPGC liaison to the Guideline panel and the Board of Directors liaison to the SPGC, and if necessary, the Conflicts of Interests Task Force of the Board. This assessment of disclosed relationships for possible COI was based on the relative weight of the financial relationship (ie, monetary amount) and the relevance of the relationship (ie, the degree to which an independent observer might reasonably interpret an association as related to the topic or recommendation of consideration). The reader of these guidelines should be mindful of this when the list of disclosures is reviewed. See the Notes section at the end of this guideline for the disclosures reported to IDSA.

Clinical Questions and Evidence Review

An initial list of relevant clinical questions for this guideline was created by the whole panel for review and discussion. The final set of clinical questions was approved by the entire panel. All outcomes of interest were identified *a priori* and explicitly rated for their relative importance for decision making. Each clinical question was assigned to a pair of panelists.

The Tufts Medical Center technical team consisted of 3 experts in systematic reviews who designed the literature searches to address each clinical question. Searches were limited to studies published in English. There was no restriction on the year of publication. The following electronic databases were searched: Ovid Medline, Cochrane database, Google Scholar, Scopus, and EMBASE. The initial literature searches were performed in March 2016 and then updated in August 2017 and in April 2019. Studies published up to April 2019 were included if pertinent to this guideline. To supplement the electronic searches, panelists had the option of manually searching journals, reference lists of conference proceedings, and regulatory agency websites for relevant articles. The technical team screened titles and abstracts of all identified citations. All potentially relevant citations were subjected to a full-text review, using predefined inclusion and exclusion criteria that were tailored to meet the specific population, intervention, and comparator for each clinical question. Conference abstracts and proceedings, letters to the editor, editorials, review articles, and unpublished data were excluded from the evidence that served as a basis for graded recommendations. The results of the literature search were thoroughly reviewed by the technical team for final selection of the relevant articles. Panel members reviewed the literature search for accuracy. Once the articles were selected, the technical team, in conjunction with panelists and methodologists, decided if a qualitative and/or a quantitative analysis were appropriate.

Evidence summaries for each question were prepared by the technical team. The risk of bias was assessed by the technical team using the Cochrane risk of bias tool for randomized controlled trials [42], the Newcastle-Ottawa scale (NOS) for nonrandomized studies [43] and QUADAS-2 tool for diagnostic test accuracy studies [44]. The certainty in the evidence was initially determined for each critical and important outcome, and

then for each recommendation using the GRADE approach for rating the confidence in the evidence [45, 46] [Figure 1]. Evidence profile tables and quality of evidence were reviewed by the guideline methodologists (Y. F. Y. and V. L.). The summaries of evidence were discussed and reviewed by all committee members and edited as appropriate. The final evidence summaries were presented to the whole panel for deliberation and drafting of recommendations. Literature search strategies, the PRISMA flow diagram detailing the search results, data extraction and evidence profile tables, and additional data (such as meta-analysis results when appropriate) can be found in supplementary materials.

Ranking of the outcomes by importance for decision-making was determined by consensus for each PICO question. In situations where a PICO question compared the use of an antimicrobial regimen to no antimicrobials, if the beneficial effects of the antimicrobial regimen were uncertain, undesirable outcomes would usually be ranked higher in importance than if benefits were certain (ie, ranked as critical for decision-making rather than important). Moreover, in situations where a PICO question compared the use of a specific antimicrobial regimen to another antimicrobial regimen (either regarding specific molecules, classes of antimicrobials, route of administration, or duration of therapy) and the beneficial effects of the 2 regimens were similar, the undesirable outcomes were ranked as critical for decision-making, although several other considerations might also have been taken into account such as stewardship issues and costs.

Development of Clinical Recommendations

All recommendations were labeled as either "strong" or "weak" according to the GRADE approach. The suggested interpretation of strong and weak recommendations for patients, clinicians, and healthcare policymakers is listed in Figure 1. For recommendations where the comparators are not formally stated, the comparison of interest is implicitly referred to as "not using the intervention" (either not using a specific treatment or diagnostic test). The strength of recommendations was established by informal consensus. Although there is arguably an ongoing need for research on virtually all of the topics considered in this guideline, "research needs" were noted for items that the panelists thought were particularly relevant.

Revision Process

Feedback was obtained from external peer reviewers. The guideline was reviewed and approved by the IDSA Standards and Practice Guidelines Committee (SPGC) as well as the IDSA Board of Directors (BOD). The guideline was endorsed by PIDS.

Revision Dates

Approximately every 2 years, but more frequently if needed, IDSA will determine the need for revisions to the guideline by an examination of the current literature and the likelihood that any new data will have an impact on the recommendations. If necessary, the entire expert panel will be reconvened to discuss potential changes. Any revision to the guideline will be submitted for review and approval to the SPGC and the IDSA Board.

I. How Should the Diagnosis of Babesiosis be Confirmed?

Recommendation:

1. For diagnostic confirmation of acute babesiosis, we recommend peripheral blood smear examination or polymerase chain reaction (PCR) rather than antibody testing *(strong recommendation, moderate-quality evidence).* **Comment:** The diagnosis of babesiosis should be based on epidemiological risk factors and clinical evidence, and confirmed by blood smear examination or PCR.

Summary of Evidence:

***Babesia microti* Infection:** A number of studies have assessed the performance of blood smear examination [47, 48] and/or PCR [49–59] for the diagnosis of acute babesiosis due to *B. microti* and at least 3 have compared the 2 approaches [49, 54, 59]. PCR (particularly real-time PCR and the recently developed 18S rRNA reverse transcriptase PCR) is more sensitive than a blood smear examination. PCR is especially useful when the parasite burden is low; however, blood smear examination is rapid and inexpensive [54, 59]. Examination of multiple thin blood smear fields is indicated (Figure 5). A review of at least 200–300 fields under oil immersion will increase sensitivity, although the number of fields has not been standardized [48]. Examination of thick blood smears may increase sensitivity because the number of red blood cells examined per field is greater than with thin smears; however, *Babesia* organisms are small and may be missed on thick blood smears. Both thick and thin smears should be prepared and examined by experienced personnel, as they can be difficult to interpret. For example, *Babesia* ring forms can be misinterpreted as *Plasmodium falciparum* trophozoites. In contrast, merozoites organized in tetrads (Maltese cross forms) are pathognomonic of babesiosis (Figure 5). If blood smears are negative and babesiosis is still suspected, PCR testing should be performed. *Babesia microti* PCR assays frequently are offered by clinical laboratories, as this species accounts for almost all cases of babesiosis in North America [3].

Babesia-specific antibody testing should not be used for routine diagnosis of acute babesiosis. Distinguishing active from past infection using serology is difficult because most patients who experience acute babesiosis remain seropositive for a year or more after resolution of disease, despite appropriate antimicrobial therapy [29, 30, 60, 61]. As with most serologic tests, optimal performance requires analysis of paired serum samples

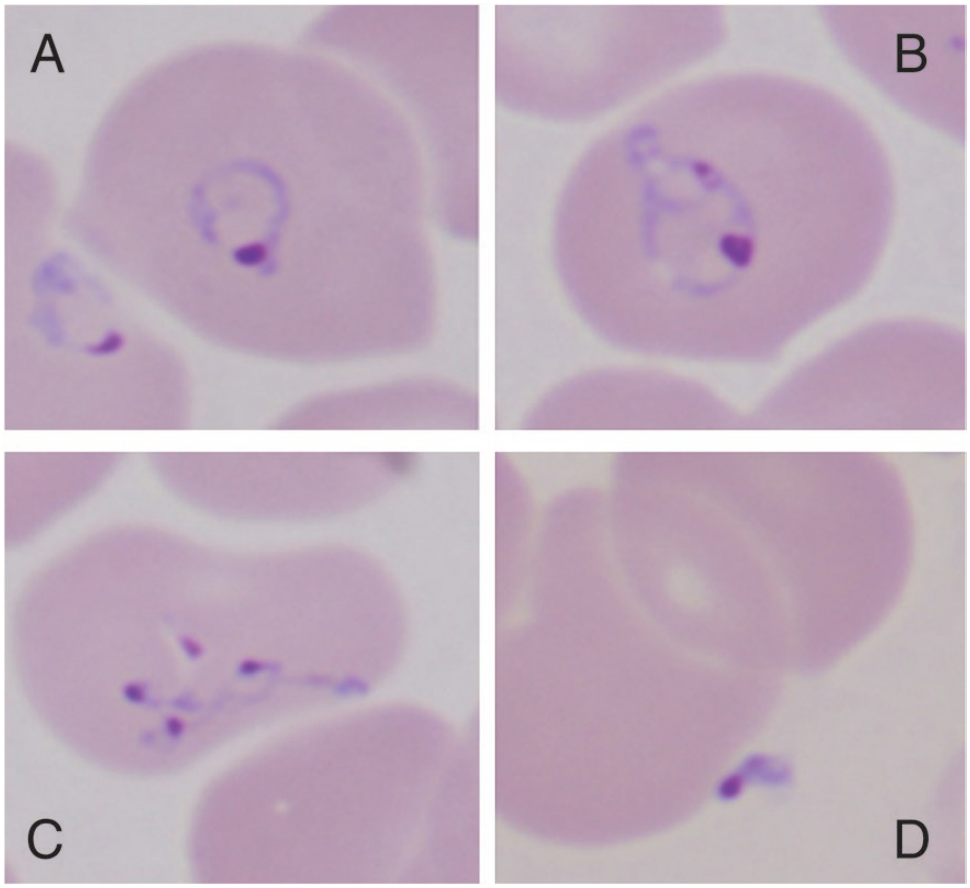

Figure 5. Giemsa-stained thin blood films showing *Babesia microti* parasites. *Babesia microti* are obligate parasites of erythrocytes. Trophozoites may appear as ring forms (*A*) or as ameboid forms (*B*). Merozoites can be arranged in tetrads (Maltese Cross forms) and are pathognomonic of babesiosis (*C*). Extracellular parasites can be noted, particularly when parasitemia is high (*D*) (adapted from [3]).

collected during the acute and convalescent phases of illness [62]. This approach is impractical for the diagnosis of acute babesiosis. Antibody testing is used to determine the seroprevalence of *Babesia* infection in epidemiological studies and may have a role in screening the blood supply [20, 29, 30, 63].

Non-*Babesia microti* Infection: Subtle morphological differences between *Babesia* species can be observed on blood smear but the basic features are common to all, including ring-form trophozoites and the pathognomonic but infrequently observed merozoite tetrads or "Maltese cross" forms (Figure 5). A *Babesia* species-specific PCR can confirm active *Babesia* infection and the infecting species. Some commercial laboratories and referral centers, such as the laboratory at the Parasitic Diseases Branch of the Centers for Disease Control and Prevention can provide PCR and DNA molecular analyses to detect non-*B. microti* species. If a *B. microti* PCR test is performed first and is negative but babesiosis is still suspected, a blood smear or pan-*Babesia* PCR test should be performed.

Symptomatic patients who test positive for *Babesia* (non-*B. microti*) antibody should either have a blood smear, a PCR assay capable of detecting all *Babesia* species (a pan-*Babesia* PCR assay), or a *Babesia* species-specific PCR that matches the *Babesia* (non-*B. microti*) antibody. The whole cell *B. microti* indirect fluorescence antibody (IFA) assay does not detect *B. duncani* antibody, just as the whole cell *B. duncani* IFA assay fails to detect *B. microti* antibody [7]. Sera from *B. venatorum* infected patients will cross-react against whole cell *B. divergens* antigen [12].

Rationale for Recommendation: Early diagnosis of symptomatic patients hastens appropriate antimicrobial therapy, which typically reduces the severity and duration of symptoms and helps prevent complications [37]. A diagnosis of babesiosis should be considered for any patient who presents with typical symptoms (especially fever, fatigue, chills, sweats, headache, and anorexia), characteristic routine laboratory test abnormalities, and who lives in, or has traveled to a *Babesia* endemic region within the previous month or who has received a blood transfusion within the previous 6 months. Most patients who acquire babesiosis through blood transfusion develop symptoms after a 1 to 9 week incubation period but it can be can as long as 6 months [27].

Borellia burgdorferi infection is more common than *B. microti* infection but their relative frequencies vary depending on geographic area. Based on a limited number of studies in areas where both *B. burgdorferi* and *B. microti* are endemic, about a tenth (median of 11%, range 2%–40%) of early Lyme disease patients experience babesiosis coinfection, whereas about half (median of 52%, range 23%–72%) of patients with babesiosis are diagnosed with Lyme disease coinfection [37, 49, 64–72]. Lyme disease patients coinfected with *B. microti* may have more severe illness than those with Lyme disease alone [49, 64, 65]. Babesiosis coinfection should be considered in Lyme disease patients with severe illness, in those whose symptoms are unlikely to be explained by *B. burgdorferi* infection alone, or in those who do not respond well to standard antibiotic therapy for Lyme disease.

The pretest probability of babesiosis in a person who does not live in or has not traveled to an endemic area within the previous month is low, and testing for *Babesia* in such individuals is not warranted. The symptoms of babesiosis are nonspecific and often consist of fever, fatigue, chills, sweats, myalgia, headache, and/or anorexia [31–33, 37, 49]. Characteristic abnormalities on routine laboratory tests include anemia, thrombocytopenia, elevated liver enzymes (aspartate aminotransferase [AST], alanine transaminase [ALT], alkaline phosphatase), and/or evidence of intravascular hemolysis (elevated lactate dehydrogenase [LDH], elevated total and indirect bilirubin levels, reduced haptoglobin) [31–33, 37, 49]. Confirmation of the diagnosis requires identification of intraerythrocytic *Babesia* parasites on blood smear or amplification of *Babesia* DNA in blood using molecular methods such as PCR. In patients with symptomatic babesiosis, parasitemia usually is high enough that blood smear examination and PCR perform similarly.

Research Needs: Additional studies are needed to assess whether CBC, liver enzymes, and markers of hemolysis are clinically useful for screening patients prior to ordering laboratory testing specific for babesiosis. Additional studies also are needed to determine whether blood smear or PCR should be the initial test used to diagnose acute babesiosis and monitor patients during therapy. More rapid, sensitive, specific, and cost-effective diagnostic tests are being developed but require clinical validation [52, 53, 55, 73–77].

II. Can an Active Case of Babesiosis Be Diagnosed Based on a Single Positive Antibody Test or Is a Blood Smear, PCR, or a Four-fold Rise in Antibody Necessary for Confirmation?

Recommendation:

1. For patients with a positive *Babesia* antibody test, we recommend confirmation with blood smear or PCR before treatment is considered *(strong recommendation, moderate-quality evidence).* **Comment:** A single positive antibody test is not sufficient to establish a diagnosis of babesiosis because *Babesia* antibodies can persist in blood for a year or more following apparent clearance of infection, with or without treatment.

Summary of Evidence: The IFA test is routinely used to detect *B. microti* antibody in blood [6, 29, 61]. A *B. microti* IgG antibody titer of ≥1:1024 or the presence of *B. microti* IgM antibody are suggestive of active or recent *B. microti* infection, while a 4-fold rise in *Babesia* IgG antibody in sera from the time of acute illness to the time of convalescence confirms the diagnosis [20, 62, 72]. *Babesia. microti* ELISA and immunoblot assays are available but have had limited use. The *B. microti* ELISA was developed for use in blood donor screening and the *B. microti* immunoblot is cumbersome to use [63, 78].

Rationale for Recommendation: A single positive *Babesia* antibody test result cannot reliably distinguish between an active and a resolved *Babesia* infection because *Babesia* antibodies can persist for more than a year following apparent clearance of infection, with or without treatment [29, 30, 60, 79]. Treatment of people with a single positive *Babesia* antibody test result but with negative blood smear and/or PCR is not indicated because of the low probability of active infection. Antibiotic treatment also incurs the risk of side effects, as well as additional costs.

Research Needs: Development of antibody and/or antigen assays that are capable of distinguishing acute from past infection would improve clinical utility.

III. What Are the Preferred Treatment Regimens for Babesiosis?

Recommendation:

1. We recommend treating babesiosis with the combination of atovaquone plus azithromycin or the combination of clindamycin plus quinine *(strong recommendation, moderate-quality evidence).* **Comment:** Atovaquone plus azithromycin is the preferred antimicrobial combination for patients experiencing babesiosis, while clindamycin plus quinine is the alternative choice. The duration of treatment is 7 to 10 days in immunocompetent patients but often is extended when the patient is immunocompromised (Table 1).

Summary of evidence:

***Babesia microti* Infection:** In a prospective, nonblinded, randomized trial in immunocompetent patients with non life-threatening babesiosis due to *B. microti*, atovaquone plus azithromycin was compared with clindamycin plus quinine (Table 2) [38]. All medications were prescribed orally for a 7-day treatment course. Based on time to resolution of symptoms, the 2 regimens had comparable efficacy. Far fewer adverse effects occurred in the atovaquone plus azithromycin-treated group (15%) than in the clindamycin plus quinine treated group (72%). Persistent symptoms were severe enough in 4 of 18 patients given clindamycin plus quinine that they required hospital

Table 2. Summary of Findings for Atovaquone/Azithromycin Compared to Clindamycin/Quinine in Patients Experiencing Non-life Threatening Babesiosis [38]

Patient or population: patients with non-life threatening babesiosis

Intervention: Atovaquone/Azithromycin

Comparison: Clindamycin/Quinine

				Anticipated absolute effects	
Outcomes (follow-up)	No of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Risk with Clindamycin/Quinine	Risk difference with Atovaquone/Azithromycin
Resolution of symptoms (follow up: 3 months)	58 (1 RCT)	⨁⨁◯◯ LOW[a,b]	(.62 to 1.30)	722 per 1000	72 fewer per 1000 (327 fewer to 182 more)
Hospitalization due to severe persistent symptoms (follow up: 1 week)	58 (1 RCT)	⨁⨁◯◯ LOW[a,c]	not estimable	222 per 1000	222 fewer per 1000 (414 fewer to 30 fewer)
Severe treatment adverse events * (follow up: 1 week)	58 (1 RCT)	⨁⨁◯◯ LOW[a,d]	(.01 to .58)	333 per 1000	308 fewer per 1000 (531 fewer to 85 fewer)
Treatment-related adverse events (follow up: 1 week)	58 (1 RCT)	⨁⨁◯◯ LOW[a,d]	(.09 to .46)	722 per 1000	572 fewer per 1000 (807 fewer to 338 fewer)
Diarrhea (follow up: 1 week)	58 (1 RCT)	⨁⨁◯◯ LOW[a,d]	(.06 to .80)	333 per 1000	258 fewer per 1000 (491 fewer to 26 fewer)
Tinnitus (follow up: 1 week)	58 (1 RCT)	⨁⨁◯◯ LOW[a,c]	not estimable	389 per 1000	389 fewer per 1000 (614 fewer to 164 fewer)
Decreased hearing (follow up: 1 week)	58 (1 RCT)	⨁⨁◯◯ LOW[a,c]	not estimable	278 per 1000	278 fewer per 1000 (485 fewer to 71 fewer)
Rash (follow up: 1 week)	58 (1 RCT)	⨁⨁◯◯ LOW[a,d]	(.12 to 3.70)	111 per 1000	36 fewer per 1000 (203 fewer to 130 more)
Vertigo (follow up: 1 week)	58 (1 RCT)	⨁⨁◯◯ LOW[a,d]	(.02 to 1.35)	167 per 1000	142 fewer per 1000 (321 fewer to 37 more)

*Severe adverse reactions were defined as those severe enough that the doses of drugs were decreased, or the drugs discontinued. These reactions included tinnitus or decreased hearing (in all the subjects) and diarrhea, cardiac arrhythmia, vertigo, and a hive-like rash.

Abbreviations: CI, confidence interval; RR, risk ratio.

Explanations

[a]Study received high risk of bias rating due to unblinded study design.

[b]95% CI is wide and crossing the null value and IOS criteria not met.

[c]Due to low event rate.

[d]Fragility due to small number of events and IOS criteria not met.

admission after 1–2 days of treatment compared with none of 40 patients given atovaquone plus azithromycin. In a subsequent retrospective study of 40 patients hospitalized because of severe babesiosis and treated exclusively with atovaquone plus azithromycin, including 11 patients who had life-threatening disease, the combination of atovaquone plus azithromycin was found to be well-tolerated and effective [39]. In some instances, the diagnosis of babesiosis is made after acute illness has resolved. Asymptomatic patients do not require antimicrobial therapy unless parasites are seen on thin blood smear for more than a month.

Numerous immunodeficiencies and comorbidities have been associated with severe babesiosis, including asplenia and hyposplenism, cancer, congestive heart failure, HIV infection, immunosuppressive drugs, and advanced age. Neonates may experience severe babesiosis after transfusion of *B. microti*-infected blood, tick transmission, or transplacental transmission [24–26]. The severity of babesiosis differs among these disease categories [3, 28, 31, 33, 37]. Some immunocompromised patients experiencing babesiosis require more intense therapy for longer duration than immunocompetent patients. A subgroup of highly immunocompromised patients reported in a case-control study required at least 6 consecutive weeks of antibiotic therapy, including 2 final weeks during which parasites were no longer detected on peripheral blood smear [28]. Eleven of 14 patients had B cell lymphoma or another malignancy, of whom 8 were also asplenic, and 7 had been treated with rituximab. One patient had an autoimmune condition that was treated with rituximab, whereas another patient had low CD4 T cell counts due to HIV/AIDS. The duration of treatment was noted to be more important than the antibiotic combination used to achieve a cure [28]. A few cases of relapse despite at least 6 consecutive weeks of atovaquone plus azithromycin demonstrate that resistance to atovaquone and/or azithromycin can emerge in highly immunocompromised patients during an extended course of this antibiotic combination [80]. Therapeutic failure in these cases was attributed to amino acid substitutions in the regions of *B. microti* proteins that are targeted by atovaquone and azithromycin [81, 82].

Non-*Babesia microti* Infection

Babesia duncani. A small number of *B. duncani* cases (<15) have been reported on the West Coast of the United States. Most were treated with IV clindamycin plus oral quinine for 7–10 days [7, 8, 19, 83, 84]. The efficacy of atovaquone plus azithromycin in treating such infection has not been evaluated.

Babesia divergens. *B. divergens* infections occur sporadically in Europe, the United States, and mainland China. To date, more than 50 cases have been reported. Almost all *B. divergens* infections have been severe and have occurred in asplenic patients [9, 10, 85, 86]. These patients usually are treated with IV clindamycin plus oral quinine. In Europe, exchange transfusion is performed early in the course of illness. Such aggressive treatment is thought to have markedly reduced the mortality rate [10, 86].

Babesia venatorum. In Europe, all 5 cases caused by *B. venatorum* have occurred in splenectomized patients, 3 of whom were being treated for lymphoma or leukemia [12, 87–89]. Initial antimicrobial therapy consisted of clindamycin plus quinine or clindamycin alone. A cure was achieved only after administration of atovaquone plus azithromycin in 2 cases. In China, *B. venatorum* infections are endemic in the Northeast, have occurred in spleen intact individuals, and disease has been mild to moderate [13]. One case was successfully treated with atovaquone plus azithromycin, while others became asymptomatic when treated with clindamycin alone [90].

Babesia crassa-like pathogen. Recently, mild to moderate illness due to a *B. crassa*-like pathogen was confirmed in 31 patients in northeastern China [15]. None received standard therapy with atovaquone plus azithromycin or clindamycin plus quinine. Three patients received clindamycin alone. Symptoms resolved by 9 months in all but 3 of the confirmed cases and no patient died.

Rationale for Recommendation: The most widely used antibiotic therapy for ambulatory patients experiencing mild to moderate *B. microti* infection is atovaquone plus azithromycin given for 7–10 days because the combination is clinically effective and well-tolerated (Table 1). High doses of azithromycin (500–1000 mg/day) have been used for treatment of highly immunocompromised patients, as such doses are thought to accelerate the resolution of symptoms and the clearance of parasites, thereby reducing the risk of developing microbial resistance [14, 80, 82, 91, 92]. For a few immunocompromised patients who experienced a relapse of symptoms while on a recommended 2-drug treatment regimen, eradication of *Babesia* infection has been reported using alternative antimicrobial regimens (Table 3) [28, 92]. Clindamycin and quinine is a second choice if atovaquone plus azithromycin cannot be used because of side effects, limited availability, or cost. Reducing the level of immunosuppression is desirable whenever possible.

Patients admitted to the hospital for severe *B. microti* infection are best treated with IV azithromycin plus oral atovaquone [28, 39]. An alternative choice is IV clindamycin plus oral quinine but this regimen should be reserved for patients unresponsive to azithromycin plus atovaquone because quinine commonly causes side effects [38]. Worsening of symptoms or increasing parasitemia despite azithromycin plus atovaquone followed by clindamycin and quinine should prompt consideration of an alternative antimicrobial regimen (Table 3). Exchange transfusion may be considered for patients with severe babesiosis who

Table 3. Antimicrobials Used for Refractory *Babesia* Infections with Limited Evidence of Efficacy

Atovaquone + azithromycin* + clindamycin
Atovaquone + clindamycin
Atovaquone/proguanil + azithromycin*
Atovaquone + azithromycin* + clindamycin + quinine

* When azithromycin is used, a 500–1000 mg daily dose should be considered.

meet specific criteria (see Section IV below). For most patients admitted to the hospital with severe babesiosis, a 7–10 day antibiotic course is sufficient to achieve cure. The duration of antibiotic therapy should be extended to at least 6 weeks for highly immunocompromised patients, especially those with impaired antibody production because these patients are more likely to fail a standard course of antimicrobial therapy [28]. Step-down therapy to an all-oral antimicrobial regimen is appropriate once symptoms and parasitemia have abated, or at time of discharge (Table 1).

Research Needs: Further research is needed to define the most effective drug combination for severe babesiosis, especially in immunocompromised patients infected with *B. microti*, *B. duncani*, *B. divergens*, *B. venatorum,* or *B. crassa*-like organisms. Research is also needed to identify alternative drug regimens, particularly for use in patients with suspected or documented microbial resistance.

IV. Is Exchange Transfusion Indicated for Severe Babesiosis?

Recommendation:

1. In selected patients with severe babesiosis, we suggest exchange transfusion using red blood cells *(weak recommendation, low-quality evidence).* **Comment:** Exchange transfusion may be considered for patients with high-grade parasitemia (>10%) or who have any one or more of the following: severe hemolytic anemia and/or severe pulmonary, renal, or hepatic compromise. Expert consultation with a transfusion services physician or hematologist in conjunction with an infectious diseases specialist is strongly advised.

Summary of Evidence: No prospective studies have assessed the indications for exchange transfusion or the benefits of exchange transfusion for severe babesiosis or compared complete with partial exchange transfusion. In a report of 34 consecutive patients hospitalized for babesiosis, one-fifth received exchange transfusion [31]. These patients had a median parasitemia of 20% (range 10%–30%) before exchange transfusion. Complicated babesiosis was associated with parasitemia >10% in this study ($P = .08$) [31] and >4% in another study ($P < .001$) [33]. In a case series of 24 patients who received exchange transfusion for severe babesiosis, the median parasitemia was 13% (range 1.6–60%) prior to exchange transfusion and 2% (range 0.1 to 13.8%) postexchange [93]. Hemolysis was the sole reason listed for exchange transfusion in over half the cases and the mean pre-exchange hemoglobin of those tested was 8.1 g/dL. Four of the 24 patients died postexchange despite low parasitemia (≤1%) at the time of death. In a recent retrospective study of 19 patients undergoing exchange transfusion, pre-exchange parasitemia >10% was associated with postexchange length of hospital stay. Postexchange parasitemia and reduction in parasitemia were not associated with postexchange length of hospital stay or mortality rate [94]. In another recent report, 3 patients with parasitemia levels >10% were successfully managed without exchange transfusion, indicating that the decision to perform exchange transfusion should not necessarily be based solely on the level of parasitemia but also on the clinical state of the patient and evidence of end-organ failure [95].

Rationale for Recommendation: Severe babesiosis can be life-threatening and fatalities have occurred despite antimicrobial therapy. Exchange transfusion rapidly decreases parasitemia by replacing parasitized with nonparasitized erythrocytes. It also removes cytokines and toxic by-products of hemolysis, particularly free hemoglobin and free heme [96]. In cases of life-threatening babesiosis, the potential benefits of exchange transfusion likely outweigh potential adverse effects, which include transfusion reactions, worsening of thrombocytopenia, and complications associated with venous access devices. No prospective study has been performed to validate the criteria for initiating exchange transfusion. While most experts would initiate exchange transfusion for high-grade parasitemia, life-threatening babesiosis, or such complications as renal insufficiency or failure, the efficacy of exchange transfusion in preventing complications or death is uncertain [40, 97].

Research Needs: Uncertainties remain regarding the indications for exchange transfusion and the efficacy of exchange transfusion. Randomized controlled trials are needed to address the safety, indications, and efficacy of exchange compared with no exchange and the optimal volume of blood to exchange.

V. How Should Immunocompetent and Immunocompromised Patients be Monitored After Babesiosis Therapy Is Initiated? How Frequently and for How Long?

Recommendations:

1. For immunocompetent patients, we recommend monitoring *Babesia* parasitemia during treatment of acute illness using peripheral blood smears but recommend against testing for parasitemia once symptoms have resolved *(strong recommendation, moderate-quality evidence).*
2. For immunocompromised patients, we suggest monitoring *Babesia* parasitemia using peripheral blood smears even after they become asymptomatic and until blood smears are negative. PCR testing should be considered if blood smears have

become negative but symptoms persist *(weak recommendation, moderate-quality evidence).*

Summary of Evidence: In otherwise healthy individuals, symptoms of babesiosis generally abate within a few days after initiation of treatment. Fever and parasites on blood smear usually clear within a week [31, 39, 60]. Fatigue sometimes persists for months after a standard course of antibiotics has been completed and by itself is not an indication for continued monitoring [38, 60, 64]. Once symptoms have resolved in immunocompetent patients, blood smears typically are negative for *Babesia* parasites but *B. microti* PCR may remain positive for months to more than a year after completion of standard treatment or for months to more than 2 years if untreated [29, 30, 60]. Persistence of *B. microti* DNA after resolution of symptoms and completion of standard treatment usually does not indicate treatment failure. Relapse of symptoms rarely is observed in immunocompetent patients, so continuing antimicrobial therapy until *Babesia* PCR becomes negative in immunocompetent patients will often result in unnecessarily prolonged therapy and is not warranted [29, 30, 32, 39, 60, 98].

Immunocompromised patients who are infected with *B. microti* are at risk for high-grade parasitemia, hospitalization, and complications that include severe hemolytic anemia, acute respiratory distress syndrome, congestive heart failure, renal impairment, shock, disseminated intravascular coagulation, warm autoimmune hemolytic anemia, relapse, and/or fatal outcome [28, 31–34, 37, 80–82, 99–102]. Immunocompromised patients differ in severity of immune suppression, risk of severe acute disease, and risk of prolonged disease with relapse. A subgroup of highly immunocompromised patients are at risk for relapse despite standard antibabesial therapy [28, 82]. They include those who (i) have received or are receiving rituximab for B cell lymphoma or an autoimmune disorder, (ii) are receiving other immunosuppressive regimens for solid organ or bone marrow transplantation or malignancy, (iii) have malignancy and are asplenic, or (iv) have HIV infection with low CD4 T cell counts (AIDS). In these patients, persistent or intermittently symptomatic infection may continue for more than 2 years [28, 100]. A retrospective case-control study of 14 such patients who were infected with *B. microti* has shown that complete cure typically requires ≥6 consecutive weeks of antimicrobial treatment, including 2 final weeks during which parasites are no longer detected on peripheral blood smear [28].

Rationale for Recommendation: Immunocompetent patients usually resolve most symptoms of babesiosis and blood smears become negative during the 7 to 10-day course of standard antimicrobial therapy. While fatigue and low-grade parasitemia detected by PCR may persist for weeks to months after treatment, further monitoring and treatment seldom are necessary because relapse rarely occurs [29, 30, 32, 39, 60, 98]. Monitoring parasitemia using PCR is not indicated in asymptomatic immunocompetent hosts.

Immunocompromised patients who experience severe illness should be monitored at least daily for the presence of *Babesia* parasites on blood smear until parasitemia has decreased to <4% [33]. Thereafter, blood smears should be obtained at least weekly until parasites are no longer detected. Blood smears should be obtained and/or *Babesia* PCR performed if symptoms consistent with babesiosis recur [28, 81, 82, 100].

There is no standardized approach to monitoring highly immunocompromised patients but close clinical and laboratory follow-up are important. Monitoring *Babesia* parasites on blood smear and treating them until the blood smear becomes negative is necessary. Until additional data become available, the use of PCR to help decide when antimicrobial therapy is discontinued should be determined on a case by case basis.

Research Needs: Additional studies are needed to determine the frequency, efficacy, and cost-effectiveness of blood smear, PCR, and other laboratory testing (such as antigen detection) for monitoring immunocompromised hosts during and following antimicrobial therapy.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. The following list is a reflection of what has been reported to the IDSA. To provide thorough transparency, the IDSA requires full disclosure of all relationships, regardless of relevancy to the guideline topic. Evaluation of such relationships as potential conflicts of interest is determined by a review process which includes assessment by the Board of Directors liaison to the Standards and Practice Guideline Committee and, if necessary, the Conflicts of Interest (COI) and Ethics Committee. The assessment of disclosed relationships for possible COI is based on the relative weight of the financial relationship (ie, monetary amount) and the relevance of the relationship (ie, the degree to which an association might reasonably be interpreted by an independent observer as related to the topic or recommendation of consideration). The reader of these guidelines should be mindful of this when the list of disclosures is reviewed. **P. J. K.** receives research funding from the National Institutes of Health (NIH), the Gordon and Llura Gund Foundation, and the Yale Emerging Infections Program; receives remuneration from Gold Standard Diagnostics for a collaborative research project; has stock in Gilead Sciences and First Trust NASDAQ Pharmaceuticals ETF; has received research funding from NIH, the Centers for Disease Control and Prevention (CDC), the Gordon and Llura Gund Foundation, and L2 Diagnostics for NIH-sponsored research; has served as a scientific consultant and provided medical education and training for Oxford Immunotec, Inc.; has a patent pending (Enhanced Chemiluminescent enzyme-linked immunosorbent assay for detection of antibodies against *Babesia microti*), for which U.S. Provisional Patent Application No. 62/580,588, was filed on November 2, 2017; serves on the Board of Directors for the American Lyme Disease Foundation and the Editorial Boards of *Pathogens* and *Plos Neglected Tropical Diseases*, the Editorial Advisory Board of *Clinical Infectious Diseases*; was on the Editorial Board of *Journal of Clinical Microbiology*, and will be on the Editorial Board of *Clinical Microbiology Reviews* starting January 2021. **P. 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B.** receives research funding from the Lyme Disease Biobank Foundation and Zeus Scientific; serves as a scientific advisor and consultant to DiaSorin, Inc.; has served as a scientific advisor and consultant for T2 Biosystems; has served on the scientific advisory board of Roche Diagnostics and AdvanDx; has received research funding from Karius, Inc., Alere, Inc., T2 Biosystems, BioMérieux. TBS Technologies, Immunetics, Inc., DiaSorin, Inc., Kephera Diagnostics, Inc., the Bay Area Lyme Foundation, the Lyme Disease; has participated in unfunded research collaborations with Karius Inc. and Kephera Diagnostics; was a member of the editorial board of the *Journal of Clinical Microbiology*; was a co-inventor on an application for a patent to protect intellectual property; and his spouse is an employee of Informed DNA. **Y. F. Y.** serves as director of the Evidence Foundation and the GRADE Network; conducts GRADE workshops with the Evidence Foundation; has served as the chair of the Guidelines Committee for the American Gastroenterological Association; and has received research funding from the Cleveland VA Medical Research and Education Foundation. **P. M. L.** has received research funding from the National Cytomegalovirus Foundation and from the NIH and educational funding from Duke University; and has served as a consultant and reviewed trial protocol for Frederick O'Connor Medical Consultants, LLC. **H. C. M.** is a current member of the CDC Workgroups; serves as a volunteer consultant on the American Academy of Pediatrics Committee on Infectious Diseases, and the NIH DSMB. **S. K. S.** has received research funding from the NIH; and has provided expert testimony for Danaher Lagnese, P.C. **E. V.** has stock in Abbott Laboratories; has filed a patent application related to compositions and methods for the prophylaxis and treatment of babesiosis (Application No: 62/939,808; has previously owned stock in AbbVie, Amgen, Baxter International, Bristol-Myers Squibb, Gilead Sciences, Johnson and Johnson, Novartis, Quest Diagnostics, and UnitedHealth Group; and received research funding from The Gordon and Llura Gund Foundation, the Dorothy Harrison Egan Foundation and the Global Lyme Alliance. **G. P. 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All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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