Review

Diagnosis, Treatment, and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babesiosis
A Review

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IMPORTANCE Lyme disease, human granulocytic anaplasmosis (HGA), and babesiosis are emerging tick-borne infections.

OBJECTIVE To provide an update on diagnosis, treatment, and prevention of tick-borne infections.

EVIDENCE REVIEW Search of PubMed and Scopus for articles on diagnosis, treatment, and prevention of tick-borne infections published in English from January 2005 through December 2015.

FINDINGS The search yielded 3550 articles for diagnosis and treatment and 752 articles for prevention. Of these articles, 361 were reviewed in depth. Evidence supports the use of US Food and Drug Administration–approved serologic tests, such as an enzyme immunoassay (EIA), followed by Western blot testing, to diagnose extracutaneous manifestations of Lyme disease. Microscopy and polymerase chain reaction assay of blood specimens are used to diagnose active HGA and babesiosis. The efficacy of oral doxycycline, amoxicillin, and cefuroxime axetil for treating Lyme disease has been established in multiple trials. Ceftriaxone is recommended when parenteral antibiotic therapy is recommended. Multiple trials have shown efficacy for a 10-day course of oral doxycycline for treatment of erythema migrans and for a 14-day course for treatment of early neurologic Lyme disease in ambulatory patients. Evidence indicates that a 10-day course of oral doxycycline is effective for HGA and that a 7- to 10-day course of azithromycin plus atovaquone is effective for mild babesiosis. Based on multiple case reports, a 7- to 10-day course of clindamycin plus quinine is often used to treat severe babesiosis. A recent study supports a minimum of 6 weeks of antibiotics for highly immunocompromised patients with babesiosis, with no parasites detected on blood smear for at least the final 2 weeks of treatment.

CONCLUSIONS AND RELEVANCE Evidence is evolving regarding the diagnosis, treatment, and prevention of Lyme disease, HGA, and babesiosis. Recent evidence supports treating patients with erythema migrans for no longer than 10 days when doxycycline is used and prescription of a 14-day course of oral doxycycline for early neurologic Lyme disease in ambulatory patients. The duration of antimicrobial therapy for babesiosis in severely immunocompromised patients should be extended to 6 weeks or longer.

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The *Ixodes scapularis* tick is responsible for transmission of at least 7 human pathogens in the United States (**Figure 1**). Three of these accounted for the majority of cases of *Ixodes*-transmitted diseases in 2015[2]: *Borrelia burgdorferi*, accounting for approximately 34 000 confirmed and probable reported cases of Lyme disease; *Anaplasma phagocytophilum*, for approximately 2600 reported cases of human granulocytic anaplasmosis (HGA); and *Babesia microti*, for approximately 1700 reported cases of babesiosis. This review summarizes current evidence regarding the diagnosis, treatment, and prevention of these 3 infections.

Methods

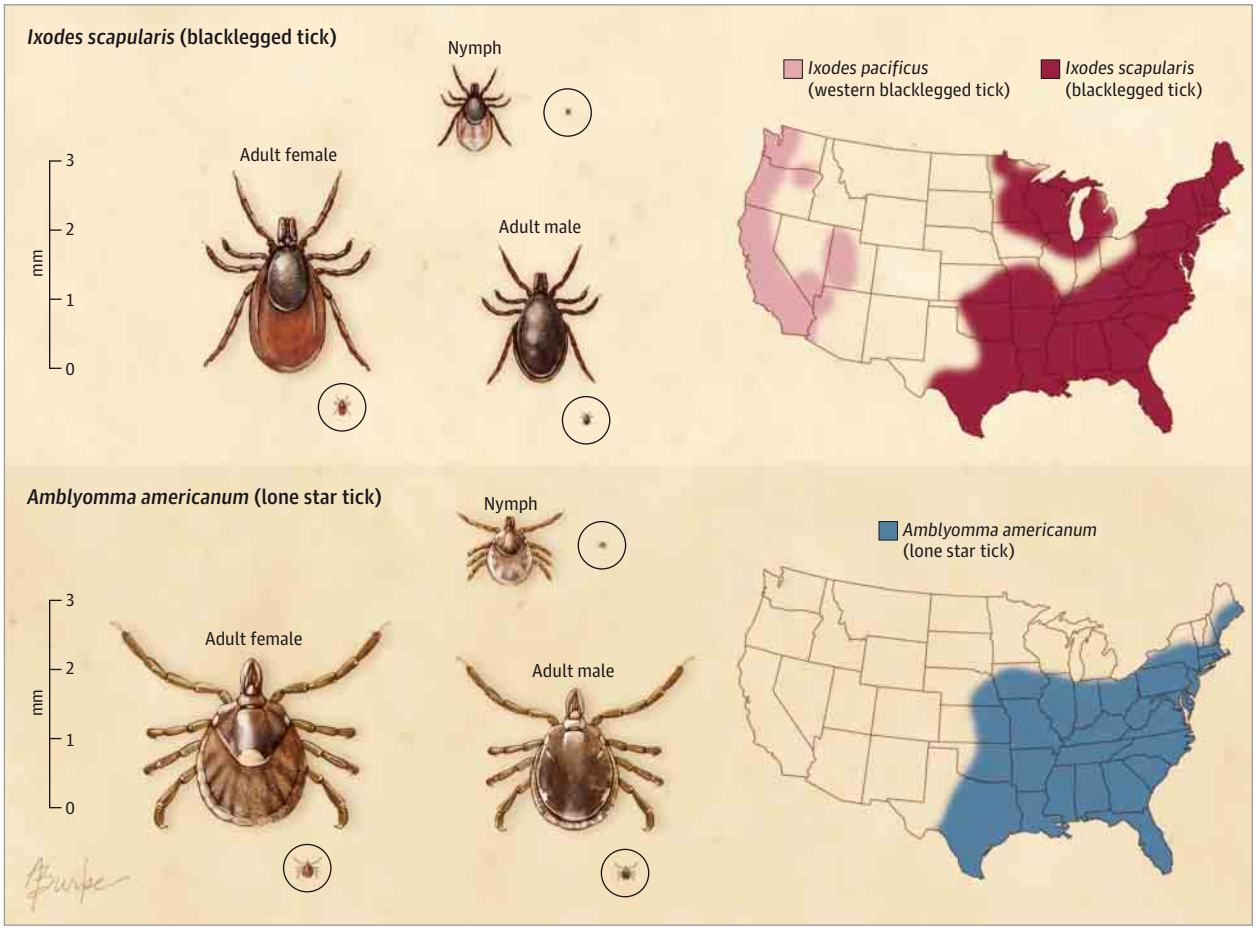
We searched PubMed and Scopus for articles published in English from January 2005 through December 2015 that pertained to the diagnosis, treatment, or prevention of Lyme disease, HGA, and babesiosis (eFigure in the Supplement). In doing so, we captured articles published shortly prior to, and since, the Infectious Diseases Society of America (IDSA) guidelines report in November 2006.[3] At least 2 authors reviewed abstracts of these publications. Any article selected by at least 1 author was reviewed in detail. Recommendations were based on the quality of the studies (randomized trials received the highest priority, and case reports received the lowest priority) and the preponderance of evidence from multiple sources.

Recommendations were independently graded by at least 2 authors using the American Heart Association scoring system[4] (eTable in the Supplement) and then reviewed and agreed on by all authors. Any discrepancies in grading were resolved by discussion and majority opinion. Scores are reported as (class-level of evidence).

Results

The searches generated 3550 articles related to diagnosis and treatment and 752 articles related to prevention. Of these articles, 361 were selected for detailed review (eFigure in the Supplement).

Figure 1. *Ixodes* and *Amblyomma americanum* Ticks and Their Geographic Distributions in the United States



Top, *Ixodes scapularis* nymphal and adult ticks (ticks in black circles are shown at actual size). The nymphs and adult females can transmit *Borrelia burgdorferi*, *Anaplasma phagocytophilum*, and *Babesia microti*; adult males may attach but do not feed and thus do not transmit these pathogens. Bottom, *Amblyomma americanum* nymphal and adult ticks linked to southern tick-associated rash illness (STARI) (ticks in black circles are shown at actual size). As shown on the right, the geographic distributions of *I scapularis* and *A americanum* in the United States overlap, with the exception of the upper Midwest. *Borrelia burgdorferi* is also transmitted by *Ixodes pacificus* ticks found along the Pacific Coast. Adapted from Tibbles et al.[1]

Diagnosis

Lyme Disease

The most common and earliest clinical manifestation of Lyme disease is a skin lesion called erythema migrans, which is present in 70% to 80% of patients.[5] Erythema migrans typically occurs within 1 to 2 weeks following a tick bite. Other relatively common clinical features include early neurologic Lyme disease (10%-15%), myopericarditis (1%-2%), and Lyme arthritis (up to 30% per Centers for Disease Control and Prevention surveillance but much lower in other studies[6,7]). Early neurologic Lyme disease presents with facial nerve palsy, lymphocytic meningitis, and radiculopathy[8]; myopericarditis typically presents with varying forms of heart block.[9] Both cardiac and early neurologic Lyme disease usually occur within weeks to a couple of months after the tick bite. Lyme arthritis is a migratory monoarticular or pauciarticular arthritis of large joints and is the hallmark of late Lyme disease, occurring months (on average >6 months) following the tick bite.[10] Diagnosis of Lyme disease is typically made by recognition of the erythema migrans skin lesion, serologic testing to identify antibodies against *B burgdorferi* antigens in patients with extracutaneous manifestations of Lyme disease such as those described above, or both.

Clinical Diagnosis

Diagnosis of erythema migrans is made by visual inspection of an expanding, erythematous skin lesion, 5 cm or larger in diameter, that develops at the site of the tick bite (**Figure 2**). These lesions may be homogeneous in color or have either central clearing or a target-like appearance. Antibodies are not consistently detectable in patients with erythema migrans (<40% sensitivity).[11] The differential diagnosis includes a number of skin conditions, such as tinea and nummular eczema.[1] One condition that can be clinically indistinguishable is southern tick-associated rash illness (STARI), a disease of unknown etiology that also follows a tick bite but is from the bite of the *Amblyomma americanum* tick.[12-16] Although there is overlap in the geographic distributions of STARI and Lyme disease (Figure 1), STARI cases are uncommon in most Lyme disease–endemic areas. All patients diagnosed with erythema migrans in Lyme disease–endemic areas should be presumed to have Lyme disease, unless there is definitive identification of *A americanum* as the biting tick (IIa-C).[17-21]

None of the extracutaneous manifestations is sufficiently specific for a definitive clinical diagnosis (IIa-C), unless there is a concomitant erythema migrans skin lesion.

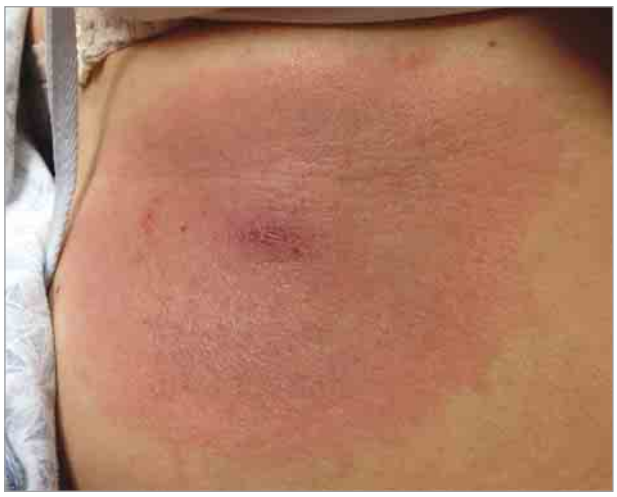
Laboratory Testing

Serologic Testing

Serologic testing is the mainstay of laboratory diagnosis for patients with extracutaneous manifestations of Lyme disease (**Table 1**). Seropositivity in a patient for whom there are objective findings of extracutaneous Lyme disease is sufficient to make a presumptive diagnosis.

Current recommendations are for 2-step testing that typically consists of an enzyme immunoassay (EIA) followed, if the EIA is reactive, by Western blot testing.[3] Most EIAs use a whole-cell sonicate of *B burgdorferi* as antigen. For patients with an illness of 4 weeks or less duration whose first-step EIA is reactive, separate IgM and IgG Western blot tests are recommended as second-step testing.[3] If symptoms have been present for more than 4 weeks, IgG Western blot alone is recommended, as it is highly sensitive for Lyme disease of more than 4 weeks' duration (I-B).[3,27] To avoid loss of specificity, the following practices should be avoided (all III-B): using assays not approved by the US Food and Drug Administration; omitting the first-step assay; performing Western blot testing despite a negative first-step test; and using IgM Western blots to confirm the diagnosis in a patient with long-standing symptoms and a negative IgG Western blot.[28] In addition, use of unconventional criteria for Western blot interpretation can substantively degrade the performance of these tests (III-B).[29]

Figure 2. Erythema Migrans Skin Lesion at the Site of a Tick Bite on the Abdomen of a Patient



The lesion is circular and homogeneous, a pattern more common than the well-recognized "bull's-eye" appearance. The primary erythema migrans lesion typically is at least 5 cm in diameter. Photograph courtesy of Roger Clark, DO, Faulkner Hospital, Boston, Massachusetts.

Serologic testing is highly sensitive for patients with neurologic or cardiac manifestations at time of presentation (≥80%).[30] If initial testing is negative but early neurologic or cardiac Lyme disease remains suspected, serologic testing should be repeated in 2 to 4 weeks (IIa-C).

Attempts have been made to simplify and improve the accuracy of the 2-step testing strategy while also minimizing time and costs. For example, the use of "striped" Western blots in which purified antigens are placed at defined locations on a strip ensures a greater standardization between test runs and allows objective quantification using densitometric scanning.[31] Another approach has been to develop EIAs with fewer cross-reactive antigens. For example, the C6 peptide EIA, which uses a highly invariant region of the *B burgdorferi* VlsE (variable major protein-like sequence, expressed) protein, has greater specificity than most whole-cell sonicate–based EIAs.[32,33] Although use of C6 as a stand-alone test is not routinely recommended owing to a small reduction in specificity compared with 2-step testing,[33,34] C6 testing alone should be considered when patients are suspected to have acquired the disease in Europe. The rationale for this recommendation is that Western blots designed for use in the United States have relatively poor sensitivity for European species of Lyme *Borrelia* and that the C6 epitope is conserved across different species and strains, making it a useful diagnostic antigen in Europe, where most cases of Lyme disease are caused by *Borrelia garinii* and *Borrelia afzelii*[35,36] (IIa-B). PepC10, an invariant epitope of *B burgdorferi* outer surface protein C, is another peptide antigen that has been approved by the US Food and Drug Administration for diagnosing Lyme disease and shows increased sensitivity in early disease.[37]

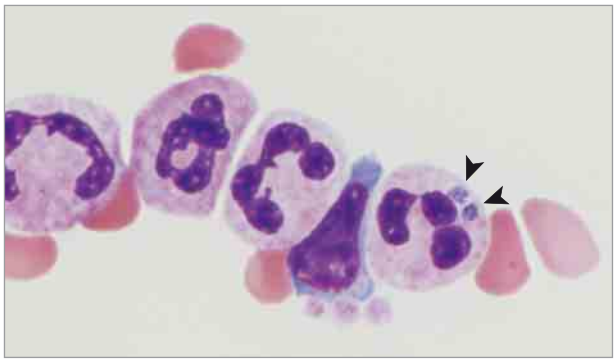
Table 1. Diagnosis of Lyme Disease, Human Granulocytic Anaplasmosis, and Babesiosis

Disease	Manifestation	Diagnostic Approach	Additional Considerations
Lyme disease	Erythema migrans	Visual inspection of skin lesion[1]	Serology not recommended because sensitivity of seropositivity is <40% on acute-phase serum sample[11]
	Extracutaneous manifestations include but are not limited to facial nerve palsy, meningitis, radiculopathy, myopericarditis, arthritis	Serologic testing[22]: EIA followed by Western blot (IgM and IgG Western blots if ≤4 weeks of symptoms; IgG Western blot only if >4 weeks or for Lyme arthritis)[a]	In Lyme meningitis, consider testing CSF for intrathecal borrelial antibody production and for borrelial DNA[8]; in Lyme arthritis, consider testing synovial fluid for borrelial DNA[23]
HGA	Fever, typically with leukopenia, thrombocytopenia, and/or increased transaminases	Blood smear[24]; buffy coat smear; PCR for *Anaplasma phagocytophilum* DNA	Serology not routinely recommended except for retrospective diagnosis in treated patients Sensitivity of seropositivity <50% on acute-phase serum sample and seropositivity alone does not establish the presence of active infection[25] Failure to defervesce within 48 h of initiation of doxycycline is evidence against the diagnosis[3]
Babesiosis	Fever, typically with anemia, thrombocytopenia, elevated lactate dehydrogenase, hyperbilirubinemia, and/or increased transaminases	Blood smear preferred[26]; PCR for *Babesia microti* DNA is an alternative	Serologic testing for IgM/IgG antibodies by indirect immunofluorescent assay can be performed, but seropositivity per se does not indicate active infection[26]

Abbreviations: CSF, cerebrospinal fluid; EIA, enzyme immunoassay; HGA, human granulocytic anaplasmosis; PCR, polymerase chain reaction.

[a] See text for potential alternative testing strategies under consideration.

Figure 3. *Anaplasma phagocytophilum* Bacteria in Human Neutrophils



Anaplasma phagocytophilum microcolonies (often called morulae) are observed within a neutrophil on a Giemsa-stained buffy coat smear (original magnification ×1000). Arrowheads indicate the morulae. Micrograph courtesy of Maria Aguero-Rosenfeld, MD, New York University, New York, New York.

Testing strategies that omit the IgM Western blot are being developed to avoid its recognized potential for false-positive test results.[28] One approach is to incorporate the VlsE band into the IgG Western blot, because IgG reactivity to this antigen is highly specific and often obtained in early infection.[31] Another approach is to use an EIA with 1 or several highly specific antigens (eg, C6 or VlsE/PepC10) as the second-step test instead of the Western blot.[38-40] In several studies, a whole-cell sonicate–based EIA followed by the C6 EIA has shown a specificity similar to that of traditional 2-step testing (IIa-B).[38,40] No serologic diagnostic approach is 100% specific, reinforcing current recommendations to not test patients with a low clinical pretest probability of Lyme disease, such as those who lack objective findings and have only nonspecific symptoms such as fatigue (I-B).[3,41,42] Serologic tests also have a poor predictive value in geographic areas with a low prevalence of disease.[43]

Laboratory Testing Other Than Serology

Central nervous system involvement can be established by testing cerebrospinal fluid (CSF) for intrathecal borrelial antibody production, borrelial DNA, or both, but these tests have variable or poor sensitivity such that their negative predictive value may be low (IIa-B).[44,45] CXCL13 in CSF has been proposed as a marker of neurologic Lyme disease, but sensitivity (88%-100%) and specificity (63%-98%) are not consistently high enough to recommend its routine use for clinical diagnosis (IIb-B).[46-49] Another limiting factor of the CXCL13 assay is that CSF samples must be acquired before starting antibiotic therapy.

The most common application of polymerase chain reaction (PCR) in Lyme disease diagnosis is for establishing a diagnosis of Lyme arthritis. PCR assay of synovial fluid has a greater than 75% sensitivity in IgG-seropositive patients with Lyme arthritis.[23]

Culture of *Borrelia* species from blood, skin biopsies, CSF, and synovial fluid is difficult and has poor sensitivity.[30] The following tests are not recommended for diagnosing Lyme disease: certain novel techniques to culture *Borrelia* in blood,[50,51] CD57 cell numbers in blood,[52,53] borrelial antibody testing of CSF without correcting for passive diffusion of antibody present in blood,[54] *Borrelia* antibody testing of synovial fluid,[55] tests of cellular immunity,[56] and urine antigen testing (all III-B).[57]

Human Granulocytic Anaplasmosis

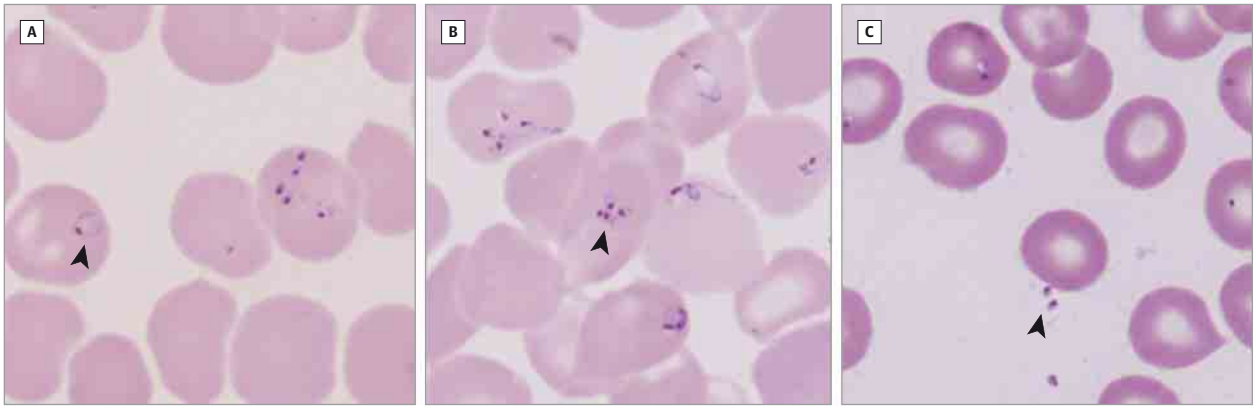
HGA occurs in all Lyme disease–endemic areas in the United States and is caused by *A phagocytophilum*, a rickettsial bacterium. The diagnosis of HGA should be considered for a patient with tick exposure in an endemic area who presents with unexplained nonspecific symptoms such as fever, chills, headache, and myalgias, especially in the setting of abnormal laboratory features, which may include leukopenia, thrombocytopenia, and/or mild elevation of liver enzyme levels.[58-60]

Anaplasma phagocytophilum infection can be diagnosed by microscopic identification of morulae in neutrophils on blood smear or in buffy coat (**Figure 3**), by PCR assay of blood, and by serologic testing (acute plus convalescent titers, as acute serology alone is too insensitive) (all I-B) (Table 1). Antibody titers typically reach at least 1:640 during acute infection.[25] A recent study showed that both PCR and buffy coat examination for morulae have sensitivities in the range of 77% to 80% for patients who are culture positive for *A phagocytophilum.* Culture is available only as a research tool.[58]

Babesiosis

Babesiosis, an infection caused by hemoprotozoan parasites of the genus *Babesia*, is prevalent in the Northeast and upper Midwest

Figure 4. *Babesia microti* Parasites in Human Red Blood Cells



A, *Babesia microti* trophozoites often appear as rings with 1 chromatin dot. Arrowhead indicates a classic ring form of babesia. B, Asexual division of the parasite yields up to 4 merozoites that can arrange in a tetrad, also known as a Maltese cross (arrowhead). Maltese crosses can be formed by *B microti*, *B duncani,* and *B divergens* in human red blood cells. C, After rupture of an infected red blood cell, free merozoites (arrowhead) quickly seek to adhere and invade an intact red blood cell. Original magnification ×1000; Giemsa stain. Micrographs courtesy of Rouette Hunter, BS, MT(ASCP), and Stephen Johnson, BS, from the Hematology Laboratory, Tufts Medical Center, Boston, Massachusetts.

regions of the United States.[26] In these regions, *B microti* is the etiologic agent and has a narrower geographic range than *B burgdorferi*.[61] *Babesia duncani* has sporadically caused disease along the Pacific Coast (from northern California to Washington), whereas *Babesia divergens*–like organisms have been implicated in only 3 patients in the Midwest (Kentucky, Missouri) and the Northwest (Washington). Babesiosis is now a nationally reportable disease for 27 states. Most cases of babesiosis are tick transmitted; however, only *B microti* is transmitted by *I scapularis*.[26] Transfusion-transmitted babesiosis has increased in the past decade.[62] Vertical transmission has also been reported.[63,64]

Babesiosis should be considered in a patient with tick exposure in an endemic area who presents with unexplained nonspecific symptoms such as fever, often in conjunction with fatigue, chills, sweats, headache, myalgia, arthralgia, and/or anorexia, especially if laboratory features include thrombocytopenia, hemolytic anemia, and/or elevation of liver enzyme levels.[3,26]

Diagnosis of active babesiosis is typically made by visualization of *Babesia* parasites on Giemsa- or Wright-stained thin blood smears (Table 1 and **Figure 4**) (I-B).[3,26] Thick blood smears are not recommended because *B microti* and *B duncani* parasites are small organisms (diameter <3 µm) that may be missed (III-C). Several real-time PCR assays are useful to detect low-grade *B microti* parasitemia in human blood and are more sensitive than blood smears. These assays have high diagnostic sensitivity and specificity, do not amplify DNA from the *Plasmodium* species that cause human malaria, and are designed to avoid cross-reactivity with *B duncani*.[65-69] PCR should be considered early in the infection, when parasites are difficult to visualize on blood smears.[26] PCR should be used with caution when monitoring the response to therapy, because *B microti* DNA can be detected for weeks to months after parasites are no longer visualized on blood smears (IIb-B).[67,68,70]

Serology can confirm the diagnosis of babesiosis (I-B) but cannot replace microscopy or PCR because *Babesia*-specific antibody may be absent or undetectable early in the course of illness and because antibody persists beyond resolution of infection.[3,26] Antibody is detected in serum using an indirect immunofluorescence assay (IFA), but other modalities of detection are under development.[71,72] A positive IgM titer is only suggestive of infection and must be accompanied by a positive IgG titer.[26] IgG titers to *B microti* of 1:1024 or greater signify active or recent infection. The IFA should use antigens for the *Babesia* species relevant to the geographic area of the patient because of lack of cross-reactivity.[73,74] The IFA that uses whole *B microti* antigen has a 88% to 96% sensitivity and a 90% to 100% specificity.[75] There have been too few cases of *B duncani* infection to validate an IFA.[74]

Treatment

Lyme Disease

Suggested treatments for adult patients in the United States who present with the most common objective clinical manifestations of Lyme disease are shown in **Table 2**. The first-line antibiotics for treating Lyme disease are doxycycline, amoxicillin, and cefuroxime axetil orally and ceftriaxone intravenously (all I-A). Macrolides are considered second-line agents (IIa-A) reserved for patients unable to tolerate beta-lactams and doxycycline, owing to higher rates of treatment failure in some but not all studies.[3,83-86]

Older treatment trials used a 20-day course of antibiotic therapy for erythema migrans,[87,88] but more recent studies provide evidence that a 10-day course of doxycycline is highly effective and as effective as longer treatment durations (I-A).[18,76,77] There is now stronger evidence that oral doxycycline is effective treatment for Lyme meningitis, cranial neuropathy, and radiculopathy.[78-82] In a prospective, randomized, double-blind study, Ljøstad et al[78] compared doxycycline (200 mg once daily orally) with ceftriaxone (2 g once daily intravenously) for 14 days in 102 participants from Norway with neurologic Lyme disease and found no treatment failure in either treatment group. The Lyme *Borrelia* species found in Europe do not strictly overlap with those found in the United States, but there are no data to suggest a differential response to antibiotics among Lyme *Borrelia* species. Based on these studies, oral doxycycline at the dose of 200 mg daily for adults given for 14 days can be considered first-line therapy for neurologic Lyme disease in Europe (I-A) and for ambulatory patients with early neurologic Lyme disease in the United States (IIa-C) (Table 2).

Table 2. Suggested Treatments for Adult Patients With the Most Common Clinical Manifestations of Lyme Disease in the United States

Manifestation	Antibiotic	Duration	Evidence Grade[a,b]
Erythema migrans	Doxycycline, 100 mg orally twice daily	10 d[c]	I-A
	Amoxicillin, 500 mg orally 3 times daily	14 d[c]	IIa-C
	Cefuroxime axetil, 500 mg orally twice daily	14 d[c]	IIa-C
Erythema migrans in a patient unable to take beta-lactams or tetracyclines	Azithromycin, 500 mg orally once daily	7-10 d	IIa-A
Lyme meningitis			
Ambulatory	Doxycycline, 100 mg orally twice daily or 200 mg once daily[d]	14 d[c]	IIa-C[e]
Hospitalized	Ceftriaxone, 2 g intravenously once daily	14 d[c,f]	I-B
Lyme cranial neuropathy or radiculopathy	Doxycycline, 100 mg orally twice daily or 200 mg once daily	14d[d,g]	IIa-B[e]
Lyme cranial neuropathy or radiculopathy in a patient unable to take tetracyclines	Amoxicillin, 500 mg orally 3 times daily	14d[c,g]	IIa-B
	Cefuroxime axetil, 500 mg orally twice daily	14d[c,g]	IIa-B
Cardiac Lyme disease			
Ambulatory	Same as for erythema migrans	14 d (range, 14-21 d)	IIa-C
Hospitalized	Ceftriaxone, 2 g intravenously once daily until stabilized or discharged Complete course with oral antibiotic recommended for erythema migrans	14 d (range, 14-21 d)[f]	IIa-C IIa-C
Lyme arthritis			
Initial	Doxycycline, 100 mg orally twice daily	28 d	IIa-B
	Amoxicillin, 500 mg orally 3 times daily	28 d	IIa-B
	Cefuroxime axetil, 500 mg orally twice daily	28 d	IIa-C
Persistent Lyme arthritis after first course of oral therapy	Re-treat using 1 of the above oral regimens	28 d	IIb-C
	Ceftriaxone, 2 g intravenously once daily	14-28 d	IIb-C

[a] Gradings pertain to the antibiotic at the specific dosage and duration. All listed antibiotics have activity against *Borrelia burgdorferi* (I-A).

[b] See eTable in the Supplement for American Heart Association evidence-based scoring system.

[c] Represents a change from the 2006 Infectious Diseases Society of America (IDSA) guidelines[3] by virtue of elimination of a longer range in duration of therapy (of up to 21 days for erythema migrans and of up to 28 days for meningitis or radiculopathy).[18,76,77]

[d] Represents a change from the 2006 IDSA guidelines[3] by suggesting oral doxycycline rather than parenteral antibiotic therapy (for meningitis or radiculopathy).[78-82]

[e] For patients who acquire Lyme disease in Europe, this recommendation is I-A.

[f] On hospital discharge, may complete the course of treatment with oral doxycycline for neurologic Lyme disease; for cardiac Lyme disease, may complete the course of therapy with any of the first-line oral regimens used for erythema migrans.

[g] Treatment does not accelerate rate of recovery of facial palsy but is recommended to prevent other sequelae.

No new evidence was found to alter the existing antibiotic recommendations from IDSA for treatment of other extracutaneous manifestations of Lyme disease.[3]

Human Granulocytic Anaplasmosis

There is no new evidence to alter the existing IDSA recommendations for treatment of HGA.[3] The IDSA guidelines state that all patients suspected of having HGA should receive empirical therapy with doxycycline for 10 days and do not need laboratory confirmation (**Table 3**) (I-B).[95] Response to doxycycline therapy for HGA is typically rapid and often seen after a single dose of antibiotic.[96] Failure to improve within 48 hours of initiation of doxycycline therapy should raise concern that the patient does not have HGA or has a coinfection that is not responsive to doxycycline, such as babesiosis.

Doxycycline is not considered safe in pregnancy. In the case of life-threatening HGA, however, use of doxycycline may be warranted.[24] A treatment period shorter than 10 days may be reasonable depending on the clinical response, but systematic studies are lacking. There have been reports of successful use of rifampin in treating HGA in pregnant women and young children, but data are limited (IIb-C, Table 3).[97,98]

Babesiosis

Current guidelines recommend therapy for symptomatic patients only.[3] Patients with mild to moderate babesiosis should be treated with a 7- to 10-day course of oral azithromycin combined with oral atovaquone (I-B) (Table 3). This recommendation is supported by data from a prospective, nonblinded, randomized trial in 58 patients with non–life-threatening babesiosis caused by *B microti*.[99] In this trial, azithromycin plus atovaquone was not different from clindamycin plus quinine in resolving symptoms but was associated with fewer adverse effects. In addition, clearance of parasite DNA in blood, an indirect measure of parasitemia, did not differ significantly between the 2 regimens.[99]

The IDSA guidelines for treating severe babesiosis recommend a 7- to 10-day course of intravenous clindamycin combined with oral quinine (I-C).[3] This recommendation is based on expert opinion, as the efficacy and benefit-risk ratio of this regimen have not been addressed in a clinical trial. Because quinine therapy often is interrupted because of drug toxicity, consideration should be given to a regimen of intravenous azithromycin plus oral atovaquone when treating severe babesiosis in hospitalized patients (IIb-C). Some patients have been successfully treated with a combination of intravenous clindamycin and oral atovaquone,[63,92,93] but the efficacy of this regimen, like those of most antibabesia drug regimens, has not been tested in a clinical trial (IIb-C).

Persistent or relapsing babesiosis often occurs in highly immunocompromised individuals, particularly in patients with B-cell lymphoma who are or were recently treated with rituximab.[100-102] Other risk factors have not been clearly defined but appear to include human immunodeficiency virus infection with low CD4 cell counts[100,103] and immunosuppressive therapy for solid organ[101] or stem cell[104] transplants. Evidence from a recent retrospective case-control study supports treating such highly immunocompromised patients

Table 3. Suggested Treatments for Adult Patients With Human Granulocytic Anaplasmosis or Babesiosis in the United States

Disease	Antibiotic(s)	Evidence Grade[a]	Alternative Option	Evidence Grade[a]
Human granulocytic anaplasmosis	Doxycycline, 100 mg orally or intravenously twice daily for 10 d	I-B	Rifampin, 300 mg orally twice daily for 10 d	IIb-C
Babesiosis				
Mild	Azithromycin, 500 mg orally on day 1 and 250 mg orally once daily from day 2 to days 7-10 plus atovaquone, 750 mg orally twice daily from day 1 to days 7-10	I-B		
Severe	Clindamycin, 300-600 mg intravenously 4 times daily plus quinine, 650 mg orally 3 to 4 times daily for 7-10 d	I-C[b,c,d]	Azithromycin, 500 mg intravenously once daily plus atovaquone, 750 mg orally twice daily for 7-10 d, or:	IIb-C[b,e]
			Clindamycin, 300-600 mg intravenously 4 times daily plus atovaquone, 750 mg orally twice daily for 7-10 d	IIb-C[b,c,d,f]
	Consider adjunctive exchange transfusion	IIa-C[b]	Consider adjunctive exchange transfusion	IIa-C[b]
In severely immuno-compromised patients	Drug regimen(s) administered for at least 6 wk, including 2 wk with no parasites on blood smear See text for the various drug regimens	I-B[g]		

[a] See eTable in the Supplement for American Heart Association evidenced-based scoring system.

[b] Recommended for the treatment of severe babesiosis in hospitalized patients.

[c] Quinidine may be used in lieu of quinine (when poorly tolerated or intravenous administration is desired) or atovaquone (when intravenous administration is desired), although efficacy data are scarce.[89] Quinidine requires cardiac monitoring, owing to the risk of QT interval prolongation and torsade de pointes.[90]

[d] Intravenous clindamycin may be replaced with oral clindamycin (600 mg administered 3 times per day) once the patient has improved.

[e] This regimen was not included in the 2006 Infectious Diseases Society of America (IDSA) guidelines[3] but should be considered when intravenous administration is desired. Intravenous azithromycin may be replaced with oral azithromycin (500 mg per day) once the patient has improved. Atovaquone should not be replaced with intravenous quinidine because patients receiving both azithromycin and quinidine may be at increased risk of cardiac arrhythmias.[90,91]

[f] This regimen was not included in the 2006 IDSA guidelines[3] but has been used successfully in several cases.[63,92,93]

[g] When treating highly immunocompromised patients, higher doses of azithromycin (600-1000 mg per day orally) should be considered.[3,94]

for 6 weeks or longer, including negative blood smears for 2 weeks or longer prior to discontinuation (I-B).[100] Several antimicrobial regimens have been used, including 2-drug regimens such as azithromycin + atovaquone or clindamycin + atovaquone or 3-drug regimens such as atovaquone + azithromycin + clindamycin or atovaquone + clindamycin + artemisinin.[100,101,105] Atovaquone/proguanil has been included in various drug regimens.[101,103-105] No particular antibabesia drug regimen appears to be superior,[100] but systematic studies are lacking. Reducing or discontinuing immunosuppressive therapy is desirable. Higher doses of oral azithromycin (from 600 to 1000 mg per day) should be considered for severely immunocompromised patients (IIb-C),[94] because several cases of antibiotic resistance have developed with lower dosages.[101]

Partial or complete red blood cell exchange transfusion should be considered for patients with high-grade parasitemia (≥10%), severe hemolysis, or pulmonary, renal, or hepatic compromise (IIa-C).[3] However, there are no systematic studies on this therapeutic modality, nor are there data on the benefit and optimal use of red blood cell exchange vs whole blood or plasma exchange. A review of 24 cases of life-threatening babesiosis revealed that hemolysis is the most frequent indication for exchange transfusion in babesiosis.[106] This series, although limited in size, suggested that (1) early use of exchange transfusion may prevent organ dysfunction and possibly death, (2) a 90% reduction in parasitemia should be the minimally desired target of red blood cell exchange, and (3) this target can be achieved by exchanging with 2.5 times the patient red blood cell volume.[106]

Splenic infarct and splenic rupture may complicate the course of babesiosis.[107] Patients with splenic infarct or rupture often experience low levels of parasitemia and do not present with the complications typically associated with severe babesiosis.[108,109] Nonsurgical control of splenic rupture is preferred, particularly when the patient is at risk of recurrent exposure to *Babesia* species, because splenectomy predisposes to severe babesiosis.[107,110]

Co-infections

Co-infections that include Lyme disease plus either HGA or babesiosis are well documented.[61] The number of symptoms in patients with concurrent Lyme disease and babesiosis is greater than in patients with Lyme disease alone.[111,112] The same observation has been reported for Lyme disease and HGA in some studies but not all.[112-114] Co-infection should be considered for patients with Lyme disease who have fever for more than 48 hours while receiving antibiotic therapy or for those with unexplained leukopenia, thrombocytopenia, and/or anemia. Doxycycline may be included empirically in the treatment regimen for babesiosis when Lyme disease or HGA co-infection is suspected. When a co-infection has been documented, patients should receive therapies appropriate for the treatment of each infection (I-C).

Other *Ixodes*-Transmitted Infections

Borrelia miyamotoi, *Borrelia mayonii*, deer tick virus, and *Ehrlichia muris*–like agent are transmitted by the *I scapularis* tick and are recognized as emerging human pathogens. *Borrelia miyamotoi* is most closely related to relapsing fever borrelia and causes an undifferentiated febrile illness that may include findings of increased liver enzyme levels, leukopenia/thrombocytopenia, and, in immunocompromised patients, chronic meningoencephalitis.[115-119] *Borrelia miyamotoi* can be diagnosed by detection of antibody to the GlpQ protein or PCR amplification of the *glpQ* gene, which is not present

Box. Take-Home Messages

Lyme Disease
- Erythema migrans is diagnosed based on visual inspection rather than laboratory testing
- Two-step serologic testing that consists of an enzyme immunoassay followed by supplemental Western blot testing is a sensitive and specific approach to diagnose extracutaneous manifestations of Lyme disease
- Most manifestations of Lyme disease can be successfully treated with oral doxycycline (100 mg twice daily for 10-14 days, except for arthritis, which has been traditionally treated for 28 days)

Human Granulocytic Anaplasmosis
- Buffy coat smear and polymerase chain reaction assay of blood are the preferred diagnostic modalities
- Doxycycline (100 mg orally twice daily) is a highly effective therapy

Babesiosis
- Thin blood smear examination and polymerase chain reaction assay are the preferred diagnostic modalities
- Azithromycin (500 mg orally on day 1, then 250 mg orally once daily) plus atovaquone (750 mg orally twice daily) should be used to treat patients with mild babesiosis
- Clindamycin (300-600 mg intravenously 4 times daily) plus quinine (650 mg orally 3 to 4 times daily) is recommended for patients with severe babesiosis
- Highly immunocompromised patients require at least 6 weeks of therapy, with negative blood smears for at least 2 weeks prior to discontinuation

in *B burgdorferi*.[119-121] The first-line antibiotics used to treat erythema migrans appear effective against *B miyamotoi*,[115,119] but no systematic study has been carried out. A new Lyme *Borrelia* species, *B mayonii*, has been reported in the Midwestern United States as causing a Lyme disease–like illness.[122] Criteria for diagnosis and appropriate treatment have not been definitively determined but are likely to be similar to those for *B burgdorferi*. Deer tick virus is a discrete subtype of Powassan virus that can cause a severe meningoencephalitis, although there is likely a spectrum of severity from asymptomatic to severe.[123] Diagnosis is made by serologic testing, PCR, or both.[124,125] Treatment is supportive only. The *E muris*–like agent has only been reported in Minnesota and Wisconsin.[126] It also causes an undifferentiated febrile illness that can be associated with increased liver enzyme levels and cytopenias. Diagnosis is typically made by PCR on a blood specimen.[125] Serology can cross react with *Ehrlichia chaffeensis* but not *A phagocytophilum*. Treatment with doxycycline appears effective.[125] Diagnostic testing for each of these pathogens is performed by only a few specialized laboratories.

Disease Prevention

There are no available human vaccines for Lyme disease, HGA, or babesiosis. A single 200-mg prophylactic dose of doxycycline following a tick bite was 87% effective in preventing the development of erythema migrans at the bite site,[127] but the confidence interval surrounding this efficacy rate was wide. Prophylaxis is only recommended when an *Ixodes* tick from a Lyme disease–endemic area has been attached for 36 hours or longer and prophylaxis can be started within 72 hours.[3] The effect of single-dose prophylaxis with doxycycline on other *I scapularis*–transmitted infections is unknown.

Current recommendations to reduce risk of transmission include daily body checks for ticks, use of tick repellents containing DEET, use of clothing impregnated with acaricides such as permethrin, and minimizing skin exposure to ticks.[128] Bathing or showering within 2 hours of tick exposure helps prevent attachment of ticks and reduces the odds of contracting Lyme disease, as does use of protective clothing.[129] Tick checks and use of tick repellents have yielded inconsistent results,[129,130] but adherence to these measures was not assessed, and failures may be attributable to lack of full adherence to preventive measures during exposures. Placing clothes in a dryer for up to 1 hour effectively kills ticks[131] but has not been evaluated for reduction of Lyme disease cases. These interventions have minimal potential risks, so although they may have limited benefit, they can be recommended.

Modifications of the home environment have not clearly been shown to affect transmission risk. Spraying pesticides around the home effectively reduces tick populations but is not associated with the incidence of Lyme disease.[129,132] This discrepancy may be attributable to risks of exposure away from home. Alternatively, the decrease in tick numbers, while large, may need to be even larger to reduce risk of tick-borne diseases. Targeted application of acaricides to mice or deer has yielded mixed results[133-136] or, in the case of the 4-poster device (a feeding station designed to apply acaricides), has raised concerns about the spread of other diseases such as chronic wasting disease in deer. Altering landscape characteristics by removing leaf litter or having a barrier to adjacent wooded areas has not consistently reduced the incidence of Lyme disease.[129]

Conclusions

Evidence is evolving regarding the diagnosis, treatment, and prevention of Lyme disease, HGA, and babesiosis. Important considerations for clinicians are summarized in the **Box**. Recent evidence supports treating patients with erythema migrans for no longer than 10 days when doxycycline is used and prescription of a 14-day course of oral doxycycline for early neurologic Lyme disease in ambulatory patients. The duration of antimicrobial therapy for babesiosis in severely immunocompromised patients should be extended to 6 weeks or longer.

ARTICLE INFORMATION

Author Contributions: Dr Hu had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: All authors.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: All authors.
Administrative, technical, or material support: Sanchez.
Study supervision: Hu.

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and babesiosis; serving as an unpaid board member of the American Lyme Disease Foundation; and serving as a consultant to Baxter for Lyme disease vaccine development. Dr Hu reported receiving research funding from Massbiologics at the University of Massachusetts Medical School; working as a consultant for Abzyme; and being supported by National Institutes of Health grants U01AI109656, R21AI111317, R21AI103905, and R42AI078631 and by the Steven and Alexandra Cohen Foundation.

Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Edward Livingston, MD, at Edward.livingston@jamanetwork.org or Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

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