A Clinical Review of Tick-Borne Diseases in Arkansas

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ABSTRACT:

Tick-borne diseases are illnesses transmitted by ticks harboring a wide variety of pathogens. Arkansas is reported as one of the states with a high incidence of tick-borne diseases. In Arkansas the four most frequently occurring tick-borne diseases are Rocky Mountain Spotted Fever (RMSF, also known as Spotted Fever Rickettsiosis), Ehrlichiosis, Tularemia and Anaplasmosis. Lyme disease, on the other hand, is not acquired in Arkansas and is only acquired by traveling to states where Lyme disease is endemic. The majority of tick-borne diseases are diagnosed based on a history of tick bite or exposure and the individual's clinical presentation. The recognition of specific symptoms requires prompt treatment to prevent long-term sequelae. Hence, knowledge of tick-borne diseases and preventive measures can help reduce the risks associated with the infection.

KEYWORDS:
RMSF, Ehrlichiosis, Tularemia, Anaplasmosis, Lyme, tick-borne diseases

Introduction

TICK-BORNE DISEASES (TBDS) ARE CAUSED BY A WIDE VARIETY OF PATHOGENS THAT CAN BE TRANSMITTED TO HUMANS THROUGH THE BITE OF INFECTED TICKS. They are diagnosed based on history of exposure to infected ticks (e.g. outdoor activities) and the presence of clinical symptoms such as fever, headache, nausea, vomiting, rash and/or joint pains. However, the varied and overlapping clinical presentations of TBDs complicate diagnosis and treatment of these diseases and represent a clinical challenge. Over the last decade, the incidence of TBDs in the United States (U.S.) has increased and this has been attributed to climate changes, tick activity, changes in human population density (for instance, more people prefer to live in wooded/grassland transitions where ticks and animal reservoirs are abundant) and improvements in diagnosis and reporting.[1,2] Most cases of TBDs can be cured with antibiotics when diagnosed early. Late diagnosis, however, can lead to serious clinical outcomes such as neurological, cardiovascular and respiratory complications.

Arkansas is among the states with the highest overall incidence of TBDs. The state's geography, which ranges from mountains to densely forested lands to the Mississippi delta, serves as habitat for host animals, which is essential for the tick's survival. According to the Arkansas Department of Health (ADH), in 2014 the number of individuals afflicted with TBDs approximately doubled, with a total of 1,108 cases reported compared to 690 cases the previous year (2013), which is attributed to better surveillance (3; Table 1). Rocky Mountain Spotted Fever (RMSF) is the most frequently reported TBD in the state, while Ehrlichiosis, Tularemia and Anaplasmosis are also common (in descending order) but of lesser frequency than RMSF. Lyme disease, the most commonly reported TBD in the U.S., has not been acquired in Arkansas but can be acquired by traveling to endemic areas such as the Northeast, Northwest and Midwest.[4,5]

An in-depth understanding of the nature of TBDs and awareness of preventive measures can help reduce TBDs. This review will highlight the four most common TBDs in Arkansas, namely RMSF, Ehrlichiosis, Tularemia and Anaplasmosis, and provide knowledge in terms of their etiology, symptomatology, diagnosis, treatment and prevention. Lyme disease is also presented here and although it is not acquired in Arkansas, it is common in the U.S. and can lead to significant morbidity and mortality if left undiagnosed and untreated. A brief outline of some emerging TBDs is presented so that providers are aware of these when formulating a diagnosis.

Tick Life Cycle and Hosts

Ticks are arthropods that require a blood meal from an animal host to survive and complete a life cycle that varies from several months up to three years or longer, depending on the species of tick and how many hosts they require. Ticks undergo three life stages: hatching from eggs, transforming into a six-legged larva before developing into an eight-legged nymph, and ultimately maturing into an adult. They can feed on a variety of animal hosts such as deer, rabbits and rodents. Ticks acquire infection by feeding on the blood of an infected animal or by transovarial transmission from an infected adult female tick.[6] TBDs are initiated by inoculation of a pathogen (virus, bacterium and/or protozoan) into a person's blood via the saliva of an infected tick while feeding. This bite may go unnoticed, as ticks can secrete saliva with anesthetic, anti-coagulant, anti-inflammatory, vasodilatory, and anti-hemostatic properties for effective feeding and transmission of the pathogens they harbor.[7]

Rocky Mountain Spotted Fever

RMSF is a TBD caused by an intracellular bacterium *Rickettsia rickettsii*. In the U.S., three vectors have been identified that transmit the RMSF bacterium, the American dog tick *Dermacentor variabilis* (Figure 1, common in Arkansas), the Rocky Mountain wood tick *Dermacentor andersoni* (Figure 2), and the brown dog tick *Rhipicephalus sanguineus* (Figure 3). Besides Arkansas, the highest incidence of RMSF cases were reported from Delaware, North Carolina, Missouri, Oklahoma and Tennessee. The incidence of RMSF is higher in males than females and most commonly seen in adults aged 60-69 or children aged 5-9 years old.[8] Effective rickettsial transmission requires attachment of the tick to its human host for at least 6-10 hours, and infection usually occurs during spring and summer months.[8,9] RMSF's incubation period is 2 to 14 days and the first clinical manifestations may appear 5-10 days after the tick bite. The hallmark of

Figure A: Classic Petechial rash found in patient with RMSF

RMSF is the appearance of a rash, which is present in 90% of patients. However, 10% of patients may fail to develop the characteristic rash and are at increased risk of being misdiagnosed or undiagnosed.[9,10] The rash is usually preceded by high grade fever (>102°F), headache, and muscle aches. Macular rash first develops on the wrists and ankles and spreads to the chest, face and rest of extremities (Figure A). Other non-specific symptoms of RMSF include abdominal pain, nausea, vomiting and diarrhea. If left untreated, widespread vasculitis can result in intravascular coagulation affecting the kidney (leading to kidney failure), heart (inflammation causing myocarditis), brain (confusions/seizures) or eyes (inflammation causing uveitis), and potentially lead to death. The clinical consequences described are due to the ability of *R. rickettsii* to invade, localize in endothelial cells that line blood vessels and induce endothelial and vascular cell injury, which is a hallmark of RMSF.[8,11]

RMSF has been described as "a great imitator of other disease" because of its diverse clinical features.[8,12] According to current data from ADH, RMSF comprises 70% of the total TBDs in Arkansas, with a mortality rate of <1%. Deaths are likely due to a delay in seeking care, diagnosis and treatment. The diagnosis of RMSF primarily relies on patient's history and clinical presentation. Serologic tests are done to establish the diagnosis in most cases. General laboratory findings include thrombocytopenia, hyponatremia and mildly elevated hepatic transaminases. Antibodies

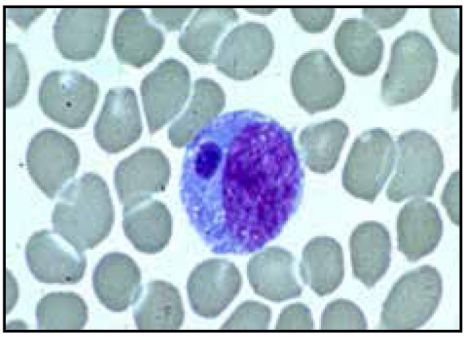

Figure B: Ehrlichia laden morulae in a white blood cell

for *R. rickettsii* are detectable 7-10 days after onset of symptoms. A four-fold increase in IgG or IgM antibody titers is confirmatory of RMSF infection.[13]

Prompt initiation of antibiotic therapy is recommended in a patient with a strong history of tick exposure and clinical presentations highly suggestive of RMSF. Doxycycline is the treatment of choice for RMSF infected patients of all ages. While there remains reluctance among providers to use doxycycline in children under 8 years of age, it is still the drug of choice, and a week long course of doxycycline will not increase the risk of tooth staining. This known side effect occurs after at least 6 weeks of cumulative treatment.[14] Minimum treatment is 5-7 days or at least 2-3 days after fever subsides. Once infected and treated, an individual develops permanent immunity against future RMSF infections.

Ehrlichiosis

Ehrlichiosis is another TBD occurring frequently in Arkansas and in the neighboring states of Oklahoma and Missouri. Based on current reports, Human Monocytic Ehrlichiosis (HME) accounts for 20% of total cases of TBDs in Arkansas, ranking second to RMSF. HME in the U.S. is caused by three species of *Ehrlichia*, namely *Ehrlichia chaffeensis* (common in Arkansas, named after Fort Chaffee, Arkansas), *Ehrlichia ewingii,* and *Ehrlichia muris*-like (EML). The lone star tick *Amblyomma americanum* (Figure 4), the most abundant tick in Arkansas, is the primary vector that transmits *Ehrlichia chaffeensis* and *Ehrlichia ewingii* in humans.[15,16] *Ehrlichia* are gram-negative intracellular coccobacilli which belong to the family Rickettsiae. They cause disease by targeting macrophages in liver, spleen, lung, kidney and central nervous system. They multiply in phagosomes and form aggregates called morulae that can be detected in the blood of 20% of patients (Figure B).[17] Some evidence suggests that HME can also be transmitted through blood transfusions, between mother and fetus via the placenta, and through direct contact with an infected dead animal.[18] The incubation period for HME is 1-2 weeks. Typical presentations of HME include fever, headache, chills, body malaise, muscle aches and other flu-like symptoms. Rash is more common in children than in adults. Untreated HME can result in serious complications such as renal failure, respiratory failure, myocarditis, encephalopathy and coagulopathy. Similar to RMSF,

Figure C: Erythema migrans rash found in patient with Lyme disease

HME is primarily diagnosed based on clinical symptoms and confirmed by serologic tests. Anemia, leukopenia, thrombocytopenia, elevated hepatic transaminases are classic laboratory abnormalities. Detection of morulae in the blood, 4-fold increase in IgG or IgM titers, and detection of DNA by PCR in the blood confirm the diagnosis. Ehrlichiosis is treated in the same manner as RMSF with doxycycline for 5-7 days or at least 2-3 days after fever subsides.

Tularemia

Tularemia is a febrile, granulomatous TBD caused by *Francisella tularensis,* a gram- negative, pleomorphic bacillus that can cause illness with as few as 10-50 organisms.[19,20] Reports show that 40% of tularemia cases in the U.S. are found in Arkansas, Oklahoma and Missouri. Arkansas had the highest tularemia incidence in the nation from 2009-2013, with rates 21 times the national average, representing 18% of all U.S. cases.[21] In Arkansas, 4% of the total tick borne cases are tularemia infections. Most cases of tularemia are transmitted to humans through the bite of an infected lone star tick *Amblyomma americanum* (Figure 4), American dog tick *Dermacentor variabilis* (Figure 1), or Rocky Mountain wood tick *Dermacentor andersoni* (Figure 2). Other routes of transmission are through deer fly bites, contact with or ingestion of contaminated animals, animal products and water, and handling of infected animal carcasses. *F. tularensis* is reported to remain viable for long periods in dead hosts' bodies. Infection with *F. tularensis* produces an acute inflammatory response which gives rise to granuloma and abscess formation. After 48-72 hours, several cytokines and chemokines, such as interferon gamma (IFN) and tumor necrosis factor (TNF), are activated, causing serious tissue injury and organ failure.[22,23] The average incubation period is 2-5 days but it may also take up to 21 days before symptoms manifest. Six forms of the disease have been identified based on the host, clinical symptoms, and route of transmission. These forms include: a) the ulceroglandular form (most common; 70-80% of cases), where *F. tularensis* enters the circulation through a tick bite or skin abrasions and then spreads to regional lymph nodes; skin ulcer and swollen lymph nodes are the main clinical symptoms; b) the glandular form (rare), which is similar to ulceroglandular, except that no ulcer is present; c) the oculoglandular form (1% of cases, Parinaud syndrome), where *F. tularensis* enters through the conjunctiva, resulting in eye inflammation and lymphadenopathy; d) the oropharyngeal form (rare) results from ingestion of contaminated food and water, with symptoms including sore throat, tonsillitis and swollen neck lymph nodes; e) pneumonic tularemia (worst form), which results from inhalation of contaminated dusts or aerosols; pneumonia is the presenting symptom and without treatment, can lead to 60% mortality rate; f) and the typhoidal form (septicemic; 10-15% cases), which may result from ingestion; pneumonia can be the presenting symptom. High grade fever is the common clinical symptom in all forms of tularemia infection. Similar to other TBDs, there is difficulty in diagnosing tularemia due to its non-specific clinical symptoms. The most common method of diagnosing tularemia is through testing and identification of antibodies to the bacteria in the blood. However, a confirmatory culture, PCR or convalescent serological test showing a four-fold rise in titers is required to support the diagnosis. Other laboratory test results that are commonly seen include the presence of thrombocytopenia, hyponatremia, elevated transaminases and creatine phosphokinases. A chest x-ray is also required to diagnose pneumonia in pneumonic and typhoidal forms of tularemia.[24] Gentamicin or streptomycin given by injection is the treatment of choice for severe tularemia, while mild cases can be treated with oral ciprofloxacin or doxycycline. Approximately 10% of patients relapse after oral treatment. Length of treatment is 10 to 21 days depending on the severity of illness. Mortality rate increases to 5-15% without treatment and presence of elevated creatine kinase and renal failure indicates poor prognosis.

Anasplasmosis

Anaplasmosis is a TBD caused by a gram-negative intracellular coccobacilli *Anaplasma phagocytophilum.* It was formerly known as human granulocytic ehrlichiosis (HGE) and recently renamed as human granulocytic anaplasmosis (HGA), as it targets granulocytes.[25] It is transmitted to humans through the bite of an infected blacklegged tick *Ixodes scapularis* (Figure 5, common in Arkansas) or Western blacklegged tick *Ixodes pacificus* (Figure 6). HGA infection mostly occurs in the Northeast and upper Midwest states, however a small percentage of cases (approximately 1.5%) have also been reported in Arkansas. Anaplasmosis is closely related to Ehrlichiosis and shares the same pathology, incubation period, clinical features, diagnosis, treatment and prognosis. Early treatment should be initiated to prevent life-threatening complications.[26, 27]

Lyme disease

Lyme disease is a TBD caused by the spirochete bacterium *Borrelia burgdorferi* and is transmitted to humans through the bite of an infected blacklegged tick *Ixodes scapularis* (Figure 5) in the Northeast and upper Midwest, and the Western blacklegged tick *Ixodes pacificus* (Figure 6) in the Northwest. This disease carries the Lyme moniker because the first case was diagnosed in 1975, in Old Lyme, Connecticut.[5] Most reported cases of Lyme disease occur in the upper Midwestern, Northeastern and North Central U.S. According to the Centers for Disease Control and Prevention (CDC), in 2013 there were over 35,000 total reported cases of Lyme disease with 95% of these cases reported from 14 states: Connecticut, Delaware, Maine, Maryland, Massachusetts, Minnesota, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont, Virginia, and Wisconsin.[13,28] A recent CDC report estimates that greater than 90% of people are undiagnosed and that there are 300,000 people infected in the U.S.[29] In northern areas of the U.S., where Lyme disease is common, the spirochete is transmitted by nymphal black-legged ticks, which commonly bite humans. However, in southern states, it is the adult black-legged tick that bites humans. Lyme disease is not reported in Arkansas and the most recent confirmed case occurred in 2007 in a traveler to an endemic area.[5]

The incubation period of Lyme disease is usually 3-30 days in endemic areas, but the rash most commonly develops within 7-14 days.[30] During the early or localized stage of illness, Lyme disease may be diag-

Table 1. Arkansas Deparment of Health (ADH) Current Tickborne Disease Infections Report

Year	Anaplasmosis	Ehrlichiosis	Lyme Disease	RMSF	Tularemia	Total Cases	Deaths
2012	8	84	0	837	22	951	5
2013	7	165	0	480	38	690	4
2014	15	236	0	816	41	1,108	4

nosed clinically in patients who present with the classic erythema migrans (EM) rash (Figure C). The rash is described as a red ring-like or homogenous expanding rash, often looking like a "bull's-eye".[28] However, only 70-80% of patients develop the classic rash, thus making early diagnosis difficult in some patients.[31] Other early clinical presentations include flu-like symptoms such as malaise, headache, fever, myalgia, arthralgia and lymphadenopathy. If left untreated, early symptoms may resolve spontaneously; however, spirochetes remain in the body and more serious symptoms can develop months to years later. The disseminated stage is characterized by the appearance of multiple secondary annular rashes and presence of flu-like symptoms and lymphadenopathy. Lyme disease at this stage becomes severe and chronic, and patients may experience intermittent rheumatologic (e.g. transient migratory arthritis and effusion, migratory tendon and bone pain, Baker's cyst), cardiac (e.g. AV blocks, myocarditis, pericarditis), and/or neurologic (e.g. Bell's palsy, encephalopathy, meningitis) manifestations.[32,33] Uveitis, hepatitis and splenomegaly may also occur in patients with late stage or disseminated Lyme disease. Serologic tests are not helpful during the early stage of the disease and only become positive after a few weeks of infection. The diagnosis of Lyme disease is usually confirmed by a series of two serologic tests as per CDC guidelines. Aside from an effective diagnosis, another advantage of a two-tier testing protocol is it distinguishes active from past Lyme infection. Enzyme immunoassay (EIA) or IFA test is performed first to detect antibodies to the spirochete; if positive or equivocal, it is followed by a Western Blot test. The patient is considered positive if both EIA or IFA and Western Blot tests are positive.[34-36] The IgM Western Blot is considered positive if two of the three bands are positive within the first month of illness (23, 39, or 41 kDa). The IgG Western Blot is positive when five of the ten bands are present (18, 23, 28, 30, 39, 41, 45, 58, 66 and 99 kDa). Localized (early) Lyme disease is commonly treated with oral amoxicillin, doxycycline or cefuroxime axetil for 14-21 days. A 100% recovery rate is typical upon successful completion of treatment in this early stage. However, patients in the disseminated (late) stage of Lyme disease require a more complicated and a longer duration of treatment up to four weeks.[34] Longer duration of antibiotics has not shown to be of any benefit for chronic sequelae of Lyme disease. Early diagnosis and treatment is essential to prevent the chronic and serious effects of Lyme disease.[34, 35]

Emerging Tick-Borne Diseases

Southern tick-associated rash illness (STARI) is an emerging TBD that produces an erythema migrans-like rash (similar to the characteristic rash of Lyme disease) following the bite of an infected lone star tick *Amblyomma americanum* (Figure 4).[17] STARI is reported in areas such as central Texas, Oklahoma, Arkansas and as far north as Maine where the lone star tick is abundant. This similarity may lead clinicians to suspect Lyme disease instead of STARI in these areas (34). Recent evidence suggests that a spirochete called *Borrelia lonestari* is the possible etiology of STARI; however, this needs further investigations.[5, 37] Diagnostic tests for STARI are not available; therefore diagnosis relies solely on the history of exposure to the tick *Amblyomma americanum.* Flu-like symptoms may also be present but are less severe than the symptoms of Lyme disease. Unlike Lyme disease, long-term sequelae have not been reported. Because of STARI's clinical resemblance to early Lyme disease, patients diagnosed with the disease are often treated with the same antibiotics recommended for localized Lyme disease.[38]

Heartland virus disease is an emerging TBD first identified in Missouri in 2009.[39] Heartland virus is different than other reported TBD in Arkansas, as the causative agent is a *Phlebovirus*, rather than a bacterium. It is believed that the virus is transmitted following the bite of an infected lone star tick *Amblyomma americanum* (Figure 4).[39] As of March 2014, there have been eight known cases of Heartland virus disease, in Missouri, Oklahoma and Tennessee. Heartland virus cases have presented similarly to *Ehrlichiosis*, with symptoms including fever, fatigue, diarrhea, leukopenia and thrombocytopenia.[39] There is no commercially available testing for Heartland virus disease, nor is there a specific treatment.[40] The CDC has established a study protocol for the investigation of Heartland virus disease.[39] Arkansas is participating in the CDC Heartland virus disease study.

Bourbon virus disease, like Heartland virus, is caused by a virus rather than a bacterium. Bourbon virus was first identified in the spring of 2014 in Bourbon County Kansas, and is a novel RNA virus in the genus *Thogotovirus* (family *Orthomyxoviridae*). Little is known about Bourbon virus at this time, but it is speculated that it is transmitted through tick or other insect bites. There has been one documented case to date.[41] The case patient had a recent history of tick bites and presented with fever, fatigue, anorexia, nausea, vomiting, and a maculopapular rash as well as thrombocytopenia and leukopenia. The patient was given doxycycline empirically for a presumed TBD, but his condition worsened, and he died eight days post illness onset.[42] There is no routine testing available for Bourbon virus. However, protocols are being developed to allow for investigational diagnostic testing of acute disease.[42]

Prevention of Tick Bites

Prevention for TBDs is divided into personal, environmental and prophylactic strategies.[2]

1. Avoid places where ticks are commonly found, such as brushy and wooded areas and areas with tall grass.
2. Wear permethrin treated clothing, light-colored clothing or repellant containing at least 20% diethyltoluamide (DEET). Children greater than 6 months old may wear up to 30% DEET. Adults may use higher concentrations.
3. Check for ticks after returning home from tick infected areas. Regularly inspect children for ticks. Look for ticks on the hairline and scalp, around the ears, under the arms, inside the belly button, behind the knees, between the legs, and around the waist.
4. Take a shower as soon as possible after returning from tick infected areas.
5. Promptly and effectively remove tick(s) when found. Use fine-tipped tweezers to grasp the tick as close to the skin's surface as possible. Pull upward with steady even pressure. Do not squeeze the abdomen of the tick. Avoid twisting

Figure 1: American dog tick

Figure 2: Rocky Mountain wood tick

Figure 3: Brown dog tick

Figure 4: Lone star tick

Figure 5: Blacklegged tick

Figure 6: Western blacklegged tick

Table 2. Summary of tick borne diseases in Arkansas

	RMSF	Ehrlichiosis	Tularemia	Anaplasmosis	Lyme Disease
Organism	Rickettsia Rickettsii	Ehrlichia chaffeensis	Francisella tularensis	Anaplasma phagocytophilum	*Borrelia burgdorferi*
Vector	Dermacentor variabilis and/or *Dermacentor andersoni* and/or *Rhipicephalus sanguineus*	Amblyomma americanum	*Amblyomma americanum,* and/or *Dermacentor variabilis* and/or *Dermacentor andersoni*	*Ixodes Scapularis* and/or *Ixodes pacificus*	*Ixodes scapularis* and/or *Ixodes pacificus*
Symptoms	Maculopapular rash, ± flu-like symptoms	Flu-like symptoms	High grade fever + symptoms depending on port of entry: (ulcero) glandular: +cutaneous ulcer; oculoglandular: +conjunctivitis, photophobia; oropharyngeal: +sore throat; pneumonic: +pneumonia; typhoidal: combination of symptoms ± pneumonia	Flu-like symptoms	Localized stage: +Erythema migrans, ± flu-like symptoms Disseminated stage: multiple annular rashes, + rheumatologic, cardiac or neurologic symptoms
Diagnostics	+ antibody titer by IFA detected 7-10 days after onset of disease	+ antibody titer by IFA detected 7-10 days after onset of disease, leukopenia, anemia, +morulae in blood	+ antibody titer by IFA	+ antibody titer by IFA detected 7-10 days after onset of disease, leukopenia, anemia, +morulae in blood	Early stage: clinical symptoms; Late stage: + antibody titer by EIA AND +western blot test
Treatment	Oral Doxycyline for all ages x 5-7 days or 3 days after fever subsides	Oral Doxycyline for all ages x 5-7 days or 3 days after fever subsides	Streptomycin (IM) or Gentamicin (IM or IV)	Oral Doxycyline for all ages x 5-7 days or 3 days after fever subsides	Oral amoxicillin, doxycycline or cefuroxime axetil x 14-21 days
Complications	Vasculitis resulting in kidney failure; myocarditis, confusion; seizures; uveitis	Renal failure; respiratory failure; myocarditis; encephalopathy; coagulopathy	Pneumonia; meningitis; osteomyelitis; pericarditis	Renal failure; respiratory failure; myocarditis; encephalopathy; coagulopathy	Migratory arthritis; Atrioventricular block; myocarditis; Bell's palsy; encephalopathy; uveitis; hepatitis

the tick because it can break off the tick's mouth that will remain in the skin. If this happens, try to remove the mouth parts and if unsuccessful, leave them alone and let the skin heal. After removal of the tick, thoroughly clean the bite area and hands with soap and water, rubbing alcohol or iodine (5, 13). Tumble clothes in a dryer on high heat to destroy remaining ticks.

6. Clear tall grasses and brush around homes. Keep areas around the home free from ticks through habitat modification and insecticide application.
7. Read more on TBDs commonly reported in your area and know how they present.
8. Antibiotic prophylaxis is not generally recommended except in areas highly endemic for Lyme disease; a single dose of doxycycline may be given in some situations, but prompt consultation with an infectious disease specialist may be helpful.

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