

What's Eating You? *Ixodes* Tick and Related Diseases, Part 1: Life Cycle, Local Reactions, and Lyme Disease

Kelsey D. Wilson, MD; Dirk M. Elston, MD

PRACTICE POINTS

- Lyme disease is transmitted by *Ixodes* ticks in the northeastern, midwestern, and far western United States.
- Most tick-borne illnesses, including Lyme disease, respond to treatment with doxycycline.
- Babesiosis, a malarialike illness, can be transmitted concurrently with Lyme disease.

The *Ixodes* tick is an important arthropod vector in the transmission of human disease. This 3-part review highlights the biology of the *Ixodes* tick and manifestations of related diseases. Part 1 addresses the *Ixodes* tick biology and life cycle; local reactions; and Lyme disease, the most prevalent of associated diseases. Part 2 will address human granulocytic anaplasmosis, babesiosis, Powassan virus infection, *Borrelia miyamotoi* disease, tick-borne encephalitis, and tick paralysis. Part 3 will address coinfection with multiple pathogens as well as methods of tick-bite prevention and tick removal.

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Ticks are ectoparasitic hemophages that feed on mammals, reptiles, and birds. The Ixodidae family comprises the hard ticks. A hard dorsal plate, scutum, and capitulum that extends outward from the body are features that distinguish the hard tick.¹ *Ixodes* is the largest genus of hard ticks, with more than 250 species localized in temperate climates.² It has an inornate scutum and lacks festoons (Figure 1).¹ The *Ixodes ricinus* species complex accounts for most species relevant to the spread of human disease (Figure 2), with *Ixodes scapularis* in the

northeastern, north midwestern, and southern United States; *Ixodes pacificus* in western United States; *I ricinus* in Europe and North Africa; and *Ixodes persulcatus* in Russia and Asia. *Ixodes holocyclus* is endemic to Australia.^{3,4}

Life Cycle

Ixodes species progress through 4 life stages—egg, larvae, nymph, and adult—during their 3-host life cycle. Lifespan is 2 to 6 years, varying with environmental factors. A blood meal is required between each stage. Female ticks have a small scutum, allowing the abdomen to engorge during meals (Figure 3).

Larvae hatch in the early summer and remain dormant until the spring, emerging as a nymph. Following a blood meal, the nymph molts and reemerges as an adult in autumn. During autumn and winter, the female

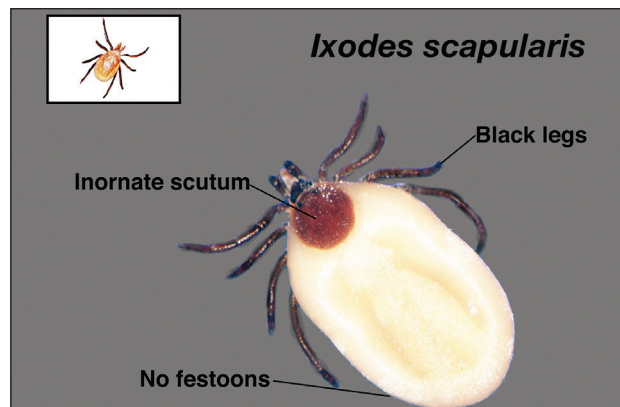


FIGURE 1. Adult *Ixodes scapularis* tick with identifiable features such as 8 black legs, an inornate scutum, and an absence of festoons.

From the Department of Dermatology and Dermatologic Surgery, Medical University of South Carolina, Charleston, South Carolina.

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Correspondence: Dirk M. Elston, MD, Department of Dermatology and Dermatologic Surgery, Medical University of South Carolina, 135 Rutledge Ave, MSC 578, Charleston, SC 29425 (elstond@musc.edu).

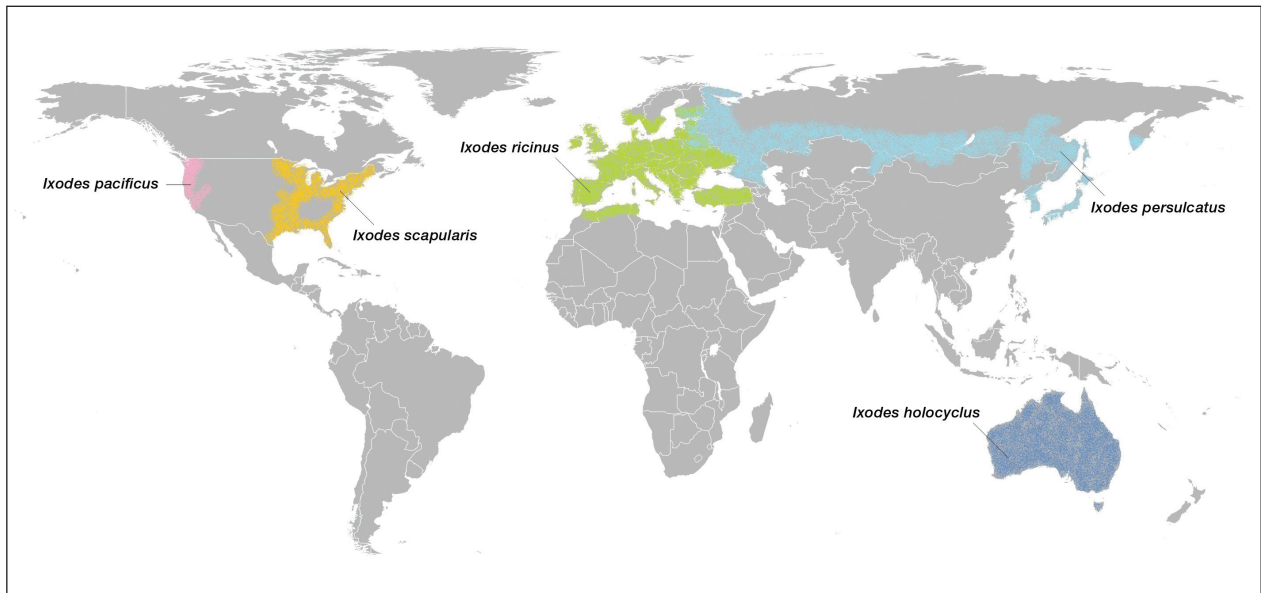


FIGURE 2. Geographic distribution of *Ixodes* species most commonly involved in disease transmission (approximation).

lays as many as 2000 eggs that emerge in early summer.⁵ Nymphs are small and easily undetected for the duration required for pathogen transmission, making nymphs the stage most likely to transmit disease.⁶

The majority of tick-borne diseases present from May to July, corresponding to nymph activity. Fewer cases present in the autumn and early spring because the adult female feeds during cooler months.⁷

Larvae have 6 legs and are about the size of a sesame seed when engorged. Nymphs are slightly larger with 8 legs. Adults are largest and have 8 legs. Following a blood meal, the tick becomes engorged, increasing in size and lightening in color (Figure 3).¹

Ticks are found in low-lying shrubs and tall grass as well as on the forest floor. They search for a host by detecting CO₂, warmth, the smell of sweat, and the color white, prompting attachment.⁸ Habitats hospitable to *Ixodes* have expanded in the wake of climate, environmental, and socioeconomic changes, potentially contributing to the increasing incidence and expansion of zoonoses associated with this vector.^{9,10}

Local Reactions

A tick bite may induce local hypersensitivity, leading to a red papule or plaque at the bite site, followed by swelling, warmth, and erythema. A cellular immune reaction induces induration and pruritus. Hard ticks are less likely than soft ticks to cause a serious local reaction.^{11,12}

A variety of clinical and histologic features are observed following an arthropod bite. Histologically, acute tick bites show a neutrophilic infiltrate with fibrin deposition. Chronic reactions demonstrate a wedge-shaped, mixed infiltrate with prominent endothelial swelling. Eosinophilic cellulitis, or Wells syndrome, reveals tissue



FIGURE 3. Female adult *Ixodes scapularis* tick (top) engorges following a blood meal, increasing in size as the light-colored abdomen expands beyond the dark-brown scutum (bottom).

eosinophilia and flame figures.¹³ Tick mouthparts may be identified in the tissue. B-cell hyperplasia is seen in *Borrelia lymphocytoma* and is more common in Europe, presenting as erythematous to plum-colored nodules on the ear and areola.¹⁴

Lyme Disease

Disease manifestations vary by location. Lyme disease is associated with *Borrelia burgdorferi* and the recently identified *Borrelia mayonii* in the United States¹⁵; in Europe and Asia, acrodermatitis chronica atrophicans is associated with *Borrelia afzelii* and neuroborreliosis, with *Borrelia garinii*. Lyme disease is the most common tick-borne illness in the United States.¹⁶ The *I ricinus* species complex is the most common vector harboring *Borrelia* species.¹⁷ At least 36 hours of tick adherence is required

Recommended Treatment of Lyme Disease

Patient Factors	Treatment	Treatment Duration
Acrodermatitis chronica atrophicans		
Ambulatory	Doxycycline 100 mg twice daily orally	21 d
Pregnant women; children <8 y; tetracycline allergic	Amoxicillin 500 mg 3 times daily orally	21 d
	Cefuroxime axetil 500 mg twice daily orally	21 d
Arthritis		
Ambulatory	Doxycycline 100 mg twice daily orally	28 d
Pregnant women; children <8 y; tetracycline allergic	Amoxicillin 500 mg 3 times daily orally	28 d
	Cefuroxime axetil 500 mg twice daily orally	28 d
Cardiac Lyme disease		
Ambulatory	Doxycycline 100 mg twice daily orally	14 d
Hospitalized	Ceftriaxone 2 g once daily IV	14 d
Erythema migrans		
Ambulatory	Doxycycline 100 mg twice daily orally	10 d
Pregnant women; children <8 y; tetracycline allergic	Amoxicillin 500 mg 3 times daily orally	14 d
	Cefuroxime axetil 500 mg twice daily orally	14 d
Meningitis		
Ambulatory	Doxycycline 100 mg twice daily orally	14 d
Hospitalized	Ceftriaxone 2 g once daily IV	14 d
Neuropathy		
Ambulatory	Doxycycline 100 mg twice daily orally	14 d
Hospitalized	Doxycycline 100 mg twice daily orally	14 d

Abbreviation: IV, intravenous.

for disease transmission.¹⁸ The incubation period is 3 to 20 days (median, 12 days).¹⁹

Clinical Findings—Erythema migrans is the most characteristic sign, seen in 80% of cases of Lyme disease. The typical rash is a centrifugally spreading, erythematous, annular patch with central clearing at the site of the tick bite.²⁰ Atypical rashes include vesicular, indurated, ulcerated, and follicular variants.²¹ Histopathology commonly shows a superficial and deep perivascular lymphocytic infiltrate with plasma cells, histiocytes, and eosinophils.²² Typically, the rash resolves in 3 to 5 weeks.¹⁸

Early disseminated Lyme disease can present with any of the following findings: multiple erythema migrans; neurologic involvement, including cranial nerve palsy and meningitis; and Lyme carditis, which may result in atrioventricular block.^{23,24} Late findings include arthritis, encephalopathy, and polyneuropathy. A late cutaneous manifestation, acrodermatitis chronica atrophicans, is rare in the United States but occurs in as many as 10% of Lyme disease cases in Europe. An initial inflammatory response manifests as blue-red erythema and edema of the extensor surfaces of the extremities, commonly on the dorsal hands,

feet, elbows, and knees. Firm fibrotic nodules may develop later over the olecranon and patella.^{23,24}

The term *chronic Lyme disease* has been used to describe the persistence of symptoms after treatment; however, large clinical trials have not detected a difference in symptom frequency between patients with a history of Lyme disease and matched controls.^{25,26} Many patients with chronic Lyme disease may instead have posttreatment Lyme disease syndrome, described as nonspecific symptoms including fatigue, arthralgia, and decreased mental acuity following treatment of confirmed Lyme disease. Symptoms generally improve within 1 year.²⁷

Laboratory Testing—The gold standard for laboratory diagnosis of Lyme disease is 2-tiered serologic testing. First, an enzyme immunoassay or immunofluorescence assay is used to screen for antibodies. A Western blot follows if the result of the screen is positive or equivocal. Western blot testing for IgM and IgG is used when illness duration is less than 4 weeks; after 4 weeks, a Western blot for IgG alone is sufficient.^{27,28} The 2-tiered test has 99% specificity. Sensitivity increases with duration of disease (29%–40% with erythema migrans; 42%–87% in

early disseminated disease; 97%–100% in late disease).^{29,30} A false-positive result can occur in the presence of infectious mononucleosis, an autoimmune disorder, and syphilis. If serologic testing is negative and suspicion remains high, testing should be repeated in 2 to 4 weeks.³¹ When a patient in a Lyme-endemic area presents with typical erythema migrans, serologic testing is unnecessary prior to treatment.³²

Management—Treatment of Lyme disease centers on antibiotic therapy (Table). First-line treatment of early disseminated disease is doxycycline for 14 days (range, 10–21 days).²⁷ In pregnant women, children younger than 8 years, and tetracycline-allergic patients, amoxicillin or cefuroxime axetil for 14 days (range, 14–21 days) may be used.³³ For erythema migrans without complications, doxycycline for 10 days is effective. Complications that require hospitalization are treated with intravenous ceftriaxone.²⁷ Re-treatment in patients with posttreatment Lyme disease syndrome is not recommended.³⁴ Prophylaxis with a single dose of doxycycline 200 mg may be indicated when all of the following conditions are met: (1) the patient is in an area where more than 20% of *Ixodes* ticks are infected with *B burgdorferi*, (2) the attached tick is *I scapularis*, (3) the tick has been attached for more than 36 hours, and (4) treatment is begun within 72 hours of tick removal.²⁷

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