

# Diagnosis and treatment of tick infestation and tick-borne diseases with cutaneous manifestations

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**ABSTRACT:** Hard and soft ticks may be associated directly or indirectly with a number of dermatoses, both infectious and inflammatory in origin. Morbidity may occur as a result of tick bites, tick toxicosis, and even infestation. These arthropod vectors may transmit life-threatening protozoan, bacterial, rickettsial, and viral diseases with systemic and cutaneous findings. Additionally, ticks may transmit more than one pathogen with subsequent human coinfection. This article reviews the presentation of tick-borne illnesses and the medical management of these diseases. Among others, diseases such as ehrlichiosis, anaplasmosis, babesiosis, tularemia, borreliosis, tick-borne encephalitis, rickettsial spotted fevers, and tick typhus are discussed in this article. The recognition of skin manifestations associated with these diseases is paramount to early diagnosis and treatment initiation.

**KEYWORDS:** arthropod, babesia, borrelia, ehrlichia, flaviviruses, rickettsia, tick, tularemia, vector-borne

## Introduction

Ticks may be divided into two taxonomical families of medical importance: the Ixodidae and Argasidae. The family Ixodidae contains the hard ticks, which may be identified by their hard, sclerotized dorsal plate. This family contains ticks of the genera *Ixodes*, *Amblyomma*, *Hemaphysalis*, *Hyalomma*, *Dermacentor*, *Boophilus*, and *Rhipicephalus*, which are the major tick vectors for a number of arthropod-borne diseases. The family Argasidae, or the soft ticks, may be recognized by the soft leathery cuticle and contains only a handful of medically important genera: *Ornithodoros*, *Argas*, and *Otobius*. In the United States, the majority of tick-borne diseases are transmitted

by ticks belonging to the genera *Amblyomma*, *Dermacentor*, *Ixodes*, and *Ornithodoros*. The biology of hard and soft ticks has been recently reviewed and will be briefly summarized (1).

Hard and soft ticks have a similar life cycle with several important differences. Both hard and soft ticks have the developmental stages of egg, larva, nymph, and adults, but, unlike hard ticks, soft ticks may have more than one nymphal stage. Each generation of hard ticks may last 1–6 years, and these ticks may take a single blood meal from one to three hosts, depending on the developmental period and tick species. Soft ticks take multiple blood meals from the same host, may feed on several hosts, and may complete a generation in several months. Hard ticks are slower feeders than soft ticks, taking from several days to weeks to complete a blood meal. This prolonged feeding period is required for their hard ventral cuticle to expand as it accommodates the increased body size from ingested blood, which may reach 100× their initial

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body weight. Soft ticks, with their soft, leathery cuticle, may feed more quickly and leave their host after several hours. The mouthparts of ticks contain sharp chelicerae, which penetrate the skin. In the process of feeding, the dermis is traumatized, creating a pool of blood from which the tick feeds. Ticks secrete a number of proteins with anticoagulant and anti-inflammatory properties to optimize feeding and, in the process, may secrete pathogens in their saliva. Depending on the species of tick, habitat preferences range from exposed areas such as forests, savannahs, and brush to more covered areas like caves, burrows, and nests. In general, soft ticks and *Ixodes* species prefer secluded habitats. Depending on tick species, host-seeking strategies may consist of actively crawling toward a host or resting on vegetation waiting for a host to pass by.

Ticks may transmit a number of different pathogens that cause human diseases including bacteria, viruses, and protozoan. The present study focuses on the infectious diseases that are transmitted by hard and soft ticks and the current recommendations for their treatment. These diseases and their clinical findings and treatment are summarized in Table 1. Lyme borreliosis will not be included in this review as the multiple presentations of infection with *Borrelia burgdorferi* and their treatment have been reviewed recently in this journal (2).

## Tick bite reactions and infestation

Tick bites may be associated with local, secondary infection at the bite site, foreign body granuloma because of retained mouthparts, local contact/irritant allergic dermatitis, ascending paralysis, and even anaphylaxis. Tick bite-site reaction may appear as a 0.5–2.0-cm erythematous macule, papule, or finely elevated plaque within 1–3 days following tick exposure (3). Bites associated with soft ticks may result in necrotic ulcerations, vesiculobullous lesions, or even significant edema involving an extremity. Chronic lesions such as tick bite granulomas may form following retention of tick mouthparts after incomplete removal, although salivary secretions have also been implicated in the pathogenesis. Tick bites may become secondarily infected with *Staphylococcus aureus* and group A *Streptococcus*, with resultant cellulitis, erysipelas, ecthyma, and impetigo. Flu-like symptoms such as headache, fever, vomiting, and malaise may also occur without cutaneous findings following a tick bite.

Once ticks have attached and commenced blood feeding, an individual may develop a phe-

nomenon known as tick paralysis. Tick paralysis, or tick toxicosis, is rare and presents with acute, ascending, flaccid paralysis. Tick paralysis may occur worldwide, and more than 60 species of ticks that cause this condition have been identified (4). Tick paralysis is associated with ixodid ticks more often than argasid ticks, although representative species from both families have been implicated as causative agents. The majority of cases of tick paralysis occur in North America and Australia. In the Western regions of the United States and Canada, *Dermacentor andersoni* is associated with tick paralysis. Sporadic cases of tick paralysis have been reported from the Eastern United States, particularly the southeast, and involve *Dermacentor variabilis* (4). Along the Eastern regions of Australia, tick paralysis is most commonly a result of *Ixodes holocyclus*, although *Ixodes cornuatus* has also been found (5). Similar to other tick-borne diseases, most cases occur during the spring months, such as April to June in the United States, when adults are actively seeking hosts (6).

Although no one specific protein has been identified, tick paralysis is thought to be a result of a tick protein injected into the human host during blood feeding. In *I. holocyclus*, the toxin has been identified as holocyclotoxin and is secreted in the saliva (7). This toxin is most likely not the same protein as seen in tick paralysis secondary to *Dermacentor* ticks because the clinical syndromes differ. Tick paralysis due to holocyclotoxin is usually associated with hypertension and typically does not resolve following detachment of the tick, unlike tick paralysis associated with *Dermacentor* (4). Depending on tick species, this neurotoxin reduces motor neuron action potentials or the action of the neurotransmitter acetylcholine (4). Symptoms usually begin 4–7 days following the commencement of tick feeding. Individuals are afebrile, and the ascending flaccid paralysis progresses over several hours or days. Typically, there is no sensory loss, and pain is absent (4,8). Clinical findings may be similar to Guillain–Barre Syndrome: patients may have ophthalmoplegia, dysarthria, generalized weakness with difficulty ambulating, deep tendon areflexia, and nerve conduction studies with decreased conduction velocities and marked reduction in the amplitude of muscle action potential, without impairment of neuromuscular transmission (9,10). Unlike tick paralysis in North America, focal neurological deficits may be apparent in addition to pupillary changes in Australian tick paralysis (4). Following *Dermacentor* tick removal or detachment, the symptoms of tick paralysis may regress within several hours and completely resolve by 24

**Table 1.** Characteristics and treatment of tick-borne diseases.

Disease agent	Recognized or potential tick vector(s)	Disease	Diagnostic features	Treatment (adults)	Alternative treatment (adults)	Treatment (children)	Alternative treatment (children)
<i>R. conorii conorii</i>	<i>Rhipicephalus sanguineus</i> , <i>Rhipicephalus simus</i> , <i>Haemaphysalis leachi</i> , <i>Haemaphysalis punctateachi</i>	Mediterranean spotted fever	Fever, single eschar, maculopapular rash	Doxycycline 200 mg PO every 12 hours × 1 day (or 100 mg PO every 12 hours until 1 day after apyrexia)	Tetracycline 500 mg PO every 6 hours × 10 days or Ciprofloxacin 750 mg PO every 12 hours × 8 days (or until 1 day after apyrexia)	Doxycycline 4.4 mg/kg PO every 12 hours × 1 day (or 2.2 mg/kg PO every 12 hours until 1 day after apyrexia)	Clarithromycin 7.5 mg/kg/day PO in two divided doses × 7 days or Azithromycin 10 mg/kg PO daily × 3 days or Chloramphenicol 50 mg/kg/day divided in four doses × 7 days (or until 1 day after apyrexia)
<i>Rickettsia conorii israelensis</i>	<i>R. sanguineus</i>	Israeli spotted fever	Fever, eschar, maculopapular rash	Doxycycline 100 mg PO or IV every 12 hours until 3 days after apyrexia			
<i>Rickettsia conorii caspia</i>	<i>R. sanguineus</i> <sup>a</sup> , <i>Rhipicephalus pumilio</i> <sup>a</sup>	Astrakhan spotted fever	Fever, eschar, maculopapular rash, conjunctivitis	Doxycycline 100 mg PO or IV every 12 hours until 3 days after apyrexia			
<i>Rickettsia conorii indica</i>	<i>R. sanguineus</i> , <i>Boophilus microplus</i> , <i>H. leachi</i>	Indian tick typhus	Fever, eschar, maculopapular rash (may be purpuric)	Doxycycline 100 mg PO or IV every 12 hours until 3 days after apyrexia			
<i>Rickettsia africana</i>	<i>Amblyomma hebraeum</i> , <i>Amblyomma variegatum</i> , <i>Amblyomma lepidum</i>	African tick bite fever	Fever, often multiple eschars, maculopapular rash (may be vesicular), aphthous stomatitis	Doxycycline 100 mg PO or IV every 12 hours until 3 days after apyrexia			
<i>Rickettsia sibirica</i> subspecies <i>mongolitimoniae</i>	<i>Hyalomma asiaticum</i> <sup>a</sup> , <i>Hyalomma truncatum</i> <sup>a</sup>	Lymphangitis-associated rickettsiosis	Fever, multiple eschars, maculopapular rash, lymphangitis	Doxycycline 100 mg PO or IV every 12 hours until 3 days after apyrexia			
<i>Rickettsia slovaca</i>	<i>Dermacentor marginatus</i> , <i>Dermacentor reticulatus</i>	Tick-borne lymphadenopathy (TIBOLA), Dermacentor-borne necrosis and lymphadenopathy (DEBONEL)	Fever and rash rare, eschar, cervical lymphadenopathy	Doxycycline 100 mg PO or IV every 12 hours until 3 days after apyrexia			
<i>Rickettsia raoultii</i>	<i>D. marginatus</i>	Tick-borne lymphadenopathy (TIBOLA), Dermacentor-borne necrosis and lymphadenopathy (DEBONEL)	Fever and rash rare, eschar, cervical lymphadenopathy	Doxycycline 100 mg PO or IV every 12 hours until 3 days after apyrexia			

Table 1. Continued

Disease agent	Recognized or potential tick vector(s)	Disease	Diagnostic features	Treatment (adults)	Alternative treatment (adults)	Treatment (children)	Alternative treatment (children)
<i>Rickettsia helvetica</i>	<i>Ixodes ricinus</i> , <i>Ixodes ovatus</i> <sup>a</sup> , <i>Ixodes persulcatus</i> <sup>a</sup> , <i>Ixodes monospinus</i> <sup>a</sup>	Unnamed	Fever and rash rare, possible myocarditis	Doxycycline 100 mg PO or IV every 12 hours until 3 days after apyrexia			
<i>Rickettsia aeschlimannii</i>	<i>Hyalomma marginatum</i> , <i>Hyalomma marginatum rufipes</i> , <i>Rhipicephalus appendiculatus</i> <sup>a</sup>	Unnamed	Eschar, maculopapular rash	Doxycycline 100 mg PO or IV every 12 hours until 3 days after apyrexia			
<i>Rickettsia massiliae</i>	<i>Rhicephalus sanguineus</i> <sup>a</sup> , <i>Rhicephalus turanicus</i> <sup>a</sup> , <i>Rhicephalus</i> <i>mushamae</i> <sup>a</sup> , <i>Rhicephalus sulcatus</i> <sup>a</sup> , <i>Rhicephalus houlattus</i> <sup>a</sup>	Unnamed	Fever, eschar, maculopapular rash	Doxycycline 100 mg PO or IV every 12 hours until 3 days after apyrexia			
<i>Rickettsia monacensis</i>	<i>Ixodes ricinus</i>	Unnamed	Fever and maculopapular rash	Doxycycline 100 mg PO or IV every 12 hours until 3 days after apyrexia			
<i>Rickettsia rickettsii</i>	<i>Dermacentor andersoni</i> , <i>Dermacentor variabilis</i> , <i>Rhipicephalus sanguineus</i> , <i>Amblyomma cajennense</i> , <i>Amblyomma aureolatum</i>	Rocky Mountain spotted fever	Fever, eschar rare, maculopapular rash (may be purpuric)	Doxycycline 100 mg PO or IV every 12 hours until 3 days after apyrexia	Tetracycline 500 mg PO (or 250 mg IV) four times daily (maximum dose 2 g/day) or Chloramphenicol 50–75 mg/kg PO or IV four times daily (maximum dose 4 g/day) until 3 days after apyrexia	Doxycycline 2.2 mg/kg PO or IV every 12 hours (if less than 45 kg) until 3 days after apyrexia	Chloramphenicol 12.5–25 mg/kg PO or IV every 6 hours × 5–10 days until 3 days after apyrexia
<i>Rickettsia honei</i>	<i>Aponomma hydrosauri</i> , <i>Ixodes granulatus</i> <sup>a</sup> , <i>Am. cajennense</i> <sup>a</sup>	Flinders Island spotted fever	Fever, eschar, maculopapular rash (may be purpuric), lymphadenopathy	Doxycycline 100 mg PO or IV every 12 hours until 3 days after apyrexia			
<i>Rickettsia australis</i>	<i>Ixodes holocyclus</i> , <i>Ixodes tasmani</i> <sup>a</sup>	Queensland tick typhus	Fever, eschar, vesicular rash	Doxycycline 100 mg PO or IV every 12 hours until 3 days after apyrexia			
<i>Rickettsia japonica</i>	<i>Ixodes ovatus</i> <sup>a</sup> , <i>Dermacentor taiwanensis</i> <sup>a</sup> , <i>Haemaphysalis longicornis</i> <sup>a</sup> , <i>Haemaphysalis flava</i> <sup>a</sup>	Japanese (Oriental) spotted fever	Fever, eschar, maculopapular rash	Doxycycline 100 mg PO or IV every 12 hours until 3 days after apyrexia			

<i>Rickettsia sibirica</i>	<i>Dermacentor nuttalli</i> , <i>Dermacentor marginatus</i> , <i>Haemaphysalis concinna</i> , <i>Dermacentor sinicus</i>	North Asian (Siberian) tick typhus	Fever, eschar, rash (may be purpuric), lymphadenopathy	Doxycycline 100 mg PO or IV every 12 hours until 3 days after apyrexia
<i>Rickettsia heilongjiangi</i>	<i>Dermacentor silvarum</i>	Far Eastern spotted fever	Eschar, maculopapular rash, lymphadenopathy	Doxycycline 100 mg PO or IV every 12 hours until 3 days after apyrexia
<i>Rickettsia parkeri</i>	<i>Amblyomma maculatum</i> , <i>Amblyomma americanum</i> , <i>Amblyomma triste</i> <sup>a</sup>	Unnamed	Fever, multiple eschars, maculopapular rash	Doxycycline 100 mg PO or IV every 12 hours until 3 days after apyrexia
<i>Rickettsia marmionii</i>	<i>Haemaphysalis novaeaguineae</i>	Australian spotted fever	Fever, eschar, maculopapular rash	Doxycycline 100 mg PO or IV every 12 hours until 3 days after apyrexia
<i>Coxiella burnetii</i>	<i>Dermacentor occidentalis</i> , <i>Amblyomma americanum</i> , <i>Haemaphysalis leporis-palustris</i> , <i>Ixodes dentatus</i> , <i>Otobius magnini</i> , <i>Rhipicephalus sanguineus</i> , <i>Haemaphysalis humerosa</i> , <i>Amblyomma triguttatum</i> , others	Q fever	Fever, macules, petechiae, and purpura	Doxycycline 100 mg PO every 12 hours × 15–21 days
<i>Francisella tularensis</i>	<i>Amblyomma americanum</i> , <i>Dermacentor andersoni</i> , <i>Dermacentor variabilis</i> , <i>Rhipicephalus sanguineus</i> , <i>Dermacentor reticulatus</i> , <i>Ixodes ricinus</i>	Tularemia	Fever, ulcerative papule, lymphadenopathy, eschar	Streptomycin 1 g IM every 12 hours × 10 days or Gentamicin 5 mg/kg IM or IV once daily × 10 days Doxycycline 100 mg IV every 12 hours × 14–21 days or Chloramphenicol 15 mg/kg IV every 6 hours × 12–21 days or Ciprofloxacin 400 mg IV every 12 hours × 10 days
<i>Borrelia parkeri</i>	<i>Ornithodoros parkeri</i>	Tick-borne relapsing fever	Episodic fever, macular rash, eschar	Streptomycin 15 mg/kg IM every 12 hours (maximum 2 g/day) × 10 days or Gentamicin 2.5 mg/kg IM or IV every 8 hours × 10 days Doxycycline 2.2 mg/kg IV every 12 hours (if weight <45 kg) × 14–21 days or Chloramphenicol 15 mg/kg IV every 6 hours × 14–21 days or Ciprofloxacin 15 mg/kg IV every 12 hours × 10 days Erythromycin 30–50 mg/kg/day (max 2 g/day) PO divided in 2–4 doses × 7 days Penicillin V 25–50 mg/kg/day (maximum 500 mg/dose) PO divided in four doses × 7 days or Penicillin G 25,000–50,000 IU/kg/day IM divided in 1–2 doses × 7 days or Penicillin G 25,000–50,000 IU/kg/day IV divided into four doses × 7 days Tetracycline 500 mg PO (or 250 mg IV) every 6 hours × 7 days or Erythromycin 500 mg PO or IV every 6 hours × 7 days or Chloramphenicol 500 mg PO or IV every 6 hours × 7 days or Penicillin G 600,000 IU IV or IM daily × 7 days

**Table 1. Continued**

Disease agent	Recognized or potential tick vector(s)	Disease	Diagnostic features	Treatment (adults)	Alternative treatment (adults)	Treatment (children)	Alternative treatment (children)
<i>Borrelia hermsii</i>	<i>Ornithodoros hermsi</i>	Tick-borne relapsing fever	Episodic fever, macular rash, eschar	Doxycycline 100 mg PO or IV every 12 hours × 7 days	Tetracycline 500 mg PO (or 250 mg IV) every 6 hours × 7 days or Erythromycin 500 mg PO or IV every 6 hours × 7 days or Chloramphenicol 500 mg PO or IV every 6 hours × 7 days or Penicillin G 600,000 IU IV or IM daily × 7 days	Penicillin V 25–50 mg/kg/day (maximum 500 mg/dose) PO divided in four doses × 7 days or Penicillin G 25,000–50,000 IU/kg/day IM divided in 1–2 doses × 7 days or Penicillin G 25,000–50,000 IU/kg/day IV divided into four doses × 7 days	Erythromycin 30–50 mg/kg/day (max 2 g/day) PO divided in 2–4 doses × 7 days
<i>Borrelia turicatae</i>	<i>Ornithodoros turicata</i>	Tick-borne relapsing fever	Episodic fever, macular rash, eschar	Doxycycline 100 mg PO or IV every 12 hours × 7 days	Tetracycline 500 mg PO (or 250 mg IV) every 6 hours × 7 days or Erythromycin 500 mg PO or IV every 6 hours × 7 days or Chloramphenicol 500 mg PO or IV every 6 hours × 7 days or Penicillin G 600,000 IU IV or IM daily × 7 days	Penicillin V 25–50 mg/kg/day (maximum 500 mg/dose) PO divided in four doses × 7 days or Penicillin G 25,000–50,000 IU/kg/day IM divided in 1–2 doses × 7 days or Penicillin G 25,000–50,000 IU/kg/day IV divided into four doses × 7 days	Erythromycin 30–50 mg/kg/day (max 2 g/day) PO divided in 2–4 doses × 7 days
<i>Borrelia lonestari</i>	<i>Amblyomma americanum</i>	Southern tick-associated rash illness (STARI)	Erythema migrans-like (Lyme-like) erythematous annular rash	Doxycycline 100 mg PO every 12 hours × 14–21 days	Amoxicillin 1000 mg PO every 8 hours × 14–21 days or Azithromycin 500 mg PO every 12 hours × 1 day then 500 mg PO daily × 4–9 days or Cefuroxime 500 mg PO every 12 hours × 14–21 days	Amoxicillin 50 mg/kg PO every 8 hours × 14–21 days	Azithromycin 20 mg/kg PO every 12 hours × 1 day then 10 mg/kg PO daily × 4–9 days or Cefuroxime 30–40 mg/kg PO every 12 hours × 14–21 days
Crimean-Congo Hemorrhagic Fever virus	<i>Hyalomma</i> spp.	Crimean-Congo Hemorrhagic Fever	Hemorrhagic fever	Supportive treatment, Ribavirin 30 mg/kg PO initial loading dose, then 15 mg/kg every 6 hours × 4 days, and then 7.5 mg/kg every 8 hours × 6 days			

Kyasanur Forest Disease virus	<i>Haemaphysalis spinigera</i>	Kyasanur Forest Disease	Hemorrhagic fever	Supportive treatment
Omsk Hemorrhagic Fever virus	<i>Dermacentor pictus</i>	Omsk Hemorrhagic Fever	Hemorrhagic fever	Supportive treatment
Alkhurma virus	<i>Ornithodoros savignyi</i> <sup>a</sup>	Alkhurma Hemorrhagic Fever	Hemorrhagic fever	Supportive treatment
Tick-borne encephalitis virus subtype Western (European), Siberian, and Far-Eastern (Russian Spring-Summer Encephalitis)	<i>Ixodes ricinus</i> , <i>Ixodes persulcatus</i> , <i>Haemaphysalis concinna</i>	Tick-borne Encephalitis	Encephalitis	Supportive treatment
Louping-ill virus	<i>Ixodes spp</i>	Louping-ill	Encephalitis	Supportive treatment
Powassan encephalitis virus	<i>Ixodes cookei</i> , <i>Dermacentor andersoni</i>	Powassan encephalitis	Encephalitis	Supportive treatment
Langat virus	<i>Ixodes granulatus</i>	Langat	Encephalitis	Supportive treatment
Colorado Tick Fever virus	<i>Dermacentor andersoni</i> , <i>Haemaphysalis leporispalustris</i> , <i>Dermacentor occidentalis</i> , <i>Dermacentor albopictus</i> , <i>Dermacentor arumapterus</i> , <i>Otobius lagophilus</i> , <i>Ixodes sculptus</i> , and <i>Ixodes spinipalpis</i>		Fever, macules, petechiae, and purpura	Supportive treatment
Eyach virus	<i>Ixodes ricinus</i>	Eyach	Fever, macules, petechiae, and purpura	Supportive treatment
<i>Ehrlichia ewingii</i>	<i>Amblyomma americanum</i>	Human Ewing Ehrlichiosis	Maculopapular rash	Doxycycline 100 mg PO or IV every 12 hours × 5–14 days
<i>Ehrlichia chaffeensis</i>	<i>Amblyomma americanum</i> , <i>Dermacentor variabilis</i>	Human monocytic ehrlichiosis	Maculopapular rash	Tetracycline 500 mg PO every 6 hours × 5–14 days or Rifampin 300 mg PO every 12 hours × 7–10 days
				Doxycycline 2.2 mg/kg PO every 12 hours × 5–14 days
				PO in four divided doses × 5–14 days or Rifampin 10 mg/kg PO every 12 hours × 7–10 days
				Tetracycline 2.2 mg/kg PO every 12 hours × 5–14 days
				PO in four divided doses × 5–14 days or Rifampin 10 mg/kg PO every 12 hours × 7–10 days

Table 1. Continued

Disease agent	Recognized or potential tick vector(s)	Disease	Diagnostic features	Treatment (adults)	Alternative treatment (adults)	Treatment (children)	Alternative treatment (children)
<i>Anaplasma phagocytophilum</i>	<i>Ixodes scapularis</i> , <i>Ixodes pacificus</i> , <i>Ixodes ricinus</i> , <i>Ixodes persulcatus</i>	Human granulocytic anaplasmosis	Maculopapular rash	Doxycycline 100 mg PO or IV every 12 hours × 5–14 days	Tetracycline 500 mg PO every 6 hours × 5–14 days or Rifampin 300 mg PO every 12 hours × 7–10 days	Doxycycline 2.2 mg/kg PO every 12 hours × 5–14 days	Tetracycline 25–50 mg/kg/day PO in four divided doses × 5–14 days or Rifampin 10 mg/kg PO every 12 hours × 7–10 days
<i>Babesia microti</i>	<i>Ixodes scapularis</i>	Babesiosis	Fever, petechiae, ecchymosis, jaundice	Atovaquone 750 mg PO every 12 hours × 7–10 days and Azithromycin 500–1000 mg PO on day 1 then 250–1000 mg on subsequent 6–9 days +/- Exchange transfusion	Clindamycin 600 mg PO every 8 hours (300–600 mg IV every 6 hours) and Quinine 650 mg PO every 6–8 hours × 7–10 days +/- Exchange transfusion	Atovaquone 20 mg/kg (maximum 750 mg/dose) PO every 12 hours × 7–10 days and Azithromycin 10 mg/kg (maximum 500 mg/dose) PO on day 1 then 5 mg/kg on subsequent 6–9 days +/- Exchange transfusion	Clindamycin 7–10 mg/kg (maximum 600 mg/dose) PO or IV every 8 hours and Quinine 8 mg/kg (maximum 650 mg/dose) PO every 8 hours × 7–10 days +/- exchange transfusion
<i>Babesia divergens</i>	<i>Ixodes ricinus</i>	Babesiosis	Fever, petechiae, ecchymosis, jaundice	Atovaquone 750 mg PO every 12 hours × 7–10 days and Azithromycin 500–1000 mg PO on day 1 then 250–1000 mg on subsequent 6–9 days +/- Exchange transfusion	Clindamycin 600 mg PO every 8 hours (300–600 mg IV every 6 hours) and Quinine 650 mg PO every 6–8 hours × 7–10 days +/- Exchange transfusion	Atovaquone 20 mg/kg (maximum 750 mg/dose) PO every 12 hours × 7–10 days and Azithromycin 10 mg/kg (maximum 500 mg/dose) PO on day 1 then 5 mg/kg on subsequent 6–9 days +/- Exchange transfusion	Clindamycin 7–10 mg/kg (maximum 600 mg/dose) PO or IV every 8 hours and Quinine 8 mg/kg (maximum 650 mg/dose) PO every 8 hours × 7–10 days +/- exchange transfusion
<i>Babesia duncani</i>	Unknown	Babesiosis	Fever, petechiae, ecchymosis, jaundice	Atovaquone 750 mg PO every 12 hours × 7–10 days and Azithromycin 500–1000 mg PO on day 1 then 250–1000 mg on subsequent 6–9 days +/- Exchange transfusion	Clindamycin 600 mg PO every 8 hours (300–600 mg IV every 6 hours) and Quinine 650 mg PO every 6–8 hours × 7–10 days +/- Exchange transfusion	Atovaquone 20 mg/kg (maximum 750 mg/dose) PO every 12 hours × 7–10 days and Azithromycin 10 mg/kg (maximum 500 mg/dose) PO on day 1 then 5 mg/kg on subsequent 6–9 days +/- Exchange transfusion	Clindamycin 7–10 mg/kg (maximum 600 mg/dose) PO or IV every 8 hours and Quinine 8 mg/kg (maximum 650 mg/dose) PO every 8 hours × 7–10 days +/- exchange transfusion

IM, intramuscular; IV, intravenous; PO, potential vector, circumstantial evidence for transmission.

hours (9). However, tick paralysis may be fatal, and approximately 10% of affected individuals may die from respiratory paralysis if the tick is not removed expediently (11). Whereas many cases resolve following tick removal or detachment, further treatment is supportive, and patients may require admission to an intensive care unit with mechanical ventilator support, depending on case severity. Hyperimmune serum is available as treatment for tick paralysis in Australia although administration has been associated with serum sickness and acute allergic reactions (4).

Tick bite anaphylaxis is a rare IgE-mediated allergy, unlike tick paralysis, that occurs within hours of tick attachment (12). Additionally, removal of a feeding tick may precipitate urticaria and anaphylaxis (5). The tick proteins implicated as potential antigens are salivary digestive enzymes. During tick removal, the tick body should not be compressed as squeezing may result in bolus injection of saliva (5).

Ticks may infest humans, especially when adults and children are exposed to areas with greater tick abundance. Tick infestation may present as erythematous pruritic papules, which, upon closer inspection, may reveal partially embedded ticks. Several case reports of *Amblyomma* tick larvae infestation have been reported (13–18). Tick larvae, also known as seed ticks, have only six legs, unlike nymphal and adult forms, which have four legs, and, given their smaller size, may be confused with mites. Tick infestation may be treated with a single, overnight application of permethrin 5% cream (16). Infestations may be prevented with protective clothing such as long-sleeved shirts, pants, and a hat. Clothing may be treated with an “insect” repellent containing N,N-diethyl-m-toluamide (DEET) or permethrin, or DEET may be applied directly to the skin (19). Ticks may be removed with a number of tick-removal devices or by using forceps, although the body of the tick should not be squeezed during the removal process (20). Methods used to suffocate the tick such as petrolatum application should be avoided because the delay in tick withdrawal allows increased time for possible pathogen transmission (16).

## EHRlichiosis

*Ehrlichia* and *Anaplasma*, small intracellular gram-negative cocci, infect the hematopoietic cells causing ehrlichiosis. A tick-borne febrile illness, ehrlichiosis typically occurs in the spring and summer months, April until September, when ticks



FIG. 1. *Amblyomma americanum* (Image courtesy of Dirk M. Elston, MD).

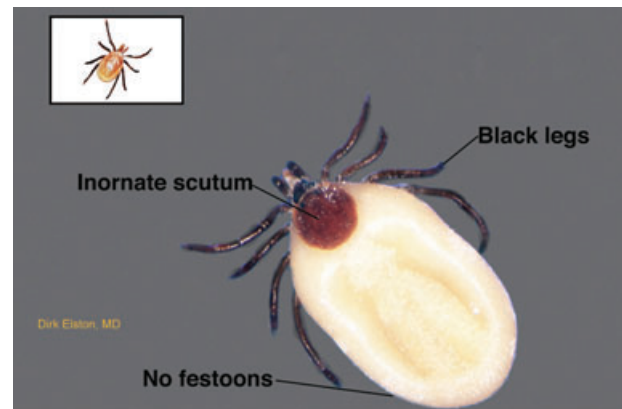


FIG. 2. *Ixodes scapularis* (Image courtesy of Dirk M. Elston, MD).

are most abundant (21). Three bacteria that cause ehrlichiosis have been described including *Ehrlichia chaffeensis*, *Anaplasma* (formerly *Ehrlichia*) *phagocytophila*, and *Ehrlichia ewingii*. In the United States, these bacteria are typically transmitted by *Amblyomma americanum* (FIG. 1), *Ixodes scapularis* (FIG. 2), and *Ixodes pacificus*.

Although ehrlichiosis is a tick-borne disease in 60% of cases, contaminated tissue and fluid may also be a source of infection. Cases of ehrlichiosis have been associated with butchers cutting fresh deer carcasses (30–32). Ehrlichiosis occurs as three distinct clinical conditions, human monocytic ehrlichiosis (HME), human granulocytic anaplasmosis (HGA; formerly human granulocytic ehrlichiosis) and human ewingii ehrlichiosis (HEE). HME is caused by *E. chaffeensis* infection of macrophages and monocytes, whereas HGA and HEE are caused by infection of neutrophils by *A. phagocytophila* and by *E. ewingii*, respectively.

## Human Monocytic Ehrlichiosis (HME)

HME develops following infection with *E. chaffeensis* and is primarily transmitted by *Am. americanum* but is also transmitted by *Dermacentor*. Diagnosed in 47 states, HME most commonly occurs in the south central and southeastern United States, especially in Arkansas, in areas with large populations of white-tailed deer (*Odocoileus virginianus*) and *Amblyomma* ticks (22). *E. ewingii* can also be transmitted by *Am. americanum* ticks and is distributed solely in the United States. This organism, previously thought to only infect dogs, has been shown to cause human disease. The clinical syndrome of HEE presents similarly to HME, although unlike *E. chaffeensis*, the organism propagates in neutrophils.

Groups at risk for the development of HME include elderly, immunocompromised, or asplenic individuals (21,23). Following tick exposure, the majority of individuals with HME develop an abrupt high-grade fever, headache, and a rash after 1–2 weeks. Other symptoms include malaise (30–80%), nausea (40–50%), myalgia (40–60%), arthralgia (30–35%), low-back pain (30–40%), and gastrointestinal symptoms (20–25%) (23). Rash will develop in more than 1/3 of individuals with ehrlichiosis, especially if immunocompromised (24). The rash may be petechial, macular, maculopapular, or erythematous and typically manifests 5 days after tick bite (23). Less likely to involve the palms and soles, the rash appears on the face, trunk, and extremities (25,26). Pancytopenia is the most common clinical sign with thrombocytopenia (70–90%) and leukopenia (60–70%) occurring early in the course of illness and anemia developing 2 weeks after tick exposure. Additionally, individuals with ehrlichiosis may develop elevations the liver transaminases (80–90%) and hyponatremia (50–70%) (27). Infection with *Ehrlichia* may cause severe illness requiring hospitalization. During infection, patients may develop acute renal, respiratory, or hepatic failure with metabolic acidosis, hypotension, coagulopathy, and myocardial or neurological dysfunction. Fatal infections occur in 3% of affected individuals (22).

Diagnosis may be based on Wright- or Giemsa-stained peripheral blood smears demonstrating the presence of morulae, which are small intracytoplasmic inclusions found in leukocytes. However, they are present in only 5% of circulating leukocytes (28). During the first week of illness, the IgG antibody is negative in 80% of patients, and IgM results are equivocal. By using an indirect immunofluorescence assay, diagnosis may be con-

firmed serologically with a fourfold rise in convalescent immunoglobulin titers between the acute and convalescent disease phases or by a single reciprocal antibody titer of 256 or greater (reciprocal titer of 64 or greater constitutes probable disease) (29). Some laboratories are able to perform polymerase chain reaction (PCR) tests as an alternative to immunoassays.

## Human Granulocytic Anaplasmosis (HGA)

Transmitted primarily by Ixodes ticks, *A. phagocytophila* has been diagnosed in North America, Europe, and Asia. The ticks that transmit HGA are *I. scapularis* in the Eastern United States, *I. pacificus* in the Western United States, *Ixodes ricinus* in Europe, and *Ixodes persulcatus* in Asia. In the United States, the majority of cases have occurred in the northeast and upper Midwest states, with the most reported cases occurring in Connecticut (22).

HGA presents similarly to HME with high-grade fever and severe headache 7–10 days following tick exposure. Other symptoms include rigors, non-specific myalgia, malaise, nausea, nonproductive cough, arthralgia, and anorexia. In contrast to HME, rash presents following tick bite only in 11% of individuals, and usually is a result of coinfection with Lyme disease (30). Leukopenia and thrombocytopenia are present in 75% of individuals affected by HGA 1 week after infection although, unlike HME, blood cell count may be normal. Similarly, acute phase reactants may be elevated including C-reactive protein and liver enzymes. Although half of individuals with HGA require hospitalization, HGA is associated with less morbidity and mortality (22).

Similar to HME, PCR-based assays, microscopic examination of peripheral blood smears, and indirect immunofluorescence assays may be used to diagnose HGA. Evaluation of the peripheral blood smear demonstrated intracytoplasmic inclusions in the monocytes, a feature suggestive of *Ehrlichia* (33).

## Treatment

Both HME and HGA are treated the same despite their being two distinct clinical entities. Tetracyclines are the treatment of choice for *E. chaffeensis* and *A. phagocytophilum* infections. In vitro testing has demonstrated excellent efficacy of tetracycline antibiotics for both *E. chaffeensis* and *A. phagocytophilum* (34,35). In the tetracycline class, doxycycline is preferred because of twice-daily oral dosing and less adverse effects. Recommended therapy for

adults is doxycycline 100 mg orally every 12 hours intervals (36). Children older than 8 years who weigh less than 45 kg may be treated with doxycycline given in divided doses, based on patient's weight (4.4 mg/kg/24 hours, maximum dose 100 mg) (36). In children younger than 8 years, tetracycline antibiotics have been associated with staining of teeth, dental enamel hypoplasia, and even bone growth interference (37). In severe cases, doxycycline should still be used in children <8 years of age despite relative contraindication (36). Treatment with doxycycline therapy typically results in rapid clinical improvement, usually within 24–48 hours of initiation of this antibiotic, except in individuals who have had a delay in diagnosis and treatment (36). The duration of antibiotic therapy is not well established and usually ranges from 7–10 days. The treatment duration should extend at least 3 days beyond fever defervescence.

If doxycycline is contraindicated, that is, allergy or pregnancy, effective alternative treatment regimens are limited. Tetracycline may be used as an alternative to doxycycline (25 mg/kg/day in four divided doses; maximum, 500 mg/dose). Typically, tetracyclines are avoided after the first trimester in pregnancy to prevent discoloration of the deciduous teeth and abnormal bone growth of the fetus. Although doxycycline presents therapeutic risks in pregnant women, this antibiotic is still the drug of choice. However, rifampin may be a safer alternative. Although *E. chaffeensis* is susceptible to both tetracyclines and rifampin in vitro, the clinical effectiveness of rifampin in adults and children with ehrlichiosis is not well established (36). Despite the fact that rifampin may cross the transplacental barrier, this medication has not been associated with birth defects in neonates born to pregnant mothers treated for tuberculosis with this antibiotic (38). Two case series have documented the efficacy of rifampin therapy in the treatment of pregnant women with ehrlichiosis. Treatment recommendations were rifampin, 300 mg orally twice daily or 600 mg orally once daily for 7 days (39,40). Rifampin therapy (20 mg/kg/day given in divided doses every 12 hours for 5–7 days, maximum of 600 mg) was recommended in children who are not severely ill and are less than 8 years of age (41).

*E. chaffeensis* is resistant to representatives of most classes of antibiotics including aminoglycosides (gentamicin), fluoroquinolones (ciprofloxacin), penicillins (penicillin), macrolides and ketolides (erythromycin and telithromycin), and sulfa-containing drugs (cotrimoxazole), based on in vitro susceptibility testing (23). Although *Ehrlichia* spp. exhibit intermediate susceptibility to the

fluoroquinolones in vitro, an infected individual developed a relapse of HGA following an almost 2-week course of levofloxacin (35,42). Resistance to fluoroquinolones in *E. chaffeensis* has been linked to mutations in the quinolone resistance-determining region of the DNA gyrase gene (43). Chloramphenicol also shows some bactericidal activity against *Ehrlichia* spp. in vitro (44). Yet, clinical results are conflicting with both treatment success and failures published (23). In HGE, oral chloramphenicol, 500 mg four times per day for 10 days, was a successful treatment in one case (45). Until further evidence concerning the efficacy of chloramphenicol and fluoroquinolones is demonstrated, treatment with these antibiotics currently is not recommended.

As an additional consideration, individuals with ehrlichiosis may also be coinfecting with *Bo. burgdorferi*, and it is recommended to continue doxycycline therapy for a 2-week course in adults and a 1-week course in pediatric patients, given the risk of teeth staining (36). If there is concern for coinfection in children less than 8 years old, a 1-week course of doxycycline may be completed, followed by switching to another antibiotic with a better pediatric safety profile, such as amoxicillin, for the treatment of Lyme borreliosis (36). Regardless, if treatment with doxycycline does not result in clinical improvement within 3 days, the clinician should consider an alternate diagnosis.

## BABESIOSIS

A small, 1- to 5- $\mu$ m, oval- to pear-shaped obligate parasite, *Babesia* is an arthropod-borne parasite that infects erythrocytes, similar to the malaria parasite. *Babesia* is an apicomplexan protozoan and historically has been associated with Texas cattle fever. To date, four strains have been identified as human pathogens after the first reported human infection in the United States in the 1960s (46). In the United States, *Babesia microti* is the most prominent pathogen, whereas, in Europe, *Babesia divergens* causes the most human infections. Additionally, the two strains WA-1 and MO-1 were identified as causative agents of human disease in the United States in 1993 and 1996, respectively (47,48). WA-1 has now been identified as *Babesia duncani* (49).

*I. scapularis* is the primary vector for *Ba. microti* in the Northeastern United States, especially along the coastal areas of Massachusetts, Connecticut, New York, and Rhode Island (50,51). *Ba. microti* is less often reported from Maryland, Virginia,

Georgia, and New Jersey (52,53). The tick feeds on the white-footed mouse, and, in endemic areas, more than half of the white mouse population may be infected, and almost 40% of *I. scapularis* nymphs may be carriers of this disease. The nymphs are the main transmitters of *Babesia* and may introduce the parasite into new vertebrate hosts, such as humans, following blood feeding. Although *Ba. duncani* and MO-1 have been reported along the Pacific Coast and in Missouri, respectively, the vectors and reservoirs for these pathogens have not been identified. The majority of cases of babesiosis occur during the Spring and Summer, June to August, with almost half occurring in the month of July (54).

The *Babesia* parasite reproduces intraerythrocytically, and, following rupture of the erythrocyte, the parasites infect new red blood cells. Consequently, hemolytic anemia develops as the infected red blood cells rupture and new cells are infected.

Clinical manifestation varies on the degree of parasitemia and ranges from an asymptomatic to fatal. Fever (85% of patients), fatigue (79%), chills (63%), and headache (39%) may appear 1–6 weeks after tick exposure (52). Additionally, myalgia, anorexia, cough, nausea, vomiting, arthralgia, depression, sore throat, abdominal pain, conjunctival injection, photophobia, and weight loss may develop (55). *Ba. divergens* and *Ba. duncani* cause more disease severity than infections with *Ba. microti* (56). Fatal in 5–9% of cases, acute respiratory failure (21% of cases), disseminated intravascular coagulation (18%), heart failure (12%), coma (9%), and renal failure (6%) may be developed in individuals with severe illness (54,57). Clinically, infected individuals may present with hepatomegaly and splenomegaly. Rash is not typically present, but other signs of hemolytic anemia such as jaundice may be evident. Laboratory findings reflect hemolytic anemia and include decreased hemoglobin and hematocrit, hyperbilirubinemia, hemoglobinuria. Additionally, thrombocytopenia, leukopenia, elevated liver transaminases, and lactate dehydrogenase may be present (52).

Microscopic examination of Giemsa-stained peripheral blood smears will demonstrate intraerythrocytic parasites. Babesiosis can also be detected by serology, indirect IFA, and PCR amplification (58,59).

## Treatment

For mild to moderate infections with babesiosis, most are self-limited and may resolve without treatment. In general, babesiosis is self-limited, and

asymptomatic individuals with parasitemia should not be treated unless parasitemia persists for more than 3 months (60). The recommended treatment for mild to moderate cases is a combination of an antimalarial drug with an antibiotic. Historically, combination therapy with clindamycin (600 mg four times per day) and quinine (650 mg three to four times per day) for 7–10 days is the standard treatment. Additionally, azithromycin when used alone or in combination with quinine may suppress parasitemia (61).

Quinine is associated with significant drug toxicities including hearing loss, tinnitus, and vertigo, and clindamycin is associated with diarrhea. Therefore, alternate drug regimens have been explored. A naphthalene with antiprotozoal activity, atovaquone, has been used in conjunction with azithromycin for treatment of babesiosis. In a recent study comparing the efficacy of this treatment regimen with a 7-day course of oral clindamycin–quinine combination therapy, resolution of parasitemia was similar in both groups, although patients receiving atovaquone–azithromycin experienced less adverse reactions than those receiving clindamycin–quinine (15 vs. 72% of cases, respectively) (62). Currently, atovaquone and azithromycin administered for 7–10 days are the treatment of choice for mild to moderate babesiosis. Atovaquone as a monotherapy is not recommended because of the emergence of resistant organisms and recrudescence of disease (63).

Limited data concerning treatment of babesiosis in children currently exist. Review of reported neonatal cases of babesiosis demonstrates treatment efficacy with the following regimens: 7- to 10-day combination course of clindamycin (5–7.5 mg/kg/dose divided in an interval based on corrected gestational age) and quinine (25 mg/kg/day divided every 8 hours) or combination of azithromycin (12 mg/kg/day) and atovaquone (40 mg/kg/day divided twice daily) for 7–10 days. Additionally, atovaquone or azithromycin may be added to the clindamycin and quinine combination (64).

Drugs including pyrimethamine, tetracyclines, primaquine, halofantrine, artesunate and artemisinin, and pentamidines have been tested in vitro for activity against *Babesia*. Because of variable results and associated drug toxicities, they have not been used in therapeutic regimens in human cases of *Babesia* infection (65). Pentamidine isothionate may decrease clinical severity but does not decrease parasitemia, making it an ineffective treatment for human cases of babesiosis (66). However, this medication has been successfully used as an adjunct in other treatment regimens. A mild case of babesiosis

was resolved after combination treatment with pentamidine and cotrimoxazole (67). Also, pentamidine and trimethoprim-sulfamethoxazole were used successfully to treat a case of *Ba. divergens* infection (67).

Antimalarials have also had both therapeutic failures and successes. If necessary, the antimalarial quinine may be used instead of quinidine in combination with clindamycin (63). Currently not licensed for human use, Imidocarb (Imizol®; Schering Plough Animal Health, Union, NJ) is effective treatment of babesiosis in bovines and, under special license, was used successfully to treat two human cases (68). In contrast, chloroquine, mefloquine, and artemisinin are all considered ineffective against *Babesia* spp. (65,69). An antitrypanosomal drug, Diminazene aceturate (Berenil®, Hoechst Ltd., Frankfurt, Germany) is effective in animal infection but failed to cure a patient with a severe *Ba. divergens* infection (68).

In severe life-threatening cases of babesiosis, exchange blood transfusions in conjunction with antimicrobial therapy reduce parasitemia and remove toxic by-products of protozoal infections. Because *Babesia* has no extra-erythrocytic stage, exchange blood transfusion significantly reduces parasitemia and may even be curative. Infection with *Ba. divergens* is considered a medical emergency, and individuals should undergo exchange transfusion in addition to treatment with intravenous (IV) quinine and clindamycin (68). Regardless, apheresis should be considered in patients with more than 5% parasitemia, coma, hypotension, congestive heart failure, pulmonary edema, or renal failure (70). Additionally, erythrocyte exchange should be considered in individuals at high risk for fulminant infections including splenectomized, elderly patients, or otherwise immunocompromised individuals. In general, an exchange of 8–10 units of erythrocytes (or 2–3× blood volume depending on the weight of the patient) should significantly decrease parasitemia; however, if parasitemia remains greater than 1% post exchange, apheresis should be repeated (71,72).

In immunocompromised individuals, higher dosage regimens and longer treatment durations may be required for successful treatment (56,73). In a patient with HIV/AIDS with an allergy to quinine, combination therapy with clindamycin, doxycycline (200 mg/day), and azithromycin (2000 mg/day) was used successfully (74,75). A patient with AIDS with babesiosis who had increasing parasitemia despite combination therapy of azithromycin and atovaquone followed by quinine and clindamycin was successfully treated with

red blood cell exchange and a five-drug regimen: atovaquone–proguanil (250 mg/100 mg twice daily), azithromycin (500 mg intravenously daily), atovaquone (500 mg twice daily), clindamycin (600 mg intravenously daily), and quinine (325 mg orally daily). He later experienced recrudescence of parasitemia and was successfully treated with atovaquone–proguanil therapy (76). Despite successful treatment, immunosuppressed individuals are at increased risk for relapsing babesiosis, and blood smears with complete blood counts should be repeated if symptoms recur. In a study of babesiosis infection in immunocompromised adults, successful treatment was associated with the duration of therapy rather than specific antibabesial treatment administered. Eradication of disease occurred typically following 6 weeks of treatment and for at least 2 weeks after parasitemia was no longer detected on blood smear (56).

## TULAREMIA

The cause of tularemia, *Francisella tularensis*, is a small, pleomorphic, aerobic, gram-negative coccobacillus that can be both intracellular and extracellular. Three main biovars have been identified, A, B, and C, all of which are found in the Northern hemisphere. The most virulent biovar, Type A, is found mainly in the United States. Biovar B, *F. tularensis* biogroup *holartica*, predominates in Europe and Asia but also occurs in North America. A low virulent strain, Biovar C, *F. tularensis* biogroup *novicida*, also occurs in select areas of North America (77).

In the United States, tularemia has been reported from every state except Hawaii (78). In 2000, almost half of all reported cases of tularemia were reported from Arkansas, Missouri, South Dakota, and Oklahoma (78). An arthropod-borne disease, tularemia may be transmitted by ticks, deerfly, mites, and other biting flies. The primary tick vectors of *F. tularensis* are *Am. americanum*, *D. andersoni* (FIG. 3), and *D. variabilis* (FIG. 4) (79). There are multiple vertebrate hosts that serve as a reservoir for tularemia. Also, tularemia may be spread by contaminated food and water in addition to blood. When transmitted by ticks, tularemia is more prevalent between the spring and the summer, accounting for the majority of outbreaks in humans (79–81). Transmission may peak again in the fall and early winter during hunting season. Hunters are exposed to infected animals and may contract the disease while preparing animal pelts or cleaning carcasses for food. For this reason, this bacterial infection has a bimodal seasonal distribution, unlike the other tick-borne diseases.

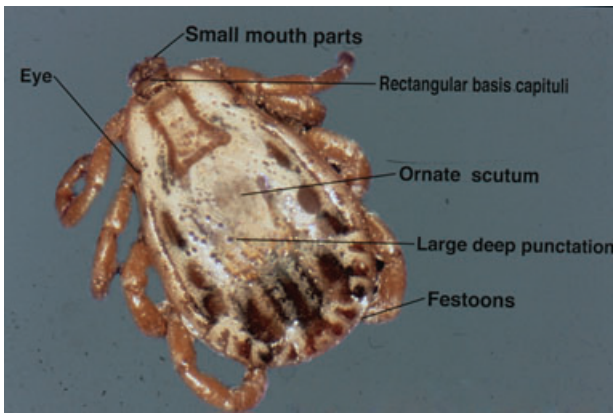


FIG. 3. *Dermacentor andersoni* (Image courtesy of Dirk M. Elston, MD).

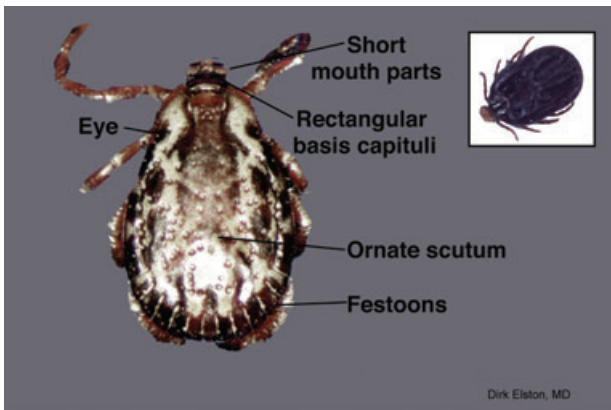


FIG. 4. *Dermacentor variabilis* (Image courtesy of Dirk M. Elston, MD).

There are several clinical variants of tularemia that may range in severity from asymptomatic infection to death. Tularemia may cause six distinct syndromes: ulceroglandular, glandular, oculoglandular, oropharyngeal, typhoidal, and pneumonic.

The most common form, ulceroglandular tularemia accounts for 80% of tularemia cases (80). In ulceroglandular tularemia, a painful erythematous papule, between 25 mm and 4.0 cm in size, develops at the inoculation site. In tick-borne diseases, the site of tick bite is often on the lower extremities and presents as a solitary lesion. When individuals are inoculated following handling of infected mammals, the sites of entry are typically the upper extremities, and the lesions may be multiple (3). This papule may develop into a pustule that then ulcerates. The punched-out ulcer may have raised ragged edges and a grayish-red or beefy-red necrotic base with scant serous or mucopurulent, yellowish, gelatinous discharge (3). A necrotic eschar may develop at the site, and, following lym-

phatic spread of bacteria, the regional lymph nodes enlarge and become tender. Biovar Type B infections are less likely to cause ulcerations, although an eschar may form at the site of necrotic papulopustule (82). Following several weeks to months, the eschar may heal with scarring (3). Following inoculation, the incubation period may last from 1 day to 3 weeks, although most symptoms develop within 4–5 days following infection and present with sudden onset of flu-like symptoms, especially chills, fever, headache, myalgias, nausea, vomiting, and anorexia (3). Bacteria may spread hematogenously to other sites including the spleen, liver, lungs, kidneys, intestine, central nervous system, and skeletal muscles. Although the bacteria may spread systemically, less than 3% of individuals with ulceroglandular tularemia die (79).

Occurring in 15% of individuals, glandular tularemia presents similarly to ulceroglandular tularemia, except there is no identifiable primary skin lesion (80). Oculoglandular tularemia occurs in less than 1% of cases and may develop following removal of tick with accidental inoculation of contaminated tick fluid in the eye (80). Individuals may develop conjunctivitis with lymphadenopathy and lymphadenitis, periorbital edema, and erythema.

Oropharyngeal tularemia may develop following the ingestion of infected raw meat or contaminated water. Individuals develop fever, exudative pharyngitis, or oropharyngeal ulcerations. Typhoidal tularemia may present with fever and chills or a systemic inflammatory response syndrome. Patients may develop pneumonia, rhabdomyolysis, and subsequent acute renal failure (8). A fatal variant, pneumonic tularemia develops following hematogenous spread, although inhalation of the bacteria may occur, such as in handling of the organism by laboratory workers (8).

Following hematogenous dissemination of bacteria in 8–20% of all forms of tularemia, secondary eruptions, or tularemids, may occur. Tularemids may present as macular, maculopapular, nodular, acneiform, papulovesicular, or plaquelike eruptions on the extensor surfaces of the extremities, face, neck, or hands. These pruritic eruptions may have a variable bodily distribution and develop more than 1 week after the onset of other systemic symptoms and may persist for another 2 weeks even after initiation of antibacterials (3).

Serologic tests are preferred for diagnosis, given that *Francisella* is a highly contagious bacterium that is fastidious and requires an enriched medium to grow in culture. Diagnosis of tularemia is confirmed with the development of antibodies 2 weeks after exposure. Diagnosis by latex agglutination

methods requires that a single antibody response  $>1:20$  be present. In contrast, diagnostic tube agglutination tests require a fourfold increase in antibody titers between the acute and convalescent phases of the disease or a single titer of more than  $1:160$  to be considered significant. Agglutination tests lack sensitivity because *F. tularensis* may fail to agglutinate. PCR-based methods are sensitive methods of diagnosis (78).

### Treatment

Because tularemia is a rare disease, there are no published, randomized control studies addressing antibiotic regimens. A 7- to 10-day intravenous course of aminoglycosides, such as streptomycin and gentamicin, is considered first-line therapy, based on anecdotal evidence. In a meta-analysis review of treated tularemia cases, treatment with streptomycin resulted in a 97% cure rate in 224 individuals treated (83). Successful in 86% (31/36) of treated cases, gentamicin is considered to be an acceptable alternative to streptomycin. In six individuals treated with another aminoglycoside, tobramycin, only half were successfully treated, and, consequently, tobramycin is not recommended as an alternative. Because of concern that *F. tularensis* may be used as a bioterrorist agent, the Working Group on Civilian Biodefense published guidelines for the treatment of this disease in 2001. For affected adults and pregnant women, streptomycin 1 g intramuscular (IM) twice daily or gentamicin 5 mg/kg IM or IV once daily for 10 days is recommended. For pediatric patients, schedules are weight based: streptomycin, 15 mg/kg IM twice daily (maximum dose 2 g/day), or gentamicin, 2.5 mg/kg IM or IV three times daily for 10 days (84).

Several other antibiotics have been shown to have good efficacy in the treatment of tularemia and may be used as alternatives if aminoglycosides are contraindicated or cannot be tolerated. Alternative treatment regimens for adults are doxycycline, 100 mg IV twice daily, or chloramphenicol 15 mg/kg IV four times daily for 14–21 days, or ciprofloxacin, 400 mg IV twice daily for 10 days (84). Chloramphenicol is not recommended for pregnant women. In children, alternatives include doxycycline 2.2 mg/kg IV twice daily (if weight  $<45$  kg) or chloramphenicol 15 mg/kg IV 4 times daily for 14–21 days, or ciprofloxacin, 15 mg/kg IV twice daily (maximum dose 1 g/day) for 10 days. In the same meta-analysis, tetracycline therapy was successful in 44 of 50 (88%) patients and resulted in no treatment failures, but 12% of individuals developed relapse (83). Because recrudescence of tula-

remia has been reported following discontinuation of therapy with the bacteriostatic antibiotics tetracycline and chloramphenicol, these antibiotics should be continued for at least 14 days (83,84). In individuals with meningeal tularemia, chloramphenicol should be considered initially for treatment because of increased penetration into the central nervous system. This medication was used to successfully treat an individual with meningeal tularemia who had failed therapy with gentamicin (85).

Evidence for the efficacy of fluoroquinolones in the treatment of tularemia is increasing. In a review of 79 tularemia cases treated with fluoroquinolones between 1966 and 2000, 86% of infected individuals were successfully treated, and only 14% relapsed, failed therapy, or had to discontinue treatment because of side effects (78). In a tularemia outbreak in Spain, ciprofloxacin had the highest treatment success rate and the least adverse events (86). Both ciprofloxacin and levofloxacin have been used as successful treatment for tularemic pneumonia (87). Ciprofloxacin has also been used to successfully treat a child who had failed gentamicin therapy (88). Ciprofloxacin currently has not been approved as treatment in children less than 12 years of age because of potential risk of cartilage damage.

In addition to in vitro studies that show *F. tularensis* resistance to b-lactams, treatment failures have occurred with b-lactam and macrolide antibiotics. For this reason, they are not recommended as alternative therapies (84,89). Eight individuals treated with ceftriaxone all failed therapy with this antibiotic (83). The ketolide telithromycin showed in vitro bactericidal activity against *F. tularensis* and, following further investigation, may prove to be a possible alternative treatment for tularemia (90).

## BORRELIOSIS

*Borrelia* species are spirochetes, gram-negative helically coiled bacteria, which cause several arthropod-borne diseases including Lyme disease, tick-borne relapsing fever (TBRF), and Southern tick associated rash and illness (STARI). The manifestations and treatment of Lyme disease, caused by *Borrelia burgdorferi*, has been reviewed recently and will not be discussed in this text (2).

### Tick-borne relapsing fever (TBRF)

Characterized by recurring febrile periods, TBRF is caused by the closely related spirochete bacteria

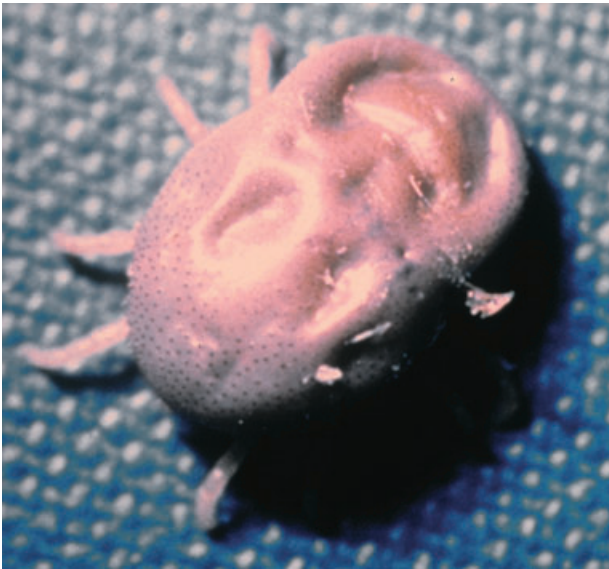


FIG. 5. *Ornithodoros* tick (Image courtesy of Dirk M. Elston, MD).

*Borrelia hermsii*, *Bo. turicatae*, and *Borrelia parkeri*. TBRF caused by *Borrelia* is transmitted by soft ticks of the genus *Ornithodoros* (FIG. 5). In the United States, *Ornithodoros parkeri*, *Ornithodoros hermsii*, and *Ornithodoros turicata* are the primary ticks involved in transmission. *O. hermsii* and *O. turicata* are the most common vectors of TBRF in the United States. *O. hermsii* transmits *Bo. hermsii*, *O. turicata* transmits *Bo. turicatae*, and *O. parkeri* transmits *Bo. parkeri*. Both *O. hermsii* and *O. parkeri* thrive in the coniferous forests of mountainous regions located at elevations between 1500 and 8000 ft. Found at lower elevations, *O. turicata* prefers drier habitats and may also be found in underground burrows, especially in Texas. Over a 25-year period, almost 500 cases were reported in the Western United States, particularly California, Colorado, and Washington. The majority of cases occurred between June and September, with the peak months of July and August. In contrast, in Texas, most cases occur in the fall and winter, especially November to January. This discrepancy may be a result of *Bo. turicatae* infections acquired in caves in contrast with the *Bo. hermsii* cases that occur in the Northwest mountainous regions. Most cases occur in individuals residing in a rural dwelling or spending significant time outdoors, that is, hiking or spelunking (91).

TBRF presents with fever, headache, myalgia, arthralgia, nausea, and vomiting approximately 1 week after tick bite (range: 4–18 days). An eschar may develop at the site of tick bite. Fever may be greater than 104°F and may last 3 days (range: 12

hours to 17 days), followed by an afebrile period of 1 week (92). Symptoms suddenly recur and last for an invariable length. Followed once again by remission, these relapses may occur as many as five times in the absence of treatment. The *Borrelia* spread hematogenously and become sequestered in the internal organs during the afebrile periods. They are capable of altering the outer surface membrane antigens, variable small proteins, and variable large proteins, to evade host immunity and, when present in the bloodstream, cause fever (93). They are capable of changing their outer surface membrane proteins multiple times, a phenomenon known as antigenic variation. As the fever defervesces, a macular eruption may occur, described as 1- to 2-cm rose-colored to erythematous macules with irregular borders (may also be circular and sharply demarcated), or other skin findings such as papules, petechiae, purpuric lesions, and facial flushing may appear in almost 20% of infected individuals (3). Other symptoms may be nonspecific and include abdominal pain, diarrhea, dry cough, eye pain, dizziness, photophobia, confusion, and neck pain. The most common hematologic abnormality, thrombocytopenia, develops in more than one-third of infected individuals, who also may develop hepatomegaly with splenomegaly, and rarely splenic rupture. Other complications include ocular abnormalities and myocarditis. Neurological sequelae such as cranial nerve palsies and meningismus occur in the majority of *Bo. turicatae* infections (27–80%), whereas neuroborreliosis caused by *Bo. hermsii* is less common (less than 5%). Laboratory findings include normal white blood cell count, proteinuria (46%), and hematuria (30%) (78).

TBRF can be diagnosed based on the presence of spirochetes in Giemsa- or Wright-stained peripheral blood smear obtained during the febrile episodes. *Borreliae* species may be visualized by microscopy by direct or indirect immunofluorescent techniques. Because of antigenic variation, serological identification of *Borrelia* is not sensitive, and few laboratories can perform the test (92).

### Treatment

Spirochetes responsible for causing TBRF are susceptible to several antibiotics. Tetracyclines are considered the treatment of choice, although no controlled studies concerning treatment of TBRF have been published. Other antimicrobials that have been used with success include penicillin, chloramphenicol, and erythromycin, and no evidence of drug resistance has been identified in TBRF spirochetes. The standard treatment regimen

is doxycycline, 100 mg every 12 hours for 7–10 days (94). If doxycycline is contraindicated, tetracycline, erythromycin, or chloramphenicol (all at dosages of 500 mg every 6 hours) may be given. Because of possible tooth discoloration and abnormal bone growth with doxycycline administration, children younger than 8 years of age and pregnant women should be treated with penicillin or erythromycin. Patients with neuroborreliosis should receive intravenous therapy with penicillin G, cefotaxime, or ceftriaxone for at least a 2-week course (95).

Following initiation of antibiotic therapy, individuals should be monitored for the development of the Jarisch–Herxheimer reaction for at least the first 4 hours after the first dose of antibiotic and even for the first 12 hours of antimicrobial treatment (96,97). Reported in 54% of patients treated for TBRE, this reaction may manifest as hypotension, tachycardia, chills, rigors, diaphoresis, and fever within 1–4 hours of antibiotic administration (96). Although the Jarisch–Herxheimer reaction is reportedly milder in children than in adults, symptoms may be severe. The opioid partial agonist, meptazinol, may reduce the severity of the symptoms (98).

#### **Southern tick-associated rash illness (STARI)**

STARI presents similarly to Lyme disease as an expanding erythematous annular rash, or Erythema Migrans. This disease is thought to be caused by *Borrelia lonestari* and is transmitted by *Amblyomma americanum* (99–101). *Bo. lonestari* has been detected in ticks in Alabama, Georgia, New Jersey, Tennessee, and Texas (78). Cases of erythema migrans associated with *Am. americanum* have been reported in the south central and southeastern United States. STARI has been identified in Alabama, Missouri, Georgia, South Carolina, North Carolina, and Maryland (78). Although *Bo. lonestari* has been detected in white-tailed deer, the natural reservoir for this spirochete has not been identified yet (102).

STARI presents with an erythema migrans-like rash but unlike erythema chronica migrans, the erythematous annular patches are more likely to be singular and smaller and develop greater central clearing (103). Unlike Lyme borreliosis, systemic symptoms are less common, but individuals may present with fatigue and cough. Laboratory findings may include an elevated serum alkaline phosphatase level (101).

Although there is no standard serological test for *Bo. lonestari*, the serology for Lyme borreliosis is negative. Experimentally, PCR amplification of the

16S ribosomal DNA and the flagellin gene may identify *Bo. lonestari* in humans and ticks (102).

#### **Treatment**

Although the causative agent of STARI is not definitively known, it has been recommended that, because of its similarities with Lyme disease, it be treated with antimicrobials. Similar treatment guidelines for STARI are recommended as would be used in the treatment of Lyme disease: 10–30 days of oral doxycycline at 3 mg/kg in divided doses; amoxicillin, 500 mg three times daily; or cefuroxime, 500 mg orally twice daily (103). A longer treatment duration is suggested if there is fever, a flu-like illness, severe headache, lymphadenopathy, multiple lesions, or other evidence of dissemination beyond the rash. Previous reports of STARI or Lyme-like illness have been treated with a 14- to 21-day course of doxycycline, 100 mg PO twice daily, or a course of amoxicillin (duration and dosage not specified) (101,104,105).

## **TICK-BORNE VIRUSES**

Arboviruses may cause syndromes characterized as primarily encephalitis, hemorrhagic fever, or systemic febrile illness. Ticks are responsible for transmitting a number of different viral diseases including Crimean-Congo hemorrhagic fever (CCHF), Colorado tick fever (CTF), tick-borne encephalitis (TBE) complex of flaviviruses, Alkhurma hemorrhagic fever, Louping-ill, Kyasanur forest disease, Omsk hemorrhagic fever, and Powassan encephalitis.

#### **Crimean-Congo hemorrhagic fever (CCHF)**

Belonging to the family Bunyaviridae, CCHF virus is a Nairovirus. Although CCHF virus has been isolated from more than 30 species of ticks, *Hyalomma* ticks are the principal vectors (106,107). Natural hosts of *Hyalomma* ticks include large herbivores, fowl, and small mammals (106). Similar to the distribution of *Hyalomma* ticks, CCHF occurs primarily in Africa, the Middle East, and central and southwestern Asia, although cases have occurred in parts of Europe. In addition to tick bite, CCHF virus may be transmitted by infected tick tissue and fluid, respiratory inhalation in laboratory setting, or contact with infected livestock blood, milk, or meat (106).

After 2–7 days following tick bite, infected individuals may develop sudden onset of fever, chills,

myalgia, arthralgia, headaches, nuchal rigidity, photophobia, retro-orbital pain, nausea, vomiting, diarrhea, and abdominal pain. Several days later, a petechial eruption may precede other hemorrhagic manifestations such as ecchymoses in the axillae and inguinal regions, bleeding from venipuncture sites, hematemesis, and melena. Individuals are jaundiced, and hepatitis may present as hepatomegaly and elevated transaminase levels. Clinical findings may include tachycardia, bradycardia, and/or hypotension. Laboratory findings include thrombocytopenia and leukopenia. Case fatality ranges from 10 to 60%, depending on route of transmission, and usually is secondary to profuse hemorrhaging, disseminated intravascular coagulation, hemorrhagic pneumoniae, and cardiogenic shock. Diagnosis may be based on serological or PCR assays.

In patients with CCHF and other hemorrhagic viral diseases, supportive therapy is essential to treatment and may require the administration of thrombocytes, fresh frozen plasma, and erythrocytes to correct hematological abnormalities. Ribavirin exhibits antiviral activity against CCHF virus in vitro and has been shown to reduce mortality in a mouse model (108,109). In a case report of health-care workers infected with CCHF in Pakistan, three individuals were successfully treated with oral ribavirin 4 g/day for 4 days, then 2.4 g/day for 6 days (intravenous ribavirin was unavailable) (110). More recently, ribavirin had an 80% efficacy in 69 Iranian individuals suspected of having CCHF (111). These individuals were treated with ribavirin administered orally (30 mg/kg initial loading dose, then 15 mg/kg every 6 hours for 4 days, and then 7.5 mg/kg every 8 hours for 6 days) (111). Post-exposure prophylaxis with oral ribavirin is recommended for persons exposed to CCHF-contaminated blood (111). In an in vitro assay, ribamidine demonstrated antiviral activity that was at least 4.5-fold less than that of ribavirin, and 6-azauridine, selenazofurin, and tiazofurin, also structural analogs of ribavirin, did not show any significant antiviral activity (112). Interferon-induced MxA protein, a GTPase of the dynamin superfamily, may prevent CCHF virus replication in vitro and in vivo. However, its role in clinical management remains to be determined (113,114).

### Colorado tick fever (CTF)

CTF is caused by a coltivirus (serotypes CTFV-F1 and CTFV-Ca) in the Reoviridae family. In the Western United States, CTF is transmitted to humans by *D. andersoni*. Other ticks including

*Dermacentor occidentalis*, *Dermacentor albopictus*, *Dermacentor arumapertus*, *Haemaphysalis leporispalustris*, *Otobius lagophilus*, *Ixodes sculptus*, and *Ixodes spinipalpis* are also infected with the virus. In endemic areas, 3.5–25% of rodents are viremic (115). Affecting a wide range of hosts, CTF virus has been isolated from wild rodents, rabbits, deer, elk, sheep, and coyotes. CTF virus can also be transmitted by exposure to contaminated blood (116). CTF occurs in the northwestern regions of North America between April and June. It has been isolated from humans or ticks in Colorado, Utah, Montana, California, Wyoming, Idaho, Oregon, South Dakota, Washington, New Mexico, Nevada, Southern Alberta, British Columbia, and Canada (117).

Following tick exposure, symptoms may manifest abruptly anywhere from less than 24 hours to 14 days later (mean 4 days) as fever, chills, headache, conjunctival injection, retro-orbital pain, photophobia, malaise, abdominal pain, nausea, vomiting, and severe myalgia (117). Typically occurring over a 1-week period, fevers may be biphasic or triphasic, with high fever lasting 2–3 days followed by defervescence for several days and then recurrence. Approximately 20% of infected individuals are hospitalized, and CTF may progress to disseminated intravascular coagulopathy, aseptic meningitis and encephalitis, pericarditis, hepatitis, myocarditis and orchitis, although rarely is CTF fatal (115,118). A faint transient morbilliform rash may be present in less than 12% of infected individuals (3). The rash may be morbilliform or petechial and even has been described as facial flushing or branny desquamation of the skin. The maculopapular eruption typically appears on the neck, face, arms, and legs, whereas the petechial eruption may appear over the flexor surfaces of the arms, forearms, and diffusely over the legs and body. CTF may be diagnosed by isolating CTF virus from blood samples or immunofluorescent antibody (IFA) test detection of a nonacute rise in antibody titer. CTF virus is present in circulating erythrocytes for as long as 4 months (119). This virus is isolated following intracerebral injection of blood into suckling mice. Enzyme-linked immunosorbent assay (ELISA) may be used to detect anti-CTF virus antibodies, which are typically present 1 or 2 weeks after the onset of illness (115). PCR analysis for CTF virus has also been developed (120).

An antigenically related coltivirus, the Eyach virus, has been implicated in encephalitis and polyradiculoneuritis in the former Czechoslovakia. The European rabbit (*Oryctolagus cuniculus*)

is the probable reservoir of Eyach virus, although the natural life cycle of the virus is not completely known (121). This virus has been isolated from *I. ricinus* in southwestern Germany, and antibodies have been detected in both humans and lagomorphs.

For both Eyach and CTF virus infections, there is no specific treatment nor is there a vaccine. Typically, supportive care is recommended, and aspirin as an antipyretic should be avoided because of possible exacerbation of thrombocytopenia-induced hemorrhage. Currently, there is no evidence to support the use of ribivirin in CTF human infections despite increased survival in animal models and anti-CTF virus activity in vitro (122).

### Tick-borne Flaviviruses

TBE virus, a flavivirus, is a single species with three subtypes: Western (European) TBE, Siberian TBE, and Far-Eastern (Russian Spring-Summer Encephalitis) TBE. Isolated in Northern Asia, Central and Western Europe, this virus has been found in at least 25 European countries and seven Asian countries. The principal ticks that transmit TBE virus to humans are *I. ricinus* in Europe, and *I. persulcatus* and *Haemaphysalis concinna* in Russia (106). Small rodents are the natural hosts of these ticks. TBE typically occurs during tick activity between April and November. In addition to tick-borne transmission, TBE virus may be acquired from ingestion of raw goat's milk, inhalation, or needle-stick exposure to contaminated blood in a laboratory setting (106,123). All three subtypes are responsible for approximately 12,000 cases of encephalitis annually (124). The majority of human infections are subclinical or asymptomatic. After 1–2 weeks following the tick bite, an infected individual develops sudden onset of fever, headache, myalgia, nausea, and vomiting that typically lasts 4 days (range: 1–8 days) (125,126). During this phase, thrombocytopenia and leukopenia may be present. Symptoms may resolve after 1 week (range: 1–33 days), and then 20–30% of infected individuals can develop meningoencephalitis (127). Typically self-limited, neurological sequelae such as hearing defects, ataxia, spinal nerve paralysis, and paresis may be debilitating.

Chronic forms may develop in which progressive neurological symptoms are present in the absence of an acute phase and manifest as progressive neuritis, sclerosis, Parkinsonian disease, or progressive muscular atrophy. In the Far East, human infections manifest as more severe encephalitic syndromes and may be more fatal

(case fatality rate of 5–35%), although chronic forms of the disease are less common. In Siberia, less severe diseases (case fatality rate of 1–3%) are present; however, chronic forms are more prevalent. In Europe, case fatality is less than 1%, and chronic forms are less prevalent. TBE may be diagnosed serologically, and the three subtypes, Western TBE virus, Siberian TBE virus, and Far-Eastern TBE virus, can be distinguished by IFA. Similar to that in other arboviruses, treatment is supportive, although, currently, two vaccines are available in Western Europe (106).

The only tick-borne flavivirus in the United States, Powassan virus is related to tick-borne encephalitis from East Asia and presents with fever, seizures, vomiting, respiratory distress, and encephalitis. The main vector is *Ixodes cookei*, but other ixodid ticks including *D. andersoni* have been implicated (128–130). Clinical disease with Powassan encephalitis is rare, with less than 50 cases reported in the last half century (118,129,130). Widely distributed in Canada and the United States, more recent cases of Powassan virus have occurred in New York, Maine, Vermont, and Ontario (128–130).

Another related tick-borne encephalitis virus, Louping-ill virus, mainly affects sheep in the moorlands of the British Isles (131). Also transmitted by *Ixodes* spp., this virus causes encephalomyelitis of sheep and is responsible for only one human death (132). Langat virus was originally isolated from ticks in Thailand and Malaysia, and, although there are no documented human cases, encephalitis was reported in 1 of 10,000 individuals who had been vaccinated with a live-attenuated Langat virus vaccine to protect against tick-borne encephalitis viruses (133).

Flaviviruses are not only responsible for encephalitic syndromes but also may present with hemorrhagic diatheses. Kyasanur forest disease virus and the closely related Alkhurma virus cause hemorrhagic diseases in humans. Transmitted by *Haemaphysalis* ticks, the natural reservoir is most likely forest animals with rare human involvement until widespread urbanization occurred. Because of deforestation in India, Kyasanur forest disease has emerged as sporadic epidemics of hemorrhagic disease in humans, affecting 100–500 people, with a case fatality rate of 2–10% (134). A closely related virus, Alkhurma was first documented in Saudi Arabia in 1992. This virus may have originated in India and emerged in Saudi Arabia because of inter-coastal trade. *Ornithodoros savignyi* has been proposed as the vector, and the virus has been isolated from sheep and camels (134). Another flavivirus

isolated in west Siberia, Omsk hemorrhagic fever virus is associated with muskrats that were reintroduced into Siberia from Canada to repopulate the region to allow the fur trade to prosper. There are only sporadic reports of Omsk hemorrhagic fever in Siberia (72,98,134,135). Human infection is similar to that seen with Kyasanur forest disease virus.

Similarly for other tick-borne viruses, treatment is supportive because no specific antiviral therapy exists. Ribavirin, interferon-alpha, 6-azauridine, and glycyrrhizin were tested in vitro for their antiviral activities against representative pathogenic flaviviruses. Interferon (IFN)-alpha was a selective and potent inhibitor of flavivirus replication, and ribavirin, and 6-azauridine, glycyrrhizin also demonstrated antiviral activity (136). However, the role of these antiviral compounds in human infection still needs to be established. In general, antiviral therapy may be required in addition to mechanical ventilation for apnea and compromised airway (117). In India, a vaccine against Kyasanur forest disease may be administered to immunize laboratory personnel (134).

No specific therapy for TBE virus currently exists, and preventive measures are achieved with vaccination and tick-control measures. In Europe and in Russia, several vaccines are available, and successful vaccination programs have nearly eliminated TBE virus from Austria (133,137). In Russia, passive immunization may be achieved with the administration of TBE virus immunoglobulins within 3 days following tick bite. In Europe, TBE immunoglobulin therapy is no longer available because of concerns that administration resulted in worsening encephalitic diseases (106,138).

## RICKSETTIAL DISEASES

### Rocky Mountain spotted fever (RMSF)

*Rickettsiae* are obligate, intracellular, short, gram-negative rods that invade endothelial cells. In the early 1900s, RMSF was shown to be transmitted by ticks and caused by *Rickettsia rickettsii* (139). In the Western United States, *R. rickettsii* is transmitted by *D. andersoni*, whereas, in the Eastern United States, this rickettsia is transmitted by *D. variabilis* (140). The ticks *Rhipicephalus sanguineus* (FIG. 6) and *Amblyomma cajennense* are also vectors of RMSF in Mexico and Central and South America, respectively (78). *R. rickettsii* may be transmitted to humans in 6–8 hours after tick attachment, although 24 hours is typically required for transmission (78). RMSF is more prevalent in the

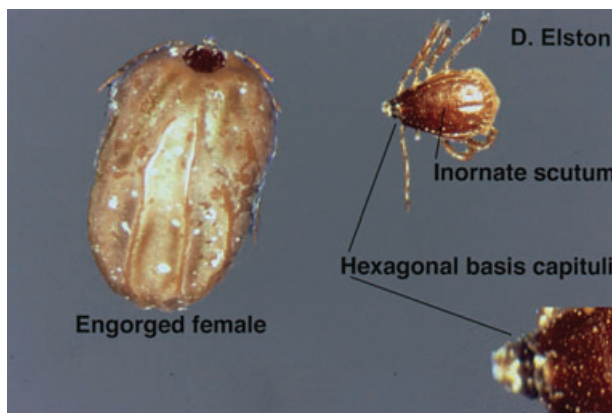


FIG. 6. *Rhipicephalus* tick (Image courtesy of Dirk M. Elston, MD).

Eastern United States but has been reported in every state except Maine and Vermont (141). The majority of cases occur in the southeastern and Midwestern states and 56% of reported cases of RMSF between 1997 and 2002 were from the states North Carolina, South Carolina, Tennessee, Oklahoma, and Arkansas (142). The majority of RMSF cases occur between April and September (90%), and almost half occur in May and June (40%) (78). Cases have been reported in every month, and human infection may result from handling *R. rickettsii* in the laboratory or from exposure to tick fluid and tissue while removing infected ticks (141,143).

Five days following tick exposure, as many as 96% of infected individuals may develop a morbilliform eruption that is more prominent in younger or fair-skinned individuals. The rash starts on the palms and soles and may progress to a petechial eruption involving the hands, feet (FIG. 7), and trunk (3). In some individuals, rash may develop within the first 24 hours of tick bite. In general, the clinical findings of RMSF typically appear within 3–5 days following tick exposure. Fever and headache are present in 80% of patients with RMSF, but in less than half are these two clinical findings present simultaneously with rash (141). Other symptoms include myalgia, nausea, and vomiting. Rickettsial infection and subsequent vasculitis may result in end-organ damage of the brain, heart, kidney, and spleen (144). Additionally, thrombocytopenia, leukopenia or leukocytosis, elevated transaminase levels, hyponatremia and lymphocytic cerebrospinal pleocytosis may be present (145). Although children are affected more commonly than adults, RMSF is more fatal in the elderly population, and 25% of infected individuals may die without treatment (139).



**FIG. 7.** Rocky Mountain spotted fever (Image courtesy of Dirk M. Elston, MD).

The indirect immunofluorescence assay is greater than 90% sensitive and is the most commonly employed serological test for evaluation of *R. rickettsii* infection (145). Antibodies may not be present until after 10–14 days of the illness. Additionally, a fourfold rise between acute and convalescent titers taken 3 weeks apart may also be used to confirm diagnosis. Positive immunofluorescence of a skin or organ-tissue biopsy, or positive PCR test for *Rickettsia rickettsii* may also confirm diagnosis.

**Treatment.** In vitro studies have shown that *Rickettsiae* are susceptible to chloramphenicol, tetracycline, rifampin (except for *Rickettsia aeschlimanii* and *Rickettsia massiliae*), and some fluoroquinolones but are resistant to penicillins, cephalosporins, aminoglycosides, trimethoprim-sulfamethoxazole, and erythromycin (146–148). Despite in vitro activity against *Rickettsia*, there are no clinical data to support the use of rifampin or fluoroquinolones in the treatment of RMSF. The fluoroquinolones enrofloxacin, and trovafloxacin have demonstrated efficacy in the treatment of canine RMSF, but no human data are available (149,150). Consequently, tetracyclines are still the first-line treatment for RMSF, and, among this class of antibiotics, doxycycline is preferred. This medication is also recommended in the treatment of children <9 years old and pregnant women, despite concerns over

adverse events including tooth discoloration and abnormal bone growth in children and fetuses and hepatotoxicity and pancreatitis in mothers. A prospective study of children with RMSF treated with doxycycline showed that these children did not develop significant tooth discoloration compared with those who had not received this medication (151). In the pediatric population and pregnant women, shorter courses of doxycycline may be administered to minimize possible side effects. The recommended dose of doxycycline is 100 mg per dose administered twice daily (orally or intravenously) for adults. For children weighing <45.4 kg, therapy with doxycycline 2.2–5 mg/kg per dose administered orally or intravenously twice daily (maximum 200 mg daily) may be used (152). For mild cases of RMSF, oral therapy with doxycycline is sufficient, and individuals who are hospitalized with more severe cases should receive intravenous therapy.

If doxycycline is contraindicated, chloramphenicol may be considered an alternative, although the use of this medication may be associated with aplastic anemia, reversible bone marrow suppression, and gray-baby syndrome. Chloramphenicol may be administered as 50–75 mg/kg per day in four divided doses in adults and as 50–100 mg/kg per day in four divided doses in children (152). Because of increased penetration of the blood brain barrier, chloramphenicol via intravenous administration is preferred if severe neurological involvement is present (8). However, epidemiologic studies suggest that chloramphenicol is less effective than tetracyclines and may be associated with increased risk of fatality from RMSF (142,153,154). If chloramphenicol is used to treat RMSF, serum drug concentrations and reticulocyte counts should be monitored when the treatment course extends beyond 3 days.

Although the duration of treatment is not well established, antibiotics should be continued for at least 3 days after the last febrile episode. Most patients treated with doxycycline or chloramphenicol defervesce within 2–3 days and are treated with a 5- to 7-day course of antibiotics. Individuals with complications such as multiorgan involvement or gangrene may require a longer duration of treatment (145). Individuals with severe cases of RMSF require supportive treatment in addition to IV antibiotics. They may need hospitalization for mechanical ventilation, fluid management with dialysis, blood transfusions or even seizure treatment (145). Anticoagulation with heparin should be avoided in individuals with RMSF as it may promote hemorrhaging (155).

Short courses of systemic corticosteroids have been used as adjunct therapy in cases of RMSF vasculitis, although clinical data are lacking (155).

### American tick bite fever

In the United States, the first documented human case of *Rickettsia parkeri* was described in 2004 (156). There are only a handful confirmed cases of *R. parkeri* infection, and several of these cases were individuals originally diagnosed as having RMSF. The vector has been identified only in one case as *Amblyomma maculatum*. *R. parkeri* has also been isolated from *Am. americanum* and *Amblyomma triste*, a tick found mainly in South America, suggesting that *R. parkeri* may also be transmitted by these ticks (156–158).

In a human case described in 2004, the afflicted individual developed fever, headache, diffuse myalgias and arthralgias, and multiple eschars on his lower extremities, followed by an erythematous maculopapular rash on his trunk and his extremities, including the palms and soles (156). In another case, the infected individual had an erythematous macular and papular eruption with a solitary eschar, leukopenia, and mild transaminitis. Both cases responded to doxycycline therapy. Either cell culture or PCR amplification from skin biopsy may be used to identify *R. parkeri* infection, especially because serological tests are not widely available (159).

### Mediterranean spotted fever (MSF) (Boutonneuse fever)

MSF is caused by *Rickettsia conorii* and is transmitted by dog ticks *Rhipicephalus sanguineus* in urban and suburban areas. Although the disease is endemic in the Mediterranean, cases have occurred in Europe, Africa, and Asia and more than 100 cases have been described in travelers returning from these areas, especially France and Spain. There are several strains of *R. conorii* that, although genotypically related, are considered as members of an *R. conorii* complex because of differences in ecology and disease manifestations (160). In addition to the causative agent of MSF, *Rickettsia conorii conorii*, the other members include *Rickettsia conorii indica* (Indian Tick Typhus), *Rickettsia conorii israelensis* (Israeli Spotted Fever) and *Rickettsia conorii caspia rickettsia* (Astrakhan Fever).

*Rhipicephalus sanguineus* is the most important known vector for *R. conorii conorii* in Europe and North Africa. The natural host of *R. conorii conorii* is the domestic dog, and in its absence this

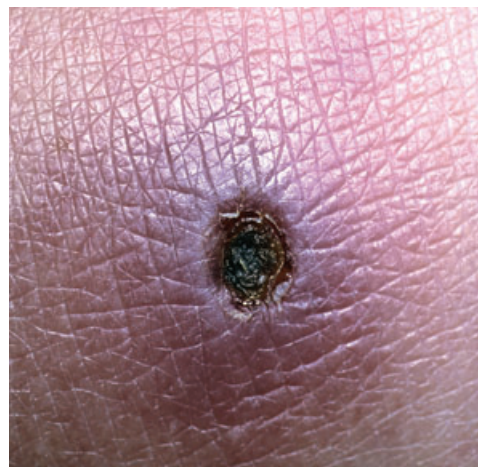


FIG. 8. Rickettsial eschar (Image courtesy of Dirk M. Elston, MD).

tick will feed on humans. In Africa, the ticks *Haemaphysalis leachi* and *Haemaphysalis punctaleachi* are also thought to transmit *R. conorii conorii*.

After an incubation period of 6 days (range: 1–16 days), infected individuals develop sudden onset of high fever, headaches, chills, arthralgias and myalgias, a generalized maculopapular cutaneous rash, and an inoculation eschar (FIG. 8) at the site of the tick bite (161). Gastrointestinal symptoms may be present in approximately one-third of patients. Typically solitary, the eschar may be found in 13–86% of cases and is usually located on the extremities or trunk (161). Rarely, it may be located on the scalp, axillary, or genital region. Regional adenopathy is not typically found in adults with MSF, although children may present with cervical lymphadenopathy (161). Despite the fact that a generalized rash may not be present in 1–4% of cases, a maculopapular eruption involving the palms and soles but sparing the face usually develops within 2–3 days of fever. Initially, the rash may be faint and macular and, in more severe cases, may progress to a purpuric eruption. Untreated, most cases of MSF last 2–3 weeks and are fairly mild in disease severity. MSF may result in severe complications affecting the kidneys, heart, and brain but is fatal in less than 1% of cases (161).

Diagnosis may be confirmed by serology or PCR assay because culture methods may not reliably identify rickettsia. Unfortunately, the different species of rickettsia are not readily differentiated by using immunoassays. Western blot may be used especially in early sera. PCR amplification of rickettsia genes including citrate synthase, ompA, ompB, or gene D may identify *Rickettsia* from tissue obtained from skin biopsies at the eschar site or blood samples (161).

**Treatment.** Similar to that of RMSE, the recommended treatment for MSF is tetracycline therapy, particularly doxycycline. MSF was successfully treated with doxycycline 200 mg PO twice daily for 1 day in adults, and this regimen is considered to be as effective as a 10-day course of tetracycline hydrochloride (162). Compared with tetracycline, erythromycin has reduced in vitro antimicrobial activity and is not as effective as a treatment. Therefore, it is not recommended as treatment for *R. conorii* (163,164). However, another macrolide, josamycin, has also been used successfully to treat MSF (this antibiotic is not currently available in the United States). A randomized clinical trial demonstrated that doxycycline (200 mg PO twice daily for 1 day in adults, 5 mg/kg of body weight PO twice daily  $\times$  1 day in children) was as efficacious as josamycin (1 g PO every 8 hours for 5 days in adults, 50 mg/kg of body weight at 12-hour intervals for 5 days in children) in the treatment of MSF (165). Josamycin may also be used in pregnant woman (3 g/day for 7 days (165)). Duration of therapy should continue until 24 hours following defervescence. Regimens with the newer macrolides clarithromycin (15 mg/kg/day in two divided doses for 7 days) and azithromycin (10 mg/kg/day in one dose for 3 days) have been used in the treatment of children with MSF, and one-dose azithromycin has been suggested for prophylaxis (166,167).

In vitro studies have demonstrated that some fluoroquinolones may be sufficient against spotted fever rickettsioses (164,168). A comparison of a 7-day course of ciprofloxacin (750 mg/12 hours) with doxycycline (100 mg/12 hours) demonstrated that MSF resolved more quickly with ciprofloxacin (169). However, a previous comparison of a 2-day course of ciprofloxacin versus a 2-day course of doxycycline suggested that symptoms resolved more quickly with doxycycline, although patients were successfully treated with both regimens (170).

Similar to the treatment of *R. rickettsii*, broad spectrum antibiotics such as penicillins, cephalosporins, and aminoglycosides are ineffective antimicrobials for *R. conorii*. In a clinical trial, rifampin did not successfully treat MSF in children (171). Treatment with trimethoprim-sulfamethoxazole not only is ineffective but may also promote the pathogenicity of *R. conorii* and increase the severity of disease (172). For this reason, sulfa-containing antimicrobials are not recommended.

### African tick bite fever

A member of the spotted fever group, *Rickettsia africae* has been recently identified as the causative

organism of African tick bite fever. This rickettsial organism is transmitted in rural sub-Saharan Africa by ticks of the *Amblyomma* genus that typically feed on cattle and wild game. The two main vectors are *Amblyomma hebraeum* in Southern Africa and *Amblyomma variegatum* in West, Central, and East Africa (173). The seroprevalence in Africa ranges from 30 to 56%, and most cases of human infection occur between November and April. In travelers, African tick bite fever may be acquired during game hunting, leisure travel, sports competitions, and volunteerism in rural Africa.

After 6–7 days, individuals may develop severe headache, myalgia, eschars with regional lymphadenitis, vesicular or maculopapular rash, and aphthous stomatitis (173–176). In half of infected individuals, multiple eschars may be present (175). The increased number of bite sites is thought to be a result of the absence of host specificity because *Amblyomma* ticks feed readily on humans (176).

The usual method of diagnosing rickettsiosis is serological immunofluorescence assay. Additionally, in skin biopsies, PCR amplification of the ompA gene has been used to identify *R. africae* (177).

Treatment of African tick bite fever has been based on case reports and limited case series. Treatment with tetracyclines is the current recommendation, although therapy with fluoroquinolones may be used (178). Recommended regimens include doxycycline, 200 mg per day for 5–7 days, although shorter durations may be possible, as seen in MSF (175,179).

### Japanese spotted fever (JSF) (Oriental spotted fever)

*Rickettsia japonica* has been identified as the cause of JSF. JSF was first characterized in several individuals who had been collecting bamboo shoots in a rural area of Japan in 1984. During April to October, more than 30 cases have been reported each year along the southwestern and central coast of Japan since the mid-1980s (180). The vector for JSF is unknown, although *R. japonica* has been isolated from at least six species of ticks in Japan and *Haemaphysalis flava*, *Haemaphysalis longicornis*, *Dermacentor taiwanensis*, and *Ixodes ovatus* are considered the most likely vectors (139). There is circumstantial evidence that the *Apodemus speciosus* rodent is the natural hosts for this disease in endemic areas (181).

JSF presents similarly to other spotted fevers. Infected individuals all develop rash and fever, and may even have an eschar or headache. Patients

develop sudden onset of high fever, headache, chills, and a maculopapular rash after 2–3 days. The rash affects the body, palms, and soles and may become petechial after 3–4 days, followed by resolution in 2 weeks. More than one-third of patients recall a tick bite, and as many as 91% have reported an eschar (180). JSF may result in severe disease including encephalitis, disseminated intravascular coagulopathy, and multiorgan failure and can even result in fatality (180).

Doxycycline and minocycline are extremely effective in treating JSF, unlike penicillins, beta-lactams and aminoglycosides (180). In vitro, minocycline is the most effective antibiotic against *R. japonica*, although quinolones and other tetracyclines are almost equally effective (182). Case reports suggest that minocycline (200 mg/day) alone may not be sufficient for cure, and additional therapy with a fluoroquinolone, such as ciprofloxacin (600 mg/day), is recommended (180,182,183).

#### Far Eastern spotted fever

A newly emerging spotted fever, Far Eastern spotted fever is a relatively mild spotted fever that peaks at the end of June and July in Russia. Neither the vector nor the natural host has been established definitively. PCR amplification assays have isolated *Rickettsia heilongjiangensis* DNA fragments from *Haemaphysalis* ticks, and this rickettsia has been isolated from *Dermacentor silvarum* in China (139). Although human infection was suggested in 1992, direct evidence for the pathogenicity of this *Rickettsia* was provided in 1996 when *R. heilongjiangensis* isolates were obtained from several individuals with a spotted fever (139). In a recent report of 13 patients from the Russian Far East who were infected by *R. heilongjiangensis*, all individuals were exposed to ticks, and almost all developed eschars (184). After 4–7 days, the majority of individuals developed fever and a faint macular or maculopapular rash, with two developed lymphangitis and regional lymphadenopathy. All patients were successfully treated with oral doxycycline.

#### Flinders Island spotted fever

*Rickettsia honei*, the causative agent of Flinders Island spotted fever, has been isolated in Flinders Island, the Island of Tasmania, Thailand, and Texas (185). The transmitting arthropod is thought to be the reptile tick *Aponomma hydrosauri*, which feeds on blue-tongue lizards, tiger snakes, and copperhead snakes (139,186,187). Typically, human infec-

tion occurs in the spring and summer, during the months of December and January in Australia.

Flinders Island spotted fever has a similar presentation to RMSE. Infected individuals present with sudden onset of fever, headache, arthralgias, myalgias, joint swelling, and cough, followed by the development of an erythematous maculopapular eruption, although the rash may appear purpuric in the setting of thrombocytopenia (188). An eschar may be present at the inoculation site (25% of cases), with enlarged regional lymph nodes (55%) (188).

A rickettsia with >99% sequence similarity to *R. honei*, *Rickettsia marmionii* was isolated from six patients with a spotted fever from Australia between 2003 and 2005. These affected individuals all developed fever and other symptoms including headache (83%), arthralgia (50%), cough (50%), maculopapular rash (33%), and pharyngitis (33%). One patient developed an eschar. Potential vectors include *Haemaphysalis novaeguineae* (139). It is unclear whether *R. marmionii* is a distinct species separate from *R. honei*, but the name Australian spotted fever has been used to distinguish this clinical syndrome from Flinders Island spotted fever.

Flinders Island spotted fever is treated with oral doxycycline, 200 mg daily for 7–10 days (189).

#### Queensland tick typhus

In 1950, *Rickettsia australis* was characterized as the etiological agent of Queensland tick typhus, a spotted fever that had affected several military troops training outdoors in Eastern Australia (190). Two ticks have been associated with transmission of *R. australis*: *I. holocyclus* and *Ixodes tasmani*. The former, an avid biter of humans, is thought to be important in human infection, whereas the latter is zoophilic and probably responsible for enzoonotic maintenance in small animals. In Queensland, *I. holocyclus* is distributed particularly along the coastal regions but also may be found in the rainforests (191). *I. tasmani* is prevalent along the coast and the interior regions of south and west Australia (191). In both urban and suburban areas, the majority of cases occur between June and November and may range in severity from mild to severe, although it is rarely fatal.

The majority of patients recall a tick bite, and more than half develop an eschar (65% of cases) at the inoculation site with regional lymphadenopathy (71%). Disease onset is heralded by high fever, headache, myalgia, and a maculopapular or vesicular eruption that develops 10 days later

(192). This spotted fever is similar to other rickettsial spotted fevers except that the rash may be vesicular.

This spotted fever is treated similarly to other spotted fevers. Doxycycline (200 mg daily) is the preferred treatment, and chloramphenicol is an alternative. More recently, quinolone antibiotics have been suggested as an alternative (193).

### Siberian tick typhus

In Asiatic Russia, Siberian tick typhus may occur during the spring and summer months. The causative agent of Siberian tick typhus, *Rickettsia sibirica* subspecies *sibirica* has been isolated from several species of ticks. These include *Dermacentor nuttalli* in (Western and Eastern Siberia), *Dermacentor marginatus* (Western Siberia and Northern Kazakhstan), *D. silvarum* and *H. concinna* (Southern and far Eastern Siberia) (139). Prevalent in China, infection with *R. sibirica* subspecies *sibirica* is referred to as North Asian tick typhus. In Northern China, *D. nuttalli* is the transmitting arthropod vector (194).

Similar to those of the other spotted fevers, symptoms develop 4–7 days after tick bite. Patients usually present with high fever and an eschar at the inoculation site, with regional lymphadenopathy. Other symptoms include headache, myalgia, and gastrointestinal complaints, although the clinical course is typically mild. A rash may develop several days after symptom onset and may be purpuric (139). Doxycycline is the recommended treatment (194).

### Emerging rickettsial spotted fevers

In the last 20 years, the number of *Rickettsiae* implicated in spotted fevers has been increasing. A newly recognized member of the spotted fever group, *Rickettsia aeschlimannii* was first isolated from *Hyalomma marginatum* in 1992. There are two reports of human infection with *R. aeschlimannii*. In 2002, a European traveler to Morocco developed an eschar on the ankle, fever, and a generalized maculopapular rash. That same year, another traveler returning from South Africa developed an eschar on the thigh, and the OmpA gene for *R. aeschlimannii* was identified in the associated *Rhipicephalus appendiculatus* tick (195,196). Transmitted by ticks of the genus *Rhipicephalus*, *Rickettsia massiliae* was first identified as a cause of spotted fever in 2005 (197,198). This rickettsia was identified from an isolate 20 years after the patient presented in Italy with fever, necrotic eschar and maculopapular rash involving palms and soles and

mild hepatomegaly. *Rickettsia monacensis* has been identified in *I. ricinus* from both Germany and Morocco (199,200). This rickettsia has been isolated from cultures in two separate cases of human infection in Spain. In both cases, the infected individuals presented with fever and maculopapular rash in the absence of an eschar (201). *Rickettsia helvetica* has been detected in *I. ricinus* ticks in Europe, Asia and Africa (199). Based on serological assay, *R. helvetica* has been implicated in human infections in Sweden, France, Italy, Thailand, and Australia. This rickettsia has been suggested to be a cause of fatal myocarditis and is associated with a mild, self-limited illness characterized by headache, myalgias, and, less commonly, with rash or eschar (139, 202–205). Other rickettsia such as *Rickettsia canadensis*, *Rickettsia amblyommi*, and *Rickettsia texiana* have been implicated as pathogens in the spotted fever group, although little is known about their natural history.

### Tick-borne lymphadenopathy (TIBOLA)/ Dermacentor-borne necrosis erythema lymphadenopathy (DEBONEL)

TIBOLA is a newly recognized tick-borne rickettsial disease associated with eschar at the tick bite site and painful lymphadenopathy (176,206). TIBOLA is caused by *Rickettsia slovaca* and is transmitted by the vector *D. marginatus* (207). Additionally, *Rickettsia raoultii*, also identified in *Ixodes* and *Dermacentor* ticks, has been associated with a human case of TIBOLA, based on PCR amplification of a blood sample (208). Described at the same time, DEBONEL is similar to TIBOLA. DEBONEL is thought to be transmitted by *D. marginatus* and caused by infection with *R. slovaca*, although an incompletely characterized *Rickettsia* belonging to the *R. massiliae* group has also been isolated from the same tick.

TIBOLA/DEBONEL is seen most often in the pediatric population and the vast majority of tick bites are associated with the scalp. In TIBOLA, following tick bite, clinical findings were apparent from 1 to 45 days later (mean 11.5 days). Lymphadenopathy was present in all cases and in 80% of children a necrotic eschar with peripheral erythema with or without alopecia was present at the bite site (209). Other symptoms included headache (61%), fever (53%), muscle pain (33%), confusion and irritability (11%), and facial edema (8%) (209). Laboratory findings may include leukopenia or lymphocytosis, eosinophilia, elevated hepatic transaminases, and increased muscle enzymes (209).

As in other rickettsial diseases, doxycycline is the preferred treatment of TIBOLA/DEBONEL (210). Azithromycin has also been used to treat TIBOLA, and the newer macrolides have been suggested as a possible alternative in the pediatric population (209,210).

### Lymphangitis-associated rickettsiosis

A newly recognized rickettsial disease, lymphangitis-associated rickettsiosis is caused by *Rickettsia sibirica mongolitimonae*, which is considered a subspecies of *R. sibirica*. Transmitted by *Hyalomma* ticks, *R. sibirica mongolitimonae* is widely distributed throughout Africa, Asia, and Europe. The natural hosts of *Hyalomma* ticks are cattle and camels. In the Mediterranean, lymphangitis-associated rickettsiosis occurs from March to early July (211). Infected individuals develop fever, headache, multiple eschars, regional lymphadenopathy, and lymphangitis that extend from the eschar to the regional lymph nodes. Unlike infections with *Rickettsia sibirica sensu stricto*, lymphangitis-associated rickettsiosis is associated with lymphangitis and multiple eschars. Successful treatment may be achieved with doxycycline therapy (211).

### Q FEVER

*Coxiella burnetii* is a short gram-negative bacterium that causes Q fever and is transmitted by inhalation of contaminated aerosols, parenteral administration of infected blood transfusions, ingestion of contaminated milk, transplacentally, and by arthropod vectors (212). Q fever is typically acquired from occupational exposure to infected domestic animals such as sheep, cattle, and goats. Although *C. burnetii* has been isolated from more than 40 species of tick, vector-borne transmission to humans comprises a small number of cases (3). Tick vectors in the United States include *D. andersoni*, *D. occidentalis*, *Am. americanum*, *Haemaphysalis leporis-palustris*, *Ixodes dentatus*, and *Otobius magnini* (213). *Coxiella* is concentrated in tick fluids and feces, and crushing of the tick *D. andersoni* may have resulted in Q fever in an infected individual (214).

Following 2–3 weeks of incubation, Q fever typically presents with abrupt high fever, headache, malaise, and myalgias. Acute hepatitis, myocarditis, pericarditis, or pneumonia may also manifest in severe cases of *Coxiella* infection (213). Q fever causes rash in less than 22% of infected individuals, and this rash may be non-

specific (3). The rash may appear 2 weeks following infection and may be described as 2–5-mm blanching erythematous macules or, less commonly, as petechial, purpuric, urticarial or vesicular (3). As many as half of individuals who developed rash did not present with other clinical findings (3). There is a wide range of possible clinical findings in acute infection including meningitis, pancreatitis, splenic rupture, orchitis, glomerulonephritis, and lymphadenopathy, among others (212). Years after acute infection, approximately 1–5% of individuals may develop chronic Q fever, which is most often characterized by endocarditis, although the liver and bones may also be affected (212). People who have heart valve and vascular abnormalities, or who are pregnant or immunosuppressed, are more likely to develop chronic Q fever infection.

*Treatment.* Acute infection with Q fever is often a mild, self-limited disease that generally does not require antibiotic treatment. In vitro studies have shown that amoxicillin, amikacin, and erythromycin have minimal efficacy in the treatment of *C. burnetii*, whereas co-trimoxazole, rifampin, tetracycline, doxycycline, and minocycline were effective. Chloramphenicol was bacteriostatic, and the fluoroquinolones had varying efficacy with ofloxacin having the greatest effect (215). In symptomatic patients, tetracyclines, especially doxycycline, are the recommended antibacterials. For acute illness, doxycycline (100 mg PO twice daily for 14 days) is the recommended regimen (216). Although the use of erythromycin is discouraged as a result of inefficacy, treatment with the newer macrolides is more promising (217).

There are mixed reports of successful treatment of acute pneumonia secondary to *C. burnetii* with erythromycin, and treatment response may vary with the severity of pneumonia (213). In several anecdotal reports, Q fever pneumonia had been successfully treated with lincomycin, cotrimoxazole, or chloramphenicol (213,218,219). Fluoroquinolones such as ofloxacin (200 mg three times a day) and pefloxacin (400 mg twice per day) have been used successfully to treat acutely infected patients, but 2–3 weeks of treatment is required (213). More recently, clarithromycin and moxifloxacin have been shown to have similar efficacy to doxycycline in the treatment of *Coxiella* pneumonia (220).

As a result of increased CSF penetration, fluoroquinolones have been recommended as an alternative in the treatment of meningoencephalitis as a result of *Coxiella* (221). However, a case review

of 29 individuals with neurological symptoms did not demonstrate decreased severity of neurological sequelae in patients treated with a fluoroquinolone compared with those treated with doxycycline (222).

The most common manifestation of chronic Q fever is endocarditis. In the treatment of endocarditis associated with Q fever, doxycycline is not effective as a monotherapy. Additionally, patients with Q fever endocarditis and tetracycline intolerance who were treated with co-trimoxazole, rifampin, or fluoroquinolone monotherapy relapsed following withdrawal of the antibiotics (213). Previously, patients treated with combination therapy of a tetracycline with either lincomycin, cotrimoxazole, or rifampin did no better than those treated with tetracycline monotherapy (213). Typically, hydroxychloroquine (600 mg daily) in combination with doxycycline (200 mg daily) is used to treat endocarditis (223). The combination of doxycycline with either a fluoroquinolone such as pefloxacin or ofloxacin was effective in the treatment of Q fever endocarditis, although individuals relapsed following discontinuation of treatment (224). For chronic endocarditis, a longer duration of treatment is recommended; 18 months of doxycycline (100 mg, twice daily) and hydroxychloroquine (200 mg, three times daily) may be sufficient therapy (223). Raising the pH in the phagolysosome, chloroquine potentiates the bactericidal activity of this tetracycline in the treatment of *Coxiella*. The serum hydroxychloroquine concentration should be maintained between 0.8 and 1.2 mg/L, and doxycycline serum concentrations should be no less than 5 mg/L (223). Chloroquine therapy may be initiated at 200 mg three times a day for the first 3–6 months and then decreased to 200 mg twice a day or even once a day to minimize intolerance (213). Individuals treated with chloroquine require eye exams every 6–12 months to screen for eye toxicity (212,225). An alternate regimen is 3-year administration of doxycycline (100 mg twice daily) and ofloxacin (200 mg three times daily) in individuals with chronic infection who cannot receive hydroxychloroquine. Another possible alternative for the treatment of endocarditis is combination treatment with doxycycline and rifampin, although rifampin administration may complicate anticoagulation therapy in these individuals (226). Duration of treatment should continue until antiphase I antigen IgA and IgG antibodies decrease below 1:200, although some authors recommend levels of IgG < 1:800 or IgA < 1:50 (213,223). In hemodynamically unstable individu-

als, valve replacement may be necessary and should be combined with antibiotic therapy to prevent relapse and the development of prosthetic valve infection (213). Combination therapy with doxycycline and hydroxychloroquine for 1 year may be required in patients with valvulopathy who develop acute Q fever so as to prevent development of endocarditis (227).

For other chronic infections with *C. burnetii* such as endovascular complications or osteoarticular infections, surgical treatment or debridement is recommended in addition to prolonged combination antibiotic therapy (225).

Hepatitis and chronic fatigue also may result from chronic infection with *Coxiella*. Treatment of hepatitis associated with Q fever is similar to acute infection. However, the addition of systemic glucocorticoids to doxycycline therapy is recommended in the treatment of Q fever hepatitis. Individuals affected with hepatitis who do not defervesce following 3 days of antibiotic treatment should receive a tapering dose of prednisone (40 mg for 48 hours, then 20 mg for 48 hours, and then 10 mg for an additional 48 hours) (213).

In pregnancy, long-term cotrimoxazole therapy (320 mg/day of trimethoprim and 1600 mg/day of sulfamethoxazole for 35 days) may be used to decrease the risk of placentitis, obstetric complications, and maternal chronic Q fever (212,228,229). If used in the last trimester prior to delivery, cotrimoxazole may induce neonatal hyperbilirubinemia (230). An alternative suggested treatment regimen is combination doxycycline (200 mg/day) and rifampin (900 mg/day), although formal data are lacking. Following delivery, mothers should be treated with one year of doxycycline and chloroquine, as above. Mothers should be made aware that *C. burnetii* may be transmitted via breast feeding and that doxycycline is excreted in breast milk (229).

Following discontinuation of antibiotics, individuals treated for chronic infection with *Coxiella* should be reevaluated for persistent occult infection. Recommendations include complete blood count (CBC), liver function tests, lymphocytic typing, and Q fever serology every month for 6 months after antibiotic discontinuation, then biannual evaluation for 2 years, and annual evaluation indefinitely. Serology may be obtained every 3 months following discontinuation of treatment to monitor for relapse (fourfold increase in immunoglobulin titer) (225). Additionally, an echocardiogram should be performed even in asymptomatic individuals biannually for the first 2 years following cessation of antibiotics (213). Vaccination is cur-

rently limited to those individuals who are at occupational risk of developing Q fever (213).

## COINFECTIONS

*Ixodes* ticks may be carriers of more than one human pathogen concurrently. Additionally, many tick-borne diseases have similar geographic distributions and vector ecologies. Almost one-third of *I. scapularis* ticks collected in Lyme-endemic regions of the United States carry more than one pathogen (231). As a result, individuals may develop coinfections with bacteria, protozoa, and even tick-borne viruses. Varying combinations of infection with *Bo. burgdorferi*, *Ba. Microti*, and *Anaplasma phagocytophilum* are evident in the Midwest United States, based on serological prevalence (232,233). In one prospective study, almost 10% of individuals residing in Wisconsin who had Lyme borreliosis also had serologies suggestive of previous *A. phagocytophilum* infection. Rates of *Bo. burgdorferi* and *Babesia* coinfection range from 11 to 23% depending on the geographic area surveyed (54,234,235). For instance, the seroprevalence of *Bo. burgdorferi* and *Babesia* coinfection in individuals living in Long Island, New York, was 66% in one study (236). *E. chaffeensis* coinfection with a spotted fever group *rickettsia* has been reported, and even one individual developed fatal encephalitis following dual infection with tick-borne encephalitis virus and *Bo. burgdorferi* (237,238).

Coinfection may alter disease severity and treatment decisions. *Babesia* coinfection with Lyme borreliosis results in prolonged duration of illness and increased severity of disease (235). First-line treatment for babesiosis will not be effective for *Borrelia* or *Anaplasma*, and if coinfection is suspected an additional antibiotic, such as doxycycline, should be administered (60). Also both chloramphenicol and the fluoroquinolones lack efficacy in the treatment of *Ehrlichia* (36,239). When considering treatment of a tick-borne disease, doxycycline is an adequate antibiotic choice for treatment of both RMSF and ehrlichiosis (142). If coinfection with *Borrelia burgdorferi* is suspected, patients with ehrlichiosis should be treated with a longer duration of doxycycline, i.e. 10–14 days, to provide appropriate therapy for Lyme disease (239).

## Summary

Arthropod vectors, such as ticks, are of extreme importance in public health. Ticks are responsible

for transmitting bacteria, viruses, and protozoa that cause human disease. Often, tick-borne clinical syndromes will have similar presentations that may delay appropriate treatment as a result of lack of recognition. Clinicians should bear in mind that, if infected individuals are not improving, coinfection may exist, or an alternative diagnosis should be considered. Antibiotics, if indicated, should be started early in the course of illness to prevent the development of acute, chronic, and/ or fatal infection.

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