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# 298 Ticks, Including Tick Paralysis

*James H. Diaz*

## SHORT VIEW SUMMARY

### Definition
- Ticks can transmit the broadest range of infectious microbes among all arthropods, including bacteria, viruses, and parasites.
- Gravid ticks may also transmit paralytic salivary toxins during blood-feeding.

### Epidemiology
- Ticks are among the most competent and versatile of all arthropod vectors of infectious diseases.
- Tick-transmitted Lyme borreliosis or Lyme disease is now the most common arthropod-borne infectious disease in the United States and Europe.
- Most tick-borne infectious diseases can also be transmitted to humans by blood transfusions and organ transplants, and babesiosis can be transmitted congenitally.

### Microbiology
- Ticks of all ages and both genders may remain infectious for generations without having to reacquire infections from host reservoirs.
- New tick-transmitted pathogenic species are constantly being described in the United States.

### Diagnosis
- Ticks can transmit several pathogens during one blood-feeding, resulting in coinfections that can complicate differential diagnosis and treatment.
- The diagnosis of tick-transmitted infectious diseases is based on combinations of tick-bite history and characteristic lesions, such as erythema migrans and eschars, microscopic identification of pathogens in blood and tissue biopsy specimens, serologic and immunocytologic tests, and nucleic acid serotyping.

### Therapy
- Most tick-transmitted bacterial diseases remain sensitive to doxycycline, amoxicillin, and chloramphenicol.
- The tick-transmitted viral diseases can be managed only supportively.
- Babesiosis is caused by a malaria-like parasite and must be treated with combinations of antimalarial agents and azithromycin or clindamycin.

### Prevention
- Combinations of immunization, prophylactic antibiotics, personal protective measures, landscape management, and wildlife management are all effective strategies for the prevention and control of tick-borne infectious diseases.
- A single 200-mg dose of doxycycline administered within 72 hours of a tick bite is more than 80% effective in preventing Lyme disease.

Ticks are the most competent and versatile of all arthropod vectors of zoonotic infectious diseases for several reasons. First, ticks are not afflicted by most of the microorganisms that they may transmit or the paralytic salivary toxins that they may transfer during blood-feeding. Second, and unlike mosquitoes, ticks can transmit the broadest range of infectious microbes among all arthropods, including bacteria, viruses, and parasites. In addition, tick-transmitted coinfections appear to be increasing and complicate differential diagnosis and antimicrobial treatment. Third, ticks can vertically transmit infectious microorganisms congenitally to their offspring of both genders (transovarian transmission) and then disseminate carrier state infections among all generational growth stages (trans-stadial transmission). Tick-borne infectious diseases can also be transmitted to humans by blood transfusions and organ transplants, and babesiosis, a tick-borne infection caused by malaria-related parasites, can be transmitted congenitally. Fourth, ticks have capitalized on many competitive advantages afforded them by evolving changes in climate and human lifestyle, including the following: wider geographic distributions and longer active breeding and blood-feeding seasons as a result of increases in global mean temperatures and humidity; greater abundance of wild animal reservoir hosts no longer effectively controlled, especially deer, rabbits, and rodents; greater residential construction in recently cleared woodlands adjacent to pastures and yards frequented by wildlife, domestic animals, and humans; and more vacation and leisure-time activities enjoyed by humans and their pets during prolonged tick host-questing and blood-feeding seasons from earlier springs through later falls and milder winters.[1] In short, ticks of all ages and both genders may remain infectious for generations without having to reacquire infections from host reservoirs and environmental and behavioral changes now place humans and ticks together outdoors for longer periods for tick breeding, blood-feeding, and infectious disease transmission.

## TICK BIOLOGY, BEHAVIOR, AND TAXONOMY

With the exception of toothed hypostomes for blood-feeding and clawless palps, adult ticks resemble large mites with eight legs and disk-shaped bodies.[2] There are four stages in the tick life cycle—egg, six-legged larva, nymph, and adult. Ticks are classified into three families: the Ixodidae, or hard ticks; the Argasidae, or soft ticks; and the Nuttalliellidae, a much lesser known family, with characteristics of both hard and soft ticks.[2] Ixodid ticks have a hard dorsal plate or scutum, which is absent in the soft-bodied, argasid ticks. Ixodid ticks also exhibit more sexual dimorphism than argasid ticks, with both genders looking alike. However, all blood-fed ticks, especially females, are capable of enormous expansion and engorged ixodid females are often confused with engorged argasid females. Although ticks from all families may serve as disease vectors, the ixodid or hard ticks are responsible for most tick-borne diseases in the United States.

Ixodid ticks have mouth parts that are attached anteriorly and visible dorsally. They live in open exposed environments, such as woodlands, grasslands, meadows, and scrub brush areas. Argasid ticks are leathery and have subterminally attached mouth parts that are not visible dorsally. Argasid ticks prefer to live in more sheltered environments, including animal nests, caves, crevices, woodpiles, and uninhabited rural cabins. All ticks feed by cutting a small hole in the host's epidermis with their chelicerae and then inserting their hypostomes into the cut, with blood flow maintained by salivary anticoagulants.[2] Ticks are attracted to warm-blooded hosts by vibration and exhaled carbon dioxide. Ixodid ticks actually "quest" for hosts by climbing onto vegetation with their forelegs outstretched; waiting to embrace passing hosts (Fig. 298-1). Ticks spend relatively short periods of their lives mating and blood-feeding on hosts: soft ticks feed rapidly for hours and then drop off, whereas hard ticks blood-feed for days (6 to 12) before dropping off for egg laying.

**KEYWORDS**

anaplasmosis; argasid ticks; *Babesia;* babesiosis; *Borrelia;* borreliosis; ehrlichiosis; *Francisella;* ixodid ticks; Lyme disease; rickettsialpox; Rocky Mountain spotted fever; tick paralysis; tick-borne coltiviruses; tick-borne encephalitis viruses; tick-borne hemorrhagic fever viruses; tick-borne relapsing fever viruses; tick-borne rickettsioses; ticks; tularemia

**FIGURE 298-1** ***Amblyomma americanum,*** **the lone star tick, "questing" for a host.** Shown is the dorsal view of a female lone star tick, the vector of southern tick-associated rash illness (STARI) caused by the spirochete *Borrelia lonestari.* Note the "lone star" mark in the center of the dorsal surface. *(From Centers for Disease Control and Prevention [CDC], Atlanta, GA. Public Health Image Library, image 8683.)*

**FIGURE 298-3** ***Rhipicephalus sanguineus,*** **the brown dog tick, "questing" for a host.** This is a dorsal view of a male tick, a new and unanticipated vector for Rocky Mountain spotted fever (RMSF) in addition to the historical vectors, *Dermacentor andersoni,* the Rocky Mountain wood tick, and *Dermacentor variabilis,* the American dog tick. *(From Centers for Disease Control and Prevention [CDC], Atlanta, GA. Public Health Image Library, image 7646.)*

**FIGURE 298-2** ***Borrelia burgdorferi,*** **the causative bacterium of Lyme disease.** Note the characteristic coiled spring appearance of a spirochete (peripheral blood smear, immunofluorescent stain under darkfield microscopy, ×1000). *(From Centers for Disease Control and Prevention [CDC], Atlanta, GA. Public Health Image Library. Courtesy Dr. Robert D. Gilmore.)*

## EPIDEMIOLOGY OF TICK-BORNE INFECTIOUS DISEASES

Tick-borne infectious diseases have challenged researchers and physicians since Dr. Howard T. Ricketts identified the wood tick, *Dermacentor andersoni,* as the vector of Rocky Mountain spotted fever (RMSF) in 1906 and firmly established the insect vector theory of infectious disease transmission.[3] The emergence and recognition of Lyme disease in the early 1970s in the United States, whose causative agent, the spirochete *Borrelia burgdorferi,* was not identified until 1982, sparked renewed interest in tick-borne diseases in the United States and Europe (Fig. 298-2).[4]

By the early 1990s, Lyme borreliosis had become the most common arthropod-borne infectious disease in the United States and Europe.[5] Since the 1970s, every decade now describes emerging or rediscovered tick-borne infectious disease and new vectors for previously described tick-borne diseases, such as RMSF.[6] These latest discoveries have been spawned by new immunodiagnostic technologies, especially by nucleic acid identification technologies, particularly the polymerase chain reaction (PCR) assay.

By the 1980s and 1990s, the causative agents of the ehrlichioses were stratified as newly emerging, *Rickettsia*-like species, and later (2001) were completely reorganized into separate genera, *Ehrlichia* and *Anaplasma.*[7,8] In 1997, Kirkland and colleagues described a new erythema migrans–like rash illness in North Carolina, a nonendemic region for Lyme disease, transmitted by the lone star tick, *Amblyomma americanum* (see Fig. 298-1).[9] This new borreliosis would soon be named the southern tick-associated rash illness (STARI) or Masters' disease, but its causative agent, *B. lonestari,* a new *Borrelia* species, would not be identified until 2004 (see Fig. 298-2).[10,11]

By 2004, ticks were recognized as the most common vectors of all arthropod-borne infectious diseases in Europe, five new spotted fever–causing rickettsiae were described, four new subspecies of the Lyme disease–causing *B. burgdorferi* complex were identified, a new relapsing fever *Borrelia* species was isolated, and anaplasmosis was exported to Europe from the United States.[12] In a seemingly unending era of new discoveries in tick-transmitted diseases, another new and unanticipated vector for RMSF, *Rhipicephalus sanguineus,* the brown dog tick, was identified in the United States in 2005 (Fig. 298-3).[13]

In 2011, the first human cases of relapsing fever caused by tick-transmitted *Borrelia miyamotoi* were reported from Russia, and by 2013, 1% to 3% of surveyed residents of New England states where Lyme disease is endemic were seropositive for prior *B. miyamotoi* infection.[14] In 2009, a new pathogenic *Ehrlichia* species in addition to endemic *Ehrlichia chaffeensis* and *Ehrlichia ewingii* was identified in four febrile patients in Minnesota or Wisconsin and presumed to be related to *Ehrlichia muris.*[15]

Because most tick-borne diseases are caused by obligate intracellular organisms, many of which infect erythrocytes, granulocytes, or vascular endothelial lining cells, many tick-borne infections may also be transmitted congenitally (e.g., babesiosis) and by blood product transfusions and organ transplants. Blood product–transmitted infections have now been described for the tick-borne rickettsial diseases (including Q fever), babesiosis, and ehrlichiosis. In 2008, the Centers for Disease Control and Prevention (CDC) reported the first case in which transfusion transmission of *Anaplasma phagocytophilum,* the tick-borne causative agent of anaplasmosis (formerly, human granulocytic ehrlichiosis [HGE]) was confirmed microscopically and serologically by testing of both the recipient and donor.[16]

Today, the seroprevalence of tick-borne diseases is increasing significantly among blood and organ donors in the United States,

combined tick-transmitted coinfections have been described in regional U.S. populations, and an unexplained increase in the virulence of tick-borne infectious diseases has been described in the United States (RMSF), Europe, and North Africa (Mediterranean spotted fever) and Australia (Queensland tick typhus). Several tick-borne infectious diseases have now been reclassified by the CDC as potential biologic terrorism agents, including the following: *Francisella tularensis* (tularemia), a category A agent (highly likely microorganism to be weaponized); *Coxiella burnetii* (Q fever), a category B agent (less likely to be weaponized); and the tick-borne encephalitis and hemorrhagic fever viruses, category C agents (least likely to be weaponized). In the future, the tick-transmitted infectious diseases will increase in prevalence over wider distributions at higher altitudes in a warmer world. Unexpected tick vectors of emerging infections caused by obligate intracellular microorganisms will continue to be discovered as people spend more leisure times outdoors in temperate climates in tick-preferred ecosystems.

## TICK-BORNE BACTERIAL INFECTIONS

### Spirochetal Infections (Borrelioses)

The borrelioses are a large group of tick-borne spirochetal diseases caused by several species of *Borrelia,* with unique geographic distributions, tick vectors, and host animal reservoirs (Table 298-1). The borrelioses are stratified into three separate epidemiologic and clinical presentations—Lyme borreliosis, STARI, and the tick-borne relapsing fevers (Table 298-2).

Lyme borreliosis (LB) or Lyme disease is now the most common tick-borne infectious disease in the Northern Hemisphere and the most common arthropod-borne infectious disease in the United States.[5,17] In the United States, LB is caused by *Borrelia burgdorferi (sensu stricto),* first identified as a novel bacterial spirochete in 1982, and transmitted to humans by *Ixodes* spp. hard ticks in U.S. regional pockets, specifically the Northeast *(I. scapularis),* upper Midwest *(I. scapularis),* and Pacific Coast (*I. pacificus;* Fig. 298-4; see also Fig. 298-2). Although *B. burgdorferi* is the sole agent of LB in the United States and has been exported to Europe, most cases of LB in Europe and northern Asia are caused by *B. afzelii* and *B. garinii* (see Table 298-1). Collectively, the three *Borrelia* species are often referred to as *B. burgdorferi (sensu lato).* Ticks usually acquire *Borrelia* infections as larvae or nymphs by blood-feeding on small reservoir hosts, most commonly birds and rodents, and may transmit LB to humans during blood-feeding, which may go unnoticed (see Fig. 298-4). *Borrelia* organisms are further maintained in nature as infected adult *Ixodes* ticks blood-feed on larger mammals, especially deer.

Unlike argasid or soft ticks, *Ixodes* ticks prefer temperate ecotonal zones of canopied forests abutting cleared scrub or grasslands and transmit *B. burgdorferi* to humans during outdoor exposures in such habitats. Because *Borrelia* spirochetes must migrate from the tick's midgut to the salivary gland during blood-feeding, tick attachments for less than 24 hours rarely result in LB in humans.[18] After an incubation period of 1 to 2 weeks, the hallmark of spirochete transmission manifests as solitary erythema migrans, a maculopapular erythematous rash with a bull's eye pattern, at the site of tick attachment (Fig. 298-5). Erythema migrans also occurs in STARI at the site of *Amblyomma americanum* or lone star tick attachment and results from the subcutaneous centrifugal movement of the spirochetes from the bite sites to the central circulation and target organs (see Fig. 298-5).

In a meta-analysis of 53 longitudinal studies of LB in the United States and Europe, Tibbles and Edlow have reported that many patients do not recall a tick bite (74% in the United States, 36% in Europe), constitutional symptoms of low-grade fever (<39°C [102.2°F]) and headache are common but nausea and vomiting are rare, and a solitary erythema migrans lesion is the most common initial presentation of LB (81% in the United States, 88% in Europe).[19] Although deaths from LB are rare, the greatest morbidity from target organ damage in LB occurs in patients with prolonged or untreated infections, with 5% to 8% developing cardiac manifestations, 15% to 20% developing neurologic manifestations, and 40% to 60% developing chronic arthritis.[18-20] However, if LB is recognized and treated early in the erythema migrans stage, cure rates will exceed 90%, late manifestations of chronic arthritis will be avoided, and outcomes will be excellent (see Table 298-2).

**TABLE 298-1 Tick-borne Spirochetal Borrelioses**

| *BORRELIA* SPECIES | TICK-BORNE DISEASES | GEOGRAPHIC DISTRIBUTION | TICK VECTORS | WILD ANIMAL RESERVOIRS |
|---|---|---|---|---|
| *B. afzelii* | European Lyme borreliosis (LB) | Europe, Scandinavia | *Ixodes ricinus* | Mammals—deer, rodents |
| *B. burgdorferi* | American LB | North America, specifically U.S. Northeast, Midwest, Pacific Northwest; Europe | *I. scapularis* (eastern United States), *I. pacificus* (western United States) | Mammals—deer, rodents (preferred by nymphs) |
| *B. crocidurae* | North African tick-borne relapsing fever (TBRF) | North Africa, Mediterranean Basin | *Ornithodoros erraticus* | Mammals—rodents, birds |
| *B. duttonii* | East African TBRF | East, Central, and South Africa | *O. moubata* | Humans are main reservoir |
| *B. garinii* | European LB | Northern Europe, Russia, Asia | *I. ricinus* (Europe), I. *persulcatus* (Asia) | Mammals—rodents, birds |
| *B. hermsii* | American TBRF | Western United States and Canada | *O. hermsi* | Mammals—rodents, chipmunks, squirrels |
| *B. hispanica* | Hispano-African TBRF | Iberian peninsula—Spain, Portugal; northwestern Africa—Algeria, Morocco, Tunisia | *O. marocanus* | Mammals—rodents |
| *B. latyschewii* | White TBRF | Russian Caucasus regions (Tajikistan, Uzbekistan), Central Asia | *O. tartakovskyi* | Mammals—rodents |
| *B. lonestari* | Southern tick-associated rash illness (STARI) or Masters' disease | Southeastern United States from southeastern Atlantic coast west to Central Texas, Oklahoma, Missouri | *Amblyomma americanum* | Mammals—rodents, cattle, other domestic animals; some reptiles, especially lizards |
| *B. mazzottii* | Southern TBRF | Southern United States, Mexico, Central America, South America | *O. talaje* | Mammals—rodents |
| *B. miyamotoi* | Russian TBRF | Japan, Eastern Europe, northeastern United States | *O. scapularis* | Mammals—rodents |
| *B. parkeri* | Western TBRF | Southwest and south central United States, Mexico | *O. parkeri* | Mammals—rodents |
| *B. persica* | Asiatic-African TBRF | Middle East (Egypt, Iran), Central Asia, Western China, Northern India | *O. tholozani* | Mammals—rodents |
| *B. turicatae* | American Southwestern TBRF | Southwest and south central United States, Mexico, Central America | *O. turicata* | Mammals—rodents, armadillos, opossums, pigs, and monkeys (Panama) |
| *B. venezuelensis* | Venezuelan TBRF | Central and South America | *O. rudis* | Mammals—rodents, opossums, armadillos, monkeys (Panama, Colombia) |

**TABLE 298-2 Clinicopathophysiologic Comparison of Lyme Borreliosis, Southern Tick-Associated Rash Illness (STARI), and Tick-borne Relapsing Fever**

| INFECTIOUS DISEASE CHARACTERISTICS | LYME BORRELIOSIS | SOUTHERN TICK-ASSOCIATED RASH ILLNESS | TICK-BORNE RELAPSING FEVER |
|---|---|---|---|
| Microbial agents | *Borrelia burgdorferi* (United States, Europe), *B. afzelii* (Europe, Asia), *B. garinii* (Europe, Asia) | *Borrelia lonestari*—has now been isolated from a skin biopsy of patient with STARI and cultured in vitro from infected *Amblyomma americanum* ticks | Many *Ornithodoros* species of soft ticks (see Table 298-1) |
| Preferred tick vectors | *Ixodes* spp. hard ticks | *A. americanum* | *Ornithodoros* spp. soft ticks |
| Preferred animal reservoirs | Rodents—nymphs; deer, birds—adults | Lizards | Rodents—nymphs; humans—*B. duttonii* only; deer, birds—adults |
| Endemicity | Highly endemic in United States and Europe | Southeastern United States | Highly endemic among vector-populated regions worldwide |
| Fever ≥39°C (102.2°F) | Very uncommon | Absent; low-grade fever may occur rarely | Present in relapsing episodes 1-3 days each; may reach 43°C (109.4°F) |
| Relapsing fevers | Not present | Not present | Present |
| Erythema migrans, or other rash | Present as annular or target-like maculopapular rash (mean diameter, 7 cm); more common on extremities | Present and mimics that of Lyme disease but with a smaller mean diameter of 4.5 cm; more common on trunk | Absent |
| Arthritis | May be present in untreated (up to 60%) late, or "chronic" infections, manifesting as oligoarthritis | Arthralgias, myalgias, and neck stiffness may occur less commonly than with Lyme disease; no chronic arthritic complications | Neck stiffness, arthralgias, myalgias common, not arthritis |
| Neurologic manifestations | May be present in up to 15% of cases; includes headache, cranial nerve (CN) VII neuritis—Bell's palsy | Dizziness, headache, memory loss, concentration difficulty may occur; no chronic neurologic complications | Common—meningitis, meningoencephalitis; neuritis of CN VII—Bell's palsy; CN VIII—deafness, myelitis, radiculopathy |
| Other presenting clinical manifestations | Myocarditis, conduction defects in late-onset and "chronic" cases in up to 8% of cases | Regional lymphadenopathy may occur; chronic complications have not been described | Splenomegaly in most, hepatomegaly in 10% of cases; myocarditis manifesting as prolonged QTc interval |
| Best screening serodiagnostics | Giemsa- or Wright-stained peripheral smear, phase-contrast, or darkfield microscopy for spirochetes; ELISA, IFA | Epidemiologic and clinical presentation; no screening serodiagnostics available at present; Lyme disease ruled out by ELISA, IFA, Western immunoblot | Giemsa- or Wright-stained peripheral smear, phase-contrast, or darkfield microscopy for spirochetes; ELISA, IFA |
| Best confirmatory diagnostics | In vitro cultivation, Western immunoblot, PCR assay | PCR assay on skin biopsy; in vitro cultivation | In vitro cultivation (not recommended; Biosafety Level 3 laboratory required), rodent inoculation, PCR assay |
| Recommended antibiotic therapy | Doxycycline, 100 mg PO bid, or amoxicillin, 500 mg PO tid, for 14-21 days; parenteral therapy for CNS involvement | Doxycycline, 100 mg PO bid, or amoxicillin, 500 mg PO tid, for 14-21 days | Tetracycline, 500 mg or 12.5 mg/kg PO qid, or doxycycline, 100 mg PO bid, or erythromycin, 500 mg or 12.5 mg/kg PO qid for 10 days; parenteral therapy with penicillin G or ceftriaxone recommended for CNS involvement |

CNS, central nervous system; ELISA, enzyme-linked immunosorbent assay; IFA, immunofluorescence assay; PCR, polymerase chain reaction.

**FIGURE 298-4** ***Ixodes scapularis.*** Shown are the black-legged deer tick, adult female and nymphs. These are arthropod vectors of babesiosis and Lyme disease, especially nymphs, whose bites are most often unnoticed. *(From Centers for Disease Control and Prevention [CDC], Atlanta, GA. Public Health Image Library, image 1205.)*

In LB-untreated patients, recurrent attacks of chronic arthritis were formerly referred to as chronic LB.[20,21] Later, as all patients in whom LB was diagnosed were treated with antibiotics, synovitis persisting for months to years after initial treatment was renamed "antibiotic-refractory arthritis."[21] Antibiotic-refractory arthritis was attributed to a combination of retained spirochetal antigens and postinfectious autoimmune reactions.[21] However, recent investigations by Nadelman and co-workers have now dispelled the former concept of chronic persisting *B. burgdorferi* infections and have demonstrated that repeat episodes of pathognomonic erythema migrans in appropriately treated LB patients were due to reinfections and not to recurrences.[22,23]

The Jarisch-Herxheimer reaction (JHR), an inflammatory cytokine-mediated reaction to dying spirochetes with a worsening of presenting symptoms, vasodilatation, and myocardial dysfunction, may occur during antibiotic treatment for LB but is more common after antibiotic therapy for tick-borne relapsing fevers.[18,24] There have been no reported deaths from JHR during antibiotic therapy for LB, and the very rare case fatalities from LB have been attributed to cardiac conduction abnormalities from myocarditis in untreated cases.[18]

First recognized in 1998, STARI manifests initially as erythema migrans, as in LB, but occurs in regions in which *B. burgdorferi* is not endemic and follows the prolonged attachment of blood-feeding lone star ticks, *Amblyomma americanum*, more abundant in the southeastern and south central United States (see Figs. 298-1 and 298-5).[9,18] Patients who are bitten by lone star ticks may develop LB-like erythema migrans rashes and occasionally develop milder constitutional symptoms than in LB, including fever, headache, fatigue, and generalized myalgias. However, unlike LB, STARI is not a reportable infectious disease and has no diagnostic serologic tests, such as enzyme-linked immunoassays (ELISAs), immunofluorescent assays (IFAs), and Western immunoblot assays. In addition, a microbiologic analysis of skin biopsy specimens obtained from the rashes of 30 patients in Missouri with clinical diagnoses of STARI failed to detect *B. lonestari*, suggesting that STARI could be caused by other pathogens.[25] Because some patients have recovered from STARI without antibiotic treatment

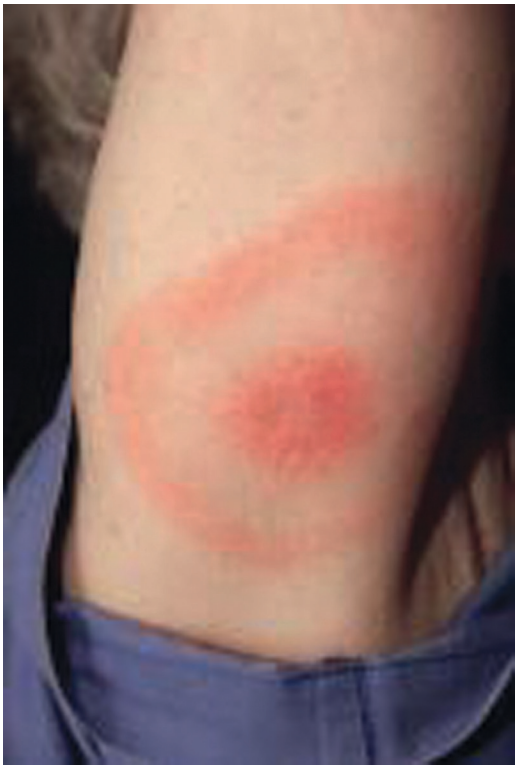

**FIGURE 298-5 Erythema migrans.** Shown is the pathognomonic "bull's eye" rash at the bite sites of *Borrelia burgdorferi*– or *B. lonestari*–infected ixodid ticks, tick vectors of Lyme disease and southern tick-associated rash illness (STARI), respectively, in endemic regions of the United States. *(From Centers for Disease Control and Prevention [CDC], Atlanta, GA. Public Health Image Library, image 9875.)*

and there have been no long-term sequelae reported in STARI cases, some have questioned whether antibiotic therapy is indicated in STARI. Because distinguishing STARI from LB may be difficult, Wormser and co-workers have recommended that the differential diagnosis rely on a combination of regional exposures, clinical presentations, serologic results, and potential for long-term sequelae based on their comparison of LB cases from New York and STARI cases from Missouri.[25] The investigators noted that the timing of rash onset was shorter (6 days) in STARI compared with LB (10 days) and that STARI patients were less likely to be symptomatic than LB patients.[25] In addition, the STARI rash was more often circular with central clearing than the LB rash.[25] Most authorities recommend antibiotic therapy for STARI with oral doxycycline or amoxicillin following the same regimen as for LB to cover any missed diagnoses of LB with potential for chronic arthritic and cardiac sequelae (see Table 298-2).[25]

The tick-borne relapsing fevers (TBRFs) comprise a worldwide group of serious bacterial infections by *Borrelia* spirochetes after brief, painless, and usually unnoticed bites by *Ornithodoros* spp. argasid or soft ticks. These ticks prefer indoor living—in cabins, caves, and crevices—and quickly abandon warm-blooded rodent hosts for egg laying (see Table 298-1).[24,25] Unlike the ixodid ticks, *Ornithodoros* ticks feed very briefly, usually for less than 30 minutes, and at night.[24,26] Adults can live for as long as 15 to 20 years and survive without blood meals for several years. Transovarian transmission of the TBRF spirochetes occurs commonly among all species and, unlike LB-causing *Borrelia* species, TBRF spirochetes are already present in the salivary glands at the onset of blood-feeding and do not need time to migrate from the gut to the mouth parts. The wild animal host reservoirs of TBRF are maintained in birds and several mammals, most commonly rodents. The bite of a TBRF-infected tick is painless, and the bite site is marked after a few days by a small red to violaceous papule with a central eschar.[18,26] One spirochete is sufficient to initiate TBRF, and the infection rate after a single bite by an infected tick is more than 50%. The incubation period to onset of the first febrile episode is 3 to 12 days.

TBRF is defined clinically by the sudden onset of two or more episodes of high fever (>39°C [102.2°F]) spaced by afebrile periods of 4 to 14 days, with the first febrile episode lasting 3 to 6 days and the relapsing episodes lasting 1 to 3 days each.[18,24,26] The first episode ends with a 15- to 30-minute "crisis" with tachycardia, hypertension, hyperpyrexia (as high as 43°C [109.4°F]), and rigors, followed by diaphoresis and defervescence.[18,26,27] All febrile episodes are accompanied by nausea, headache, neck stiffness, myalgia, and arthralgia. The relapsing febrile episodes result from the growth of new spirochete populations in the blood to replace those killed by macrophages and cytokines. Most patients have splenomegaly, 10% will have hepatomegaly, and most will have elevated aminotransferase levels, unconjugated bilirubin, and prolonged prothrombin and partial thromboplastin times.[24,27] Direct neurologic involvement is more common than in LB and may include cranial nerve neuritis (especially cranial nerves VII and VIII), radiculopathy, and myelopathy. Myocarditis is also more common than in LB; may be complicated by adult respiratory distress syndrome (ARDS), pulmonary edema, and cardiomegaly; and is often fatal. Diagnostic and treatment strategies for TBRF are outlined in Table 298-2.

The JHR is much more common, although rarely fatal, during treatment of TBRF than during treatment of LB and occurs in 30% to 40% of patients with TBRF.[18] At present, no prophylactic strategies to reduce the severity of the JHR have proved beneficial or have been adequately tested in multiple clinical trials, including therapy with antipyretics, corticosteroids, or naloxone. Treatment with penicillin instead of tetracycline has a slightly lower risk for causing JHR during antibiotic therapy for TBRF.

## Spotted Fever Group Rickettsial Infections

The family Rickettsiaceae contains two genera, the spotted fever–causing genus *Rickettsia* and the typhus-causing genus *Orientia* (see Chapters 188 and 193). The rickettsiae may be further stratified clinically into the tick-borne spotted fever group and mouse mite–transmitted rickettsialpox caused by *Rickettsia akari* (see Chapter 189). The rickettsiae are obligate intracellular, gram-negative bacteria that thrive in ixodid tick salivary glands and are transmitted during blood-feeding. Once injected into the host, rickettsiae are initially distributed regionally via lymphatics, with some species causing marked regional lymphadenopathy (e.g., *Rickettsia slovaca*). Within 2 to 14 days (mean, 7 days), rickettsiae are disseminated hematogenously to vascular endothelial lining cells of target organs, including the central nervous system (CNS), lungs, and myocardium. Rickettsiae gain entry into host endothelial cells in a Trojan horse–like manner by using their outer membrane proteins (OmpA and OmpB) to stimulate endocytosis. Once within phagosomes, rickettsiae escape to enter the cytosol or nucleus for rapid replication by binary fission, safe from host immune attack. The tick-borne rickettsial diseases that cause spotted fevers (SFs) are compared in a descending order of clinical severity of infection by preferred tick vectors and wild animal reservoirs in Table 298-3.

The global epidemiology of the tick-borne SF–causing rickettsiae has dramatically evolved since the transmission cycle of RMSF was first described by Ricketts in 1906 with the following: emerging new strains and diseases (*R. slovaca*–associated lymphadenopathy); greater understanding of the highly conserved genome of several related species (*R. africae–R. parkeri* and the *R. conorii* subspecies); wider geographic distribution and greater virulence of existing strains (*R. rickettsii, R. conorii* subspecies, *R. australis*); unanticipated new tick vectors for some SFs (*Rhipicephalus sanguineus* for RMSF in the United States); cluster outbreaks of tick-borne rickettsioses in returning travelers (*R. africae* causing African tick-bite fever); and regional clusters and epidemic cycles of more severe SFs worldwide (RMSF in the United States, Mediterranean SF [MSF] in Europe, and Queensland tick typhus [QTT] in Australia).* The reasons for such changes in rickettsial SF epidemiology are unclear and may include warming temperatures and increasing humidity, more frequent drought-rain cycles, residential development in preferred tick ecosystems, more competent tick vectors given competitive advantages by environmental and

*References 3, 4, 12, 28-30, 31, 32

**TABLE 298-3 Spotted Fever Group of Tick-borne Rickettsioses**

| *RICKETTSIA* SPECIES | TICK-BORNE DISEASES | GEOGRAPHIC DISTRIBUTION | TICK VECTORS | WILD ANIMAL RESERVOIRS (MAMMALS) |
|---|---|---|---|---|
| *R. rickettsii* | Rocky Mountain spotted fever (SF), Brazilian SF | Continental United States, Central America (Costa Rica, Mexico, Panama), South America (Argentina, Brazil) | *Amblyomma, Dermacentor, Rhipicephalus* spp. | Ungulates, rodents |
| *R. conorii* | Boutonneuse fever, Mediterranean SF, Israeli SF, Astrakhan SF, Indian tick typhus, Kenyan tick typhus | Mediterranean Basin, Africa, Middle East, Asia | *Rhipicephalus* spp. | Ungulates, rodents |
| *R. sibirica* | North Asian tick typhus (Siberian tick typhus) | Africa (Niger, Mali, South Africa), Asia (Russia, China, Mongolia, Pakistan, Kazakhstan, Kirgizia, Tajikistan), Europe (France) | *Dermacentor, Haemaphysalis, Hyalomma* spp. | Ungulates, rodents |
| *R. japonica* | Japanese SF | Japan and China | *Haemaphysalis* spp., *Ixodes ovatus* | Ungulates, rodents |
| *R. australis* | Queensland tick typhus | Eastern Australian seaboard from Cairns, Queensland, to Gippsland, Victoria | *Ixodes* spp., especially *I. holocyclus* | Rodents |
| *R. honei* | Flinders Island SF | Southern Australia, Thailand | *Aponomma* spp. | Rodents |
| *R. africae* and *R. parkeri* | African tick bite fever | Sub-Saharan Africa, North America, South America, Caribbean | *Amblyomma* spp. | Rodents |
| *R. slovaca* | Tick-borne lymphadenopathy; *Dermacentor*-borne eschar, lymphadenopathy, or necrosis | Europe | *Dermacentor* spp. | Ungulates, rodents |
| *R. aeschlimannii* | Not named at present | Southern Europe, Africa | *Hyalomma* spp. | Ungulates, rodents |

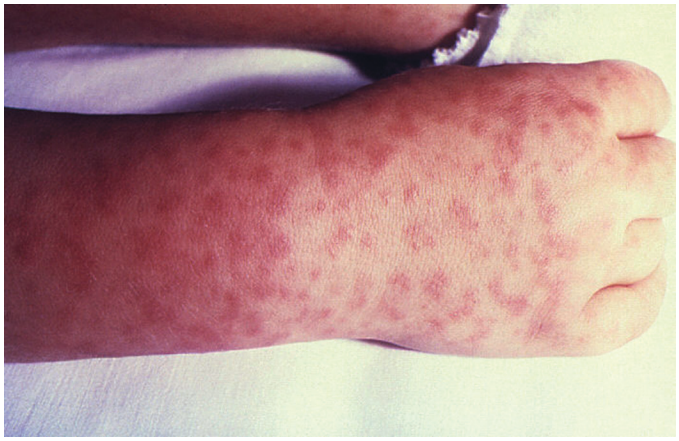

**FIGURE 298-6 Characteristic initial distal maculopapular-petechial rash of Rocky Mountain spotted fever.** This is on the dorsal aspect of a child's right hand and wrist. *(From Centers for Disease Control and Prevention [CDC], Atlanta, GA. Public Health Image Library, image 1962.)*

genetic changes, more frequent contact between ticks and humans outdoors, and international trade and travel distributing tick vectors and their preferred animal hosts quickly and widely.

The tick-borne SF rickettsioses share many common features in clinical presentations, including incubation periods of approximately 1 week, flulike prodromes of fever, headache, myalgia, nausea, vomiting, and abdominal pain (that may mimic acute appendicitis in RMSF), spotty rashes within 3 to 5 days of fever onset, and necrotic eschars at tick-bite sites (Fig. 298-6). Some SF rickettsial diseases may be "spotless," including RMSF in 10% to 15% of cases, complicating early differential diagnosis.[30] The tick-borne rickettsial infections that can cause spotty rashes include *R. rickettsii* (RMSF), *R. conorii* (MSF), *R. australis* (QTT), and *R. africae–R. parkeri* (African–North American tick bite fever) in about 50% of cases (see Fig. 298-6).[26,27] The tick-borne rickettsial infections that are associated with one or more necrotic eschars at tick-bite sites include *R. conorii, R. australis, R. africae–R. parkeri, R. japonica, R. slovaca, R. aeschlimannii,* and *R. honei.* The SF rickettsioses may vary in severity from causing multisystem organ failure (RMSF, MSF) to painful lymphadenopathy *(R. africae–R. parkeri, R. slovaca)* to mild to subclinical disease *(R. aeschlimannii).*[28,30,31]

After an average incubation period of 1 week, RMSF starts with a flulike, febrile prodrome followed by a characteristic maculopapular evolving to petechial rash in 85% to 90% of cases in 3 to 5 days.[28] The pathognomonic rash starts distally on the wrists and ankles and then spreads centripetally up the limbs (see Fig. 298-6). The pathophysiologic mechanisms of petechial rashes and target organ system damage (CNS, lungs, heart) in the SF rickettsioses include vascular endothelial cell damage by microbial replication, vascular inflammation (vasculitis), and increased widespread vascular permeability, which may result in hypovolemic shock, oliguric prerenal failure from acute tubular necrosis, cerebral edema, and noncardiogenic pulmonary edema. Distal, digital skin necrosis may occur in severe cases of RMSF and QTT from hypoperfusion.[32] Cardiac vasculitis may manifest as myocarditis with intraventricular conduction blocks. Aside from petechial rash and thrombocytopenia, other hemorrhagic manifestations in RMSF and other SFs are rare. CNS complications in RMSF and other severe SF infections may include ataxia, photophobia, transient deafness, focal neurologic deficits, meningismus, meningoencephalitis, seizures, and coma. Pulmonary complications may include cough, alveolar infiltrates, interstitial pneumonitis, pleural effusions, pulmonary edema, and ARDS.[28,30-32]

Initially, MSF caused by *R. conorii* was thought to be a more benign disease than RMSF. In 1981, severe cases of MSF with multiple eschars and multisystem disease similar to RMSF with CNS, renal, and pulmonary complications were first reported and now appear to be increasing across Europe.[30] In a 1997 outbreak of MSF in Portugal, case-fatality rates (CFRs) of 32% were recorded and exceeded those of untreated RMSF of 23%.[30] QTT, African tick bite fever (ATBF), and *R. slovaca*–associated lymphadenopathy are generally milder diseases than RMSF and MSF. However, severe cases of QTT with RMSF-like complications, including renal insufficiency and pulmonary infiltrates, were recently reported from Australia.[32]

Although ATBF caused by *R. africae,* a similar tick-bite fever in North America caused by *R. parkeri,* and *R. slovaca* infections may all cause multiple necrotic eschars and painful regional lymphadenopathy, these SF infections are often spotless (≥50%) and follow typical rickettsial SF prodromes.[31,32] A history of tick bites, eschars, and painful regional lymphadenopathy helps to establish the correct diagnosis, especially in the absence of adequate diagnostic laboratory services. The precise laboratory diagnosis of tick-borne rickettsial SFs may be established by microbiologic isolation of the causative organisms from skin biopsy specimens or blood cultures, nonspecific immunofluorescent antibody tests that cross react with many SF antigens, other immunocytologic techniques to demonstrate intracellular rickettsiae, and PCR assay to identify and speciate rickettsial DNA or RNA.

Antibiotic treatment mainstays for the tick-borne rickettsial SFs remain the tetracyclines for most cases and chloramphenicol for severe multisystem disease and during pregnancy.[28] Although the quinolones, azithromycin, and clarithromycin may be as effective as tetracyclines and chloramphenicol for rapidly managing some SFs, they are not recommended for initial therapy at this time. Although short, 1- to 2-day courses of doxycycline have been reported to be as successful as 10-day courses in some SF infections (e.g., MSF), such treatment strategies have not been tested in randomized controlled trials in other SF infections and are also not recommended at this time. Most authorities now recommend that tetracycline, chloramphenicol, or ciprofloxacin for tetracycline-allergic patients be continued for a minimum or 7 days or until the patient has been afebrile for at least 48 hours and is improving clinically.

## Q Fever

Q (query) fever was first described in Australia in 1935, and its causative organism, *Coxiella burnetii,* was isolated shortly thereafter.[33] *C. burnetii* is a gram-negative, intracellular, spore-forming bacterium that is the sole species of its genus. *C. burnetii* is genetically related to *Legionella pneumophila* and, like *L. pneumophila, C. burnetii* is usually transmitted to humans by inhalation of contaminated aerosols. Q fever is a zoonosis with worldwide distribution and extensive domestic animal (cattle, sheep, goats, cats, dogs), wild animal (birds, rabbits, reptiles), and arthropod (ticks) reservoirs. In most cases, humans are not infected by tick bites but by inhaling spores or bacteria in aerosols contaminated with infectious particles in dried animal feces, milk, or products of conception.[33,34] Q fever may also be transmitted by ingestion of contaminated milk, by vertical transmission from mother to fetus, by contaminated blood product transfusion, and even percutaneously by crushing infected ticks near breaks in the skin barrier.

*C. burnetii* is reactivated during pregnancy and multiplies extensively in the placenta, exposing abattoir workers, veterinarians, researchers (especially those working with parturient sheep), and domestic pet owners (especially of cats) to highly infectious aerosols during delivery.[33,34] Recently, several cases of Q fever were reported among U.S. military personnel deployed to Iraq and Afghanistan and in travelers returning from Asia, Latin America, and sub-Saharan Africa.[34,35] *C. burnetii* has long been considered a potential bioterrorism weapon for several reasons, including its environmental stability, spore-forming capability, ease of aerosolized dispersal, and high pathogenicity, with an ability to initiate infection with a single microorganism.

After an average 2-week incubation period (range, 2 to 29 days), Q fever may manifest as a wide variety of illnesses in humans, including the following: acute Q fever, a self-limited febrile illness with severe headache, retro-orbital pain, and nonproductive cough; Q fever pneumonia with consolidated opacities, pleural effusions, and hilar lymphadenopathy on chest radiographs; Q fever granulomatous hepatitis, usually after ingestion of contaminated milk; CNS Q fever with protean manifestations ranging from aseptic meningoencephalitis and transient behavioral and sensory disturbances to cranial nerve palsies and hemifacial pain mimicking trigeminal neuralgia; and chronic Q fever endocarditis, especially in predisposed patients with congenital valvulopathies, prosthetic heart valves, aortic aneurysms, or vascular grafts.[33,34,35] Patients who are immunocompromised by pregnancy, congenital immunodeficiency disorders, cancer, HIV infection/AIDS, organ transplant antirejection therapy, renal dialysis, or prolonged corticosteroid therapy are at greater risk for acquiring more severe and chronic Q fever infections.[35]

Because the isolation of *C. burnetii* requires Biosafety Level 3, most diagnostic laboratory strategies for Q fever rely on microscopic detection on Giemsa-stained smears of blood or sputum or tissue biopsies (liver, excised heart valves), on antibody detection by immunofluorescent assays, or on DNA detection by PCR assay.[33,35] The prognosis is usually excellent in the acute Q fever illnesses, and mortality is rare after appropriate antibiotic therapy with tetracyclines (doxycycline is preferred—100 mg PO twice daily for 14 days) or fluoroquinolones. Chronic Q fever endocarditis will require prolonged treatment with two antibiotics, either rifampin (300 mg PO twice daily) and ciprofloxacin (750 mg PO twice daily) for 3 years or doxycycline (100 mg PO twice daily) and hydroxychloroquine (200 mg PO three times daily) for at least 18 months. Such combined therapies will require close monitoring for drug toxicities, especially hepatotoxicity from rifampin and oculotoxicity from hydroxychloroquine. In addition, all patients with Q fever endocarditis should undergo screening transesophageal echocardiography for underlying valvulopathies. Chronically infected heart valves and vascular grafts will require surgical replacement.

## Tularemia

Tularemia, also known as rabbit fever or deer fly fever, was first described as a zoonosis in squirrels in Tulare County, California, in 1911. Its causative agent, *Francisella tularensis,* was later identified as a gram-negative coccobacillus by Dr. Edward Francis during an investigation of deer fly fever in Utah in 1921.[36] Tularemia occurs in regional pockets worldwide, has a very large wild and domestic animal reservoir, and is seasonally transmitted to humans by ixodid tick and deer fly bites and by contact with infected animals, especially rabbits and muskrats. The primary tick vector of tularemia in the United States is the American dog tick, *Dermacentor variabilis* (Fig. 298-7). Tick-transmitted tularemia is most commonly reported during the spring and summer (May to August) worldwide. Tularemia transmitted through contact with an infected animal occurs more often during the fall through hunting and trapping seasons, especially among male hunters who field-clean infected animal carcasses. *F. tularensis* is an extremely stable microorganism in nature, surviving in soil, water, and animal carcasses for months to years. In addition to fecal or vomit contamination of tick bites and direct inoculation of intact skin or mucosal surfaces when crushing ticks or skinning animals, tularemia may be transmitted by ingesting raw or undercooked infected game or bush meats, drinking contaminated water, or inhaling aerosolized microorganisms.[37-39]

In 2000, a cluster outbreak of primary pneumonic tularemia in 11 patients (with one fatality) was reported from Martha's Vineyard, Massachusetts.[40] A case-control investigation of the outbreak implicated aerosolized exposure to *F. tularensis* during summertime brush cutting and lawn mowing as significant (odds ratio [OR], 9.2; 95% confidence interval [CI], 1.6 to 68.0) risk factors for pneumonic tularemia.[40] Concerns about inhalation transmission and potential biologic weaponization of *F. tularensis* led to the reinstatement of tularemia as a nationally notifiable infectious disease in 2000.[37,38] The CDC reported a total of 1368 cases of tularemia from 44 states from 1990 to 2000 (period prevalence, 124 cases/yr; range, 86 to 93 cases/yr), with most cases occurring in males during May to August in regional pockets,

**FIGURE 298-7 "Questing" female American dog tick, *Dermacentor variabilis.*** This is a vector of tick paralysis in the southeastern United States and Pacific Northwest and a vector of Rocky Mountain spotted fever in addition to the Rocky Mountain wood tick, *Dermacentor andersoni,* in the western United States. *(From Centers for Disease Control and Prevention [CDC], Atlanta, GA. Public Health Image Library, image 170.)*

**TABLE 298-4 Clinical Classification of Tularemia Based on the Portal of Entry**

| CLINICAL CLASSIFICATION OF TULAREMIA CASES | CASE DEFINITION BY CLINICAL PRESENTATION | PORTALS OF ENTRY OF *FRANCISELLA TULARENSIS* | CASE FREQUENCY, UNITED STATES (%) |
|---|---|---|---|
| Ulceroglandular | Malaise, fever, bite eschars or ulcers, painful regional lymphadenopathy | Tick or deer fly bite, or direct inoculation across intact dermis | 80 |
| Glandular | Malaise, fever, suppurative lymphadenopathy | Direct inoculation across intact dermis | 15 |
| Oropharyngeal | Malaise, fever, sore throat, dysphagia, painful cervical lymphadenopathy | Ingestion of raw or undercooked infected game or bush meats | <5 |
| Oculoglandular | Malaise, fever, ocular infection, regional facial lymphadenopathy | Ocular inoculation of infectious fluids or animal danders or autoinoculation from bite eschar or ulcers | 1 |
| Typhoidal | Malaise, fever, abdominal pain, mesenteric lymphadenopathy; mimics typhoid fever | Ingestion of contaminated water | Rare |
| Pneumonic | Malaise, fever, pneumonia with multiple ill-defined infiltrates, hilar lymphadenopathy; mimics inhalation anthrax | Inhalation of contaminated aerosols, aerosolized bioweapon exposures, or hematogenous spreading from glandular or typhoidal infections | Rare, except on Martha's Vineyard after aerosolized exposures during mechanized bush trimming and lawn mowing |

including Arkansas and Missouri, eastern Oklahoma and Kansas, southern Montana and South Dakota, and Martha's Vineyard.[37]

There are two biovars of *F. tularensis,* with biovar A (*F. tularensis* biogroup *tularensis*) causing 60% to 90% of tularemia cases in North America and biovar B (*F. tularensis* biogroup *palearctica*) causing a milder disease throughout Europe and Asia.[38,39,41] The presenting clinical manifestations of infection depend on the virulence of the biovars (A > B), route of entry of microorganisms, multisystem infections, and immunocompetence of infected hosts.

The portal of entry of *F. tularensis* has historically been used to classify the clinical manifestations of tularemia, with untreated pneumonic tularemia having the highest CFRs of 30% to 60% (Table 298-4).[37-39,40,41] The differential diagnosis of ulceroglandular tularemia, the most common presentation, is extensive and includes other arthropod bites, bacterial and viral infections, and fungal diseases capable of causing skin ulcers with painful regional lymphadenopathy. Diagnostic strategies for tularemia include the following: microscopic identification or culture in Biosafety Level 3 facilities of microorganisms from blood, sputum, gastric lavage fluid, lung biopsy, or lymph node aspirates (sensitivity, 10% to 25%); acute and convalescent serology comparing antibody titers (sensitivity, >85%); direct immunofluorescent antibody testing; and antigen detection by PCR assay (sensitivity, 50% to 73%). Frequently accompanying laboratory abnormalities in tularemia include significant elevations in the erythrocyte sedimentation rate (ESR), significant leukocytosis (>10,000/μL), often with normal differential counts, and thrombocytosis. The recommended treatment strategies for tularemia have evolved considerably from historical treatments with painful intramuscular injections of streptomycin to oral therapy with the aminoglycosides and fluoroquinolones, which are effective in 86% of cases and may result in resolution of ulcers within 72 hours. Most cases in adults, including pneumonic tularemia, may be managed with fluoroquinolones alone (ciprofloxacin, 400 mg IV or 500 mg PO twice daily for 7 to 14 days, or levofloxacin, 500 mg IV or PO twice daily for 7 to 14 days), with aminoglycosides (gentamicin or amikacin, 3 to 5 mg/kg/day for 10 to 14 days) reserved for pediatric infections and widely disseminated systemic infections. Relapse rates are highest with oral tetracyclines, including doxycycline, and chloramphenicol, which may still be indicated for cases with CNS dissemination despite its potential for bone marrow toxicity.

## Tick-borne Ehrlichioses and Anaplasmosis

The human ehrlichioses and anaplasmosis (formerly known as human monocytic and human granulocytic ehrlichiosis, respectively) are classic examples of emerging tick-borne infectious diseases. Since 1986, four new tick-borne bacterial species have been identified and classified into a new family, Anaplasmataceae. The four genera of Anaplasmataceae comprise obligate, intracellular, gram-negative bacteria, closely related genetically to the family Rickettsiaceae. The Anaplasmataceae include two genera that are synergistic parasites of flatworms *(Neorickettsia sennetsu)* and filarial worms (*Wolbachia* spp.) and two

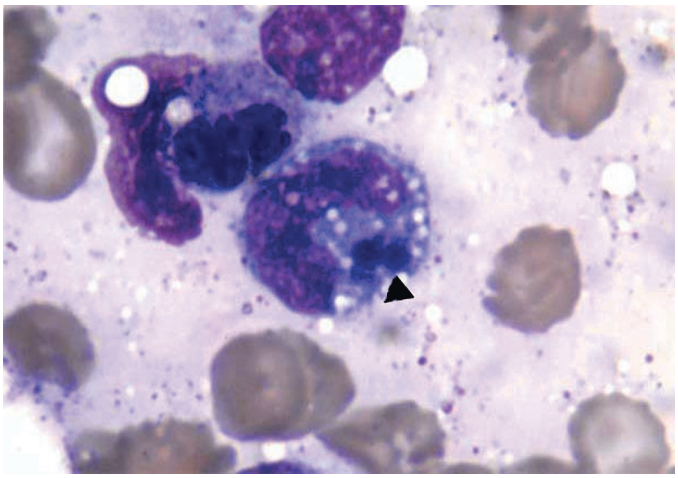

**FIGURE 298-8** ***Ehrlichia chaffeensis*** **morula** ***(arrowhead)*** **within a monocyte (peripheral blood smear, Wright stain, ×1000.)** *(From Safdar N, Love RB, Maki DG. Severe* Ehrlichia chaffeensis *infection in a lung transplant recipient: a review of ehrlichiosis in the immunocompromised patient.* Emerg Infect Dis. *2002;8:320-323.)*

genera that are tick-borne bacterial infections of many mammals, including humans, *Ehrlichia* and *Anaplasma* (Fig. 298-8).[42,43] Like rickettsiae, the Anaplasmataceae attach to molecular ligands on phagocytic cells to gain Trojan horse–like entry into leukocytes and then trick intracellular phagosomes into releasing them into the cytosol for replication (see Fig. 298-8).[43,44]

The tick-borne Anaplasmataceae are now endemic in the United States and have preferred geographic distributions, tick vectors, and wild and domestic animal reservoirs (Table 298-5). They spread from the infected tick's gut to its salivary gland, are inoculated over 24 to 36 hours into the host's dermis, and cause subclinical (especially in children) to severe and potentially fatal infections (especially in immunocompromised adults) within 1 to 4 weeks. Because transovarian transmission in ticks has not been observed, the major reservoirs of the Anaplasmataceae in nature are wild and domestic animals.[42,43] Although the presenting clinical manifestations are similar among Anaplasmataceae infections, the potential multisystem complications and resulting CFRs from these diseases are ultimately determined by the immunocompetence of human hosts (see Table 298-5). The human Anaplasmataceae are resistant to fluoroquinolones but remain susceptible to tetracyclines, which are now recommended for children and adults. Because there are no vaccines for the tick-borne ehrlichioses and anaplasmosis, the best preventive measures are tick avoidance and control and rapid removal of blood-feeding ticks by 36 hours or less.[43,44]

**TABLE 298-5 Human Ehrlichioses and Anaplasmosis**

| | HUMAN MONOCYTOTROPIC EHRLICHIOSIS | HUMAN GRANULOCYTOTROPIC EHRLICHIOSIS (HME) | HUMAN GRANULOCYTOTROPIC ANAPLASMOSIS |
|---|---|---|---|
| Former disease nomenclature | Human monocytic ehrlichiosis | Human granulocytic ehrlichiosis | Human granulocytic ehrlichiosis |
| Causative agent(s) | *Ehrlichia chaffeensis* | *Ehrlichia ewingii, Ehrlichia cani*—one asymptomatic human case reported in Venezuela | *Anaplasma phagocytophilum* |
| Leukocyte targets | Monocytic cell phagosomes | Neutrophil phagosomes | Granulocyte-neutrophil phagosomes |
| Tick vectors | *Amblyomma americanum* (lone star ticks) | *Amblyomma americanum* (lone star ticks), *Dermacentor variabilis* (American dog ticks) | *Ixodes persulcatus* complex (American deer ticks)—*I. scapularis, I. ricinus, I. pacificus* |
| Animal reservoirs | White-tailed deer, coyotes, dogs | White-tailed deer, dogs | Rodents, deer, ruminants, horses |
| U.S. regional distribution | Southeastern and south central United States | South central United States | Northeastern United States, upper Midwest, northern California |
| U.S. regional prevalence | 2-5 cases/100,000 | Up to 10% of presumed HME cases have *E. ewingii* infections in south central United States | 50-60 cases/100,000; high seroprevalence rates in children (>20%) who have had subclinical infections |
| Seasonal occurrences | April-September, peaking in July | Spring-fall | May-July |
| Incubation periods (wk) | 1-4 | 1-4 | 1-4 |
| Modes of transmission | Tick bite, blood product transfusion | Tick bite, blood product transfusion | Tick bite, blood product transfusion, nosocomial |
| Frequently presenting clinical manifestations | Fever, malaise, headache, myalgias, rash in <40% | Same initial manifestations, but much milder, except in immunocompromised individuals | Fever, malaise, headache, myalgias; rarely rash |
| Laboratory abnormalities | Leukopenia, thrombocytopenia, transaminitis | Leukopenia, thrombocytopenia, transaminitis | More pronounced and prolonged leukopenia, thrombocytopenia, transaminitis |
| Potential complications, especially in immunocompromised individuals | Meningoencephalitis, acute renal and respiratory failure, hepatitis, myocarditis | Milder and less likely, except in patients immunocompromised by HIV/AIDS, organ transplantation, prolonged corticosteroid therapy | May be significant in immunocompromised patients with high fevers, seizures, confusion, hemorrhagic diathesis, rhabdomyolysis, shock, acute tubular necrosis, adult respiratory distress syndrome; some specific CNS complications may include eighth nerve palsy, brachial plexopathy, demyelinating polyneuropathy |
| Case-fatality rate (CFR) | 3%, higher in immunocompromised individuals | No deaths reported | 0.5%, higher CFR in immunocompromised individuals |
| Recommended confirmatory diagnostic tests | Wright-stained peripheral blood smears with characteristic intracytoplasmic morulae in monocytes, DNA detection by PCR assay, culture | Wright-stained peripheral blood smears with characteristic intracytoplasmic morulae in neutrophils, DNA detection by PCR | Wright-stained peripheral blood smears with characteristic intracytoplasmic aggregates in neutrophils, DNA detection by PCR assay, increased immunofluorescent antibodies in initial and paired serum samples |
| Current antibiotic resistance | Fluoroquinolones | Fluoroquinolones | Fluoroquinolones |
| Currently recommended antibiotic therapy, adults | Doxycycline, 100 mg PO bid, or tetracycline, 250-500 mg PO qid, for minimum of 3 days after defervescence to maximum of 14-21 days | Doxycycline, 100 mg PO bid, or tetracycline, 250-500 mg PO qid, for minimum of 3 days after defervescence to maximum of 14-21 days | Doxycycline, 100 mg PO bid, or tetracycline, 250-500 mg PO qid for minimum of 3 days after defervescence to maximum of 14-21 days |
| Currently recommended antibiotic therapy, children | Doxycycline, 4.4 mg/kg PO bid, or tetracycline, 25-50 mg/kg PO qid, for minimum of 3 days after defervescence to maximum of 14-21 days | Doxycycline, 4.4 mg/kg PO bid, or tetracycline, 25-50 mg/kg PO qid, for minimum of 3 days after defervescence to maximum of 14-21 days | Doxycycline, 4.4 mg/kg PO bid, or tetracycline, 25-50 mg/kg PO qid, for minimum of 3 days after defervescence to maximum of 14-21 days |

CNS, central nervous system; HIV/AIDS, human immunodeficiency virus infection/acquired immunodeficiency syndrome; PCR, polymerase chain reaction.

## TICK-BORNE PROTOZOAL INFECTIONS

### Babesial Infections

Babesiosis is a tick-borne, malaria-like zoonosis that usually causes subclinical infections with prolonged parasitemias in humans and can be transmitted vertically in utero and horizontally by blood product transfusion.[44-48] Babesiosis was initially described in cattle with red water (hemoglobinuric) fever in 1888, when Victor Babes observed inclusions within bovine erythrocytes. Theobald Smith later identified the causative agent of bovine red water fever in 1893 as *Babesia bigemina,* accurately described the parasite's life cycle, and demonstrated for the first time the arthropod-borne transmission of an infectious disease to a mammal. Although more than 100 species of *Babesia* have now been identified as zoonoses in domestic and wild mammals, only a few species can cause babesiosis in humans, a disease characterized by fever, intravascular hemolysis, and hemoglobinuria (Table 298-6). In severe cases, usually in elderly, immunocompromised, or splenectomized human hosts, massive hemoglobinuria may be associated with severe anemia, jaundice, acute renal failure, and increased CFRs. Babesiosis is now reemerging as an arthropod-borne parasitic disease, as confirmed by increasing numbers of reported cases in the northeast United States and increasing seroprevalence rates there and in California.[45-47]

Human babesiosis may be divided into two epidemiologic and clinical patterns based on the causative *Babesia* species, their regional endemicity, and the immunocompetence of their human dead-end hosts (see Table 298-6). The first pattern is caused by *Babesia divergens* and related species or subspecies and occurs in immunocompromised, and often splenectomized, human hosts. It includes *B. divergens* babesiosis, first in Eastern and now in Western Europe, a *B. divergens*–like babesiosis in the Midwest caused by a *Babesia* species designated MO-1, and a babesiosis along the Pacific Coast caused by *B. divergens*–like species designated as WA-1 and as CA types (e.g., CA-1, CA-2).[44-48]

**TABLE 298-6 Causal Agents and Clinical Manifestations of Babesiosis**

| *BABESIA* SPECIES | GEOGRAPHIC DISTRIBUTION | TICK VECTORS | ANIMAL RESERVOIRS | EPIDEMIOLOGY | CLINICAL MANIFESTATIONS |
|---|---|---|---|---|---|
| *B. divergens* | United Kingdom, Western Europe, Eastern Europe, Sweden, Russia; not reported in United States | *Ixodes ricinus* | Cattle, reindeer | Incubation 1-4 wk<br>Occurs during summer months in cattle-raising regions<br>Targets splenectomized or immunocompromised patients primarily | Fulminant course with high case-fatality rate<br>Fever, rigors, headache, myalgia, jaundice, hemoglobinuria, hemolytic anemia, acute renal failure, multiorgan failure |
| *B. microti* | Parallels the U.S. Northeast endemic regions for *Borrelia burgdorferi*, especially the islands off New York, Massachusetts, Connecticut, and Rhode Island and focal areas in Connecticut, New Jersey, Wisconsin, and Minnesota | Deer ticks: *Ixodes dammini* and *Ixodes scapularis* | White-footed mouse *(Peromyscus leucopus)* | Incubation 1-4 wk after tick bites or 4-9 wk after blood transfusions<br>Transmission primarily by nymphal ticks<br>Targets older, not necessarily immunocompromised patients—particularly severe in those immunocompromised by HIV infection, advanced age, coinfections with *B. burgdorferi*<br>Seasonality parallels tick nymph activity; 80% of cases occur May-August | Often asymptomatic in young, healthy patients<br>Self-limited influenza-like febrile illness with onset of anorexia, malaise, lethargy, followed in 1 wk by high fever, diaphoresis, myalgias; mild splenomegaly, rarely hepatomegaly<br>Later hemolysis, hemolytic anemia, thrombocytopenia, jaundice, acute renal failure, especially in the splenectomized, elderly, or the immunocompromised<br>Complications include ARDS and DIC<br>Case-fatality rate 5% |
| MO-1 (a relative or subspecies of *B. divergens*) | Rural Missouri and Kentucky | *Ixodes dentatus* (rabbit tick) | Rabbits, birds | Incubation 1-4 wk after tick bites<br>Spring to autumn seasonality<br>Targets the splenectomized, like *B. divergens* | Same as above—often asymptomatic, except in the splenectomized, who will develop high parasitemias and multiorgan failure |
| WA-1 (a relative or subspecies of *B. gibsoni*) | Rural Washington State | Ixodid ticks, including *Ixodes dentatus* | Unknown—wild canids and ungulates suspected | Incubation 1-4 wk<br>Targets the splenectomized, elderly, immunocompromised, premature infants<br>May be transmitted by blood transfusion | Same as above—often asymptomatic, except in the splenectomized, who will develop high parasitemias and multiorgan failure |
| CA-1, CA-2, etc. subspecies (relatives or subspecies of mule deer and bighorn sheep *Babesia* species) | U.S. Pacific coast, primarily rural and semirural areas of California | Ixodid ticks | Unknown—mule deer and bighorn sheep suspected | Incubation 1-4 wk<br>Targets the splenectomized, elderly, immunocompromised, and premature infants | Same as above—often asymptomatic, except in the splenectomized, who will develop high parasitemias and multiorgan failure |

ARDS, acute respiratory distress syndrome; DIC, disseminated intravascular coagulation.

The *B. divergens*–related species are maintained in tick vectors by transovarial and trans-stadial transmission of the parasites, and most infections are transmitted by diminutive and usually unidentified and unnoticed nymphal ticks.[49] The human *B. divergens*–like cases occur primarily in cattle-ranching regions during the summer months, when tick vectors are most active and the incidence of bovine red water fever is greatest. These are the more severe cases of babesiosis, with hemolytic anemia, hemoglobinuria, and renal failure, usually in splenectomized persons.

The second and more common pattern of babesiosis in the United States occurs in regional pockets on the northeast coast (New York, Massachusetts, Rhode Island, Connecticut, New Jersey, and offshore islands [Block Island, Long Island, Nantucket]) and upper Midwest (Minnesota, Wisconsin) and is caused by *Babesia microti,* a rodent *Babesia* species transmitted to humans by the same ixodid ticks (black-legged deer ticks) that transmit Lyme disease (see Fig. 298-4).[44] Thus, *B. microti* babesiosis in the United States parallels the distribution of Lyme disease and its tick vectors, occurs in clusters in the same regional pockets as Lyme disease, and may coexist with Lyme disease in an increasing number of cases.[44,45,50,51] *B. microti*–induced babesiosis occurs during the warmest months, with 80% of cases reported between May and August, when deer ticks are most active. Humans are usually infected by unnoticed bites by nymphal deer ticks from rodent reservoirs in mice, especially the white-footed mouse *(Peromyscus leucopus),* rather than deer.

Diagnostic strategies for babesiosis include the demonstration of characteristic intraerythrocytic and extraerythrocytic organisms on Giemsa-stained thin smears and subinoculation of human blood samples into hamsters for suspected *B. microti* infections or into gerbils for suspected *B. divergens*–related infections (Fig. 298-9).[44,47,48] The serologic methods, especially useful when microscopic methods fail in low parasitemias, include indirect immunofluorescent antibody testing for specific IgM antibodies in acute infections and PCR-based assays to detect *Babesia* DNA and species-specific DNA sequences.

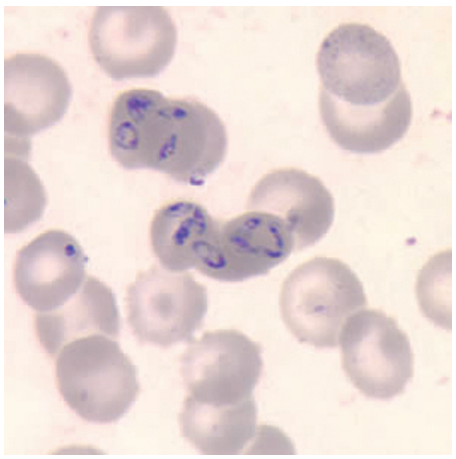

**FIGURE 298-9 *Babesia microti.*** Note the vacuolated intraerythrocytic ring forms and the clumped extraerythrocytic forms (thin blood smear, Giemsa stain, ×1000). *(From Centers for Disease Control and Prevention, Atlanta, GA: DPDx Image Library. Available at http://www.cdc.gov/dpdx/HTML/Babesiosis.htm.)*

Quinine (650 mg orally three times daily) and clindamycin (1.2 g IV twice daily or 600 mg orally three times daily), continued for 1 week or until parasitemias are in remission, can be used to treat babesiosis caused by all species.[44] Quinine and clindamycin are preferred therapies for WA-1 babesiosis and for severe *B. microti* infections, especially

**TABLE 298-7 Representative Tick-borne Viral Encephalitides and Hemorrhagic Fevers**

| VIRUS NAME | VIRAL SYNDROME | FAMILY TAXONOMY | GEOGRAPHIC DISTRIBUTION | TICK VECTORS | WILD ANIMAL RESERVOIRS |
|---|---|---|---|---|---|
| Central European tick-borne encephalitis (TBEV-Eu) | TBE | Flaviviridae | Europe, except Iberian Peninsula | Ixodid ticks, especially *Dermacentor marginatus, Ixodes persulcatus*, and *I. ricinus* | Mammals—especially rodents, including hedgehogs, wood mice, and voles; deer and other ungulates, birds, domestic livestock, especially goats |
| Powassan encephalitis | TBE | Flaviviridae | Canada, Northeastern United States, Far Eastern Russia | *Ixodes* spp., particularly *I. cookei, Dermacentor andersoni* | Mammals—rodents, skunks, other medium-sized mammals, especially woodchucks |
| Langat | TBE | Flaviviridae | Malaysia | Ixodid ticks | Mammals—monkeys, rodents |
| Louping Ill | TBE | Flaviviridae | United States, Scotland | Ixodid ticks | Sheep |
| Russian (Siberian) spring-summer encephalitis (TBEV-Sib) | TBE | Flaviviridae | Russia | *Ixodes* spp., *I. persulcatus, I. ricinus* | Mammals—rodents including hedgehogs, wood mice, voles; also birds, deer, other ungulates, domestic livestock, especially goats |
| Far Eastern TBE (TBEV-FE) | TBE | Flaviviridae | Eastern Russia, China to Far Eastern Japan | *I. persulcatus* | Mammals—rodents, including hedgehogs, wood mice, voles; also birds, deer, other ungulates, domestic livestock, especially goats |
| Turkish sheep encephalitis | TBE | Flaviviridae | Turkey | Ixodid ticks | Sheep |
| Crimean-Congo hemorrhagic fever (HF) | HF | Bunyaviridae | Asia, Eastern Europe, Africa, Middle East | *Hyalomma marginatum, Hyalomma anatolicum* | Mammals—many domestic animals (buffalo, camels, cattle, goats, sheep), rabbits, rodents (hedgehogs), birds |
| Kyasanur Forest disease | HF | Flaviviridae | Western India | *Haemaphysalis spinigera* | Mammals—especially monkeys, domestic livestock (cattle, goats, sheep), rodents, insectivores |
| Omsk HF | HF | Flaviviridae | Western Siberia | *Dermacentor reticulatus, Ixodes apronophorus* | Mammals—rodents, especially muskrats, water voles |

in older adults and splenectomized or immunosuppressed individuals.[44,48] For non–life-threatening *B. microti* infections, a 2-week course of oral atovaquone (750 mg twice daily) and azithromycin (500 mg on day 1, followed by 250 to 600 mg/day for 1 week) cleared parasitemias as effectively as quinine and clindamycin, with fewer side effects. For coinfections with *B. burgdorferi,* patients should be treated specifically for Lyme disease with doxycycline (200 mg orally twice daily for 2 weeks) and with antimalarial agents for babesiosis.[44,45,51]

## TICK-BORNE VIRAL INFECTIONS

### Tick-borne Viral Encephalitides

The tick-borne viral infections are caused primarily by flaviviruses and may be divided into two separate clinical presentations, each with preferred tick vectors and wild animal reservoirs—the viral encephalitides and viral hemorrhagic fevers (Table 298-7). The tick-borne viral infections share several common clinical and epidemiologic characteristics, including the following: incubation periods of approximately 1 week; biphasic illnesses separated by symptom-free periods beginning with flulike viremic stages and ending with CNS or hemorrhagic manifestations with increased CFRs; nonspecific serodiagnosis by comparing acute and convalescent sera for increased antibody titers or by hemagglutination inhibition; specific serodiagnosis by enzyme-linked immunosorbent assay (ELISA) and antigen detection from blood or cerebrospinal fluid (CSF) by reverse-transcriptase (RT)-PCR; no specific treatments other than supportive therapy; and significantly increased postinfection morbidity.[52]

From a global distribution perspective, the tick-borne encephalitis viruses (TBEVs) are separated into the Old World (Eastern Hemisphere) and New World (Western Hemisphere) strains, with the Old World strains having significantly higher CFRs (20% to 40%) and permanent neurologic morbidity rates (28% to 30%) than the New World strains (CFR, 10% to 15%; morbidity rate <10%).[52] Although additional Old World flaviviral strains have now been discovered in sheep reservoirs, the most common Old World TBEVs have been further stratified regionally into three major subtypes—European or Central European (TBEV-Eu), Siberian or Russian spring-summer (TBEV-Sib), and Far Eastern (TBEV-FE; see Table 298-7). Except for the Old World TBEVs with sheep reservoirs, all the TBEVs are transmitted by the injection of infected saliva from viremic ixodid ticks. During blood-feeding, viruses in tick saliva increase up to 10-fold and render early removal of the feeding tick ineffective in preventing disease. The preferred wild animal reservoirs for TBEVs include rodents, insectivores, medium-sized mammals, deer and other ungulates, birds, and, less often, domestic animals (see Table 298-7).

Powassan encephalitis, first isolated in 1958, typifies a New World TBEV with a confined regional distribution in the New England states and Eastern Canada, several ixodid tick vectors, primarily *Ixodes* spp., an extensive wild animal reservoir in rodents and medium-sized mammals, especially woodchucks and skunks, and a seasonal occurrence.[53] Cases occur from May to December and peak during June to September, when ticks are most active. Patients with Powassan encephalitis present with somnolence, headache, confusion, high fever, weakness, ataxia, and CSF lymphocytosis. Transient improvement may be followed by neurologic deterioration, evidence of ischemia or demyelination on magnetic resonance imaging, and slow recovery, often with permanent deficits including memory loss, weakness, ophthalmoplegia, and lower extremity paraparesis. Unlike the Old World TBEVs, Powassan encephalitis is uncommon, with only 31 confirmed cases reported by the CDC from 1958 to 2001. Because there is no vaccine or specific therapy for Powassan encephalitis, the best means of prevention is protection from tick bites. Since 2008, Powassan encephalitis cases historically confined to the northeastern United States and Canada have been increasingly confirmed farther westward in Minnesota and Wisconsin, with fatal cases reported in the elderly.[54]

The Old World TBEVs remain common causes of permanent neurologic morbidity from Scandinavia to Eastern Japan, with more than 10,000 cases reported per year, a third of which result in permanent neurologic deficits.[52] In addition to tick bites, the Old World TBEVs may occasionally be transmitted by ingestion of unpasteurized milk products from viremic livestock (especially goats), breast-feeding, and slaughter of viremic animals. Old World TBEV is typically biphasic in over 70% of cases, with an initial febrile flulike presentation followed by a 1-week (range, 1 to 21 days) symptom-free interval. This honeymoon or recovery period is followed by meningoencephalitis with CSF pleocytosis, with or without myelitis, and a poliomyelitis-like flaccid paralysis that targets the arms, neck, and shoulders. Magnetic resonance imaging and electroencephalographic abnormalities are common but nonspecific. Other acute neurologic complications may

include altered consciousness, seizure activity, cranial nerve palsies, and an often fatal bulbar syndrome with cardiorespiratory failure. Because no specific treatments other than supportive therapy exist, tick avoidance and immunization remain the best preventive measures. Effective vaccines have now been developed for the three subtypes of Old World TBEVs, and some have been shown to even provide cross-protection among the subtypes in experimentally infected animals.

### Tick-borne Viral Hemorrhagic Fevers

The tick-borne hemorrhagic fever (TBHF) viruses are maintained in nature in extensive wild and domestic animal reservoirs and are transmitted by infected ixodid tick bites, squashing infected ticks, creating infective aerosols, direct contact with blood or tissues from infected animals or humans, or nosocomial spread among medical personnel.[55] TBHFs may be caused by flaviviruses and bunyaviruses, which are distributed throughout Eastern Europe, Africa, and Asia. They are characterized clinically by biphasic illnesses that present as febrile flulike symptoms and end as hepatomegaly and hemorrhagic manifestations (petechiae, purpura, subconjunctival and pharyngeal hemorrhage, thrombocytopenia, cerebral hemorrhage, disseminated intravascular coagulation) separated by a few afebrile days. CFRs range from 10% to over 50%, with most deaths occurring within 5 to 14 days of symptom onset during hemorrhagic stages. Diagnoses may be confirmed by immunologic techniques, such as antibody increases in paired sera and ELISA, and by molecular techniques, such as RT-PCR. Although ribavirin can inhibit Crimean-Congo hemorrhagic fever (CCHF) virus replication in animal models, it has not been tested in clinical trials in humans with CCHF. Nevertheless, if TBHF is suspected in the tropics and laboratory confirmation is unavailable, intravenously administered ribavirin (30 mg/kg initially, followed by 16 mg/kg four times daily for 4 days, and then 8 mg/kg three times daily for 6 days) is recommended for severe cases, and oral ribavirin is recommended for high-risk contacts. All patients with TBHFs should be placed in isolation, and strict universal precautions should be practiced by all medical personnel. A mouse brain–derived CCHF vaccine has been developed in Bulgaria but is not available elsewhere. In the absence of a universal vaccine, the best preventive measures for the TBHFs are tick avoidance and control, rapid burial of dead animals, and personal protective equipment for abattoir workers and medical personnel.

### Tick-borne Coltiviruses

The tick-borne coltiviruses of the family Reoviridae are all double-stranded RNA viruses of the genus *Coltivirus* and include Colorado tick fever virus (CTFV), which is endemic in the United States and Canadian Rocky Mountain regions; the California tick fever virus (TFV) of rabbits (CTFV-Ca); the Salmon River virus (SRV) of Idaho, a serotype of the CTFVs; and the European Eyach virus (EYAV).[56] The ixodid or hard ticks are the only vectors of the coltiviruses, with *Dermacentor* ticks (mainly *D. andersoni*) being the principal vectors of CTFV and SRV in the Rocky Mountains and *Ixodes* ticks *(I. ricinus, I. ventalloi)* being the only vectors of EYAV throughout Europe. Among the coltiviruses, CTFV has the widest host range, which includes squirrels, other rodents, rabbits, porcupines, marmots, deer, elk, sheep, and coyotes. The remaining coltiviruses have fewer, more specific wild animal hosts, including the black-tailed jackrabbit *(Lepus californicus)* for CTFV-Ca and primarily the European rabbit *(Oryctolagus cuniculus)* but also rodents, deer, domestic goats, and sheep for EYAV. The coltiviruses are maintained in nature by ixodid ticks that blood-feed on wild animal hosts with prolonged viremias and then transmit coltiviruses trans-stadially but not transovarially. Infected nymphs hibernate over winter, and previously infected nymphs and newly infected adults then transmit coltiviruses to human dead-end hosts during spring-summer blood-feeding. CTFV has also been transmitted by blood transfusion and congenitally.

Both CTFV and SRV can cause biphasic to triphasic febrile illnesses that mimic mild cases of RMSF without rash. Leukopenia and thrombocytopenia are common laboratory manifestations of coltivirus infections.[56] Complications are rare but may include meningoencephalitis, orchitis, hemorrhagic fever, pericarditis, and myocarditis. EYAV infections are more often complicated by CNS manifestations than American strain coltivirus infections. The most common differential diagnoses for the tick-borne coltiviruses are other tick-borne febrile diseases, most commonly RMSF in North America, which may be distinguished from CTFV and SRV infections by its characteristic rash and leukocytosis. Serologic diagnostic methods to detect anticoltivirus antibodies include complement fixation, seroneutralization assay, immunofluorescence assay, ELISA, and Western immunoblot. The most specific and confirmatory laboratory diagnostic methods include RT-PCR assays to identify CTFV-RNA (or the RNA of its cross-reacting serotypes, CTFV-Ca and SRV) or the isolation of coltiviruses after intracerebral inoculation of infected human blood into suckling mice. Treatment of all tick-borne coltivirus infections is entirely supportive, and long-term complications are rare in uncomplicated cases.

## TICK PARALYSIS

First described in 1912 in Australia, Canada, and the United States, tick paralysis is a rare, regional, and seasonal cause of acute ataxia and ascending paralysis with an incubation period of 4 to 7 days after female tick attachment, mating, and blood-feeding.[57-60] Although 43 species of ticks have been implicated in tick paralysis cases worldwide, most cases occur in the United States and Canadian Pacific Northwest (Washington State and British Columbia) and in Australia. In the U.S. Pacific Northwest, tick paralysis is caused by the American dog tick, *D. variabilis,* or the Rocky Mountain wood tick, *Dermacentor andersoni,* during April through June, when *Dermacentor* ticks emerge from hibernation to mate and to seek blood meals (see Fig. 298-7).[57-62] The mechanism of neurotoxic paralysis in *Dermacentor* tick paralysis is unknown, but neuroelectrophysiologic studies have suggested that sodium flux across axonal membranes is blocked at the nodes of Ranvier, leaving neuromuscular transmission unimpeded.[63] In Australia, the marsupial ixodid tick, *Ixodes holocyclus,* can cause a more severe form of ascending neuromuscular paralysis by producing a botulinum-like neurotoxin that blocks neuromuscular transmission by inhibiting the presynaptic release of acetylcholine.[63]

Most cases of tick paralysis in North America have occurred sporadically in young girls with long hair concealing ticks feeding on the scalp or neck.[62] However, a four-patient cluster of *Dermacentor* tick paralysis, including a 6-year-old girl with a tick on her hairline, and three adults with ticks on the neck ($n = 1$) and back ($n = 2$), was reported from Colorado in 2006.[60]

Although botulism causes a descending neuromuscular paralysis with a preserved sensorium, tick paralysis, Guillain-Barré syndrome, acute poliomyelitis, and spinal cord tumors may all cause acute ascending paralysis with preserved mental status and must be differentiated from each other (Table 298-8).[60-62] Because poliomyelitis has been nearly eradicated by vaccination worldwide, tick paralysis is frequently misdiagnosed as Guillain-Barré syndrome, and the correct diagnosis is made accidentally by finding an engorged, usually female, tick on the scalp, head, or neck during hair combing or when applying electroencephalographic electrodes (see Table 298-8).

Before 1954, postmortem examinations of persons who died suddenly of unexplained paralytic illnesses demonstrated attached ticks on their heads and necks.[64] In a review of Canadian tick paralysis cases in the 1950s before the widespread availability of mechanical ventilation in intensive care units, Rose reported a CFR of 10% to 12% without tick removal.[64] In a review of 33 tick paralysis cases in Washington State over the period 1946 to 1966, Dworkin and co-workers reported a CFR of up to 10%, with most deaths occurring in the 1940s.[65] In a 60-year meta-analysis of confirmed tick paralysis cases in the United States, Diaz reported a CFR of 6% in the first 30 years, a seasonal pattern of case clusters in children and adults in urban and rural locations, and a significant increase in initial misdiagnoses of tick paralysis as Guillain-Barré syndrome in more recently reported cases.[66] In addition, the misdiagnoses of tick paralysis cases as Guillain-Barré syndrome often directed unnecessary therapies, such as central venous plasmapheresis with immunoglobulin G, and delayed correct diagnosis and treatment by tick removal.[66] In all cases, the diagnosis of tick paralysis was later established when attached ticks were either discovered by caregivers or by cranial neuroimaging studies.[66] The CFR from tick paralysis has steadily declined over the past 60 years, with almost all deaths in Canada and the United States reported in the 1940s and 1950s.[64-66]

**TABLE 298-8 Clinical Differential Diagnosis of Tick Paralysis vs. Ascending Neuromuscular Paralysis with Preserved Sensorium**

| PRESENTING CLINICAL FEATURES | TICK PARALYSIS | GUILLAIN-BARRÉ SYNDROME | CERVICAL SPINAL CORD LESION | POLIOMYELITIS |
|---|---|---|---|---|
| Onset of ascending paralysis | Acute, rapid, within 24-48 hr | Slower onset, days to weeks | Abrupt to gradual | Days to weeks |
| Ataxia | Present | Absent | Absent | Absent |
| Deep tendon reflexes | Hyporeflexia progressing to areflexia | Hyporeflexia progressing to areflexia | Variable | Hyporeflexia progressing to areflexia |
| Babinski sign | Absent | Absent | Present | Absent |
| Sensory loss | None | Mild | Present | None |
| Meningeal signs | Absent | Rarely present | Absent | Present |
| Fever | Absent | Rarely present | Absent | Present |
| CSF findings | | | | |
| Protein levels (mg/dL) | Normal | High (≥40) | Normal to high | High |
| White cells per $mm^3$ | <10 | <10 | | >10 |
| Differential counts | Normal | <10 mononuclear cells/$mm^3$ | Variable | Lymphocytosis |
| Nerve conduction studies | ↑ Latency in distal motor nerves<br>↓ Nerve conduction velocity<br>↓ Amplitude of motor and sensory nerve action potentials | Similar | Similar | Similar |
| Time to neurologic recovery | Rapid, ≤24 hr after tick removal | Weeks to months | Variable | Months to years |
| Permanent neurologic deficits | None after tick removal | Permanent paresis possible | Permanent paresis possible | Permanent paresis possible |

CSF, cerebrospinal fluid.

The treatment of *Dermacentor* tick paralysis simply requires removing the tick with forceps (or tweezers) to restore neuromuscular function within 24 hours. Although *I. holocyclus* tick paralysis is also treated by tick removal, transient neuromuscular deterioration may occur for 24-48 hours after tick removal.[67] The administration of *I. holocyclus* antitoxin before tick removal and prolonged observation for hypoventilation have been recommended.

## PREVENTION AND CONTROL OF TICK-BORNE INFECTIOUS DISEASES AND PARALYTIC POISONINGS

There are a number of strategies that can be used in the prevention and control of tick-borne infectious diseases, including immunization, personal protective measures, landscape management, and wildlife management. In the 1990s, a Lyme disease vaccine was developed for the United States, but it was withdrawn from the market in 2002 because of poor sales. Immunization strategies to prevent tick-borne infectious diseases have proved far more effective in Europe and Asia than in the United States, where neurologic complications from TBEVs are second only to Japanese encephalitis as causes of permanent paraparesis.[51] Current immunization programs for tick-borne viral diseases now provide primary prevention of TBEV-Eu in Europe, TBEV-Sib in Russia and the Middle East, TBEV-FE in China and the Far East, and CCHF in Bulgaria. A canine antitoxin for *I. holocyclus*–induced tick paralysis has been used to reverse tick paralysis in animals and humans in Australia.[67]

In addition to immunization, antibiotic therapy after presumed ixodid tick bites with erythema migrans has been recommended as a prophylactic therapeutic strategy for the primary prevention of some tick-borne infections. A randomized clinical trial found that a single 200-mg dose of doxycycline administered within 72 hours of a tick bite was 87% effective in preventing Lyme disease.[68]

Finally, because most tick-borne infectious diseases may also be transmitted by blood product transfusions, screening blood product donors in high seroprevalence areas for Lyme disease and other borrelioses, babesiosis, ehrlichioses, and anaplasmosis would eliminate transfusion-transmitted cases. Physicians are encouraged to order leukocyte-reduced blood components for blood product transfusions to potentially reduce the risks for ehrlichiosis and anaplasmosis, especially in regions that are highly endemic for leukocytotropic tick-borne infectious diseases.

Personal protective measures to prevent tick-transmitted diseases include wearing appropriate clothing, using insect repellents, and performing regular tick checks. Wearing long pants tucked into socks, long-sleeved shirts, and light-colored clothing can help keep ticks off the skin and make them easier to spot on clothing. Impregnating clothing with permethrin, routinely performed by the military on maneuvers, is a highly effective repellent against ticks and other insects. The topical application of insect repellents containing 20% to 50% formulations of *N,N*-diethyl-meta-toluamide (DEET) directly on the skin is another effective and recommended measure.

Most patients with Lyme disease, TBRF, babesiosis, ehrlichioses, and anaplasmosis will not recall tick bites because these diseases are often transmitted by diminutive nymphal ticks. Nevertheless, tick localization and removal as soon as possible, preferably within 36 hours, remain recommended strategies to prevent the rickettsial and viral ixodid tick-borne diseases and to reverse tick paralysis. Ticks should always be removed with forceps (or tweezers), not fingers (because squashing ticks can transmit several tick-borne diseases across dermal barriers or create infectious aerosols), and in contiguity with their feeding mouth parts, rather than burning ticks with spent matches or painting embedded ticks with adhesives or nail polishes.

Landscape management strategies to prevent tick-borne diseases include widespread application of acaricides over tick-preferred ecosystems, removal of vegetation and leaf litter near homes and recreation sites, and creation of dry barriers of gravel, stone, or wood chips between forested areas and yards or playgrounds. Wildlife management strategies to prevent tick-borne diseases include encouraging the development of better veterinary vaccines for tick-borne diseases with large domestic animal reservoirs, applying acaricides actively to domestic animals and passively to deer and cattle at baited feeding and watering stations or salt licks, and setting out acaricide-baited rodent houses for rodents to occupy or acaricide-baited cotton balls for rodents to adopt as nesting materials, especially in crawl spaces under homes and near playgrounds.

## CONCLUSION

Most emerging infectious diseases today, such as West Nile virus and severe acute respiratory syndrome, arise from zoonotic reservoirs, and many are transmitted by arthropod vectors. Because ticks are the most common insect vectors of zoonotic diseases, ticks have become common arthropod vectors of emerging zoonotic diseases, including Lyme disease, ehrlichiosis, and anaplasmosis. Ticks are highly competent and versatile vectors of infectious diseases because ticks of all ages and both genders may remain infectious for generations, without having to reacquire infections from host reservoirs. Recent environmental changes and human behaviors now place

humans and ticks together outdoors for longer periods in welcoming ecosystems for breeding, blood-feeding, and infectious disease transmission. Better prevention and treatment strategies for tick-borne diseases are indicated, before the highly conserved genomes of tick-transmitted microorganisms reassort their nucleic acids with their hosts and develop antimicrobial resistance (especially to tetracyclines) or superpathogen capabilities, either by nature's own design or human terrorist intent.

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*The complete reference list is available online at Expert Consult.*


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