FIG. 295.9 The typical self-limited, intensely pruritic, papulovesicular rash of cercarial dermatitis or swimmer's (duck hunter's) itch caused by penetration of the skin by the cercariae of avian (waterfowl) schistosomes. *(From Centers for Disease Control and Prevention. DpDx Image Library.* http://www.dpd.cdc.gov/dpdx/HTML/CercarialDermatitis.html.*)*

The demographic and behavioral features of true delusional infestations have remained constant over the years and have included: (1) onset in well-educated, middle-aged adults who are pet owners; (2) production of purported specimens of causative parasites; (3) pesticide overtreatment of themselves, their households, and their domestic pets; (4) excessive cleaning or vacuuming of households; (5) intense anger and resentment directed at physicians failing to confirm their self-diagnoses; and (6) sharing of delusional symptoms with spouses or relatives.[17] The most effective management strategies for true delusional infestations include empathetic history taking and active listening to patients; careful exclusion of the most commonly underdiagnosed true ectoparasitoses; and therapeutic regimens in consultation with mental health providers.[17]

PREVENTION OF MITE INFECTIONS AND MITE-TRANSMITTED INFECTIOUS DISEASES

Prevention and control strategies for mite ectoparasites include (1) household and campsite spraying of pyrethrin and pyrethroid-containing insecticides; (2) spraying or impregnating pyrethrin and pyrethroid-containing repellents on clothing; (3) applying diethyltoluamide–containing insect repellents (*N,N*-diethyl-meta-toluamide [DEET]) to exposed skin; (4) gently washing exposed or infested areas of the body with soap and water to remove stylostome-attached mites without decapitating them; (5) improving rodent reservoir control in campgrounds, homes, apartments, barns, sheds, and, especially, crowded public housing; (6) treating straw beds, straw mattresses, and hayride wagons with pyrethrin- and pyrethroid-containing insecticides; and (7) vacuuming bedrooms and mattresses and washing bed linens regularly, and covering mattresses and pillows with plastic covers to minimize house dust mite levels. There are no vaccines for scrub typhus or rickettsialpox. Weekly doses of 200 mg of doxycycline can prevent *O. tsutsugamushi* infections.

CONCLUSION

In summary, mites are ubiquitous and bothersome pests, and of these, most are trombiculid larvae (chiggers) and animal and plant mites that do not transmit infectious diseases. Only about 20 species can cause dermatitis or transmit infectious diseases.[3] The Asian and Eurasian *Leptotrombidium* species of trombiculid larvae (chiggers) can transmit scrub typhus in endemic regions, and the house mouse mite can transmit rickettsialpox from a mouse zoonosis in urban and rural settings, which is more widespread worldwide than initially thought.

Key References

The complete reference list is available online at Expert Consult.

2. Krusell A, Comer JA, Sexton DJ. Rickettsialpox in North Carolina: a case report. *Emerg Infect Dis*. 2002;8:727–728.
8. Ozturk MK, Gunes T, Kose ET, et al. Rickettsialpox in Turkey. *Emerg Infect Dis*. 2003;9:1498–1499.
10. Kong TK, To WK. Bird-mite infestation. *N Engl J Med*. 2006;354:172.
14. Del Giudice P, Caumes C, Boissy C, et al. An outbreak of creeping eruption in southern France. *Br J Dermatol*. 2007;157:824–825.
15. Del Giudice P, Blanc-Amrane V, Bahadoran P, et al. *Pyemotes ventricosus* dermatitis, southeastern France. *Emerg Infect Dis*. 2008;14:1759–1761.
16. Nasca MR, Lacarrubba F, Micali G. Diagnosis of trombiculosis by videodermatoscopy. *Emerg Infect Dis*. 2014;20:1059–1060.

References

1. Service MW. Scrub typhus mites (Trombiculidae). In: Service MW, ed. *Medical Entomology for Students*. London: Chapman and Hall; 1996:256–262.
2. Krusell A, Comer JA, Sexton DJ. Rickettsialpox in North Carolina: a case report. *Emerg Infect Dis*. 2002;8:727–728.
3. Goddard J. Mites. In: Goddard J, ed. *Physician's Guide to Arthropods of Medical Importance*. 4th ed. Boca Raton, FL: CRC Press; 2002:229–246.
4. Weitzel T, Dittrich S, Lopez J, et al. Endemic scrub typhus in South America. *N Engl J Med*. 2016;375:954–961.
5. Yun JS, Song JS, Choi EJ, et al. Case report: successfully managed acute transverse myelitis related to scrub typhus and serial image findings. *Am J Trop Med Hyg*. 2017;96:557–560.
6. Thipmontree W, Suwattanabunpot K, Supputtamonkol Y. Case report: spontaneous splenic rupture caused by scrub typhus. *Am J Trop Med Hyg*. 2016;95:1284–1286.
7. Watt G, Walker DH. Scrub typhus. In: Guerrant RL, Walker DH, Weller PF, eds. *Tropical Infectious Diseases: Principles, Pathogens and Practice*. 2nd ed. Philadelphia: Churchill Livingstone; 2006:557–562.
8. Ozturk MK, Gunes T, Kose ET, et al. Rickettsialpox in Turkey. *Emerg Infect Dis*. 2003;9:1498–1499.
9. Neva FA, Brown HW. Class Arachnida—ticks, mites, spiders, scorpions. In: Neva FA, Brown HW, eds. *Basic Clinical Parasitology*. East Norwalk, CT: Appleton and Lange; 1994:300–311.
10. Kong TK, To WK. Bird-mite infestation. *N Engl J Med*. 2006;354:172.
11. Fine RM, Scott HG. Straw itch mite dermatitis caused by *Pyemotes ventricosus*: comparative aspects. *South Med J*. 1965;58:416–420.
12. Centers for Disease Control and Prevention. Outbreak of pruritic rashes associated with mites—Kansas, 2004. *MMWR Morb Mortal Wkly Rep*. 2005;54:952–955.
13. Bellido-Blasco JB, Arnedo-Pena A, González-Morán F, et al. Dermatitis outbreaks caused by *Pyemotes*. *Med Clin (Barc)*. 2000;114:294–296.
14. Del Giudice P, Caumes C, Boissy C, et al. An outbreak of creeping eruption in southern France. *Br J Dermatol*. 2007;157:824–825.
15. Del Giudice P, Blanc-Amrane V, Bahadoran P, et al. *Pyemotes ventricosus* dermatitis, southeastern France. *Emerg Infect Dis*. 2008;14:1759–1761.
16. Nasca MR, Lacarrubba F, Micali G. Diagnosis of trombiculosis by videodermatoscopy. *Emerg Infect Dis*. 2014;20:1059–1060.
17. Diaz JH, Nesbitt LT Jr. Delusional infestations: case series, differential diagnosis, and management strategies. *J LA State Med Soc*. 2014;166:154–159.

296 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 (e.g., 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 (transstadial 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: (1) wider geographic distributions and longer active breeding and blood-feeding seasons as a result of increases in global mean temperatures and humidity; (2) greater abundance of wild animal reservoir hosts no longer effectively controlled, especially deer, rabbits, and rodents; (3) greater residential construction in recently cleared woodlands adjacent to pastures and yards frequented by wildlife, domestic animals, and humans; and (4) 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 mouthparts 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. 296.1). 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 (6–12) before dropping off for egg laying.

FIG. 296.1 Female *Dermacentor andersoni*, the Rocky Mountain wood tick, questing for a host. The Rocky Mountain wood tick is the preferred tick vector for *Rickettsia rickettsii,* the causative riskettsial agent of Rocky Mountain spotted fever in the US Rocky Mountains and the Canadian southwest. *(From Biggs HM, Behravesh CB, Bradley KK, et al. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever and other spotted fever group rickettsioses, ehrlichioses, and anaplasmosis—United States.* MMWR Recomm Rep. *2016;65:1–44.)*

FIG. 296.2 *Borrelia burgdorferi,* the causative bacterium of Lyme disease. Note the characteristic coiled spring appearance of a spirochete (peripheral blood smear, immunofluorescence stain under darkfield microscopy, ×1000). *(From Public Health Image Library. Atlanta, GA: Centers for Disease Control and Prevention. 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 (see Fig. 296.1).[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. 296.2).[4]

By the early 1990s, Lyme borreliosis (LB) 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) they were completely reorganized into separate genera, *Ehrlichia* and *Anaplasma.*[7,8] In 1997, Kirkland and colleagues[9] 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* (Fig. 296.3). This new borreliosis would soon be named the southern tick-associated rash illness (STARI) or Masters disease, but its causative agent, *Borrelia lonestari,* a new *Borrelia* species, would not be identified until 2004.[10,11]

By 2004, ticks were recognized as the most common vectors of all arthropod-borne infectious diseases in Europe, five new spotted fever (SF)–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. 296.4).[13]

In 2011, the first human cases of relapsing fever caused by tick-transmitted *Borrelia miyamotoi* were reported from Russia.[14] In 2013, 1% to 3% of surveyed residents of New England states where Lyme disease is endemic were seropositive for prior *B. miyamotoi* infection.[15] Since 2011, more than 50 patients with acute febrile illnesses resembling Lyme disease without erythema migrans have been described as having *B. miyamotoi* infections.[16] In most cases, patients present with fever, malaise, fatigue, headache, myalgias, and arthralgias, and they do not have recurrent fevers. This initial clinical presentation more closely resembles other hard tick–transmitted diseases, especially anaplasmosis and Lyme disease without a significant rash, rather than soft tick–transmitted classic relapsing fever. In two cases, immunocompromised patients developed meningoencephalitis.[15] *B. miyamotoi* infections are transmitted by the same ixodid ticks that carry Lyme disease: *Ixodes scapularis,* the eastern black-legged tick (Fig. 296.5), and *Ixodes pacificus,* the western black-legged tick (Fig. 296.6).[15,16] Uncomplicated cases may be effectively treated with oral doxycycline, and the cases complicated by meningoencephalitis responded to intravenous therapy with ceftriaxone or penicillin G.

In 2009, a new pathogenic *Ehrlichia* species in addition to endemic *Ehrlichia chaffeensis* and *Ehrlichia ewingii* was identified in four febrile patients in Minnesota and Wisconsin and presumed to be related to *Ehrlichia muris.*[17]

In July 2008, an 80-year-old man with a tick-bite–appearing eschar, lymphadenitis, and regional lymphadenopathy, and three additional patients with similar presenting manifestations, were reported in northern California.[18] An afebrile, "spotless" rickettsial disease was suspected initially in all cases.[18] Convalescent sera from all four patients exhibited cross-reacting immunoglobulin antibody titers to the RMSF agent *Rickettsia rickettsii,* and also to a newly recognized SF group agent, *Rickettsia* 364D (*R. philipii* [proposed]), later detected in the Pacific Coast tick *Dermacentor occidentalis* (Figs. 296.7 and 296.8).[18] All patients were effectively treated without fatalities with oral doxycycline over a 2-week course.[18]

The Heartland virus, a novel phlebovirus (family Bunyaviridae) transmitted by the Lone Star tick *A. americanum* (see Fig. 296.3), was first described in 2009 in two elderly Missouri farmers believed to have ehrlichiosis and who presented with fever, fatigue, headache, confusion, myalgia, and laboratory evidence of leukopenia and thrombocytopenia.[19] In 2013, a fatal case of Heartland virus disease was reported in an 80-year-old man in Tennessee who presented with similar clinical and laboratory findings, but he could not recall a tick bite.[20] Other than supportive care, there are no specific drug treatments for Heartland virus disease.[19,20]

In June 2014, a previously healthy man in eastern Kansas with a history of tick bite, fever, and fatigue was treated with doxycycline for a presumed tick-borne illness.[21] He later died from a critical illness characterized by high fever, thrombocytopenia, leukopenia, and multiorgan failure.[21] Given the proximity to the Heartland virus cases in adjacent Missouri, blood specimens were analyzed for antibodies against Heartland virus.[21] Subsequently, a series of serologic, culture-based, and molecular tests demonstrated the presence of a novel thogotovirus (the first representative of the family was isolated in the Thogoto forest

FIG. 296.3 ***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 Public Health Image Library. Image 8683. Atlanta, GA: Centers for Disease Control and Prevention.)*

FIG. 296.5 ***Ixodes scapularis,*** **the eastern black-legged tick.** Shown are the adult female and two nymphs. These are arthropod vectors of babesiosis and Lyme disease, especially nymphs, whose bites are most often unnoticed. *(From Public Health Image Library. Image 1205. Atlanta, GA: Centers for Disease Control and Prevention.)*

FIG. 296.4 ***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 in addition to the historical vectors *Dermacentor andersoni,* the Rocky Mountain wood tick, and *Dermacentor variabilis,* the American dog tick. *(From Public Health Image Library. Image 7646. Atlanta, GA: Centers for Disease Control and Prevention.)*

FIG. 296.6 ***Ixodes pacificus,*** **the western black-legged tick, questing for a host.** *Ixodes pacificus* is the preferred tick vector for the transmission of *Borrelia* spirochetal infections, including *B. burgdorferi,* the causative agent of Lyme borreliosis, and *B. miyamotoi,* the causative agent of a Lyme disease–like borreliosis without the characteristic erythema migrans rash. *(From Biggs HM, Behravesh CB, Bradley KK, et al. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever and other spotted fever group rickettsioses, ehrlichioses, and anaplasmosis—United States.* MMWR Recomm Rep. *2016; 65:1–44.)*

of Kenya) phylogenetically distinct from Heartland virus and named Bourbon virus after the patient's county of residence.[21]

Another novel, tick-transmitted phlebovirus (family Bunyaviridae), the severe fever with thrombocytopenia syndrome virus (SFTSV), was first described in 2009 in China and has now been detected in *Haemaphysalis* species ticks in Korea and Japan.[22] SFTSV is transmitted by at least two species of *Haemaphysalis* ticks, *H. longicornis* and *H. concinna,* and is characterized by the abrupt onset of high fever, abdominal pain, nausea, vomiting, leukocytopenia, and thrombocytopenia with hemorrhage.[22] The zoonotic reservoir for SFTSV is in domestic animals, especially goats.[22] Since 2010, about 2500 cases of severe fever with thrombocytopenia syndrome (SFTS) have been reported from central and eastern China, mostly in hospitalized patients, with a median case-fatality rate of 7.3%.[22] Other than supportive care, there are no specific drug treatments for SFTS.[22]

In each case of these newly described tick-transmitted diseases, another tick-borne disease was initially suspected. Ehrlichiosis was suspected in the Heartland virus disease cases, Lyme disease in the *B. miyamotoi* cases, and "spotless" RMSF with eschar in the *Rickettsia* 364D cases.

Because most tick-borne diseases are caused by obligate intracellular organisms, many of which infect erythrocytes, monocytes, 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) was

FIG. 296.7 ***Dermacentor occidentalis,*** **the Pacific Coast tick, adult female** ***(left)*** **and adult male** ***(right).*** *Dermacentor occidentalis,* the Pacific Coast tick, has now been identified as the tick vector of *Rickettsia* 364D (*Rickettsia philipii* [proposed]) rickettsiosis in California, which has been described as a "spotless" fever with a tick-bite eschar. *(From Shapiro MR, Fritz CL, Tait K, et al.* Rickettsia *364D: a newly recognized cause of eschar-associated illness in California.* Clin Infect Dis. *2010;50:541–548; and Centers for Disease Control and Prevention, Atlanta, GA. Photographs courtesy James Gathany.)*

FIG. 296.8 **Rickettsia 364D eschar.** A pediatric patient in California with a tick-bite eschar on the left brow from the newly discovered rickettsial species *Rickettsia* 364D, transmitted by the bite of an infected Pacific Coast tick (*Dermacentor occidentalis*). *(From Biggs HM, Behravesh CB, Bradley KK, et al. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever and other spotted fever group rickettsioses, ehrlichioses, and anaplasmosis—United States.* MMWR Recomm Rep. *2016;65:1–44. Photo courtesy Samantha H. Johnson, MD, Oakland Children's Hospital and Research Center, Oakland, CA.)*

confirmed microscopically and serologically by testing of both the recipient and the donor.[23]

In 2016, Moritz and coinvestigators from the American Red Cross reported the results of their screening intervention designed to reduce the risk of blood transfusion-transmitted babesiosis caused by *Babesia microti* in highly endemic regions of the United States, including Connecticut, Massachusetts, Minnesota, and Wisconsin.[24] *Babesia microti* is an intraerythrocytic parasite, related to the malaria parasite, that, like malaria, can be transmitted by blood transfusion. Babesiosis is a potentially fatal disease as a result of splenic rupture. The investigators screened over 89,000 blood donation samples for *B. microti* antibodies (with arrayed fluorescence immunoassays) and for *B. microti* DNA (with PCR assays) and confirmed 335 samples (0.38%) as serologically positive and 67 (20%) of these as PCR-positive.[24] In Connecticut and Massachusetts from June 2012 through September 2014, no reported cases of transfusion-transmitted babesiosis were associated with the screened donations (0 cases/75,331 screened blood donations), compared with 14 cases per 253,031 unscreened donations (1 case/18,074 donations; odds ratio, = 8.6; 95% confidence interval, 0.51–144; $P = .05$).[24] Over the reporting period, 29 cases of transfusion-transmitted babesiosis were linked to unscreened blood from infected donors.[24] Although no currently licensed tests exist to screen for *B. microti* in donated blood, the authors concluded that screening for antibodies to and DNA from *B. microti* could significantly decrease the rate of transfusion-transmitted babesiosis in highly endemic US states.[24]

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 US 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 [MSF]) and Australia (Queensland tick typhus [QTT]). Several tick-borne infectious diseases have now been reclassified by the CDC as potential biological 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 time 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 296.1). The borrelioses are stratified into three separate epidemiologic and clinical presentations: LB, STARI, and the tick-borne relapsing fevers (TBRFs) (Table 296.2).

Lyme Borreliosis

LB, or Lyme disease (see Chapter 241), 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. 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 US regional pockets, specifically the Northeast *(I. scapularis),* upper Midwest *(I. scapularis),* and Pacific Coast (*I. pacificus;* see Figs. 296.2, 296.5, and 296.6). Although *B. burgdorferi* is the sole agent of LB in the United States, most cases of LB in Europe and northern Asia are caused by *Borrelia afzelii* and *Borrelia garinii* (see Table 296.1). 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

TABLE 296.1 Tick-Borne Spirochetal Borrelioses

BORRELIA SPECIES	TICKBORNE DISEASES	GEOGRAPHIC DISTRIBUTION	TICK VECTORS	WILD ANIMAL RESERVOIRS
B. afzelii	European Lyme borreliosis (LB) or Lyme disease	Europe, Scandinavia	*Ixodes ricinus*	Mammals: deer, rodents
B. burgdorferi	American LB or Lyme disease	North America, specifically US Northeast, Midwest, Pacific Northwest; Europe	*Ixodes scapularis* (eastern United States), *Ixodes pacificus* (western United States)	Mammals: deer, rodents (preferred by nymphs)
B. crocidurae	North African tick-borne relapsing fever (TBRF)	North Africa, Mediterranean Basin	*Carios erraticus*	Mammals: rodents, birds
B. duttonii	East African TBRF	East, central, and South Africa	*Ornithodoros moubata*	Humans (main reservoir)
B. garinii	European LB	Northern Europe, Russia, Asia	*I. ricinus* (Europe), *Ixodes persulcatus* (Asia)	Mammals: rodents, birds
B. hermsii	American TBRF	Western United States and Canada	*Ornithodoros hermsii*	Mammals: rodents, chipmunks, squirrels
B. hispanica	Hispano-African TBRF	Iberian peninsula: Spain, Portugal; northwestern Africa: Algeria, Morocco, Tunisia	*Ornithodoros marocanus*	Mammals: rodents
B. latyschewii	White TBRF	Russian Caucasus regions (Tajikistan, Uzbekistan), Central Asia	*Ornithodoros 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	*Ornithodoros talaje*	Mammals: rodents
B. miyamotoi	Russian TBRF	Japan, Eastern Europe, US Northeast	*Ixodes scapularis*	Mammals: rodents
B. parkeri	Western TBRF	Southwest and south central United States, Mexico	*Ornithodoros parkeri*	Mammals: rodents
B. persica	Asiatic-African TBRF	Middle East (Egypt, Iran), central Asia, western China, northern India	*Ornithodoros tholozani*	Mammals: rodents
B. turicatae	American Southwestern TBRF	Southwest and south central United States, Mexico, Central America	*Ornithodoros turicata*	Mammals: rodents, armadillos, opossums, pigs, and monkeys (Panama)
B. venezuelensis	Venezuelan TBRF	Central and South America	*Ornithodoros rudis*	Mammals: rodents, opossums, armadillos, monkeys (Panama, Colombia)

go unnoticed (see Fig. 296.2). *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.[25,26] 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. 296.9).[25–29] Erythema migrans in LB results from the subcutaneous centrifugal movement of the spirochetes from the bite sites to the central circulation and target organs (see Figs. 296.3 and 296.9).[27] An erythema migrans -like rash also occurs in STARI at the site of *A. americanum* (Lone Star tick) attachment, but the underlying mechanisms responsible for the rash in STARI are unclear.

In a meta-analysis of 53 longitudinal studies of LB in the United States and Europe, Tibbles and Edlow[26] reported that many patients did 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 were common but nausea and vomiting were rare, and a solitary erythema migrans lesion was the most common initial presentation of LB (81% in the United States, 88% in Europe). If LB is recognized and treated early in the erythema migrans stage, cure rates will exceed 90%, and outcomes will be excellent (see Table 296.2).[28–31] Although deaths from LB are rare, 5% to 8% of patients may develop cardiac manifestations, and 15% to 20% of patients may develop neurologic manifestations.[28,29]

In patients who previously had antibiotic-treated erythema migrans, reinfections with *B. burgdorferi* may occur in subsequent summers and will be again heralded by another erythema migrans lesion.[29] Recent investigations by Nadelman and coworkers demonstrated that repeated episodes of pathognomonic erythema migrans in patients with previous appropriately treated early LB were due to reinfections and not to recurrences.[29–31] However, persistent arthritis despite adequate antibiotic treatment of LB (now called post-infectious Lyme arthritis) may occur and was formerly referred to as chronic Lyme arthritis.[31a] Despite spirochetal elimination with antibiotic therapy, the proliferative synovitis of Lyme arthritis may extend for months to years and has been attributed to retained spirochetal fragments (such as *B. burgdorferi* peptoglycan) and/or autoimmune responses to these antigens and not to recurrent LB.[31a]

Unfortunately, some practitioners continue to diagnose patients who are suffering from a variety of generalized myofascial, arthritic, and neurologic pain conditions as having "chronic Lyme disease" and have prescribed long courses of oral and intravenous antibiotics despite evidence demonstrating that such therapies provide no improvement and can cause harm. In 2017, Marzec and coauthors reported a case series of five patients diagnosed with "chronic Lyme disease" who were then treated with protracted courses of antibiotics.[32] The resulting complications from this unnecessary therapy included (1) septic shock from central venous catheter–associated bacteremia in two patients, with one fatality; (2) vertebral osteomyelitis in one patient; (3) intractable *Clostridioides difficile* (formerly *Clostridium difficile*) colitis in one patient who later

TABLE 296.2 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 a patient with STARI and cultured in vitro from infected *Amblyomma americanum* ticks	Many *Ornithodoros* species of soft ticks (see Table 296.1)
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; include headache, neuritis of cranial nerve (CN) VII (Bell palsy)	Dizziness, headache, memory loss, concentration difficulty may occur; no chronic neurologic complications	Common: meningitis, meningoencephalitis; neuritis of CN VII (Bell palsy); neuritis of CN VIII (deafness, myelitis, radiculopathy)
Other presenting clinical manifestations	Myocarditis, conduction defects in up to 8% of late-onset and "chronic" 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 d; parenteral therapy for CNS involvement	Doxycycline, 100 mg PO bid, or amoxicillin, 500 mg PO tid, for 14–21 d	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 d; 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.

died from complications of amyotrophic lateral sclerosis (ALS); and (4) a paraspinal abscess that required surgical drainage in the last case.[32]

Although the concept of chronic LB has been dispelled by carefully conducted clinical studies, lingering and unconfirmed associations continue to be made between LB cases and subsequent deaths due to four neurodegenerative disorders: ALS, Alzheimer disease (AD), multiple sclerosis (MS), and Parkinson disease (PD). If such associations truly existed, then the geographic distributions of LB cases and deaths from these four neurodegenerative disorders would be anticipated to significantly overlap. Forrester and coinvestigators compared LB incidence rates in each state from the National Notifiable Diseases Surveillance System during 2001–2010 with age-adjusted death rates for AD, ALS, MS, and PD obtained from the CDC Wide-ranging Online Data for Epidemiologic Research (CDC WONDER) database over the same reporting period.[33] LB incidence per US state was not correlated with rates of death due to ALS, MS, or PD. However, an inverse correlation was detected between LB and AD.[33] The authors concluded that their failure to accurately confirm any positive correlations between the geographic distribution of LB and the geographic distribution of deaths due to AD, ALS, MS, and PD provided further evidence that LB was not associated with the development of these common neurodegenerative conditions in an aging population.[33]

The Jarisch-Herxheimer reaction (JHR), an inflammatory cytokine-mediated reaction to dying spirochetes with a worsening of presenting symptoms, vasodilation, and myocardial dysfunction, may occur during antibiotic treatment for LB but is more common after antibiotic therapy forTBRFs.[25,34] 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.[25]

Southern Tick-Associated Rash Illness (STARI)

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 *(A. americanum),* more abundant in the southeastern and south central United States (see Fig. 296.3).[3,25–27] 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.[27] However, unlike LB, STARI is not a reportable infectious disease and has no diagnostic serologic tests, such as enzyme-linked immunosorbent assays (ELISAs), immunofluorescence assays, 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.[35] Because some patients have recovered from STARI without antibiotic treatment and there have been no long-term sequelae reported

FIG. 296.9 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 Public Health Image Library. Image 9875. Atlanta, GA: Centers for Disease Control and Prevention.)*

FIG. 296.10 *Ornithodoros* species soft tick, before *(left)* and after *(right)* a blood meal. The *Ornithodoros* species of soft ticks include *Ornithodoros hermsii, O. parkeri,* and *O. turicatae.* They are widely distributed throughout the mountainous regions of the western half of the United States and southwestern Canada at elevations above 1500 m and transmit the spirochetes that cause tick-borne relapsing fever (*Borrelia hermsii, Borrelia parkeri,* and *Borrelia turicatae*). *(From Tickborne Diseases of the United States. Soft tick. Atlanta, GA: Centers for Disease Control and Prevention.* https://www.cdc.gov/ticks/tickbornediseases/tickID.html.*)*

in STARI cases, some have questioned whether antibiotic therapy is indicated in STARI. Because distinguishing STARI from LB may be difficult, Wormser and coworkers[35] 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. 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.[35] In addition, the STARI rash was more often circular with central clearing than the LB rash.[35] 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 the potential for chronic arthritic and cardiac sequelae (see Table 296.2).[35]

Tick-Borne Relapsing Fevers

The TBRFs (see Chapter 240) 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 (Fig. 296.10). *Ornithodoros* ticks prefer indoor living—in cabins, caves, and crevices—and quickly abandon warm-blooded rodent hosts for egg laying (see Table 296.1).[34,36] 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 mouthparts. The wild animal host reservoirs of TBRF are maintained in birds and several mammals, most commonly rodents. Adult ticks can live for as long as 15 to 20 years and survive without blood meals for several years.

The *Ornithodoros* species of soft ticks in the United States include *Ornithodoros hermsii, Ornithodoros parkeri,* and *Ornithodoros turicatae* (see Fig. 296.10). These soft ticks are widely distributed throughout the mountainous regions of the western half of the United States and southwestern Canada at elevations above 1500 m and transmit the spirochetes that cause TBRF (*Borrelia hermsii, Borrelia parkeri,* and *Borrelia turicatae*). Humans typically come into contact with *Ornithodoros* soft ticks when they stay in frequently unoccupied and rodent-infested mountain cabins. The ticks emerge at night and feed briefly and unnoticed while the person is sleeping. Unlike the ixodid ticks, *Ornithodoros* ticks feed very rapidly, usually for less than 30 minutes, and always at night.[34,36,37] The bites are painless as a result of local anesthetic-like chemicals in the tick saliva. The bite site is marked after a few days by a small red to violaceous papule with a central eschar. 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 from tick bite to onset of the first febrile episode is 3 to 12 days.[36] Since most people are unaware that they have been bitten, the history of potential regional exposures in high-altitude mountainous regions is essential to the correct diagnosis.

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.[25,36,37] 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.[25,36,37] 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, and 10% will have hepatomegaly. 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, pulmonary edema, and cardiomegaly; and is often fatal.[37]

Laboratory diagnostics include identifying the spirochetes microscopically on peripheral blood smears and detecting their nucleic acids using PCR assays. Thrombocytopenia (platelets <150 μL) is a common finding on the complete blood count. Most patients will have elevated aminotransferase levels, unconjugated bilirubin, and prolonged prothrombin and partial thromboplastin times.[34,37]

Treatment strategies include tetracycline (500 mg or 12.5 mg/kg PO four times daily), or doxycycline (100 mg PO twice daily), or erythromycin (500 mg or 12.5 mg/kg PO four times daily for 10 days). Parenteral therapy with penicillin G or ceftriaxone is recommended for central nervous system (CNS) involvement.

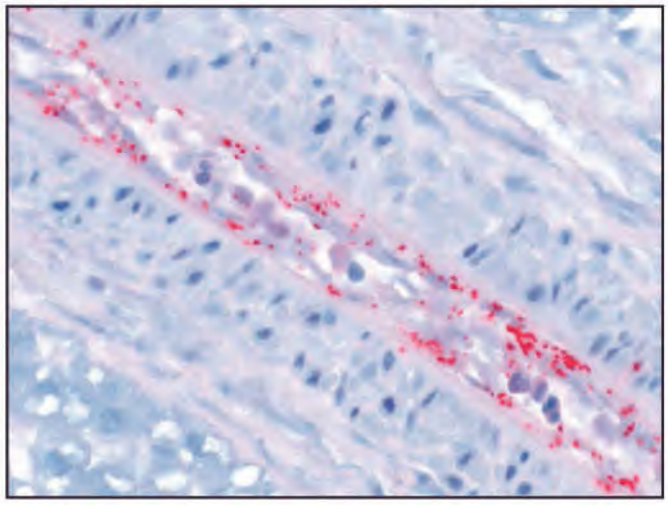

FIG. 296.11 *Rickettsia rickettsii* tissue biopsy specimen, with immunohistochemical stain. Immunohistochemical stain of a tissue biopsy specimen demonstrating intracellular gram-negative *Rickettsia rickettsii* bacteria *(red)* within vascular endothelial lining cells. Infection with *R. rickettsia* causes the systemic vasculitis of Rocky Mountain spotted fever that manifests initially as petechial skin lesions and may progress without antirickettsial therapy to microvascular leakage and ischemic vasculopathy with gangrene and autoamputation of digits and limbs (see Fig. 296.14). *(From Biggs HM, Behravesh CB, Bradley KK, et al. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever and other spotted fever group rickettsioses, ehrlichioses, and anaplasmosis—United States.* MMWR Recomm Rep. *2016;65:1–44.)*

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.[25] 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. Antispirochetal therapy for TBRF with penicillin instead of tetracycline has a slightly lower risk of associated JHR.[25]

Spotted Fever Group Rickettsial Infections

The family Rickettsiaceae contains two genera: the SF–causing genus *Rickettsia* and the scrub typhus–causing genus *Orientia* (see Chapters 186 and 191). The rickettsiae may be further stratified clinically into the tick-borne SF group and mouse mite–transmitted rickettsialpox caused by *Rickettsia akari* (see Chapter 187). 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 CNS, lungs, and myocardium (Fig. 296.11).

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 SFs are compared in a descending order of clinical severity of infection by preferred tick vectors and wild animal reservoirs in Table 296.3.

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 (*Rickettsia africae–Rickettsia parkeri* and the *Rickettsia conorii* subspecies); wider geographic distribution and greater virulence of existing strains (*R. rickettsii, R. conorii* subspecies, *Rickettsia 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, MSF in Europe, and QTT in Australia).[38–43] 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 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.

In the United States, the SF group rickettsioses are nationally notifiable infectious diseases that are primarily caused by the highly pathogenic *R. rickettsii* and less pathogenic rickettsial species such as *R. parkeri* and *Rickettsia* 364D (Fig. 296.12; see also Fig. 296.8). In 2016, Drexler and coinvestigators reported the results of their summary analysis of all passive surveillance data regarding SF group rickettsioses reported to the CDC during the period 2008–2012 in order to reassess the epidemiology of reported cases and to analyze any significant trends in incidence rates.[44] The incidence rate for SF group rickettsioses in the United States increased from 1.7 cases per million person-years in 2000 to 14.3 cases per million person-years in 2012.[44] SF group rickettsiosis cases were more frequently reported among males and persons of white race and non-Hispanic ethnicity.[44] Although the case-fatality rate (CFR) was low (0.4%), it was significantly higher for American Indian/Alaska Natives (relative risk = 5.4) and Asian/Pacific Islanders (relative risk = 5.7) and was highest overall in children under 10 years of age (CFR = 1.6%).[44] The authors recommended the increased use of PCR and the improved reporting of clinical signs, such as eschars, to better delineate the risk factors, incidence rates, and outcomes of SF group rickettsioses.[44] Following these recommendations, Herrick and coauthors utilized improved clinical reporting and molecular confirmation of *R. parkeri* infections by real-time PCR to establish a new geographic distribution and tick vector for *R. parkeri* infections in the United States (see Fig. 296.12).[45] Although all prior reported cases of *R. parkeri* rickettsiosis were described in the coastal Southeast and linked to transmission by the Gulf Coast tick (*Amblyomma maculatum*), Herrick and coauthors described one confirmed and one probable case of *R. parkeri* rickettsiosis acquired in a mountainous region of Arizona, well outside of the distribution range of the Gulf Coast tick and likely transmitted by a newly recognized tick vector, *Amblyomma triste* (see Fig. 296.12).[45]

The tick-borne SF rickettsioses share many common presenting features, including: (1) incubation periods of about 1 week; (2) flulike prodromes of fever, headache, myalgia, nausea, vomiting, and abdominal pain (that may mimic acute appendicitis in RMSF); (3) spotty rashes within 3 to 5 days of fever onset (Fig. 296.13); and (4) necrotic eschars at tick-bite sites (see Fig. 296.12B). Some SF rickettsial diseases may be "spotless," including RMSF in 10% to 15% of cases, complicating early differential diagnosis. 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. 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. helvetica, R. japonica, R. slovaca, R. aeschlimannii, R. honei,* and *R.* 364D (*R. philipii* [proposed]). 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*).

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. The pathognomonic rash starts distally on the wrists and ankles and then spreads centripetally up the limbs (see Fig. 296.13). 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 (see Fig. 296.11).

TABLE 296.3 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 Gipps Island, Victoria	*Ixodes* spp., especially *I. holocyclus* and *I. tasmania*	Rodents, bandicoots, wombats, cattle, domestic dogs
R. honei	Flinders Island SF	Southern Australia, Thailand	*Aponomma* spp.	Rodents
R. honei subspecies *marmionii*	Australian SF	Cape York, Queensland	*Haemaphysalis novaeguineae*	Similar to *R. australis:* Rodents, bandicoots, wombats, cattle, domestic dogs
R. africae and *R. parkeri*	African tick-bite fever	Sub-Saharan Africa, North America, South America, Caribbean	*Amblyomma* spp.	Rodents
R. 364D (*R. philipii* [proposed])	*R.* 364D "spotless" rickettsiosis with tick-bite eschar	California	*Dermacentor occidentalis*	Rodents, other small mammals
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

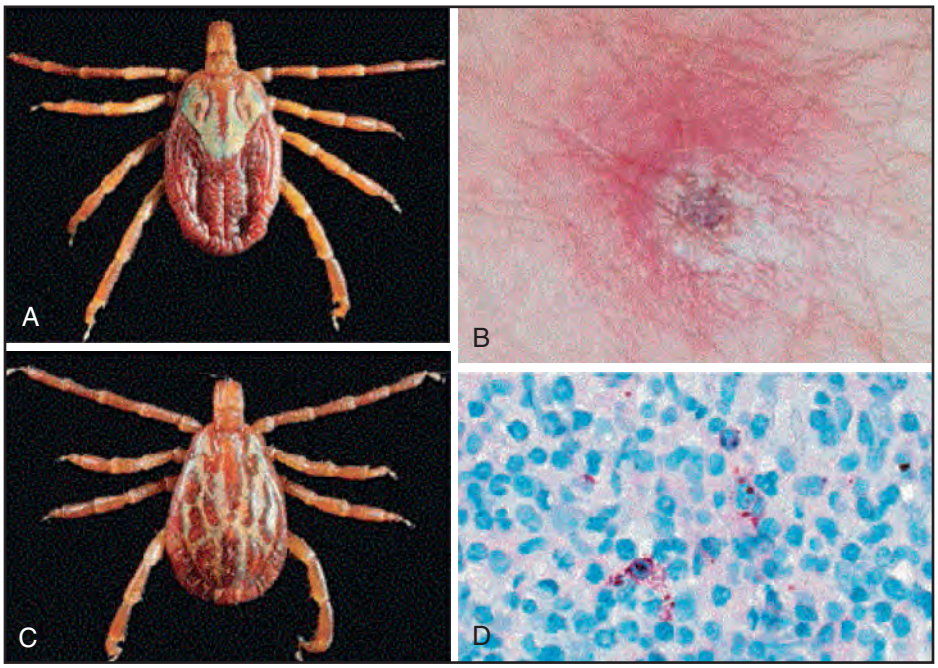

FIG. 296.12 *Rickettsia parkeri* rickettsiosis, preferred tick vectors, eschar, and immunohistochemical stain of tissue biopsy. *Rickettsia parkeri* rickettsiosis is transmitted by female (A) and male (C) Gulf Coast ticks (*Amblyomma maculatum*). Rickettsiosis is characterized by initial erythema, swelling, and itching at the bite site that ulcerates and then scabs over as an inoculation eschar (B). Patients often report fever, rash, and regional lymphadenopathy. Additional symptoms may include chills, myalgia, arthralgia, malaise, and headache. Laboratory diagnostics include immunohistochemical staining of eschar biopsy sites to demonstrate intracellular, gram-negative spotted fever group *Rickettsia* (D); growth of the organism in cell cultures from specimens; and nucleic acid speciation by quantitative polymerase chain reaction assays. Treatment is with oral doxycycline, 100 mg twice a day for a minimum of 10 days. *(From Straily A, Feldpausch A, Ulbrich C, et al. Notes form the field:* Rickettsia parkeri *rickettsiosis—Georgia, 2012–2014.* MMWR Morb Mortal Wkly Rep. *2016;65:718–719.)*

FIG. 296.13 Characteristic initial distal maculopapular-petechial rash of Rocky Mountain spotted fever. This rash is shown on the dorsal aspect of a child's right hand and wrist. *(From Public Health Image Library. Image 1962. Atlanta, GA: Centers for Disease Control and Prevention.)*

FIG. 296.14 Digital ischemia with gangrene resulting from Rocky Mountain spotted fever. Gangrene of the digits in a patient with ischemic vasculopathy from late-stage Rocky Mountain spotted fever caused by tick-transmitted infection with *Rickettsia rickettsii. (From Biggs HM, Behravesh CB, Bradley KK, et al. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever and other spotted fever group rickettsioses, ehrlichioses, and anaplasmosis—United States.* MMWR Recomm Rep. *2016;65:1–44.)*

Distal, digital skin necrosis and gangrene of the digits and limbs may occur in severe cases of RMSF and QTT from hypoperfusion (Fig. 296.14).

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 adult respiratory distress syndrome.

Initially, MSF caused by *R. conorii* was thought to be a more benign disease than RMSF. Severe cases of MSF with multiple eschars and multisystem disease similar to RMSF with CNS, renal, and pulmonary complications were first reported in 1981, and now appear to be increasing across Europe.[44] In a 1997 outbreak of MSF in Portugal, CFRs of 32% were recorded and exceeded those of untreated RMSF (CFR of 23%).[44] QTT, African tick-bite fever, and *R. slovaca*–associated lymphadenopathy are generally milder diseases than RMSF and MSF.[43] However, severe cases of QTT with RMSF-like complications, including renal insufficiency and pulmonary infiltrates, were recently reported from Australia.[43]

Although African tick-bite fever 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.[42,43] 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 immunofluorescence 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.[39] 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 of 7 days or until the patient has been afebrile for at least 48 hours and is improving clinically.

Q (Query) Fever

Q (query) fever (see Chapter 188) was first described in Australia in 1935, and its causative organism, *C. burnetii,* was isolated shortly thereafter.[46] *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.[46,47] 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.[47] In most cases, humans are infected not by tick bites but by inhaling spores or bacteria in aerosols contaminated with infectious particles in dried animal feces, milk, or products of conception.[46–48] 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.[46]

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.[46,47] Several cases of Q fever were reported among US military personnel deployed to Iraq and Afghanistan and in travelers returning from Asia, Latin America, and sub-Saharan Africa.[48,49] *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.

Over 3000 cases of acute Q fever presenting as pneumonia in most cases (62%) were reported from the Netherlands during the period 2007–2009. Most of the patients were males, smokers, and adults 40 to 60 years old. Very few patients worked in agriculture (3.2%) or in meat-processing plants, including abattoirs (0.5%). Public health investigators determined that the Q fever epidemic was caused by the aerosolization of contaminated dust particles from commercial dairy goat farms located in densely populated areas that were experiencing waves of Q fever–induced abortions in infected goats. Strict veterinary infectious disease control measures on dairy goat and sheep farms halted the epidemic in 2010, but left many infected patients at increased risk of developing chronic Q fever endocarditis years later.[50]

After an average 2-week incubation period (range, 2–29 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 unpasteurized 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.[49,51] Patients who are immunocompromised by pregnancy, congenital immunodeficiency disorders, cancer, human immunodeficiency virus infection/acquired immunodeficiency syndrome, organ transplant antirejection therapy, renal dialysis, or prolonged corticosteroid therapy are at greater risk for acquiring more severe and chronic Q fever infections.[47,51]

Recent reports have recommended that clinicians should consider a diagnosis of Q fever in the absence of infected livestock exposure and should preoperatively screen patients undergoing elective cardiac valve surgery for Q fever.[49,51] In an analysis of two national surveillance systems for Q fever cases in the United States during the reporting period 2000–2012, CDC investigators noted that most cases (61%) did not report any livestock exposures, but a substantial proportion reported drinking raw milk (prevalence rate, 8.4%).[49] The overall incidence rate of Q fever during the reporting period was 0.38 cases per million person-years, with a hospitalization rate of 62% and a CFR of 2.0%.[49] In 2015, Dutch investigators reported three cases of postoperatively diagnosed chronic Q fever endocarditis in patients requiring cardiac valve surgery.[51] Earlier diagnosis and antimicrobial therapy might have prevented progressive valve dysfunction from chronic Q fever endocarditis in these cases and eliminated the need for cardiac valvuloplasty or replacement.[51]

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 immunofluorescence assays, or on DNA detection by PCR assay.[46,48] The prognosis is usually excellent in the acute Q fever illnesses, and mortality is rare after appropriate antibiotic therapy with tetracyclines (doxycycline [100 mg PO twice daily for 14 days] is preferred) 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 and/or aortic aneurysms.[51] Chronically infected heart valves and vascular grafts will require surgical replacement.

Tularemia

Tularemia, also known as rabbit fever or deer fly fever (see Chapter 227), was first described as a zoonosis in squirrels in Tulare County, California, in 1911. Its causative agent, *F. tularensis,* was later identified as a gram-negative coccobacillus by Dr. Edward Francis during an investigation of deer fly fever in Utah in 1921.[52] 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. 296.15). Tick-transmitted tularemia is most commonly reported during the spring and summer (May to August) worldwide.[53] 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.[53] *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.[53–55]

In 2000, a cluster outbreak of primary pneumonic tularemia in 11 patients (with one fatality) was reported from Martha's Vineyard, Massachusetts.[56] A case-control study of the outbreak implicated aerosolized exposure to *F. tularensis* during summertime brush cutting and lawn mowing as significant (odds ratio, 9.2; 95% confidence interval, 1.6–68.0) risk factors for pneumonic tularemia.[56] Concerns about inhalational transmission and potential biological weaponization of *F. tularensis* led to the reinstatement of tularemia as a nationally notifiable infectious disease in 2000.[53,54] The CDC reported a total of 1368 cases of tularemia from 44 states from 1990 to 2000 (period prevalence, 124 cases/year; range, 86–93 cases/year), with most cases occurring in males during May to August in regional pockets, including Arkansas and Missouri, eastern Oklahoma and Kansas, southern Montana and South Dakota, and Martha's Vineyard.[53]

FIG. 296.15 *Dermacentor variabilis,* the American dog tick, questing for a host. This female American dog tick is a vector of tick paralysis in the southeastern United States and Pacific Northwest and is a vector of Rocky Mountain spotted fever in addition to the Rocky Mountain wood tick (*D. andersoni*) in the western United States. *(From Public Health Image Library. Image 170. Atlanta, GA: Centers for Disease Control and Prevention.)*

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.[54,55,57] 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 296.4).[53,55] 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.[54] 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%–25%); acute and convalescent serology comparing antibody titers (sensitivity, >85%); direct immunofluorescence antibody testing; and antigen detection by PCR assay (sensitivity, 50%–73%). Frequently accompanying laboratory abnormalities in tularemia include significant elevations in the erythrocyte sedimentation rate; significant leukocytosis (>10,000/μL), often with normal differential counts; and thrombocytosis.[55] 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.[55] Most cases in adults, including pneumonic tularemia, may be managed with fluoroquinolones alone (ciprofloxacin, 400 mg IV or 500 mg PO twice daily for 7–14 days, or levofloxacin, 500 mg IV or PO twice daily for 7–14 days), with aminoglycosides (gentamicin or amikacin, 3–5 mg/kg/day for 10–14 days) reserved for pediatric infections and

TABLE 296.4 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 inhalational 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

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 (see Chapter 192). 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 genera that are tick-borne bacterial infections of many mammals, including humans: *Ehrlichia* and *Anaplasma*.[58,59] 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 (Figs. 296.16 and 296.17).[58,59]

The human ehrlichioses are potentially fatal tick-borne infectious diseases caused by either *E. chaffeensis,* first identified in 1991, or *E. ewingii,* first identified in 1992.[60] Although the ehrlichioses became nationally notifiable infectious diseases in the United States in 1999, the case definitions did not differentiate between cases of ehrlichiosis and anaplasmosis or between *E. chaffeensis* and *E. ewingii* infections until 2008.[60] In 2016, Heitman and coworkers reported a summary analysis of ehrlichiosis cases in the United States reported to two national passive surveillance systems, the National Notifiable Diseases Surveillance System and the CDC's Case Report Forms.[60] During the reporting period 2008–2012, 4613 cases of *E. chaffeensis* infections were reported, for an incidence rate (IR) of 3.2 cases per million person-years.[60] The hospitalization rate was 57%; the CFR was 1%, and children less than 5 years of age had the highest CFRs (4%).[60] During the same period, 55 cases of *E. ewingii* infection were reported, for a national IR of 0.04 cases per million person-years with a hospitalization rate of 77% and no deaths.[60] Although prior reports had linked ehrlichiosis cases to concurrent immunocompromise, immunosuppressive conditions were only reported in 26% of cases.[60] Using improved surveillance of newly reportable diseases since 1999, the authors observed that the overall IR for ehrlichiosis infections had increased fourfold in the United States between 2000 and 2012; most cases occurred in immunocompetent persons; and children under 5 years of age had increased CFRs relative to older patients.[60]

The tick-borne Anaplasmataceae are endemic in the United States and have preferred geographic distributions, tick vectors, and wild and domestic animal reservoirs (Table 296.5). They spread from the infected

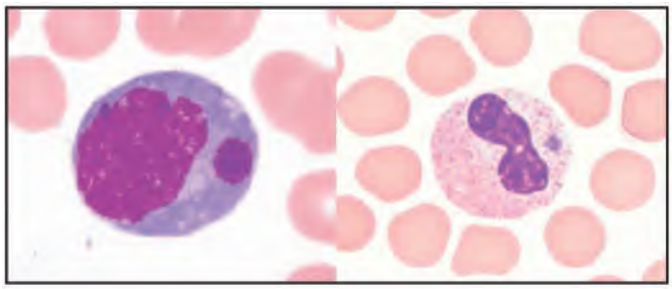

FIG. 296.16 Intracellular morulae in ehrlichiosis and anaplasmosis. Wright-stained peripheral blood smears that demonstrate an intramonocytic morula characteristic of ehrlichiosis caused by *Ehrlichia chaffeensis (left)* and an intragranulocytic morula associated with either ehrlichiosis caused by *Ehrlichia ewingii* or anaplasmosis caused by *Anaplasma phagocytophillum (right). (From Biggs HM, Behravesh CB, Bradley KK, et al. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever and other spotted fever group rickettsioses, ehrlichioses, and anaplasmosis—United States.* MMWR Recomm Rep. *2016;65:1–44. Photos courtesy J. Stephen Dumler, MD, University of Maryland, and Bobbi S. Pritt, MD, Mayo Clinic.)*

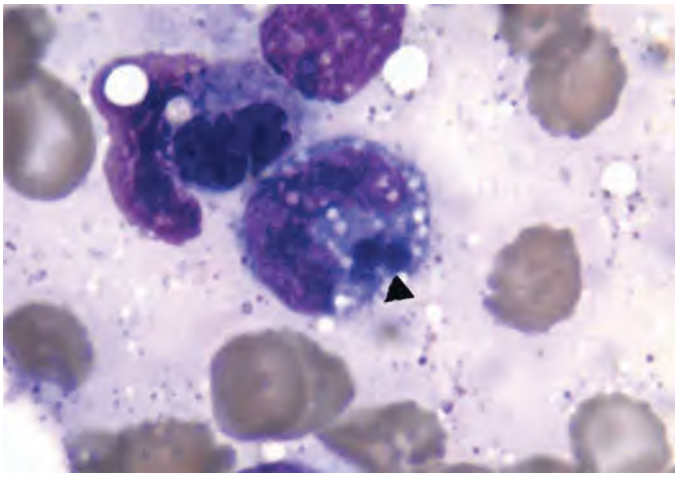

FIG. 296.17 *Ehrlichia chaffeensis* morula *(arrowhead)* within a monocyte (peripheral blood smear, Wright stain, ×1000.) *(From Safdar N, Love RB, Maki DG. Severe* Ehrlichia chaffeensis *infection in a lung transplant recipient: a review of ehrlichiosis in the immunocompromised patient.* Emerg Infect Dis. *2002;8:320–323.)*

TABLE 296.5 Human Ehrlichioses and Anaplasmosis

	HUMAN MONOCYTOTROPIC EHRLICHIOSIS	HUMAN GRANULOCYTOTROPIC EHRLICHIOSIS	HUMAN GRANULOCYTOTROPIC ANAPLASMOSIS
Former disease nomenclature	Human monocytic ehrlichiosis	Human granulocytic ehrlichiosis	Human granulocytic ehrlichiosis
Causative agent(s)	*Ehrlichia chaffeensis*	*Ehrlichia ewingii, Ehrlichia canis*—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 tick)	*Amblyomma americanum* (Lone Star tick), *Dermacentor variabilis* (American dog tick)	*Ixodes persulcatus* complex (American deer tick): *I. scapularis, I. ricinus, I. pacificus*
Animal reservoirs	White-tailed deer, coyotes, dogs	White-tailed deer, dogs	Rodents, deer, ruminants, horses
US regional distribution	Southeastern and south central United States	South central United States	Northeast US, upper Midwest, northern California
US regional prevalence	2–5 cases/100,000	Up to 10% of presumed 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 assay	Wright-stained peripheral blood smears with characteristic intracytoplasmic aggregates in neutrophils, DNA detection by PCR assay, increased immunofluorescence 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'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.[58,59] 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 296.5). 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 within 36 hours from the exposure.[58,59]

TICK-BORNE PROTOZOAL INFECTIONS

Babesial Infections

Babesiosis is a tick-borne, malaria-like zoonosis (see Chapter 281) that usually causes subclinical infections with prolonged parasitemias in humans and can be transmitted vertically in utero and horizontally by blood product transfusion.[61–65] 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 296.6). In severe cases, usually in elderly, immunocompromised, or splenectomized human hosts, massive hemoglobinuria may be associated with severe nonimmune hemolytic 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 northeastern United States and Wisconsin and better laboratory detection of increasing seroprevalence rates there and in California.[62]

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 296.6). 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 recognized in Eastern and now in Western Europe, a *B. divergens*–like babesiosis in the US Midwest caused by a *Babesia* species designated MO-1, and a babesiosis along the US Pacific Coast caused by *B. divergens*–like species designated as WA-1 and as CA types (e.g., CA-1, CA-2).[61–65] The *B. divergens*–related species are maintained in tick vectors by transovarian and transstadial transmission of the parasites, and most infections are transmitted by diminutive and usually unidentified and unnoticed nymphal ticks.[66] 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 in the upper Midwest (Minnesota, Wisconsin) and is caused by *B. microti,* a rodent *Babesia* species transmitted to humans by the same ixodid ticks (black-legged or deer ticks) that transmit Lyme disease (see Fig. 296.5).[61] Thus *B. microti* babesiosis in the United States parallels the distribution of Lyme disease, occurs in clusters in the same regional pockets as Lyme disease, and may coexist with Lyme disease in an increasing number of recognized cases.[61,62,67,68] *B. microti*–induced babesiosis occurs during the warmest months (April through October), with 80% of cases reported between May and August, when black-legged ticks are most active. White-tailed deer serve as the primary hosts for adult black-legged ticks, but white-footed mice (*Peromyscus leucopus*) and other small mammals serve as the zoonotic reservoir for *B. microti*. Humans are usually infected by unnoticed bites by nymphal deer ticks.

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

TABLE 296.6 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 Occurs during summer months in cattle-raising regions Targets splenectomized or immunocompromised patients primarily	Fulminant course with high case-fatality rate Fever, rigors, headache, myalgia, jaundice, hemoglobinuria, hemolytic anemia, acute renal failure, multiorgan failure
B. microti	Parallels the US 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 scapularis*	White-footed mouse *(Peromyscus leucopus)*	Incubation 1–4 wk after tick bites or 4–9 wk after blood transfusions Transmission primarily by nymphal ticks Targets older, not necessarily immunocompromised patients; particularly severe in those immunocompromised by HIV infection, advanced age, coinfections with *Borrelia burgdorferi* Seasonality parallels tick nymph activity; 80% of cases occur May–August	Often asymptomatic in young, healthy patients 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 Later hemolysis, hemolytic anemia, thrombocytopenia, jaundice, acute renal failure, especially in the splenectomized, elderly, or immunocompromised Complications include ARDS and DIC 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 Spring to autumn seasonality Targets splenectomized patients, 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 Targets the splenectomized, elderly, immunocompromised, premature infants 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. (relatives or subspecies of mule deer and bighorn sheep *Babesia* species)	US Pacific Coast, primarily rural and semirural areas of California	Ixodid ticks	Unknown; mule deer and bighorn sheep suspected	Incubation 1–4 wk 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; *HIV,* human immunodeficiency virus.

suspected *B. divergens*–related infections (Fig. 296.18). The serologic methods, especially useful when microscopic methods fail in low parasitemias, include indirect immunofluorescence antibody testing for specific immunoglobulin M antibodies in acute infections and PCR-based assays to detect *Babesia* DNA and species-specific DNA sequences.

Quinine (650 mg PO three times daily) and clindamycin (1.2 g IV twice daily or 600 mg PO three times daily), continued for 1 week or until parasitemias are in remission, can be used to treat babesiosis caused by all species.[61] Quinine and clindamycin are preferred therapies for WA-1 babesiosis and for severe *B. microti* infections, especially in older adults and splenectomized or immunosuppressed individuals.[61,65] 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 PO twice daily for 2 weeks) and with antimalarial agents for babesiosis.[61,68]

Although the most common clinical presentation of babesiosis is a febrile viral-like illness with laboratory evidence of nonimmune hemolytic anemia and thrombocytopenia, Woolley and coinvestigators recently reported 6 cases of warm autoimmune hemolytic anemia among 86 patients treated for babesiosis at their institution over a 7.5-year period.[69] All 6 patients were asplenic ($P < .0001$) and demonstrated positive direct antiglobulin tests for immunoglobulin G and complement component 3, which confirmed production of autoantibodies against erythrocytes.[69] Unlike the non–immune-mediated hemolysis which characterizes most cases of babesiosis and resolves after appropriate antimicrobial therapy, autoimmune hemolysis continues to cause hemolysis in babesiosis patients posttreatment and requires immunosuppressive therapy with corticosteroids and/or monoclonal antibodies, such as rituximab (anti-CD20 monoclonal antibody).[69] The investigators recommended that asplenic and immunosuppressed patients with worsening or recrudescent hemolytic anemia after treatment for babesiosis be evaluated for warm autoimmune hemolytic anemia and potential immunosuppressive therapy.[69]

TICK-BORNE VIRAL INFECTIONS

Tick-Borne Viral Encephalitides

The tick-borne viral infections are caused primarily by flaviviruses (family Flaviviridae) and may be divided into two separate clinical presentations, each with preferred tick vectors and wild animal reservoirs: the viral encephalitides (Table 296.7) and the viral hemorrhagic fevers (Table 296.8). 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;

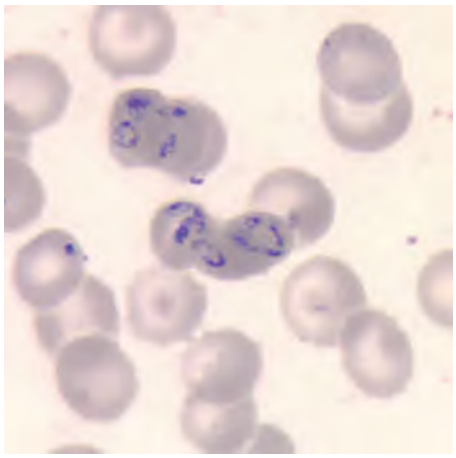

FIG. 296.18 ***Babesia microti.*** Note the vacuolated intraerythrocytic ring forms and the clumped extraerythrocytic forms (thin blood smear, Giemsa stain, ×1000). *(From DPDx Image Library. Babesiosis Image Library: Babesia sp. in thin blood smears stained with Giemsa, Fig. A. Atlanta, GA: Centers for Disease Control and Prevention.* http://www.cdc.gov/dpdx/babesiosis/index.html.*)*

TABLE 296.7 Representative Tick-Borne Encephalitis Viruses

VIRUS NAME	FAMILY TAXONOMY	GEOGRAPHIC DISTRIBUTION	TICK VECTORS	WILD ANIMAL RESERVOIRS
Central European tick-borne encephalitis virus (TBEV-Eu)	Flaviviridae	Europe, except Iberian Peninsula	Ixodid ticks, especially *Dermacentor marginatus, Ixodes persulcatus,* and *Ixodes ricinus*	Mammals: especially rodents, including hedgehogs, wood mice, and voles; also deer and other ungulates, birds, and domestic livestock, especially goats
Deer tick virus	Flaviviridae	US New England states (Connecticut, Massachusetts, New York)	*Ixodes scapularis*	Deer
Far Eastern TBEV (TBEV-FE)	Flaviviridae	Eastern Russia, China to far eastern Japan	*I. persulcatus*	Mammals: rodents, including hedgehogs, wood mice, voles; also birds, deer, other ungulates, and domestic livestock, especially goats
Langat virus	Flaviviridae	Malaysia	Ixodid ticks	Mammals: monkeys, rodents
Louping ill virus	Flaviviridae	United States, Scotland	Ixodid ticks	Sheep
Powassan encephalitis virus	Flaviviridae	Canada, US Northeast, far eastern Russia	*Ixodes* spp., particularly *I. scapularis, I. cookei; Dermacentor andersoni*	Mammals: rodents, skunks, and other medium-sized mammals, especially woodchucks
Siberian (Russian) spring-summer TBEV (TBEV-Sib)	Flaviviridae	Russia	*Ixodes* spp., particularly *I. persulcatus, I. ricinus*	Mammals: rodents, including hedgehogs, wood mice, voles; also birds, deer, other ungulates, and domestic livestock, especially goats
Turkish sheep encephalitis virus	Flaviviridae	Turkey	Ixodid ticks	Sheep
Bhanja virus	Bunyaviridae	Eastern Europe, Russia, central and West Africa	*Dermacentor* spp.; *Haemaphysalis intermedia*	Cattle, sheep, goats, hedgehogs
Crimean-Congo hemorrhagic fever virus	Bunyaviridae	Asia, Eastern Europe, Africa, Middle East	*Hyalomma marginatum, Hyalomma anatolicum*	Mammals: many domestic animals (buffalo, camels, cattle, goats, sheep), rabbits, rodents (hedgehogs), birds

TABLE 296.8 Representative Tick-Borne Hemorrhagic Fever Viruses

VIRUS NAME	FAMILY TAXONOMY	GEOGRAPHIC DISTRIBUTION	TICK VECTORS	WILD ANIMAL RESERVOIRS
Alkhurma hemorrhagic fever virus	Flaviviridae	Saudi Arabia	*Ornithodoros savignyi* (suspected)	Camels, sheep
Omsk hemorrhagic fever virus	Flaviviridae	Western Siberia	*Dermacentor reticulatus, Ixodes apronophorus*	Mammals: rodents, especially muskrats, water voles
Kyasanur Forest disease	Flaviviridae	Western India	*Haemaphysalis spinigera*	Mammals: especially monkeys, domestic livestock (cattle, goats, sheep), rodents, insectivores
Heartland virus	Bunyaviridae	Missouri, Kansas, Tennessee	*Amblyomma americanum*	Mammals: rodents, skunks, other medium-sized mammals
Crimean-Congo hemorrhagic fever virus	Bunyaviridae	Asia, Eastern Europe, Africa, Middle East	*Hyalomma marginatum, Hyalomma anatolicum*	Mammals: many domestic animals (buffalo, camels, cattle, goats, sheep), rabbits, rodents (hedgehogs), birds
Severe fever with thrombocytopenia virus	Bunyaviridae	China (mostly), Japan, Korea	*Haemaphysalis* spp., especially *H. longicornis* > *H. concinna*	Primarily domestic animals, especially goats
Bourbon virus	Orthomyxoviridae	Missouri, Kansas, Oklahoma	Unknown	Unknown

nonspecific serodiagnosis by comparing acute and convalescent sera for increased antibody titers or by hemagglutination inhibition; specific serodiagnosis by ELISA and antigen detection from blood or cerebrospinal fluid (CSF) by reverse-transcriptase PCR; no specific treatments other than supportive therapy; and significantly increased postinfection morbidity.[70]

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%–40%) and permanent neurologic morbidity rates (28%–30%) than the New World strains (CFR, 10%–15%; morbidity rate, <10%).[70] 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 296.7). 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.[70] 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 296.7).[70]

New World TBEVs: Powassan Encephalitis

Powassan encephalitis, first isolated in 1958, typifies a New World TBEV with a confined regional distribution in the New England states (especially Connecticut, Massachusetts, and New York) 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.[71] Cases occur from May to December and peak during June to September, when ticks are most active.[71] Patients with Powassan encephalitis present with somnolence, headache, confusion, high fever, weakness, ataxia, and CSF lymphocytosis.[71] Transient improvement may be followed by neurologic deterioration, evidence of ischemia or demyelination on magnetic resonance imaging (MRI), and slow recovery, often with permanent deficits including memory loss, weakness, ophthalmoplegia, and lower extremity paraparesis.[71–73] Unlike the Old World TBEVs, Powassan encephalitis is uncommon, with only 31 confirmed cases reported by the CDC from 1958 to 2001.[71] 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.[72]

Although uncommon, Powassan virus (POWV) disease can be transmitted to humans by blood-feeding ixodid ticks in as little as 15 minutes and in clinical presentation mimics other arthropod-borne viral encephalitidies, such as La Crosse encephalitis and West Nile virus neuroinvasive disease, in clinical presentation.[73] The CFR can be as high as 10%, and permanent neurologic sequelae are common.[73] Therefore clinicians should include POWV in their differential diagnosis of encephalitis in endemic regions, such as New England and Minnesota, during the mosquito-borne encephalitis season and also obtain serologic tests for POWV on CSF samples (POWV-specific neutralizing immunoglobulin M antibody titers).[72,73] Unlike the prolonged attachment time required for the transmission of LB, the short attachment time required for transmission of POWV underscores the critical importance of personal protective measures, such as repellents and clothing, in preventing tick-transmitted infectious diseases.[72,73]

The deer tick virus is closely related to Powassan virus and is also transmitted by ixodid ticks in the same endemic regions of New England.[74] It also causes a meningoencephalitis syndrome with a high CFR.[74]

Old World TBEVs

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.[70] In addition to tick bites, the Old World TBEVs may occasionally be transmitted by ingestion of unpasteurized milk products from viremic livestock (especially goats), breastfeeding, and slaughter of viremic animals.[70] Old World TBEV is typically biphasic in over 70% of cases, with an initial febrile flulike presentation followed by a 1-week (range, 1–21 days) symptom-free interval.[70] 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.[70] MRI 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.[70]

Tick-Borne Hemorrhagic Fever Viruses

The tick-borne hemorrhagic fever (TBHF) viruses (see Chapter 166) 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.[75] TBHFs are usually caused by either flaviviruses or bunyaviruses, which are distributed throughout eastern Europe, Africa, and Asia. As noted earlier, a previously unidentified tick-borne thogotovirus (family Orthomyxoviridae) was described in the United States in 2014 in a healthy man in eastern Kansas and later named Bourbon virus after the patient's county of residence.[21]

The TBHFs are characterized clinically by biphasic illnesses that present as febrile flulike symptoms and end as hepatomegaly with liver failure and hemorrhagic manifestations (petechiae, purpura, subconjunctival and pharyngeal hemorrhage, thrombocytopenia, cerebral hemorrhage, severe intrapulmonary 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 real-time 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.[75,76] All patients with TBHFs should be placed in isolation, and strict universal precautions, including personal protective equipment, should be practiced by all medical personnel because nosocomial transmission has been reported, most likely by the generation of infectious aerosols during bag-valve-mask ventilation and bronchoscopy.[76] 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 (see Chapter 149) 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 of rabbits (CTFV-Ca) and the Salmon River virus (SRV) of Idaho, serotypes of the CTFVs; and the European Eyach virus (EYAV).[77] 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.[77] Among the coltiviruses, CTFV has the widest host range, which includes squirrels, other rodents, rabbits, porcupines, marmots, deer, elk, sheep, and coyotes.[77] 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 cunniculus*) but also rodents, deer, domestic goats, and sheep for EYAV.[77] The coltiviruses are maintained in nature by ixodid ticks that blood-feed on wild animal hosts with prolonged viremias and then transmit coltiviruses transstadially but not transovarially.[77] 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.[77] CTFV has also been transmitted by blood transfusion and congenitally.[77]

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 and are strong indicators for the diagnosis.[77] 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.[77] 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.[77] Serologic diagnostic methods to detect anticoltivirus antibodies include complement fixation test, seroneutralization assay, immunofluorescence assay, ELISA, and Western immunoblot assay.[77] The most specific and confirmatory laboratory diagnostic methods include reverse-transcriptase 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.[77] 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.[78–80] 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.[81–83] In the US Pacific Northwest, tick paralysis is caused by the American dog tick (*D. variabilis*) or the Rocky Mountain wood tick (*D. andersoni*) during April through June, when *Dermacentor* ticks emerge from hibernation to mate and to seek blood meals (see Figs. 296.1 and 296.15).[81–83] 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.[82,84] 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.[84]

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.[83] 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.[81]

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 296.9).[84–87] 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 296.9).[83,87]

Before 1954, postmortem examinations of persons who died suddenly of unexplained paralytic illnesses demonstrated attached ticks on their heads and necks.[78–80] In a review of Canadian tick paralysis cases in the 1950s before the widespread availability of mechanical ventilation in intensive care units, Rose[88] reported a CFR of 10% to 12% without tick removal. In a review of 33 tick paralysis cases in Washington State over the period 1946–1966, Dworkin and coworkers[86] reported a CFR of up to 10%, with most deaths occurring in the 1940s. In a 60-year meta-analysis of confirmed tick paralysis cases in the United States, Diaz[87] reported a CFR of 6% in the first 30 years, a seasonal pattern of case clusters in children and adults in both urban and rural locations, and a significant increase in initial misdiagnoses of tick paralysis as Guillain-Barré syndrome in more recently reported cases. 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.[87] In all cases, the diagnosis of tick paralysis was later established when attached ticks were discovered either by caregivers or by cranial neuroimaging studies.[87] 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.[78,79,86,87]

The emergence of a new form of acute paralysis in children is relevant to the clinical recognition and diagnosis of tick paralysis. In 2014, 120 cases of acute-onset flaccid limb weakness in children were reported in

TABLE 296.9 Clinical Differential Diagnosis of Tick Paralysis Versus 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 h	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) White cells (per mm^3) Differential counts	 Normal <10 Normal	 High (≥40) <10 <10 mononuclear cells/mm^3	 Normal to high Variable	 High >10 Lymphocytosis
Nerve conduction studies	↑ Latency in distal motor nerves ↓ Nerve conduction velocity ↓ Amplitude of motor and sensory nerve action potentials	Similar	Similar	Similar
Time to neurologic recovery	Rapid, ≤24 h 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.

clusters of two or more cases from states throughout the continental United States.[89] These cases all shared similar presentations and diagnostic features, including short prodromes of fever and respiratory or gastrointestinal symptoms before onset of focal limb weakness in one or more limbs and scattered lesions in the gray matter of the spinal cord on MRI. The condition was later described as acute flaccid myelitis (AFM) based on its diagnostic neuroimaging findings. Temporal associations between AFM and enterovirus D68 (EV-D68) infections were reported in some cases.[89]

By 2015, the CDC established a case definition for AFM that required the following criteria: (1) acute onset of flaccid limb weakness in one or more limbs; (2) CSF leukocytosis (white blood cell count >5/mm^3, corrected for red blood cells); and (3) MRI-documented lesions confined to the gray matter of the spinal cord (later lesions were detected throughout the neuraxis).[90] By 2016, the CDC reported an increase in cases of AFM, with 144 cases confirmed by the CDC case definition in 37 states.[90]

In an outbreak in Washington State during September–November, 2016, 10 confirmed cases of AFM were reported with EV-D68 detected by PCR in nasopharyngeal swabs from two patients and with enterovirus A71 (EV-A71) detected by PCR in a stool specimen from a third patient.[91] In all cases, poliovirus and West Nile virus were ruled our as infectious causes of acute flaccid paralysis. Since both EV-D68 and EV-D71 have been associated with cluster outbreaks of acute flaccid paralysis in children in the past, an infectious or postinfectious autoimmune etiology of AFM was suspected.[92,93]

Although no deaths from AFM have been reported, several cases have required mechanical ventilatory support, and others have been treated by intravenous immunoglobulin G therapy as recommended for Guillain-Barré syndrome.[91] Some of the largest cluster outbreaks of AFM have now been reported from states also reporting the highest prevalence rates for tick paralysis in children (e.g., Colorado and Washington). Clinicians should therefore include AFM in their differential diagnosis of acute flaccid paralysis in children and should collect specimens for laboratory testing (blood, nasopharyngeal swabs, CSF, and stool); order appropriate neuroimaging studies (MRI of the entire neuraxis from the cerebrum to the cauda equina); and exclude or confirm any infectious or noninfectious etiologies, including tick paralysis.[89–91]

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 to 48 hours after tick removal.[84] The administration of *I. holocyclus* antitoxin before tick removal and prolonged observation for hypoventilation have been recommended.[84]

RED MEAT ALLERGY AFTER TICK BITES

Immunoglobulin E (IgE)-mediated urticarial and anaphylactic reactions to tick bite–injected salivary proteins were initially described in Australia in the 1980s following paralysis tick *(I. holocyclus)* bites.[93a] Between 2003 and 2007, 25 patients who lived in a paralysis tick–endemic area of Sydney, northern New South Wales, developed red meat allergies after extensive local reactions to paralysis tick bites, suggesting an immunologic cross-reaction between arthropod-injected and foodborne proteins.[93b] Although red meat allergic reactions are rare and responsible for only 3% of food allergies, red meat allergies have been reported following antigenic sensitization by ingestion of cow's milk, by exposures to bovine and porcine albumin, by intravenous chemotherapy with the chimeric mouse-human monoclonal antibody, cetuximab, and by prior allergic reactions to foods containing bovine and porcine-derived gelatin.[93c] The sensitizing foodborne allergen in all of these exposures was determined to be glalactose-alpha-1,3-galactose (α-gal), an oligosaccharide constituent of all red meats (beef, lamb, pork, horse, and game meats) that structurally resembles the human blood group antigen B.[93d] The association between tick bites and red meat allergies, however, remained uncertain until recently.

In 2018, Carter and colleagues at the US National Institute of Allergy and Infectious Diseases (NIAID) identified IgE antibodies to α-gal in 6 of 70 patients with idiopathic anaphylaxis, all of whom reported prior tick bites and lived in Lone Star tick (*A. americanum*)-endemic US states (see Fig. 296.3).[93e] Unlike typical foodborne allergies, which occur within minutes of ingestion, α-gal allergies following tick bites are delayed by 3 to 6 hours and present with combinations of urticarial reactions, angioedema, and anaphylaxis.[93e] In addition to having tick bite histories in Lone Star tick–endemic regions, all 6 patients in that study were males and had non-B blood types.[93e] Two of the 6 patients also had indolent systemic mastocytosis, a condition known to predispose patients to venom allergies, and suffered more severe anaphylactic reactions.[93e] After adopting red meat–free diets that included chicken, turkey, and seafood, all 6 patients experienced no further episodes of unexplained anaphylaxis for follow-up periods ranging from 18 months to 3 years.[93e] The authors concluded that α-gal allergy should be excluded as a cause of unexplained delayed anaphylaxis following red meat

ingestion, especially in patients residing in Lone Star tick–endemic regions of the United States. In addition, the NIAID study identified several potential risk factors for red meat allergy after tick bites including (1) male gender due to increased outdoor exposures to repeated tick bites, (2) non-B blood type as the B-blood group antigen resembles α-gal and probably provides cross-protection, and (3) a history of indolent systemic mastocytosis.[93e]

Like tick paralysis, tick-bite induced red meat allergy is a rare, noninfectious phenomenon. It results from prior sensitization to α-gal following specific tick bites and may occur in a wide geographic distribution. All life stages of ticks feed on warm-blooded mammals and absorb α-gal sugars from their hosts. During human blood-feeding, ticks inject small amounts of α-gal into bite wounds in addition to other salivary chemicals, such as anticoagulants and local anesthetics. Repeated tick bites over time may predispose certain individuals to IgE-mediated allergic responses including anaphylaxis on reexposures to α-gal antigens in red meats, dairy products, drugs and foods containing gelatin, and during cetuximab chemotherapy.[93e,93f]

TICK-TRANSMITTED COINFECTIONS

Ticks may be asymptomatically coinfected with several pathogens that can be simultaneously transmitted to human hosts during blood feeding. In 1996, Krause and coworkers initially reported increased duration and severity of illness in patients coinfected with the Lyme disease spirochete, *B. burgdorferi,* and *B. microti,* the protozoan agent of babesiosis.[94] In 1997, Schwartz and coinvestigators in the eastern United States first identified coinfections in ixodid ticks with *B. burgdorferi* and *Anaplasma phagocytophila*, the bacterial agent of anaplasmosis.[95] In 1997, Nadelman and coauthors reported the first US case of concurrent Lyme borreliosis and anaplasmosis.[96]

In 2002, Belongia reviewed the epidemiology and impact of human coinfections from ixodid tick bites in the United States and reached the following conclusions[68]:

1. Ixodid tick coinfections with *B. burgdorferi* and *B. microti* ranged regionally from 2% in New Jersey to 19% on Nantucket Island, Massachusetts.[68]
2. Ixodid tick coinfections with *B. burgdorferi* and *A. phagocytophila* were consistently less common regionally, ranging from 1% to 6% in six selected regions, with occasional regional pockets of high prevalence (26% in Westchester County, New York).[68]
3. Among patients with confirmed tick-borne coinfections, the highest regional coinfection rates reached 39%; and the most commonly diagnosed human tick-borne coinfections in the Eastern United States were Lyme borreliosis and babesiosis, which accounted for 80% of coinfections.[68]
4. Human coinfections with Lyme borreliosis and anaplasmosis were less common and accounted for 3% to 15% of coinfections in Connecticut and Wisconsin.[68]
5. As initially described by Krause and coinvestigators in 1996, coinfections with Lyme borreliosis and babesiosis were more severe, with a longer duration of illness, than Lyme borreliosis alone.[67,94]
6. Lastly, clinicians should always consider the possibility of tick-borne coinfections in overlapping endemic regions; order appropriate laboratory tests for the molecular or serologic detection of multiple tick-borne pathogens; and prescribe the most appropriate antimicrobials for each infecting agent.[67,94–97]

To date, most tick-borne coinfections have been reported from geographic areas with overlapping endemic ranges of infected ticks capable of transmitting multiple pathogens during blood-feeding. The eastern black-legged or deer tick, *I. scapularis* (see Fig. 296.5), has been implicated most often by transmitting Lyme disease and babesiosis in a northeastern coastal band extending from New Jersey north to New Hampshire. *Ixodes scapularis* has also cotransmitted Lyme disease and anaplasmosis in an upper Midwest geographic band extending from Wisconsin across Minnesota to Canada, another endemic region of overlapping tick-transmitted infectious diseases (Fig. 296.19).

Although unusual, ticks have also transmitted pathogens and paralytic toxins. In 2003, Inokuma and coauthors reported a case of tick paralysis in a 59-year-old male traveler returning to Japan from a vacation to the Gold Coast of Queensland, Australia.[98] The authors noted that the patient demonstrated both the characteristic features of Australian tick paralysis and other unusual features, suggestive of a tick-borne rickettsial coinfection.[98] The characteristic features of Australian tick paralysis included a prolonged prodrome of lethargy and weakness, ascending paralysis beginning in the right leg, external ophthalmoplegia, and constricted visual fields.[98] The more unusual features of the case included febrile prodromal and incubation periods, a tick-bite eschar with surrounding anesthesia on the scalp, and regional submandibular lymphadenopathy.[98] The results of all initial laboratory studies were within normal limits, including CSF analysis.[98] Following the self-removal of a semiengorged gravid female *I. holocyclus* tick from his scalp, the patient's paralysis and visual findings gradually resolved, but the anesthesia surrounding the tick-bite eschar persisted for over 2 weeks.[98]

Subsequent serologic comparisons of rising antibody titers to other tick-borne diseases in paired serum samples suggested that the more unusual features of the case could have been consistent with coinfection by *R. helvetica,* a common cause of tick-bite eschar with regional lymphadenopathy in Europe.[22] Additional Western blot analysis demonstrated cross-reactivity of the patient's serum against several high-molecular-weight outer membrane proteins, all species-specific for *R. helvetica.*[10] The authors concluded that the patient may have been coinfected with *I. holocyclus*–transmitted tick paralysis and *R. helvetica* tick-bite fever with eschar and regional lymphadenopathy. In addition, the authors noted that a rickettsial species closely related to *R. helvetica* had been isolated from ticks in Japan in 2002 and that further investigations of the distributions of *R. helvetica*–like rickettsia in Australia and Japan should be conducted.[98]

In summary, the ability of ixodid ticks to be coinfected with multiple pathogens and to transmit coinfections to humans during prolonged blood-feeding has now been demonstrated in the United States. The immunologic confirmation of tick-borne coinfections by rising antibody titers in paired serum samples and/or by nucleic acid determinations using PCR will take a significant period of time and may only be available in state and federal reference laboratories. Some critical tick-borne infections, such as RMSF, Lyme disease meningoencephalitis, and babesiosis with splenomegaly may require immediate, empirical intravenous antibiotic management prior to confirmatory laboratory diagnoses. In such cases, Diaz has recommended the generation of probability-based decision tree models to expose potential coinfections based on: (1) the regional distributions and prevalence rates of potentially coinfected tick vectors; (2) tick identification by experts; and (3) any cutaneous presenting manifestations of tick bites, such as eschars or erythema migrans, if present (Fig. 296.20).[99] Clinicians should suspect tick-borne coinfections in returning travelers and all patients with clinical and immunologic evidence of multiple infecting agents, especially in cases of unusual presentation or severity, prolonged duration, or nonresponse to single (typically doxycycline) antibiotic therapy.[99]

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

A number of strategies can be used in the prevention and control of tick-borne infectious diseases and paralytic poisonings, 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 virus as causes of permanent paraparesis. 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.[84]

In addition to immunization, available only for Old World TBEVs, antibiotic therapy after presumed ixodid tick bites with erythema migrans has been recommended as a prophylactic therapeutic strategy for the

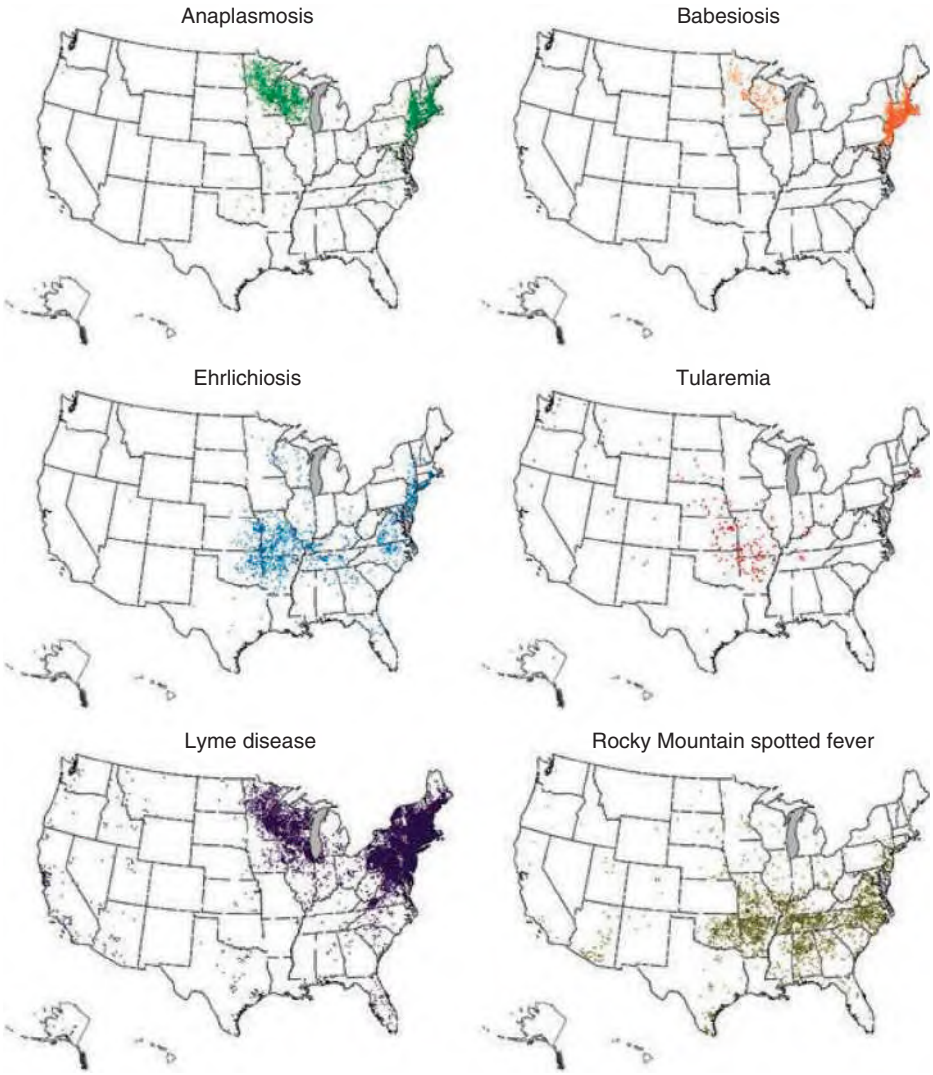

FIG. 296.19 Regional US maps of the most common tick-transmitted infectious diseases. One colored dot is one reported case in 2015. The eastern black-legged or deer tick, *Ixodes scapularis* (see Fig. 296.5), has been implicated most often in coinfections by transmitting Lyme disease and babesiosis in a northeastern coastal band extending from New Jersey north to New Hampshire. *Ixodes scapularis* has also cotransmitted Lyme disease and anaplasmosis in an upper Midwest geographic band extending from Wisconsin across Minnesota to Canada, another endemic region of overlapping tick-transmitted infectious diseases. *(From* Tickborne Diseases of the United States: A Reference Manual for Health Care Providers. *4th ed. Atlanta, GA: Centers for Disease Control and Prevention; 2017.)*

primary prevention of some tick-borne infections.[100] 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.[100]

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.[64,65,69] 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 mouthparts, 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

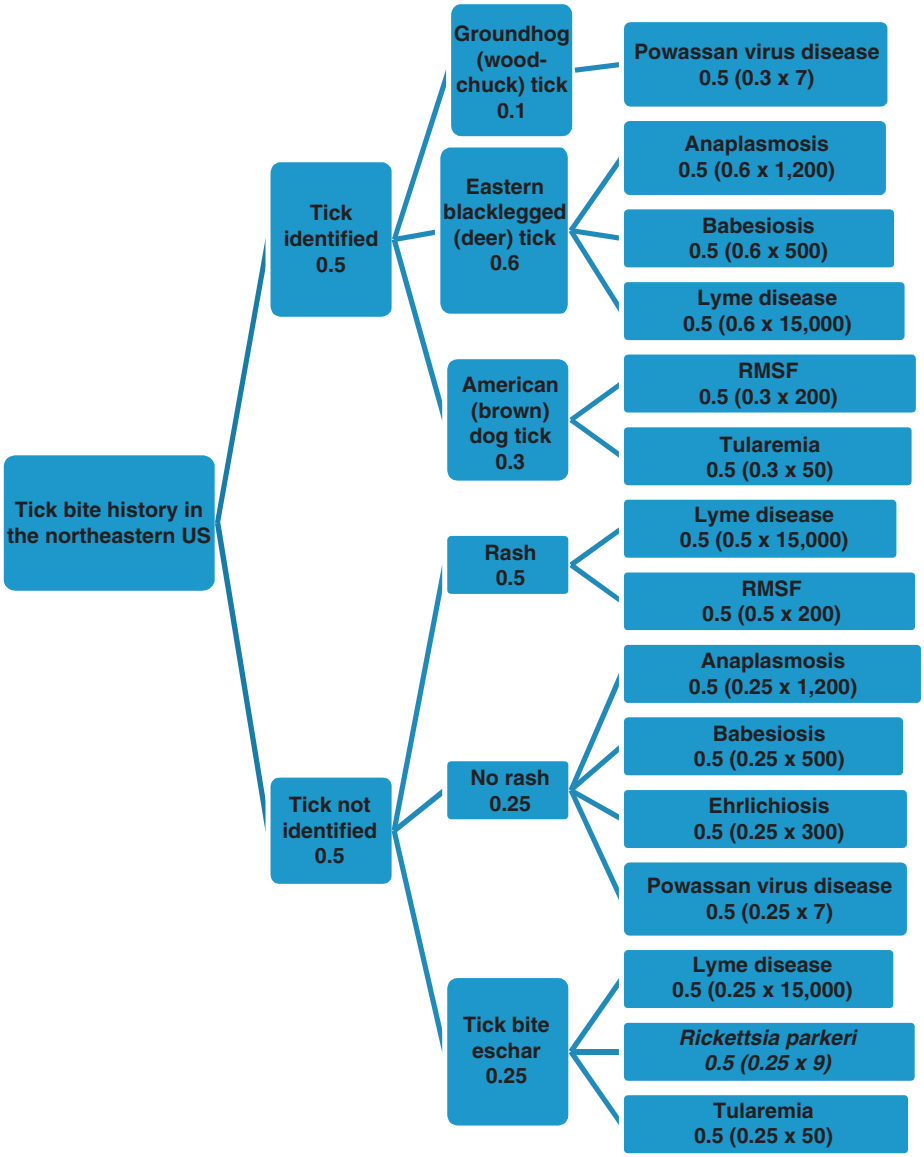

FIG. 296.20 A hypothetical probability-based decision tree model for predicting tick-borne infections and coinfections in an endemic region. This sample hypothetical decision tree illustrates the method for analyzing decision tree models of potential tick-borne infections and coinfections in the northeastern United States. Decision trees are solved from right to left. (1) The first and largest entry on the far right is the outcome of confirmed number of cases by the CDC for the given year (2015 was used here). (2) Distributions of tick vectors are expressed as a percent or as probabilities. (3) The sum of probabilities for any set of possibilities must equal 1.0. (4) Multiply from right to left to solve for the greatest expected values. The calculations for expected values are shown in the outcomes boxes on the right.*Predictions:* Based on solution of the decision tree, the most common tick-borne infections in this region will be Lyme disease transmitted by an Eastern black-legged (deer) tick, with an expected incidence rate of 21% (10,125/48,143); followed by anaplasmosis transmitted by the same tick, with an incidence rate of less than 1% (510/48,143); and followed by babesiosis transmitted by the same tick, with an incidence rate of less than 1% (213/48,143). The remaining 79% of tick-borne diseases in the northeastern United States will be caused by other pathogens and other tick vectors, including the groundhog (woodchuck) tick and the American (brown) dog tick. Coinfections, although rare, may occur more commonly with Lyme disease and babesiosis than with Lyme disease and anaplasmosis. Triple infections with Lyme disease, anaplasmosis, and babesiosis are possible but unlikely, and will be transmitted by the Eastern black-legged (deer) tick. *RMSF,* Rocky Mountain spotted fever.

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.

CONCLUSIONS

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 doxycycline) or superpathogen capabilities, either by nature's own design or human terrorist intent.