



Tick-Borne Illness for Emergency Medicine Providers

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Abstract

Purpose of Review Ticks are the most important vectors of human diseases after mosquitoes. Emergency physicians throughout the USA can be expected to encounter Lyme disease, Rocky Mountain spotted fever, ehrlichiosis, and other disorders based upon geographic location.

Recent Findings The number of identifiable disorders transmitted by these arthropods has increased in recent years. Severe fever with thrombocytopenia syndrome has only been described within the past decade, and the new millennium has seen over 10 new species of rickettsial disease discovered.

Summary Ticks transmit more pathogenic species than any other group of blood-feeding arthropods. This review provides an update on the diagnosis and management of the diseases most likely to be encountered in clinical practice.

Keywords Tick-borne illness · Rocky Mountain spotted fever · Babesiosis · Febrile illness · Lyme disease

Introduction

Ticks are small, approximately 3–5 mm, with immature forms 0.5–2 mm, arachnid obligate parasites of vertebrates and the most important vector of transmission of zoonotic diseases to humans worldwide and in the USA [1, 2]. Theobald Smith and Frederick L. Kilborne were the first to show that a tick can transmit an infection to a vertebrate host in 1893 [3]. There are two medically important families: the *Argasidae* and *Ixodidae*, commonly known as hard and soft ticks respectively [4]. Hard ticks tend to attach and feed for many hours to days with most parasites only transmitted once the tick has been attached for at least 4 h, while soft ticks feed for minutes at a time often residing in rodents' burrows or birds' nests [5]. Over one third of all species of *Ixodidae* are known to feed on humans [6]. Mites are tiny arachnids distinct from ticks

which include some parasitic forms such as *Sarcoptes scabiei* that causes scabies; infected mouse mites (*Liponyssoides sanguineus*) which spread rickettsialpox caused by *Rickettsia akari*; and *Leptotrombidium deliense*, a form of chiggers which transmits *Orientia tsutsugamushi*, the cause of scrub typhus. This review will concentrate on tick-borne illness with emphasis on those entities most likely to be encountered by emergency practitioners.

Some Background on Ticks

Ticks typically undergo three life stages that include a larva that hatches from an egg, a nymph, and an adult, with a blood meal required for each stage of development and additionally one or more for the adult female to lay eggs [4, 6]. Ticks hunt by positioning themselves on vegetation in a process called questing and respond to stimuli such as carbon dioxide, heat, shadows, and vibrations [2]. There are a wide range of hosts that ticks parasitize on, facilitating their persistence and spread in the environment.

Human Exposure

Humans typically play the role of an incidental host for any stage of a tick's development. Humans' exposure to ticks is increased during the warmer part of the year, typically from April to October in the USA. However, tick bites occur even

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in cold weather; Rocky Mountain spotted fever (RMSF) cases are reported to CDC from December to January from the north of the contiguous forty eight states [7]. The incidence of tick-borne illnesses in the USA seems to be increasing [4, 8, 9]. This may be due to a number of factors: better surveillance and reporting, increased public and clinician awareness, people spending more time in nature, natural areas incorporated into residential development, an increase in number of tick's hosts such as white tail deer [6], and, possibly, climate warming [10]. Any time a tick acquires a pathogen from an infected host, it can be passed on to the next stage of their development or to the offspring in the developing eggs.

Non-infectious Considerations

In addition to transmitting bacterial, viral, and protozoan infections, tick bites can rarely result in flaccid paralysis [11], and acute allergic and anaphylactic reactions [12], and even induce meat allergy in patients [13]. Patients can present after a known exposure seeking ways to mitigate a risk of becoming ill, or with a tick-borne illness and no recollection or knowledge of a previous tick bite. Patients can also seek help simply to remove an attached tick. See Table 1 for some non-infectious tick bite-associated medical problems. See Tables 2 and 3 for infectious diseases transmitted by ticks. Table 3 is dedicated to tick-borne viral illnesses, for which treatment is largely supportive.

Management of the Patient with a Reported Tick Bite

Ticks are ubiquitous in nature and are frequently found in and around homes [17]. Patients can present to the ED either with a tick still attached requiring its removal, or shortly after having removed one themselves seeking ways to reduce chances of developing a tick-borne infectious complication.

Removal of the Attached Tick

In rare cases of tick-induced anaphylaxis, immediate administration of epinephrine is indicated [13]. This is the only time when killing of the tick in situ with application of ether or dry freezing is recommended prior to its removal [12, 13]. Otherwise, gentle, steady, upward, and backward pulling on the tick with fine forceps is all that is necessary to remove it. *Ixodes* ticks cement their mouth parts in the skin with a special substance at the attachment time and if the tick is accidentally pulled apart, those parts can be safely left in situ [15]. The site can then be cleaned with rubbing alcohol. Numerous commercial devices are described as aids in tick removal, for example mildly heated forceps or low-energy radiofrequency devices [22] that may decrease the chances of fragmenting the tick.

Prophylaxis Against Infection: Current Status

No vaccine is currently available in the USA for any of the tick-borne illnesses [7]. A single 200 mg dose of doxycycline in adults or 4 mg/kg in children older than 8 years (there is evidence now that doxycycline is safe at any age) may be reasonable after a tick bite is highly endemic for Lyme disease provided it is given within 72 h of the bite and if the clearly identified *Ixodes scapularis* tick was attached for at least 36 h [14, 15]. The patient should be warned that this does not completely eliminate the chance of Lyme disease development and may not protect from either ehrlichiosis or anaplasmosis which commonly co-infect *Ixodes* ticks [6, 23].

Management of Selected Tick-Borne Illnesses in the Emergency Department

Several of tick-borne infectious diseases are both common and mandate an early treatment for an optimal outcome. It is important to recognize that a large proportion of patients with proven tick-borne zoonosis do not recall a tick bite [5, 7]. Ticks' larva and nymph forms are minute, spread pathogens as efficiently as the adults, will fall off to the ground after the feeding, and are commonly overlooked by their human hosts. Some of the tick-borne diseases are caused by bacteria and parasites and have specific therapies recommended (see Table 2).

Lyme Disease

In the USA, Lyme disease (LD) is the most common vector-borne illness [15] with *Borrelia burgdorferi* being the pathogen [24]. It may be carried by small rodents such as wild mice and voles, and the disease has an incubation period of 3–20 days. The number of cases has been steadily increasing over the past two decades [25]; the states of Maine, Minnesota, New Hampshire, Vermont, and Virginia now account for over 90% of all cases [15]. Children aged 5–14 have a higher incidence of LD than adults, and over half of all cases are reported in June and July [15]. *Ixodes scapularis* ticks are the vectors, and the tick must be attached for at least 36 h to transmit the pathogen [8].

Similarly to other spirochetal illnesses, Lyme disease occurs in stages. Erythema migrans, an expanding erythematous rash, with or without central clearing, should be greater than 5 cm in diameter to meet diagnostic criteria, and acute febrile illness are the earliest and most common manifestations. Erythema migrans occurs in 80% of Lyme disease; it begins at the site of a tick bite after a delay from several to up to 30 days (usually 1 to 2 weeks [8]). Initial localized erythema from local irritation appearing at the tick bite site is not a sign

Table 1 Non-infectious tick bite-associated medical conditions [1, 2•, 11–14]

Problem	Prevention	Management	Comments
Attached tick	Avoidance of areas where ticks are common such as tall grass or dense shrubs [1, 2•]; protective dress including closed toe shoes, long sleeve light clothing with pants tucked into socks, regular application of appropriate insect repellent (DEET concentration at least 10%, long acting DEET (ultrathon tm), or picaridin) to skin and wearing of permethrin-treated clothing [1, 2•, 14], regular skin and clothing checks for ticks	Remove by grasping the tick's body with fine tweezers and steady pull backwards and upwards. Careful avoidance of squeezing or disturbing the tick prior to removal to avoid regurgitation. If tick anaphylaxis is a concern, killing the tick with either permethrin or freeze drying in situ prior to removal is recommended	Common areas of attachment include groin, axilla, and scalp. Many tick-borne illnesses are not transmitted if the attached tick is promptly removed. Only local wound care is recommended if attached tick's mouth parts are left behind unless a wound infection or foreign body granuloma forms
Allergic reaction to tick bite	Avoidance of tick bites, prompt tick removal	Usual care with early administration of epinephrine for anaphylaxis [12]. EpiPen or similar at discharge	Risk is increased in individuals with atopy. Severity ranges from mild local reactions to exuberant local edema that can be mistaken for cellulitis, to anaphylactic shock [13]
Tick-induced allergies to mammalian meat and related compounds	Avoidance of mammalian meat, mammalian milks, gelatin, and gelatin-containing substances and certain medications (e.g., cetuximab) [13]		The mechanism of this acquired reaction lies in sensitization to Galactose- <i>alpha</i> -1,3-galactose (alpha gal) induced by certain tick's bites [13]
Tick paralysis	Regular tick checks and prompt removal if found especially in children [11]	Supportive care with ventilator support may be needed	Rare disease, presenting as ascending paralysis with eventual respiratory failure caused by neurotoxin produced in salivary glands of ticks, multiple tick species implicated worldwide [12]

of Lyme disease. Additional erythema migrans rashes sometimes appear with the hematogenous spread of Lyme disease.

The second phase, or early disseminated Lyme disease, occurs days to weeks after the tick bite and presents with neurological (especially meningitis and bilateral Bell's palsy) and cardiac findings (classically atrioventricular heart block that can be rapidly progressive or fluctuating from first degree to complete). As erythema migrans and fever commonly resolve by the time of cardiac and neurological manifestations, a careful consideration of the possibility of Lyme disease is necessary as both first degree AV block and a Bell's palsy are typically benign idiopathic conditions. Lyme meningitis clinically resembles that of an aseptic/viral one, with lymphocytic predominance. Serological testing from both blood and cerebrospinal fluid is necessary to confirm the diagnosis [8] in late presenters, while serologic testing is not helpful in a patient with erythema migrans [8].

Late and untreated Lyme disease causes recurring mono- (typically knee joint) or oligo-arthritis, and late neuroborreliosis is also described causing meningoencephalitis or

radiculoneuritis [15]. "Chronic" Lyme disease (essentially chronic fatigue and fibromyalgia type disease) or congenital Lyme disease are thought not to exist [7•, 8] and consequently antibiotic therapy for these patients will not be helpful. Erythema migrans is typically neither painful nor pruritic and so can be overlooked by the patient depending on its location, highlighting the importance of a complete skin exam in a febrile patient. As Lyme disease without erythema migrans has been described, antibiotic treatment should begin if there is a reasonable clinical suspicion while awaiting serologic testing [15].

Lyme Mimic

The lone star tick *Amblyomma americanum* bite causes Southern tick-associated rash illness (STARI) heralded by a "bull's eye" rash that is clinically indistinguishable from erythema migrans [8, 14]. It is thought to be an infectious disease, but the cause remains unknown and it follows a uniformly benign course. The only way to distinguish the two is through

Table 2 Infectious diseases transmitted by ticks—bacterial and parasitic infections [5, 9, 15–18]

Disease	Vector, agent, and geographical distribution	Symptoms	Treatment	Comments
Lyme disease	<i>Borrelia burgdorferi</i> , a spirochete transmitted by <i>Ixodes scapularis</i> (blacklegged tick) in Eastern US and upper Midwest, and <i>Ixodes pacificus</i> (western black legged tick) in far western US; <i>Borrelia mayonii</i> in upper Midwest; <i>B. afzelii</i> , and <i>B. garinii</i> in Europe and Asia	Characteristic rash, acute febrile illness, cardiac, neurological, and joint complications	Doxycycline, ampicillin, and cefuroxime are first-line agents; ceftriaxone and macrolides are less effective [14, 15]	Most common vector-borne illness in North America [9, 15]
Tick-born relapsing fever	<i>Borrelia hermsii</i> in Western US, <i>B. hispanica</i> and <i>Borrelia crocidurae</i> in Africa spread by soft ticks; <i>B. miyamotoi</i> in various Ixodes ticks in eastern USA, Europe, and Asia [5]	Acute febrile illness in immunocompetent hosts that is relapsing unless treated with antibiotics; subacute afebrile meningoencephalitis in immunocompromised hosts	Same antibiotics as used for Lyme disease	<i>B. miyamotoi</i> was only recently recognized as a human pathogen in 2011 [5]. After initiation of antibiotic treatment, Jarisch-Herxheimer reaction has been observed [5]
Rocky Mountain spotted fever	<i>Rickettsia rickettsii</i> spread by American dog tick <i>Dermacentor variabilis</i> , the Rocky Mountain wood tick <i>Dermacentor andersoni</i> , or the brown dog tick <i>Rhipicephalus sanguineus</i> in the USA (present in all 48 contiguous states), and Western Canada other ticks in Central and South America [17]	Acute febrile illness with microangiitis and associated complications including severe sepsis, meningitis, limb necrosis, and multiorgan failure	Doxycycline (preferred in all patients) or chloramphenicol, delay in treatment associated with poor outcome	North Carolina, Oklahoma, Tennessee, Missouri, and Arkansas count for over 60% of all cases reported in the USA, and the disease is becoming more common in certain parts of Arizona
Other rickettsial spotted fevers	<i>R. parkeri</i> rickettsiosis (first described in humans in 2002) is transmitted by Gulf Coast ticks in the southeastern and mid-Atlantic states, as well as parts of southern Arizona; Rickettsia Species 364D transmitted by Pacific Coast tick <i>Dermacentor occidentalis</i> in California (first recognized in humans in 2008); other ticks transmit <i>R. conorii</i> that causes Boutonneuse fever in Africa, Southern Europe, and Asia; <i>R. africae</i> causes African tick bite fever in Sub-Saharan Africa, Australia, and Asia [18] <i>R. japonica</i> causes Japanese spotted fever in Japan; <i>R. australis</i> causes Queensland tick typhus in Australia; <i>R. sibirica</i> causes North Asia tick typhus in Eurasia	Similar to RMSF but less severe, with <i>R. parkeri</i> an inoculation eschar commonly develops	Same as for RMSF, doxycycline is the drug of choice in all patients groups	Those acquired in the Americas can be difficult to distinguish from RMSF, treated the same, eschar develops in many rickettsial illnesses acquired in Old World [18, 19]
Tularemia	<i>R. Helvetica</i> causes aneuruptive fever in Eurasia; <i>Rickettsia slovaca</i> causes Tick-borne lymphadenopathy in Western and Central Europe <i>Francisella tularensis</i> transmitted by dog tick (<i>Dermacentor variabilis</i>), the wood tick (<i>D. andersoni</i>), and the lone star tick (<i>Amblyomma americanum</i>) occurs in all US states except Hawaii, Canada, Northern Mexico, and Eurasia	Ulceroglandular tularemia that develops after a tick bite is characterized first by development of a painless ulcer that heals, following by a febrile illness with lymphadenopathy, that suppurates without treatment and can be complicated by pneumonia, sepsis, or multiorgan failure [16]	Aminoglycosides (gentamycin preferred), fluoroquinolones (ciprofloxacin most studied), streptomycin, doxycycline [16, 20]	Two main subspecies of <i>F. tularensis</i> are <i>F. tularensis</i> or type A that is most virulent, causes more severe disease and is found in USA, and <i>F. holarctica</i> that is less virulent and is found in North America and Eurasia [16]
Babesiosis	<i>B. microti</i> transmitted by <i>Ixodes scapularis</i> ticks, primarily in the Northeast and Upper Midwest, also in parts of Europe	Acute febrile illness with hemolytic anemia, in severe cases with multiorgan failure	Atovaquone and azithromycin, or clindamycin and quinine	Malaria-like infection that can range from asymptomatic to life threatening in immunocompromised or asplenic individuals and first

Table 2 (continued)

Disease	Vector, agent, and geographical distribution	Symptoms	Treatment	Comments
Ehrlichiosis	<i>Ehrlichia chaffeensis</i> (causes most severe infections) and <i>Ehrlichia ewingii</i> spread by the lone star tick <i>Amblyomma americanum</i> in the southeastern and south-central United States, <i>Ehrlichia muris</i> is transmitted by <i>Ixodes scapularis</i> ticks in the Upper Midwest [17]	Acute nonspecific febrile illness associated with leucopenia and thrombocytopenia	Doxycycline, delay in treatment is associated with poor outcome	manifest months after exposure in newly acquired immunodeficiency or after splenectomy Oklahoma, Missouri, and Arkansas account for 35% of reported Ehrlichiosis cases in the USA
Anaplasmosis	<i>Anaplasma phagocytophilum</i> spread by <i>Ixodes scapularis</i> in the Upper Midwest and northeastern United States	Acute nonspecific febrile illness associated with leucopenia and thrombocytopenia, similar to Ehrlichiosis but usually less severe [17]	Doxycycline, delay in treatment is associated with poor outcome. Rifampin if doxycycline cannot be given	Due to the common vector and geographic overlap, co-infection of <i>A. phagocytophilum</i> with <i>B. burgdorferi</i> , <i>Babesia microti</i> , or Powassan virus is possible
Q fever	<i>Coxiella burnetii</i> can rarely be spread by lone star tick <i>Amblyomma americanum</i>	Acute febrile illness with respiratory and gastrointestinal symptoms, later complicated by pneumonia and endocarditis	Tetracycline or fluoroquinolone antibiotics	Up to 50% of infected individuals do not develop an acute illness but may still be at risk for later complications such as endocarditis

a serologic testing, as the lone star tick' range and *Ixodes scapularis*' range frequently overlap. Erythema multiforme, arthropod bite reactions, nummular eczema, and granuloma annulare are other potential erythema migrans mimics [8].

Treatment of Lyme Disease

Once Lyme disease diagnosis is established, the patient should be treated with antibiotics. Diagnosis is confirmed by Western blot testing. Either oral doxycycline, ampicillin, or cefuroxime can be used. In sick patients with neurological or cardiac complications when parenteral antibiotics are needed, ceftriaxone, cefotaxime, or penicillin G are additional choices. Macrolides are less effective and should only be used if the above-mentioned more effective antibiotics cannot be given.

In addition to *Borrelia burgdorferi*, *Ixodes scapularis* ticks are commonly co-infected with several other important human pathogens. In the USA, concurrent babesiosis is seen in up to 20% of all patients with proven Lyme disease and approximately 10% are infected with either human granulocytic anaplasmosis agent or *Borrelia miyamotoi*, the cause of hard tick relapsing fever [5, 24].

Babesiosis

Human babesiosis is a nationally notifiable disease caused by *Babesia microti* in the Northeast and Upper Midwest, *Babesia duncani* in the Pacific Northwest, and *Babesia divergens* in Kentucky, Missouri, and Washington State. *Babesia* spp. are intraerythrocytic protozoan parasites belonging to the same phylum as malaria-causing plasmodiums. *Babesia microti* is the most common pathogen transmitted by a blood transfusion as reported to the FDA [3], likely due to the large number of subclinical and very mild cases of this infection. Most symptomatic cases manifest anywhere from 1 week to 1 month after the tick bite. High fever and chills are the most common symptoms along with several other nonspecific signs including nonproductive cough, pharyngeal erythema, and conjunctivitis. Splenomegaly, hepatomegaly, and jaundice if present are more helpful in suggesting the clinical diagnosis. Laboratory findings of hemolytic anemia with elevated lactate dehydrogenase levels and reticulocyte counts and thrombocytopenia are usually seen. A definitive diagnosis is made by visualizing parasites on thin blood smear Giemsa or Wright stains or with specialized PCR testing for babesia DNA in blood [14].

Clinical Features of Babesiosis

Babesiosis clinically ranges from an asymptomatic to a fatal illness mostly depending on the immune status and age of the patient. Asplenic patients, those with HIV infection, lymphoma, those receiving immunosuppressive chemotherapy for

Table 3 Infectious diseases transmitted by ticks—viral infections [1, 4, 9*, 19, 21]

Disease	Vector, agent, and geographical distribution	Symptoms	Comments
Colorado tick fever	Colorado tick fever virus spread by Rocky Mountain wood tick <i>Dermacentor andersoni</i> in the Western United States, especially in Colorado, Utah, Montana, and Wyoming	Acute nonspecific febrile illness with leucopenia and thrombocytopenia often biphasic with symptoms abating after 2 to 4 days, then recurring 1 to 3 days later, rarely progresses to meningoencephalitis and disseminated intravascular coagulation	Only tick-borne viral encephalitis in North America, while known in Eurasia for decades, it was first described in the USA in 2010 severe disease with high mortality
Powassan virus disease	<i>Powassan</i> virus spread by several types of <i>Ixodes</i> and <i>Dermacentor</i> ticks in Northeastern and Upper Midwest regions of the USA, Canada, and Russia	Acute febrile illness progresses to severe meningoencephalitis [9*]	
Heartland and Bourbon Virus diseases	Probable tick-borne illness, sporadic cases described in the Midwest and South east of the USA	Nonspecific viral febrile illness following a tick bite with gastrointestinal symptoms and a rash that progressed to multiorgan failure in a few cases	
Tick-borne encephalitis	Tick-borne encephalitis virus transmitted by <i>Ixodes ricinus</i> and <i>I. persulcatus</i> throughout Eurasia with highest rates in western Siberia, Slovenia, and the Baltic States [4]	Nonspecific febrile illness that lasts for several days and may be followed by an afebrile and relatively asymptomatic period then in one third of patients central nervous system involvement resulting in aseptic meningitis, encephalitis, or myelitis	High morbidity and mortality
Crimean-Congo hemorrhagic fever	Crimean-Congo hemorrhagic fever virus spread by <i>Ixodes</i> ticks in Eastern Europe, throughout the Mediterranean, in central Asia, and Africa [4, 19]	Acute febrile illness with characteristic nonsuppurative conjunctivitis followed by hemorrhagic complications starting at day four	High mortality and slow recovery
Omsk hemorrhagic fever	Omsk hemorrhagic fever virus spread by <i>Ixodes</i> and <i>Dermacentor</i> ticks in South Western Siberia	Acute onset of high fever followed by hemorrhagic complications starting on day four of the illness	Rarely biphasic course with encephalitis developing after resolution of the fever and hemorrhagic symptoms
Kyasanur Forest disease	Kyasanur Forest disease virus spread by <i>Hemaphysalis spinigera</i> ticks	Acute febrile illness followed by vomiting, diarrhea, and hemorrhagic complications starting on day three	Rarely biphasic course with return of fever and neurologic complications
Severe fever with thrombocytopenia syndrome (SFTS)	SFTS virus is thought to be spread by <i>Haemaphysalis longicornis</i> tick in parts of China, Korea, and Japan first described in 2012	Onset of high fever with GI or respiratory symptoms, followed by decline in leucopenia and thrombocytopenia and in severe cases multiorgan failure	There is a vaccine being developed. [21] Heartland virus, a phlebovirus closely related to SFTS agent [21] was isolated from patients in the USA [1]

cancer, patients with organ transplantation, or those receiving anticytokine immunomodulating drugs are at risk for severe and fatal disease as are those with severe chronic lung, heart, or liver disease and those at the extremes of age [14]. Acute respiratory distress syndrome, splenic infarct or spontaneous splenic rupture, disseminated intravascular coagulation, coma, and multiorgan failure have been described [3].

Treatment Considerations

Any symptomatic patient with babesiosis requires treatment. Atovaquone and azithromycin are used for mild to moderate disease and are an option for severe disease while clindamycin with either quinine or quinidine are used for severe disease along with exchange transfusions when high parasitemia or organ failure develops [3, 14]. Usual treatment duration is 7 to 10 days in immunocompetent patients, while the immunocompromised may require up to 6 weeks of antibiotics.

Anaplasmosis

Human granulocytic anaplasmosis is caused by *Anaplasma phagocytophilum* that invades neutrophils and causes a systemic inflammatory response that is the mechanism for tissue damage in this disease [17]. One to 2 weeks after the tick bite, acute febrile illness develops usually without accompanying rash, pronounced gastrointestinal symptoms, or central nervous system involvement. In most cases, it is a self-limiting disease with clinical findings of fever, headache, myalgias, chills, nausea, and abdominal pain; however, the elderly, immunocompromised, and those with severe comorbid conditions are at risk for severe disease. Acute respiratory distress syndrome, hemorrhagic manifestations, acute renal failure, and serious opportunistic viral and fungal infections have been reported [17]. Pancytopenia with left shift and elevated transaminases are the usual laboratory findings.

Diagnosis and Treatment

PCR, serology, and peripheral blood smear examination looking for intragranulocyte inclusions called morulae establish the diagnosis. Treatment should begin promptly if anaplasmosis is suspected. Doxycycline is the drug of choice in all patients, including children of all ages and pregnant women [17].

Ehrlichiosis

Similar to human granulocytic anaplasmosis, human monocytic ehrlichiosis is a rickettsial disease found in the southeast and south central United States. This may also be detected by the presence of morulae intracellularly, along with decreased

white blood count and thrombocytopenia. Treatment is with doxycycline as well.

Borrelia myamotoi

Borrelia myamotoi is a recently discovered relapsing fever pathogen that is present in *Ixodes* ticks, unlike other relapsing fever-causing *Borrelia* species that are spread by soft-bodied ticks or lice [5]. In immunocompetent hosts, it appears to cause acute febrile illness, usually without a rash, that is relapsing without antibiotic treatment. Leukopenia, thrombocytopenia, and elevated transaminases are characteristic laboratory findings, and PCR on blood or cerebrospinal fluid can be diagnostic during an acute infection. In immunocompromised patients, a progressive afebrile meningoencephalitis was reported. Antibiotics used in treatment of Lyme disease appear to be uniformly effective in curing *Borrelia myamotoi* relapsing fever [25].

Tularemia

Tularemia, caused by the agent *Francisella tularensis*, may be transmitted by contaminated water, contact with contaminated animals, or by tick bites. It is listed also as a category A bioterrorism agent. Specific symptoms are listed in Table 2. It is treatable with streptomycin, gentamicin, ciprofloxacin, or doxycycline.

Tick-Borne Viral Illness

A variety of viruses have been reported as tick-borne illness and are listed in Table 3. Tick-borne encephalitis is a flavivirus, and the most important tick-borne illness in Europe. Crimean-Congo hemorrhagic fever has the largest known distribution of any tick-transmitted virus, ranging from the Crimea through Eastern Europe, Iran, and India. Powassan disease agent is another flavivirus, notable because it is fatal in 10% of patients who develop encephalitis. In 2010, severe fever with thrombocytopenia syndrome (SFTS) was described in China, then 2 years later in Korea and Japan. The causative agent is a phlebovirus, which causes a hemorrhagic fever, a case fatality rate of approximately 7% due to multiorgan failure, and an average time to death of 9 days. The treatment is supportive.

Rocky Mountain Spotted Fever

Rocky Mountain spotted fever (RMFS) is the most common and severe of the rickettsial infections in the USA. It is caused by *Rickettsia rickettsii* that is transmitted by American dog tick *Dermacentor variabilis*, the Rocky Mountain wood tick *Dermacentor andersoni*, or the brown dog tick *Rhipicephalus sanguineus*. Only

Table 4 Selected antibiotics used in treatment of tick-borne illnesses [8, 14, 17, 20]

Antibiotic	Indications	Dosing and duration
Doxycycline	Lyme disease, other borreliosis, tick-borne rickettsiosis including RMSF, human granulocytic anaplasmosis, ehrlichiosis, tularemia (second line)	100 mg BID or 2.2 mg/kg/dose up to 100 mg BID for children 10–21 days
Chloramphenicol	Second (and inferior) choice for RMSF	25–50 mg/kg every 6 h max single dose is 1 g, monitor serum concentration
Atovaquone	Together with azithromycin for mild or moderate babesiosis	750 mg BID for 7–10 days; up to 6 weeks in severely immunocompromised patients
Quinine	Together with clindamycin for severe babesiosis	650 mg orally 3–4 times a day for 7–10 days
Rifampin	Human granulocytic anaplasmosis if doxycycline is absolutely contraindicated	10–20 mg/kg max 600 mg daily for 7–10 days. Not active against Lyme disease or rickettsial illnesses
Gentamycin	Severe tularemia	Once daily 5 mg/kg with serum concentration monitoring for 10–21 days
Ciprofloxacin	Mild to moderate tularemia	500 mg PO BID for 7–10 days

approximately a half of patients diagnosed with RMFS recall a tick bite [17]. Delayed diagnosis or providing inappropriate antibiotic therapy for this illness increases the chances of a fatal outcome. It is transmitted everywhere in the USA except for Alaska and Hawaii, with Arkansas, Missouri, North Carolina, and Tennessee, accounting for over half of all reported cases. Most patients are seen from April to October [26]. At least 4 to 6 h of tick attachment is needed for disease transmission and only 1–3% of ticks in the endemic areas carry the bacteria, so prophylactic antibiotics to prevent RMSF are not recommended [26].

RMSF Signs and Symptoms

RMSF is an acute infectious vasculitis affecting small and medium blood vessels, accounting for the wide range of disease manifestations. After an incubation period from 2 to 14 days, an acute nonspecific febrile illness ensues with a variety of accompanying symptoms. These are classically accompanied by a severe headache. The initially macular rash begins on the wrists and ankles 2 to 5 days after fever onset. The rash spreads centrally, and eventually can develop into petechiae and purpura with tissue necrosis. The rash may be absent in up to 15% of cases and many patients seek care before the development of rash [17, 26]. Complications may occur early in severe cases and include meningoencephalitis, myocarditis, acute respiratory distress syndrome, rhabdomyolysis, and vascular vision loss. In its early stages, RMFS is a clinical diagnosis and requires a good travel and exposure history. Routine laboratory testing may reveal normal or slightly increased leucocyte count, mild thrombocytopenia, and hyponatremia. Antibody testing to *Rickettsia rickettsii* is the current diagnostic standard but is sensitive only after 7 to 10 days after disease onset [26].

RMSF Differential Diagnosis

Severe RMFS differential diagnosis includes meningococemia, other severe bacterial sepsis, or systemic vasculitis from other causes. Once RMSF is reasonably suspected and cannot be confidently ruled out by showing a presence of a different pathological process, treatment should be implemented without delay (Table 4). The antibiotic of choice in adult and pediatric patients regardless of age is doxycycline [17, 26]. The safety data for use of doxycycline in pregnancy is lacking, but a short course has been deemed to be likely safe [17]. Patients treated with chloramphenicol, the only other agent with activity against *Rickettsia rickettsia*, are at higher risk of death [17]. Use of chloramphenicol may only be appropriate in case of severe tetracycline allergy when rapid desensitization is impossible due to the nature of reaction (i.e., Stevens-Johnson) or possibly in pregnancy with joint decision-making [26]. While cephalosporins, aminoglycosides, and broad spectrum β lactams have no activity against RMFS pathogen, they may need to be administered to a sick septic patient initially while the diagnosis is established.

Conclusions

Ticks are ubiquitous in the USA and are especially active during warm weather; close to 1000 species have been described. Tick bite prevention may entail use of N, N diethyl-m-toluamide (DEET), picardin, permethrin-impregnated clothing, and gloves with protective clothing to prevent blood exposure. People frequently are unaware of being bitten by a tick. Prompt removal of an attached tick is likely protective. While some tick-borne illnesses are caused by viruses, warranting only supportive care, others are caused by rickettsial diseases and by parasites which mandate prompt and specific directed care.

It is prudent to consider several tick-borne bacterial illnesses in patients presenting with acute nonspecific febrile illness, including those who do not recall a recent tick bite. Early diagnosis and treatment may prevent serious complications, including death. All common treatable infectious tick-borne illnesses common in the USA, except for babesiosis, can be effectively treated with doxycycline, and it is likely that doxycycline can be given safely to patients of any age when necessary.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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