Rocky Mountain Spotted Fever in Children

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KEYWORDS

• Rocky mountain spotted fever • *Rickettsia rickettsii* • Rash
• Increased intracranial pressure • Sepsis • Doxycycline

KEY POINTS

- Rocky Mountain spotted fever (RMSF) is typically undifferentiated from many other infections in the first few days of illness.
- Treatment should not be delayed pending confirmation of infection when RMSF is suspected.
- Doxycycline is the drug of choice even for infants and children less than 8 years old.

INTRODUCTION

RMSF is caused by *Rickettsia rickettsii*, the prototypical member of the spotted fever subgroup of rickettsial species. RMSF was first recognized as a clinical entity in the 1890s in Idaho and Montana. In the past century, RMSF has been identified within 46 states in the United States. *R rickettsii* also causes disease in many parts of Central and South America, where the infection is given other names, such as Brazilian spotted fever or febre maculosa.[1,2]

The spotted fever subgroup of *Rickettsia* now consists of 20 known species that cause similar illnesses worldwide.[3–5] *R parkeri* and other related species are present among tick populations in the United States. Infection by these related species may account in part for the apparent increase in probable, but not confirmed, cases of RMSF in the United States in recent years.[6] RMSF remains a nationally notifiable disease, but reporting was changed in 2010 under the broader category of spotted fever rickettsiosis.[7]

The pathogenesis, clinical features, and management of infections caused by the various agents of spotted fever rickettsiosis are largely the same. Laboratory studies of *R conorii*, the cause of Mediterranean spotted fever, have provided many insights into *R rickettsii* infections.

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MICROBIOLOGY

R rickettsii is an obligate intracellular bacterium that must invade eukaryotic cells for ongoing survival and replication. The microbes are pleomorphic, nonmotile coccobacilli that are approximately 0.3 μm by 1.0 μm in size and stain weakly gram negative. The species produces no known toxins.[8,9] The circular bacterial chromosome of *R rickettsii* is highly conserved and small (approximately 1.25 Mb) compared with most other bacterial species.[5,10,11] Whole-genome sequencing indicates a repertoire of approximately 1495 genes. The species lacks many genes that encode proteins necessary for carbohydrate metabolism or synthesis of lipids and nucleic acids and thus must scavenge multiple substrates from within the host cells it invades. It cannot use glucose but instead acquires adenosine triphosphate from host cells.[12] *R rickettsii* cannot be propagated in standard culture media; specific cell lines are required.[8,13]

VECTORS AND TRANSMISSION

Spotted fever rickettsia are zoonotic tick-borne microbes that are maintained in the wild by a cycle of transmission between ixodid (hard-bodied) ticks and small mammals. Humans are accidental hosts. Domesticated animals, primarily dogs, may serve to bring infected ticks into close proximity with humans. Dogs may develop illness with infection that is usually self-limited.[8] Once a tick is infected with one rickettsial species, it is resistant to infection by other rickettsia, a phenomenon labeled rickettsial interference.[14]

R rickettsii infection is maintained through all stages of the ixodid lifecycle, which takes a year or more to complete. The lifecycle requires 3 blood meals from mammalian hosts. Larvae emerge from eggs, feed, detach, and molt into nymphs. Nymphs feed, detach, and molt into adults. Adult females feed, detach, and lay eggs on the ground. *R rickettsii* is transmitted from adult females to eggs (transovarian) and during molting (trans-stadial). Transovarial transmission reduces survival and reproductive capacity of the tick hosts. Horizontal transmission, from tick to tick via blood of an infected mammal, occurs but plays a lesser role in maintaining the zoonosis.[15–18] Frequency of *R rickettsii* carriage by *Dermacentor variabilis* in the United States is less than 1%.[17,19]

RMSF is transmitted to humans only by adult ticks, which release microbes from their salivary glands after 6 to 10 hours of feeding.[1] At least 5 ixodid tick species may harbor *R rickettsii*[5,20,21]:

- *D andersoni* (Rocky Mountain wood tick)—predominant vector in the Eastern United States
- *D variabilis* (American dog tick)—predominant vector in the Western United States.
- *Rhipicephalus sanguineus* (brown dog tick)—recently recognized vector in Arizona and Mexico
- *Amblyomma cajennense* (the cayenne tick)—vector in Central and South America and in Texas
- *A aureolatum*—vector in Central and South America

The Lone Star tick, *A americanum*, also rarely may function as a vector for RMSF.[22,23] Tick vectors in the United States are shown in **Fig. 1**.

Tick hemolymph also harbors microbes. Transmission to humans can occur when ticks are crushed during attempted removal from the skin.[8] Infection has occurred via blood transfusion,[24] health care–associated needle-stick injury,[25] and laboratory accidents.[26,27]

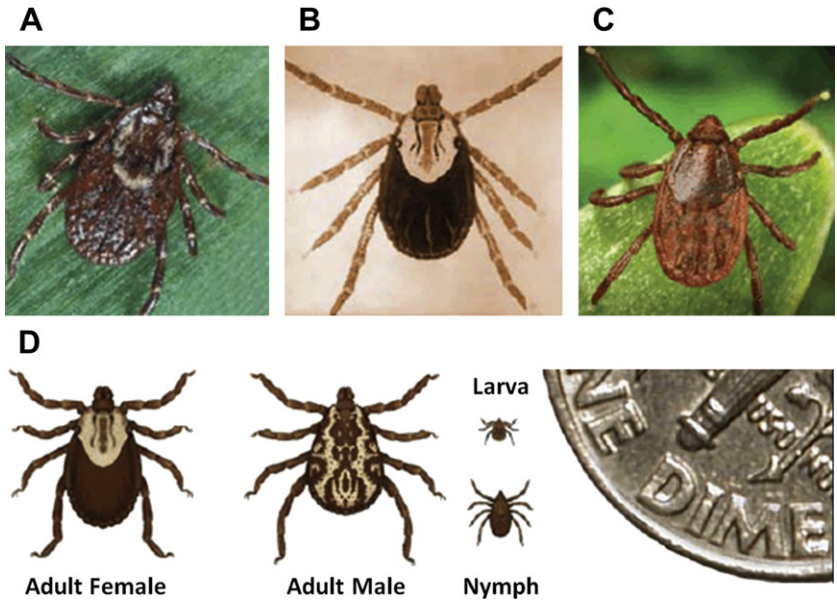

Fig. 1. Primary tick species responsible for transmission of RMSF in the United States. (*A*) Adult female *D variabilis*. (*B*) Adult female *D andersoni*. (*C*) Adult female *Rhipicephalus sanguineus*. (*D*) Relative sizes of adult female, adult male, nymph, and larval forms of *D variabilis*. (*Adapted from* Chapman AS, Bakken JS, Folk SM, et al. Diagnosis and management of tickborne rickettsial diseases: rocky mountain spotted fever, Ehrlichiosis, and Anaplasmosis—United States. A practical guide for physicians and other health-care and public health professionals. MMWR Morb Mortal Wkly Rep 2006;55(RR04):1–27.)

EPIDEMIOLOGY

The geographic distribution of RMSF correlates with presence of its tick vectors.[28] In the continental United States, only Vermont and Maine did not report cases from 2000 to 2007.[6,29] Geographic distribution of reported cases by counties in the United States in 2009 is shown in **Fig. 2**. The incidence of reported cases of RMSF in the United States since 1920 is shown in **Fig. 3**. The availability of effective antimicrobial agents in the 1950s was associated with a decline in reported cases that seemed to reverse in the 1960s. There seems to be a 30-year to 40-year cycle of disease for reasons that are unclear.[1]

Between 2000 and 2008, aggregate incidence was 2 to 4 per million among children ages 1 to 19 years old and 6 to 8 per million among adults over 40 years old.[7] Incidence in the United States rose from 1.7 per million persons (495 cases) in 2000 to 8 per million (2563 cases) in 2008. Explanations for this 4-fold increase include changes in diagnostic and surveillance practices in addition to potential increases in frequency, because most reported cases are probable rather than confirmed. Cross-reactivity of serologic tests for RMSF with other spotted fever rickettsia also may be a factor.[1,6,30]

The largest seroprevalence study in children showed a rate of 12% overall in convenience samples from 7 centers in endemic areas of the South and Midwest.[31] Seroprevalence rates were 10% to 16% among children in 2 communities in Arizona at the time of an outbreak of RMSF associated with the newly recognized brown dog tick vector in 2003 and 2004.[20,32]

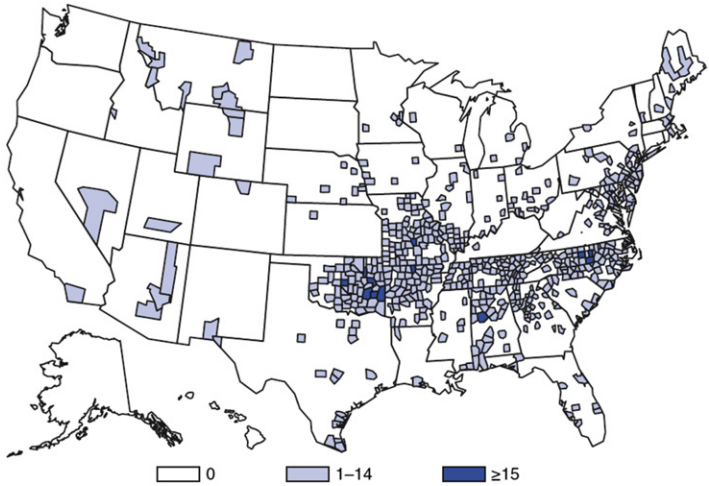

Fig. 2. Number of reported cases of RMSF by county, United States, 2009. RMSF is reported throughout most of the United States, reflecting the widespread distribution of the primary tick vectors responsible for transmission (*D variabilis* in the East, *D andersoni* in the West, and *Rhipicephalus sanguineus* in parts of the Southwest). (*From* the Centers for Disease Control and Prevention. Rocky mountain spotted fever (RMSF). Available at: http://www.cdc.gov/rmsf/stats/index.html. Accessed January 24, 2013.)

A great majority of cases in children and adults occur during April through September, but cases have been reported from all months of the year.[28,33] Male patients comprise approximately 57% of cases reported in recent years.[6] Cases are more common in rural and suburban areas due to increased opportunities for exposure to the tick vectors, but urban cases have been reported, even in New York City.[8,34] Clusters of cases among family members also have occurred.[35] Concurrent infections have been observed in humans and their dogs.[36]

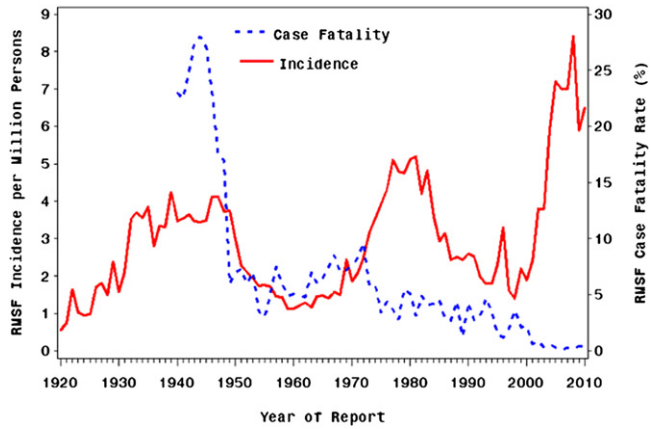

Fig. 3. Incidence and case-fatality of RMSF in the United States, 1920–2008. The recent increase in incidence and decrease in case fatality partially may reflect changes in reporting and diagnosis. Note the 30-year to 40-year cycle in incidence. (*From* the Centers for Disease Control and Prevention. Rocky mountain spotted fever (RMSF). Available at: http://www.cdc.gov/rmsf/stats/index.html. Accessed January 24, 2013.)

Host factors that may be associated with increased severity of RMSF include older age, male gender, and presence of glucose-6-phosphate dehydrogenase deficiency.[37–39] Greater severity also has been observed in African American patients. Issue of access to care, difficulties in recognizing the presence of rash, and delays in receipt of effective antimicrobial therapy may explain this racial disparity more than any host susceptibility or microbial virulence factors.[8,40]

PATHOGENESIS

R rickettsii has primary tropism for endothelial cells. As microbial replication progresses, blood vessels throughout the body, including the skin, brain, liver, spleen, lungs, and heart, become infected, with progressive focal disruptions of endothelial integrity. A distinctive perivascular infiltrate of lymphocytes and macrophages ensues. Most clinical features of RMSF derive from the resulting increased vascular permeability.[8]

Once *R rickettsii* is inoculated into the epidermis during adult tick feeding, microbes presumably spread to regional lymph nodes via lymphatic vessels.[26,41] *R rickettsii* then reach the bloodstream and begin to invade the endothelium of small and medium-sized blood vessels. Oxidative and peroxidative injury to endothelial membranes from the net effects of phospholipase, proteases, and free radical production leads to cell necrosis.[26,42–44]

Focal areas of vasculitis in the epidermis generate the erythematous spots of spotted fever. Capillaries, arterioles, and venules are involved.[45] Progressive endothelial injury can lead to microhemorrhages in addition to increased permeability. Leakage of fluid into organ tissues, such as in the lung or brain, which lack lymphatic vessels to drain interstitial fluid, can lead to pulmonary insufficiency and increased intracranial pressure, respectively.[26]

R rickettsii induces a procoagulant state, secondary to endothelial injury, with thrombin generation, platelet activation, increased fibrinolysis, and consumption of anticoagulants. Yet, development of actual disseminated intravascular coagulation is rare in RMSF. The multiorgan dysfunction that develops in some fatal cases seems more the result of vascular insufficiency than major hemorrhage or vaso-occlusive infarcts.[8,42,46,47]

At the molecular level, rickettsial outer membrane protein B (OmpB) and other microbial surface structures function as adhesins and bind microbes to endothelial cells. OmpB attaches to Ku70 molecules on the host cell surface and recruits additional Ku70 to the host cell membrane. Ku70 is a subunit of a DNA-dependent protein kinase ubiquitously expressed in mammalian cells and typically located in the nucleus and cytoplasm.[48,49] Localization of Ku70 to the cell membrane is restricted to endothelial cells and monocytes, the 2 main cellular targets in RMSF.

Attached microbes induce local rearrangement of the host cell cytoskeleton that leads to endocytosis.[26,49,50] This process is accomplished by microbial co-opting host cell actin nucleating protein complexes (Arp2/3) and various signaling processes, including those mediated by clathrin, caveolin 2, phosphoinositide 3-kinase, and other kinases.[13,51] After internalization, *R rickettsii* lyses its endosome using the enzymes phospholipase D and hemolysin C.[43] Rickettsia grow well in the high potassium concentration environs of the cytoplasm.[8]

Once free in the cytoplasm, *R rickettsii* migrate into adjacent cells by actin-based motility, which does not lyse the cells. Actin-based motility involves recruitment of host cell actin filaments, by expression of the microbial protein RickA, to form a filamentous comet tail. These actin structures propel organisms rapidly through the cytoplasm to the host cell surface, creating structures that invaginate membranes of

adjacent cells. These protrusions are engulfed by the neighboring cell, resulting in local intercellular spread of infection.[8,43,52,53]

Disruption of endothelial intercellular adherens junction complexes occurs within 48 hours of infection and is associated with phosphorylation of vascular endothelial cadherin, a major component of junctional complexes.[54,55] This leads to the characteristic vascular hyperpermeability of RMSF.

Virulence of microbes that reside in tick salivary glands declines during the prolonged winter starvation period. Virulence is restored within 24 to 72 hours of either allowing ticks to take a blood meal or exposing them to a temperature of 37°C.[56,57] This likely reflects environmental regulation of microbial genes that facilitate virulence or simply replication or both.

Higher microbial inocula in prison volunteers, in a study subsequently criticized on ethical grounds, were associated with higher frequency of symptomatic infection, shorter incubation periods, and longer duration of fever.[8,58] Modeling studies suggest an inoculum of 23 organisms lead to symptomatic infection in 50% of those exposed. Risk of infection after intradermal inoculation of a single microbe is approximately 5%.[27]

HOST IMMUNE RESPONSE

Rickettsial infection of endothelial cells induces production of interleukin (IL)-6 and IL-8 and monocyte chemoattractant protein 1 via activation of nuclear factor-κB.[59,60] Natural killer cells are activated early in infection and produce interferon-γ, which can inhibit rickettsial growth. Infection also induces production of IL-1β and tumor necrosis factor α. Human endothelial cells can produce rickettsicidal amounts of nitric oxide (via inducible nitric oxide synthetase) and hydrogen peroxide in response to interferon-γ, IL-1β, and tumor necrosis factor α. Macrophages can kill rickettsia with hydrogen peroxide and tryptophan starvation in phagosomes by degradation of tryptophan by indoleamine 2,3-dioxygenase.[43,44]

Clearance of infection is associated with homing of CD4+ and CD8+ lymphocytes and macrophages to foci of infection in the microcirculation. These and dendritic cells are presumed the sources of proinflammatory cytokines that can activate killing within infected endothelial cells. CD8+ T-lymphocytes also may induce apoptosis of infected endothelial cells.[8,44,61]

Antibody responses directed against OmpA, OmpB, and Sca2 epitopes are protective against reinfection.[13,62,63] These antibodies typically are not produced in substantial quantities until a week or 2 after infection. Serologic response may be blunted by early treatment.[64]

CLINICAL FEATURES

The course of RMSF is variable, ranging from a mild to moderate, self-limited febrile illness to a severe life-threatening infection. A history of recent tick bite is reported in 50% to 66% of patients. Tick exposure can easily go unnoticed because the bites are painless and ticks may feed for several days without producing any irritation or discomfort. Ticks also often attach to the scalp, axillae, or perineum where they are not easily spotted. Eschars are rarely produced at the site of bite. The incubation period is typically 4 to 7 days but ranges from 2 to 14 days.[8,33,39,65–69]

Early symptoms and signs of infection are nonspecific. Fever is the earliest sign, occurs in at least 97% of children with RMSF, and often exceeds 102°F (38.9°C). Onset of illness is often abrupt but gradual onset occurs in approximately one-third of children and adults. Approximately 95% of children with RMSF have a rash at

some point during the illness, compared with 80% of adults. In children, rash often appears on the first or second day of illness but may appear on the third or fourth day or beyond, which is more common in adults. The classic triad of fever, rash, and headache occurs in most but not all patients and often is not apparent early in the course.[8,33,39,65]

The typical exanthem consists of small, blanching pink macules on the ankles, wrists, or forearms (**Fig. 4**). The rash may become maculopapular and expand centripetally to involve proximal extremities and torso.[33,65,70] The spots of spotted fever are the end result of focal infection of small blood vessels in the skin. Palms and soles are involved in approximately half of cases, usually later in the course, and this is not pathognomonic for RMSF. The face is spared even when rash is diffuse. Rash may be evanescent or localized to a single area. A petechial component may develop in approximately 60% of children but usually not until 5 or more days into the illness. Patients with petechiae usually are severely ill. Skin lesions may progress to purpura or local areas of gangrene. Early skin findings may be difficult to appreciate in dark-skinned patients.[21,33,39,71]

Headache is present in 40% to 60% of children under 15 years old, more prominent in older children and adults, and often described as severe.[8,33,69] Headache is likely due to vasculitis-related increase in intracranial pressure, in addition to effects of circulating proinflammatory cytokines. Headache may manifest as irritability, inconsolability, or fussiness in infants and young children.

Malaise, myalgia, abdominal pain, nausea, vomiting, and/or diarrhea occur in at least 25% of children with RMSF.[33,69] Photophobia and conjunctival injection are sometimes seen. Lymphadenopathy, hepatomegaly, splenomegaly, and periorbital and peripheral edema are noted in approximately 20% to 25% of children. The constellation of symptoms and signs easily may be mistaken for common viral or bacterial infections that delay consideration of RMSF.

The central nervous system involvement occurs beyond headache. Altered mental status is seen in one-third or more of children ill enough to require hospitalization. Meningismus is noted in approximately 16%.[33,69] Seizures, cranial nerve palsies, coma, and hearing loss are not common but can occur. Significant neurologic manifestations are more common in older children and adults.[39] Death can result from cerebral herniation.

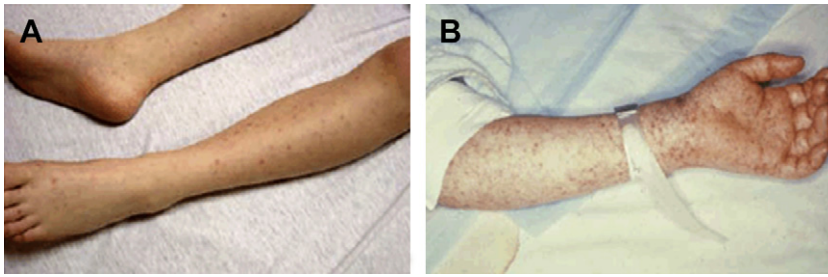

Fig. 4. Rash associated with RMSF. (*A*) Maculopapular rash on legs and feet. (*B*) Late petechial rash on forearm and hand. ([*A*] *Courtesy of* GS Marshall, University of Louisville School of Medicine, Louisville, KY; and [*B*] *From* Chapman AS, Bakken JS, Folk SM, et al. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever, ehrlichioses, and anaplasmosis—United States: a practical guide for physicians and other health-care and public health professionals. MMWR Recomm Rep 2006;55(RR-4):1–27.)

Cough and sore throat occasionally occur. Pulmonary edema can develop in severe cases. Chest radiography within 48 hours of admission may show opacities suggestive of infiltrates or pneumonia in a third of hospitalized children.[33,72] Myocarditis can occur from vasculitis. Subclinical involvement may be common,[73] but heart failure, heart block, and other cardiac manifestations appear rare in children without advanced disease.

LABORATORY FINDINGS

Complete blood counts often are normal, especially early in the course. Thrombocytopenia, due to platelet sequestration and destruction in the microcirculation, occurs in approximately 60% of hospitalized children.[33,69] Fulminant disseminated intravascular coagulation is rare.[8] Leukocytosis is present in approximately 25% and leukopenia in approximately 10% of children.[33]

Hyponatremia occurs in up to half of patients, and 20% may have serum sodium concentrations below 130 mEq/L. This almost always reflects capillary leak from endothelial damage rather than secretion of inappropriate antidiuretic hormone. Mild to moderated elevations of hepatic transaminases are seen in approximately half of patients. Hyperbilirubinemia sufficient to produce jaundice is uncommon. Serum albumin concentrations may be low, consistent with increased vascular permeability.[33]

Serum creatinine and blood urea nitrogen concentrations may be elevated in advanced infection. Renal insufficiency is common in severe disease and may be caused by ischemia-related acute tubular necrosis, vasculitis of renal vessels, or microthrombosis. Creatine kinase concentrations may increase due to vasculitis-induced muscle injury.[8]

Cerebrospinal fluid obtained in 38 children hospitalized with RMSF showed mild pleocytosis in some, with an interquartile range of 3 to 38 white blood cells/mm^3. Mononuclear cell predominance is common. Cerebrospinal fluid protein concentrations are often mildly elevated, but hypoglycorrhachia is rare.[33,69]

CNS imaging is typically done only in severe cases of altered mental status. CT studies, when abnormal, have shown diffuse white matter changes, sulcal effacement from cerebral edema, and focal attenuations consistent with infarctions. MRI studies may demonstrate punctate areas of increased signal throughout the brain on T2-weighted images, consistent with perivascular inflammation, as well as arterial infarctions or meningeal enhancement.[74,75] Electroencephalography, when abnormal, usually demonstrates nonfocal cortical disturbances reflective of diffuse cerebral vasculitis.[8]

DIAGNOSIS

Serologic testing and skin biopsy remain the best means of confirming a diagnosis of RMSF. Immunofluorescent antibody assays are considered the best serologic tests for RMSF. Latex agglutination and enzyme-linked immunosorbent assays also are available. Most commercial assays measure both IgM and IgG. Demonstration of a seroconversion or a 4-fold or greater rise in serum antibody titers between acute and convalescent sera is considered confirmatory.[21] Antibodies against other spotted fever rickettsia, including *R parkeri*, can be cross-reactive in *R rickettsii* assays.[76]

IgM and IgG antibodies against *R rickettsii* typically increase concurrently during the second week of illness and usually are not detectable during the first 7 days of illness. Convalescent titers usually should be obtained 2 weeks after onset of illness, but seroconversion may take 4 weeks in some patients. A single immunofluorescent antibody

assays titer greater than or equal to 1:64 or latex agglutination titer greater than or equal to 1:128 is suggestive of RMSF in compatible clinical settings. IgM concentrations wane after 3 to 4 months. IgG titers wane after 7 to 8 months but may persist at detectable levels for years.[21,65,77] Weil-Felix serologic tests, once a diagnostic mainstay, are not as reliable as current commercial assays.[78]

Skin biopsy (3–5 mm punch biopsy) of rash spots is useful in acute illness. Immunohistochemical staining is 100% specific and approximately 70% sensitive.[79] Polymerase chain reaction testing also can be done on skin specimens. Evaluation of skin biopsies for RMSF is not available in many locales. Health care providers can submit skin specimens to the Centers for Disease Control and Prevention for testing via their state health departments.[80]

Detection of *R rickettsii* by blood smears or polymerase chain reaction tests is insensitive due to low numbers of circulating bacteria. Culture of skin or other specimens using tissue culture methods is technically feasible but can be conducted only by laboratories, such as the Centers for Disease Control and Prevention, that can follow biosafety level 3 containment procedures.[21]

DIFFERENTIAL DIAGNOSIS

Other tick-borne infections caused by relatives of *R rickettsii* can be similar to RMSF. Human monocytic ehrlichiosis caused by *Ehrlichia chaffeensis* can be indistinguishable clinically from RMSF. In human monocytic ehrlichiosis, hepatic transaminase elevation is often more prominent, leukopenia more frequent, and rash less frequent than in RMSF.[21,81] Human granulocytic ehrlichiosis caused by *Anaplasma phagocytophilum* (and *E ewingii*) rarely has associated rash and may have more gradual onset of illness.[82] *R parkeri* and a newly recognized spotted fever group microbe, *Candidatus R andeanae*, can cause illness similar to mild RMSF. These microbes are transmitted by the Gulf Coast tick, *A maculatum*.[83]

Other infections that sometimes may mimic RMSF include human herpesvirus 6 (roseola), Epstein-Barr virus, enteroviruses, leptospirosis, human parvovirus, secondary syphilis, and *Mycoplasma pneumoniae*. Clinical courses of Kawasaki disease, drug reactions, erythema multiforme, and immune complex-mediated illnesses also can overlap substantially with RMSF. Petechial rashes can be seen with meningococcal infection, disseminated gonococcal infection, immune thrombotic thrombocytopenic purpura, and after group A streptococcal pharyngitis. Meningococcal infection usually progresses more rapidly than RMSF.[21]

Rash on palms and soles may be caused by drug hypersensitivity reactions, bacterial endocarditis, secondary syphilis, rate bite fever (*Streptobacillus moniliformis*), certain enteroviruses, ehrlichiosis, and meningococcal infection.[21]

TREATMENT

Doxycycline is the antimicrobial agent of choice for treatment of suspected RMSF in patients of all ages, even young infants.[65,84] Treatment should never be delayed while awaiting laboratory confirmation of the diagnosis.[29] When patients in endemic areas in spring and summer have fever and headache, providers should not wait for development of rash to initiate therapy.

Minimally ill febrile patients with epidemiologic risk but without other features indicative of RMSF can be observed during the first 3 days of illness, but such patients should be re-evaluated when illness continues beyond this time frame. A complete blood cell count and serum electrolyte concentrations may be helpful. Thrombocytopenia and/or hyponatremia should heighten suspicion for RMSF.[29,39]

Outpatient management is reasonable for patients who are only mildly ill. Hospitalized children generally require intravascular volume support. Intensive care monitoring and inotropic support may be necessary. Management of pulmonary edema or increased intracranial pressure may require mechanical ventilation. Dialysis may be needed for renal insufficiency develops.[65]

Because meningococcemia and RMSF can overlap substantially, a third-generation cephalosporin or other agent with activity against Neisseria *meningitidis* is usually administered when RMSF is suspected. β-Lactam antimicrobials are ineffective for RSMF.[21,65]

Doxycycline is administered at a dosage of 2.2 mg/kg per dose twice daily (every 12 hours when hospitalized) for children, up to the adult maximum dosage of 200 mg twice daily. Oral or intravenous routes may be used, depending on the degree of illness and the ability of patients to take oral medication. It is generally accepted to treat for 3 days after defervescence, which usually results in total course of 5 to 10 days. Patients initially treated intravenously can be switched to oral therapy when they can tolerate fluids or other oral therapies.[21,84]

The usual contraindication of age less than 8 years old for tetracyclines due to potential for dental discoloration does not apply when RMSF (or infections due to related microbes, including agents of human ehrlichiosis) is suspected. Short courses of doxycycline administered to young children at the dosage (indicated previously) for RMSF have not been associated with discoloration of permanent teeth.[65,85,86]

Chloramphenicol is the only other antimicrobial agent for which there is substantial clinical experience with treatment of RMSF. It is less effective for RMSF than doxycycline. Oral formulations of chloramphenicol are no longer available in the United States.[65,87]

Macrolides are not effective against *R rickettsii* and many related species and should not be prescribed for treatment of RMSF.[88] Sulfonamide antimicrobial agents also are inactive and anecdotal clinical experience and animal studies suggest that administration of these compounds may increase the severity of illness by mechanisms that are uncertain but potentially involve oxidative stress.[89,90]

PROGNOSIS

Most children with RMSF recover fully when treated. Serologic studies suggest subclinical or unrecognized symptomatic infections are somewhat common.[31] Case fatality among before availability of effective antimicrobials was usually 20% to 25%. Death can result from multiorgan system failure or cerebral herniation. Case fatality in the United States was approximately 2% in the early 1990s and decreased to 0.3% during 2003 to 2007. Children less than 10 years old (2.3%) and adults 70 years old or older (1.3%) have the highest case fatality. Patients with underlying immunosuppressive conditions have a 4.4-fold greater risk of death.[8,27,91]

Delay in therapy is associated with higher risk of death.[92,93] One large cohort study found case fatality of 5.3% among patients whose treatment was initiated on the fifth day of illness or beyond compared with 1.6% among those whose treatment was initiated earlier.[87] Delays in appropriate therapy more often result from clinician failure to consider RMSF than patient delay in seeking care.[65] In the most recent series of children hospitalized for RMSF in the United States, illness was present for a median of 6 days before admission, and 86% had at least 1 health care visit during that interval.[33] Factors associated with delay in therapy include presentation during winter or early spring; presentation with complaints other than fever, rash, and headache; and lack of history of tick bite.[39,87,93]

Neurologic deficits are the most common long-term sequelae. In the most recent pediatric series, 13 (15%) of 89 surviving patients had 1 or more neurologic deficits at the time of discharge. These included global encephalopathy, speech and/or swallowing dysfunction, ataxia or gait abnormality, and cortical blindness.[33] All had altered mental status and required initial intensive care. Other neurologic sequelae can include seizures, paresthesias, hearing loss, facial nerve palsy, and changes in personality.[94] Many neurologic deficits that occur during acute illness, including ataxia and cranial nerve palsies, improve or resolve over time.[33,69]

Avascular necrosis of digits, ear lobes, nose, and scrotum has been described.[33,69] This outcome occurs most commonly in patients who have progressed to septic shock.

PREVENTION

Tick exposure is more likely in wooded areas or areas with bushes and high grass or leaf litter. When working or recreating in such areas, wearing light-colored clothing that covers arms, legs, and other exposed areas and staying on the center of trails may be helpful. Locating play equipment in sunny, dry areas away from forest edges or creating a barrier of wood chips or gravel between recreation areas and forest may reduce likelihood of tick exposure. Permethrin-treated clothing can repel ticks and may be used by children of all ages and remains effective through approximately 20 washings. Maintaining tick-free pets also decreases tick exposure.[95,96]

For children older than 2 months of age, use of skin repellents that contain 20% to 30% diethyltoluamide on exposed skin can provide protection. Applications of newer microencapsulated formulations may be effective for 8 to 12 hours. Serious neurologic complications associated with use of diethyltoluamide in young children have been reported, but risk is low when products are used per manufacturer instructions.[65,95]

Children's bodies and clothing should be carefully inspected after possible tick exposure. Ticks often attach to exposed hairy regions, including the head, neck, and behind the ears. Risk of transmission increases the longer a tick is attached. Removal is best accomplished by grasping the tick close to the skin with fine tweezers, then gently pulling straight out without twisting.[95,96]

Because carriage of *R rickettsii* is 1% or less among its vectors, most tick bites do not result in infection. Antimicrobial prophylaxis for RMSF after tick exposure in endemic areas is not recommended. Formalin-fixed killed whole cell vaccines developed in past decades reduced disease severity but did not protect against infection. A live attenuated vaccine strain, *R rickettsii* Iowa, is protective in animal models but has not been studied in humans.[49,97]

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