Vector-Borne Diseases Potpourri

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EDUCATION GAPS

Clinicians should be aware that:

1. Doxycycline may be used for the treatment of erythema migrans in all ages, but amoxicillin is preferred for children younger than 8 years for treatment of Lyme arthritis because a 28-day course of antibiotics is required.
2. Dengue infection has a wide range of presentations; many patients have no symptoms, but a minority of severe cases can progress to shock and hemorrhage.
3. There are several malaria prophylaxis options for foreign travel.
4. Treatment of Rocky Mountain spotted fever should be initiated without waiting for laboratory confirmation.

OBJECTIVES *After completing this article, readers should be able to:*

1. Describe the epidemiology of West Nile virus, Lyme disease, dengue, malaria, and Rocky Mountain spotted fever.
2. Recognize the clinical manifestations of West Nile virus, Lyme disease, dengue, malaria, and Rocky Mountain spotted fever.
3. Determine appropriate treatment management and prophylaxis measures for these vector-borne diseases.

ABSTRACT

The Intergovernmental Panel on Climate Change has reported that the prevalence of vector-borne diseases has increased in recent decades and that the prevalence of malaria, Lyme disease, dengue, and, in particular, West Nile virus infection are expected to increase further if control measures are not strengthened. (1)(2) This review article summarizes the epidemiology, various clinical manifestations, and management strategies of these vector-borne diseases with increasing prevalence both in the United States and worldwide.

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ABBREVIATIONS

AFM	acute flaccid myelitis
CDC	Centers for Disease Control and Prevention
CSF	cerebrospinal fluid
FDA	Food and Drug Administration
PCR	polymerase chain reaction
RMSF	Rocky Mountain spotted fever
WNV	West Nile virus

WEST NILE VIRUS

Epidemiology

West Nile virus (WNV) is a single-stranded positive-sense RNA virus of the *Flaviviridae* family, which includes the Zika, yellow fever, and dengue viruses,

and is antigenically related to the Japanese encephalitis and St Louis encephalitis viruses. It is the most common arbovirus in North America. Transmission has been reported on every continent except for Antarctica. It is the leading cause of neuroinvasive arboviral disease in the United States. WNV was first detected in 1999 in New York City and subsequently has spread across the United States and Canada, except for Alaska and Hawaii. (3)(4) Human transmission occurs through bites by infected *Culex* mosquitoes, and birds are the primary host. Transmission can also occur person-to-person through solid organ transplant and blood transfusion. (3)

Most human infections in temperate or subtropical regions occur in the summer or early fall. All age groups are susceptible to WNV infection, but older adults have the highest incidence of severe disease. (3)

Clinical Manifestations

Most people infected with WNV are asymptomatic (70%–80%). (3) Fever is the most common symptom, in conjunction with headache, fatigue, and myalgia. Gastrointestinal symptoms and a maculopapular rash can also occur. (4) Neuroinvasive disease, which occurs in less than 1% of patients, presents as meningitis, encephalitis, or acute flaccid myelitis (AFM) (3). The presentation of WNV meningitis and encephalitis is similar to aseptic meningitis or encephalitis caused by other viral infections. Meningitis occurs more commonly in children, compared with encephalitis, which is more common in adults. (5) AFM presents similar to poliovirus-associated poliomyelitis as both viruses damage anterior horn cells. This damage results in rapid progressive asymmetrical paralysis and may progress to respiratory paralysis requiring mechanical ventilation. (3)

In cases of neuroinvasive disease, the cerebrospinal fluid (CSF) examination generally reveals lymphocytic pleocytosis. Testing the CSF and serum to detect WNV-specific IgM antibodies should be performed. Immunoassays for WNV-specific IgM are available commercially and through public health departments. However, the presence of IgM antibodies is not sufficient for confirming the disease because it may cross-react with other flaviviruses. (3)(4) Therefore, all positive immunoassays must be confirmed by neutralizing antibody testing of acute- and convalescent-phase serum specimens. IgM antibodies are detectable within 3 to 8 days of symptom onset and can remain detectable for up to 90 days. Brain magnetic resonance imaging is frequently normal in these patients, but occasionally signal abnormalities are seen in the basal ganglia, thalamus, and brain stem for patients presenting with encephalitis and in the spinal cord with AFM (3).

Management

There are currently no effective treatments for patients with WNV aside from supportive care.

Prognosis

For WNV neuroinvasive disease and meningitis, most patients recover completely, although symptoms such as fatigue, weakness, and general malaise may persist for weeks to months. WNV encephalitis and AFM often take weeks to months to recover from, and patients may have residual neurologic deficits. (3) The Centers for Disease Control and Prevention (CDC) reported an estimated mortality rate of 4% among all patients with WNV and 9% in neuroinvasive cases between 1999 and 2016. (4)(5) Children with neuroinvasive disease have a better overall prognosis compared with older adults (case fatality of 1%). (5)

LYME DISEASE

Epidemiology

Lyme disease was first identified in 1977 after a report of several children with arthritis in Old Lyme, Connecticut. (6) Lyme disease is the most common vector-borne infection in the United States, with approximately 35,000 reported cases annually. (6)(7) Most cases (up to 80%) occur in New England and the Mid-Atlantic states, with lower rates of infection in the Midwest and on the west coast. (6)(8) Lyme disease is caused by the spirochete *Borrelia burgdorferi* and is transmitted by infected ticks, primarily *Ixodes scapularis* in the eastern United States along with *Ixodes pacificus* in the western United States. Hosts include mice, rodents, deer, and humans. (6) Transmission of infection occurs from April to October, with a peak incidence of 50% of infections occurring in June and July. (8) The highest incidence of infection occurs in children aged 5 to 9 years along with adults aged 55 through 69 years. (7)(8) The incubation period from tick bite to appearance of rash is 3 to 32 days. (8) *Ixodes* ticks can also transmit other infections, although routine testing for coinfections is not typically necessary. Anaplasmosis and babesiosis are the 2 most commonly transmitted infections by *Ixodes* ticks after Lyme disease, and these infections rarely cause clinically significant disease in children. However, anaplasmosis can be tested for in patients with abnormal cell counts or liver enzyme levels, and babesiosis can be tested for in children who have splenic dysfunction, are immunocompromised, or are neonates, as these children are at risk for more severe infection. (7)

Clinical Manifestations

There are 3 identified stages of the clinical manifestation of Lyme disease: early localized, early disseminated, and late Lyme disease. Early localized Lyme disease is characterized by the classic skin lesion erythema migrans (Fig 1), which occurs at the site of the tick bite. The lesion begins as an erythematous macule that is either homogeneous or has a pale center and if untreated progresses to the typical "bull's-eye" lesion. (7)(8) Children often have lesions on the upper body, whereas adults tend to manifest lesions on the legs and feet. (9) Early localized Lyme disease can be associated with systemic symptoms such as fever, fatigue, headaches, and body aches. In early disseminated Lyme disease, which occurs several weeks after the initial bite, multiple, smaller erythema migrans lesions may develop. Patients can develop neuroborreliosis, which is characterized by cranial nerve palsies (usually cranial nerve VII, as seen in Fig 2), lymphocytic meningitis, and radiculitis. Patients may also develop Lyme carditis with atrioventricular heart block that can progress to life-threatening arrhythmias. Carditis is less commonly seen in children. (7) Late Lyme disease is characterized by monoarticular or oligoarticular inflammatory arthritis, typically of the knee joint (Fig 3). Patients develop joint swelling with white blood cells in the synovial fluid, and swelling is often out of proportion and more severe compared with the degree of pain that is present. (8) The mean time to development of Lyme arthritis after the initial tick bite is 3.4 months, and patients usually do not have a history of earlier manifestations of Lyme disease. (7)(8)

Lyme disease is diagnosed by a 2-tiered testing serologic approach to increase diagnostic specificity because there is a high false-positive rate due to cross-reactivity of antibodies against *B burgdorferi* that are also produced

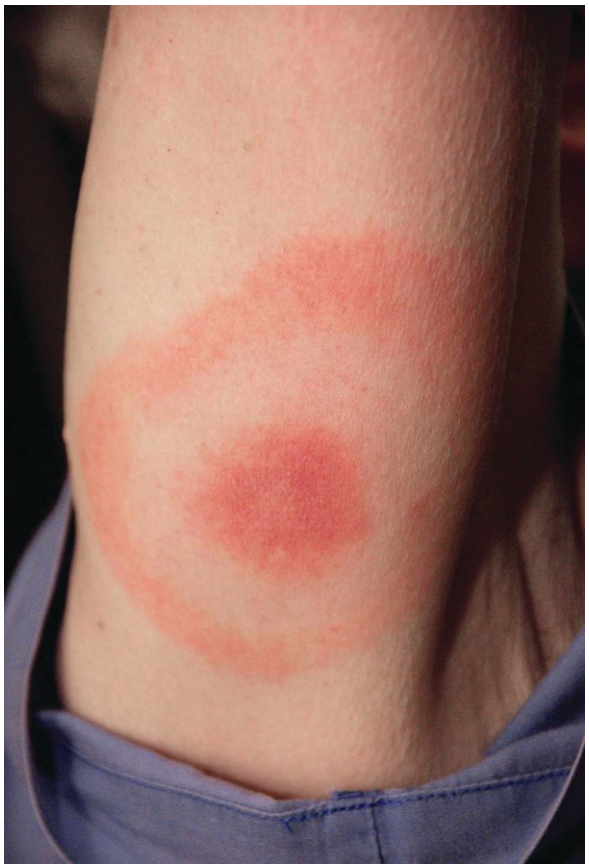

Figure 1. Photograph of the pathognomonic erythematous rash (erythema migrans) in the pattern of a bull's-eye that developed at the site of a tick bite on this Maryland patient's posterior right upper arm. The expanding rash reflects migration of the spirochetes after introduction of the organism during the tick bite. (Reprinted with permission from the Centers for Disease Control and Prevention.)

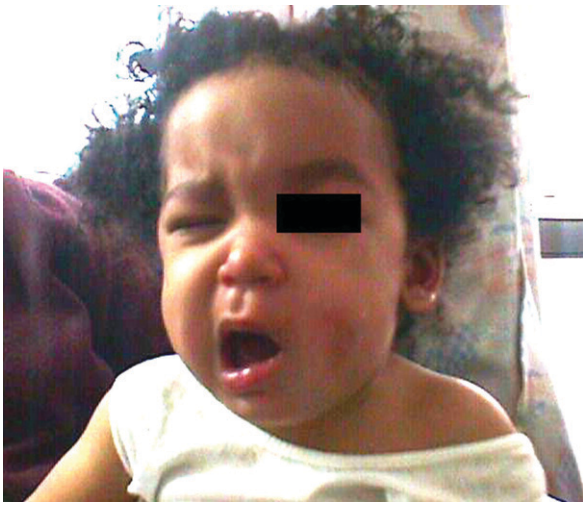

Figure 2. A 15-month-old with left facial nerve palsy complicating Lyme disease. (Reprinted with permission from the American Academy of Pediatrics.)

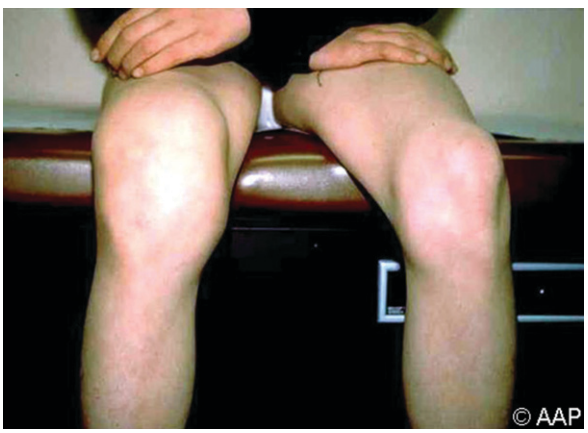

Figure 3. *Borrelia burgdorferi* synovitis with marked swelling and only mild tenderness. Arthritis occurs usually within 1 to 2 months after the appearance of erythema migrans, and the knees are the most commonly affected joints. (Reprinted with permission from the American Academy of Pediatrics.)

against other spirochete infections, spirochetes present in normal oral flora, other infections, and autoimmune disorders. First, an enzyme-linked immunosorbent assay or an immunofluorescent antibody test is performed. If testing is negative, the patient is considered to be seronegative and no additional testing is indicated. If either test is positive, a Western blot should be performed that examines IgM to 3 antigens and IgG to 10 antigens. A positive test requires identifying at least 2 IgM bands or 5 IgG bands. (8) There is no Food and Drug Administration (FDA)–approved polymerase chain reaction (PCR) test, although it can be used to test synovial fluid in patients with persistent joint swelling despite therapy. The CSF may be tested by PCR, although a negative test result does not exclude the diagnosis. Testing should not be conducted for patients with erythema migrans because antibodies take 2 to 4 weeks to develop, so patients should undergo treatment without confirmatory testing. (8) It is important to use Lyme testing only in patients with the appropriate clinical manifestations and geographic exposure because Lyme testing is frequently inappropriately used and misinterpreted, creating a source of diagnostic confusion for both physicians and families. (7)(8)

Management

The Infectious Diseases Society of America established guidelines in 2020 for treatment of the different stages of Lyme disease (Table 1). Doxycycline, amoxicillin, or cefuroxime may be used to treat erythema migrans in children of all ages. Previously, doxycycline had not been recommended in children younger than 8 years due to risk of dental staining. However, more recent evidence demonstrates that doxycycline is safe to use for short durations of therapy. Azithromycin is the second-line for treatment of erythema migrans for patients intolerant of other therapies. Doxycycline is the drug of choice for all facial palsies because amoxicillin is not as likely to reach therapeutic levels in the central nervous system. Ceftriaxone or oral agents for treatment of erythema migrans may be used for cardiac manifestations. For late disseminated infection, treatment is a 28-day course of oral antibiotics (doxycycline, amoxicillin, or cefuroxime). Amoxicillin is preferred for children younger than 8 years due to the prolonged course. Children with a partial response to therapy may require a second 28-day course or a course of parenteral ceftriaxone for 14 to 28 days. (7)(8)

Chemoprophylaxis may be used in high-risk endemic areas, with a single dose of doxycycline in patients with a tick attached for at least 36 hours and where prophylaxis can be started within 72 hours of tick removal. (6)(8) In endemic areas, routine tick precautions should be exercised, including minimizing exposed skin with protective clothing, using clothing treated with 0.5% permethrin, applying repellant with *N,N*-diethyl-*meta*-toluamide (DEET) at 30% concentrations, and checking for ticks after potential exposure. (6)

Prognosis

Children with Lyme disease who are treated in earlier stages rarely develop late symptoms. Between 10% and 15% of patients with Lyme arthritis will have persistent synovitis that may last for months to years, and they may

Table 1. Lyme Disease Management in Children

DISEASE CATEGORY	DRUGS AND DOSING
Erythema migrans	Doxycycline, 4.4 mg/kg per day, orally, divided into 2 doses (maximum, 200 mg/d) for 10 d OR Amoxicillin, 50 mg/kg per day, orally, divided into 3 doses (maximum, 1.5 g/d) for 14 d OR Cefuroxime, 30 mg/kg per day, orally, divided into 2 doses (maximum, 1 g/d) for 14 d Second-line for patients intolerant of β-lactams or doxycycline: azithromycin, 10 mg/kg per day, orally, once daily for 7 d
Facial palsy	Doxycycline, 4.4 mg/kg per day, orally, divided into 2 doses (maximum, 200 mg/d) for 14 d
Arthritis	Any of the oral agents for early localized disease for 28 d If persistent arthritis after completion of therapy: Retreat as for first episode for second 28-d course OR Ceftriaxone, 50–75 mg/kg, intravenously, once daily (maximum, 2 g/d) for 14–28 d
Atrioventricular heart block or carditis	Any of the oral agents for early localized disease for 14 d OR Ceftriaxone, 50–75 mg/kg, intravenously, once daily (maximum, 2 g/d) for 14 d (range, 14–21 d for hospitalized patient); oral therapy with agent for early localized disease can be substituted when patient is stabilized or discharged to complete course
Meningitis	Doxycycline, 4.4 mg/kg per day, orally, divided into 1 or 2 doses (maximum, 200 mg/d) for 14 d OR Ceftriaxone, 50–75 mg/kg, intravenously, once daily (maximum, 2 g/d) for 14 d

Adapted from Meissner HC, Steere AC. Management of pediatric Lyme disease: updates from 2020 Lyme guidelines. *Pediatrics*. 2022;149[3]:e2021054980.

need to be referred to a rheumatologist for joint corticosteroid injections. There is no scientific evidence of treatment-refractory chronic Lyme disease, and patients with persistent symptoms will recover gradually after treatment. (8)

DENGUE

Epidemiology

Dengue is the most common mosquito-borne virus globally, with an annual incidence of 390 million infections. (2)(10)(11) Dengue is the leading cause of fever in travelers from the Caribbean, Latin America, and South Asia, so it is critical to have a high index of suspicion for dengue in return travelers from these areas. In the United States, dengue is endemic in Puerto Rico, the Virgin Islands, and American Samoa, (11) although there has been a rising number of cases of local transmission in Florida, Hawaii, and Texas in recent years. (10) There are 4 dengue virus serotypes (DENV 1–4), which are closely related RNA viruses belonging to the *Flavivirus* genus. Viruses are transmitted to humans through the bite of an infected mosquito, primarily *Aedes aegypti* but also *Aedes albopictus* and *Aedes polynesiensis*. The incubation period ranges from 3 to 14 days before the development of symptoms. Humans are the main host of dengue viruses. (11) Lifetime immunity is conferred against a specific serotype after infection, although patients are at risk for future infections from other serotypes. (10) In children, 95% of cases occur in youths younger than 15 years, and infants are at highest risk for severe infection and septic shock. (12)

Clinical Manifestations

There is a wide range of clinical presentations of dengue, from asymptomatic to a self-limited febrile illness to severe shock. (10)(11) The categories of severity of dengue infection as defined by the World Health Organization are dengue without warning signs, dengue with warning signs, and severe dengue (Table 2). Most patients with dengue will be asymptomatic or have mild symptoms. (13) For symptomatic patients, the illness is divided into 3 phases. In the febrile phase, patients will have fever for 2 to 7 days that is often associated with muscle, bone, and joint pain that is the origin for the term *break-bone fever*. Patients may also have headache, retro-orbital pain, nausea, vomiting, abdominal pain, malaise, and a convalescent maculopapular rash. (11)(13) There are often bleeding manifestations, including petechiae, purpura, and bleeding around venipuncture sites. Underlying capillary fragility causes easily provoked petechiae, which can be elicited on a tourniquet test (Fig 4). (11)(13) Most children will recover after the initial stage. However, some children progress to the critical phase during defervescence on days 3 to 7 of illness with development of increased capillary permeability and plasma leakage that lasts for 24 to 48 hours. These patients present with warning signs (Table 2). Critical-phase patients can develop pleural effusions, ascites, hypovolemic shock, and hemorrhage. This phase is followed by the convalescent phase with gradual improvement in hemodynamic stability. Less commonly, patients can develop myocarditis, pancreatitis, hepatitis, hemophagocytic lymphohistiocytosis, acute meningoencephalitis, and postdengue acute disseminated encephalomyelitis. (11)

Diagnostic testing is performed by reverse transcription PCR to detect dengue RNA, a test that has high sensitivity and specificity, or by immunoassay to detect dengue virus nonstructural protein 1 antigen. (10)(11) IgM antibodies form between days 3 and 5 of illness and will be detectable in up to 99% of patients by day 10 of illness. IgM antibodies peak 2 weeks after illness and will wane over months. IgG antibodies are detectable for life. (11) Associated supporting laboratory abnormalities include leukopenia, thrombocytopenia, and elevated liver transaminase levels. (11)(13)

Table 2. Dengue Severity Classification

DENGUE WITHOUT WARNING SIGNS	DENGUE WITH WARNING SIGNS	SEVERE DENGUE
Live in/travel to endemic area Fever + 2 of the following: • Nausea/vomiting • Rash • Aches and pains • Leukopenia • Positive tourniquet test (>10 petechiae present per square inch of skin on a tourniqueted arm)	Dengue as defined in the first column plus: • Abdominal pain or tenderness • Persistent vomiting • Clinical fluid accumulation (ascites, pleural effusion) • Mucosal bleed • Lethargy • Restlessness • Liver enlargement >2 cm • Increase in hematocrit concurrent with rapid decrease in platelet count	Severe plasma leakage leading to: • Shock • Fluid accumulation with respiratory distress Severe bleeding Severe organ involvement: • Liver: transaminases >1,000 IU/L • Central nervous system: impaired consciousness • Heart failure

Adapted with permission from World Health Organization. *Dengue Hemorrhagic Fever: Diagnosis, Treatment, Prevention and Control*. Geneva, Switzerland: World Health Organization; 2009.

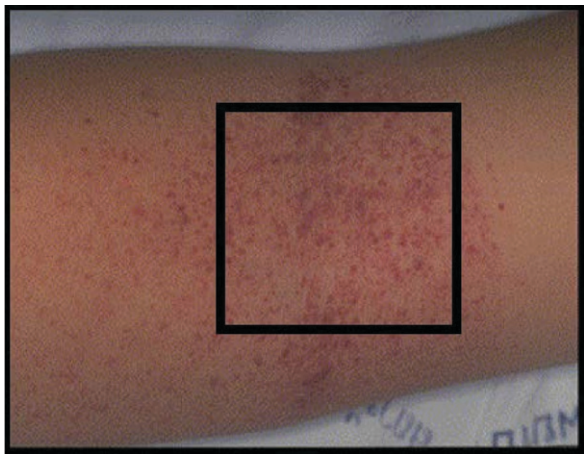

Figure 4. Positive tourniquet test with greater than 10 petechiae per square inch. (Reprinted with permission from the Centers for Disease Control and Prevention.)

Management

There are no current antiviral treatments for dengue infection, and the mainstay of treatment is supportive care. Patients without warning signs may be treated in the outpatient setting. Patients with warning signs or who are at risk for progression to severe infection (eg, young infants) should be monitored in an inpatient setting. (10)(11) Patients should be adequately hydrated to account for insensible losses, and medications that increase bleeding risk (nonsteroidal anti-inflammatories, salicylates) should be avoided. Patients in the severe phase require close monitoring for shock. Patients with evidence of refractory shock or hemorrhage may be treated with intravenous colloid fluid, vasoactive support, and blood products. (11) During the convalescent phase, extracellular fluid is reabsorbed, and patients require a careful balance of maintaining intravascular volume status while preventing fluid overload. There has been no demonstrated benefit of corticosteroids, immunoglobulins, or prophylactic platelet transfusions. (10)

Travelers to endemic areas should follow prevention recommendations to reduce risk of mosquito bites. *Aedes* mosquitoes most commonly bite during the daytime, so travelers should wear protective clothing, apply US Environmental Protection Agency–approved repellents, use screened windows and doors, and use bed nets for children sleeping during the daytime. There is a recombinant, live-attenuated tetravalent vaccine approved by the FDA and the CDC for children aged 9 to 16 years who live in endemic areas and have previous laboratory evidence of dengue infection. (10)(11) Patients without previous infection who are vaccinated are at increased risk for severe dengue when infected with a different serotype. Thus, only patients who are seropositive are approved for vaccination. (11)

Prognosis

The overall mortality rate for dengue is less than 1%. In patients with severe dengue, the mortality rate may be as high as 13%. (10) Prompt recognition of severe dengue and early management of shock has been shown to lower the mortality rate in patients with severe dengue to less than 1%. (10)(11)

MALARIA

Epidemiology

Protozoa of the genus *Plasmodium* cause malaria. There are 5 species that infect humans: *Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae,* and *Plasmodium knowlesi*. Coinfections with multiple species can occur. Malaria is endemic throughout the tropical regions of the world, including Africa, Asia, the South Pacific, Latin America, and parts of the Caribbean. It can also be found in Eastern Europe. *P vivax* and *P falciparum* are the most prevalent species worldwide. (14) Most cases reported in the United States are acquired outside the United States. However, locally acquired cases can occur. There were 9 cases of locally acquired malaria reported in 2023, of which 7 were *P vivax* malaria infections in Florida, 1 was *P vivax* in Texas, and 1 was *P falciparum* in Maryland. (15)

Infection transmission occurs by the bite of a female *Anopheles* genus of mosquito, and the incubation period ranges from 7 to 30 days. Less commonly, transmission can occur through organ transplant, blood transfusions, and contaminated needles and by vertical transmission from mother to fetus. (14) Relapses can occur months after initial infections by *P vivax* and *P ovale* because of the persistent hepatic (hypnozoite) stage of the infection.

Clinical Manifestations

The classic presentation of malaria, which may be paroxysmal, includes high fever with chills, headaches, rigors, and diaphoresis. Other manifestations include gastrointestinal symptoms, arthralgia, myalgia, back pain, cough, and shortness of breath. Severe malaria infections, usually caused by *P falciparum*, can present with altered mental status or other central nervous system symptoms (cerebral malaria); signs of end-organ involvement, including renal failure, respiratory failure, jaundice with hepatic dysfunction, vascular collapse, and shock; severe anemia; thrombocytopenia; and/or hypoglycemia. Congenital malaria infections are rare, and most cases are caused by *P vivax* and *P falciparum* with manifestations resembling neonatal sepsis with nonspecific symptoms.

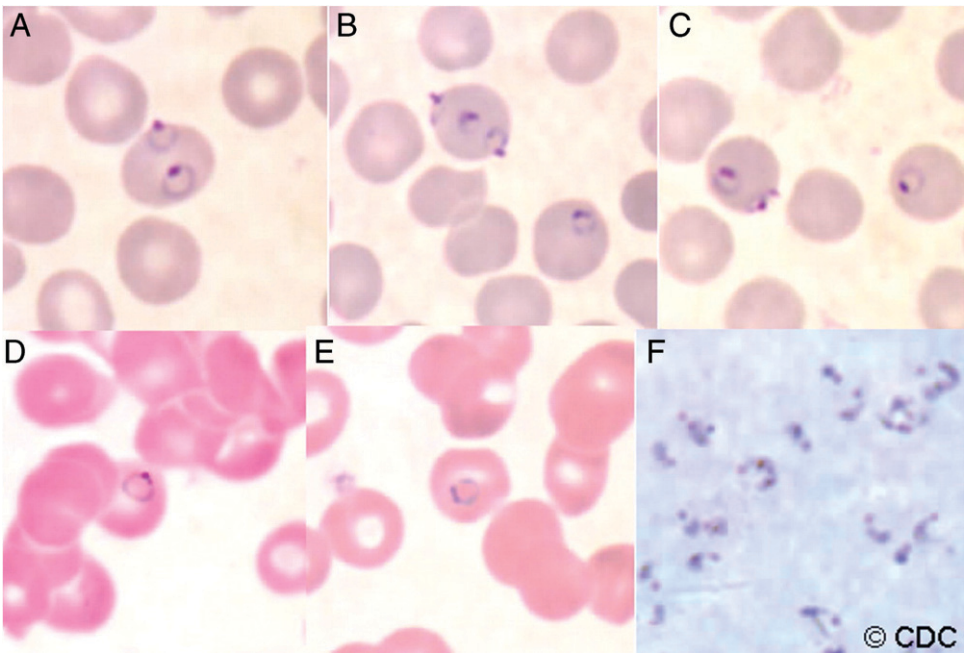

Figure 5. *Plasmodium falciparum* ring-stage smears from patients. *P falciparum* rings have delicate cytoplasm and 1 or 2 small chromatin dots. Red blood cells (RBCs) that are infected are not enlarged; multiple infection of RBCs is more common in *P falciparum* than in other species. Occasional appliqué forms (ie, rings appearing on the periphery of the RBC) can be present. A–C. Multiply infected RBCs with appliqué forms in thin blood smears. D. Signet ring form. E. Double chromatin dot. F. A thick blood smear showing many ring forms of *P falciparum*. (Reprinted with permission from the Centers for Disease Control and Prevention.)

Definitive diagnosis is the identification of *Plasmodium* parasites microscopically. Both thick and thin smears are examined. A thick smear is more sensitive for detection of the parasite, whereas the thin smear enables species identification and determines the parasitemia (Figs 5 and 6). If the smears are negative but malaria remains a possibility, repeated smears should be obtained every 12 to 24 hours in a 72-hour period, with ideally obtaining at least 3 sets of smears. PCR assay is highly sensitive, but it can take days for results to return because these assays are performed in reference laboratories and by state health departments. Rapid parasite-specific antigen testing is available, but limitations of the test are that it cannot be used for species identification and parasite count, or to distinguish new infections from recently treated infections.

Management

Malaria treatment is based on the infecting species, drug resistance in the locations where malaria was acquired, and severity of disease. Selection of appropriate therapies based on CDC recommendations for uncomplicated infections caused by *P falciparum*, *P vivax,* and *P ovale* are

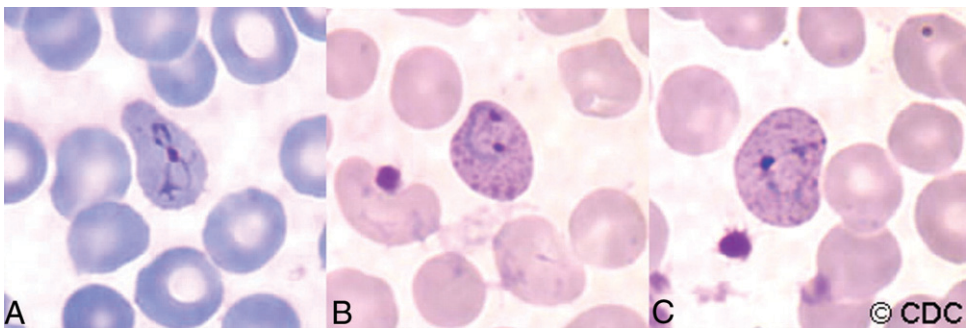

Figure 6. *Plasmodium vivax* ring-stage parasite smears from patients. *P vivax* rings have large chromatin dots and can show ameboid cytoplasm as they develop. Red blood cells (RBCs) can be normal to enlarged up to 1.5 times and may be distorted. Under optimal conditions, Schüffner dots may be seen. A–C. Rings in thin blood smears. A and C. Rings are ameboid and the RBCs are enlarged and distorted. B. Ring with double chromatin dot. Schüffner dots can be seen in B and C. (Reprinted with permission from the Centers for Disease Control and Prevention.)

Table 3. Treatment Recommendations for Uncomplicated Malaria Infection

DRUG SUSCEPTIBILITY (BASED ON WHERE ACQUIRED)	RECOMMENDED PEDIATRIC REGIMENS
Uncomplicated Malaria: *Plasmodium falciparum* or unknown species	
Chloroquine resistant or unknown resistance (All malaria-endemic regions except those in Central America west of Panama Canal, Haiti, and Dominican Republic)	A. Artemether-lumefantrine[a] (1 tablet: 20 mg of artemether and 120 mg of lumefantrine) 5 to <15 kg: 1 tablet po per dose 15 to <25 kg: 2 tablets po per dose 25 to <35 kg: 3 tablets po per dose ≥35 kg: 4 tablets po per dose 3-d course: day 1, initial dose and second dose 8 h later; days 2 and 3, 1 dose twice daily B. Atovaquone-proguanil[a] (adult tablet: 250 mg of atovaquone and 100 mg of proguanil; pediatric tablet: 62.5 mg of atovaquone and 25 mg of proguanil) 5 to <8 kg: 2 pediatric tablets po once daily × 3 d 8 to <10 kg: 3 pediatric tablets po once daily × 3 d 10 to <20 kg: 1 adult tablet po once daily × 3 d 20 to <30 kg: 2 adult tablets po once daily × 3 d 30 to <40 kg: 3 adult tablets po once daily × 3 d ≥40 kg: 4 adult tablets po once daily × 3 d C. Quinine sulfate[b] plus doxycycline[c] tetracycline, or clindamycin[d] Quinine sulfate: 8.3 mg base/kg (10 mg salt/kg) po 3 times daily × 3 or 7 d[c] Doxycycline: 2.2 mg/kg po twice daily × 7 d Tetracycline: 25 mg/kg per day po divided 4 times daily × 7 d; clindamycin: 20 mg/kg per day po divided 3 times daily × 7 d D. Mefloquine[e] Dose 1: 13.7 mg base/kg (15 mg salt/kg) po Dose 2 at 6–12 h: 9.1 mg base/kg (10 mg salt/kg) po
Chloroquine sensitive (Central America west of Panama Canal, Haiti, and Dominican Republic)	Chloroquine phosphate Dose 1: 10 mg base/kg (16.7 mg salt/kg) po Doses 2–4 (3 additional doses) at 6, 24, and 48 h: 5 mg base/kg (8.3 mg salt/kg) po per dose; or Hydroxychloroquine Dose 1: 10 mg base/kg (12.9 mg salt/kg) po Doses 2–4 (3 additional doses) at 6, 24, and 48 h: 5 mg base/kg (6.5 mg salt/kg) po per dose
Uncomplicated Malaria: *Plasmodium vivax* or *Plasmodium ovale*	
Chloroquine sensitive (All malaria-endemic regions except Papua New Guinea and Indonesia)	Acute treatment[f]: Chloroquine phosphate Dose 1: 10 mg base/kg (16.7 mg salt/kg) po Doses 2–4 (3 additional doses) at 6, 24, and 48 h: 5 mg base/kg (8.3 mg salt/kg) po per dose; or Hydroxychloroquine Dose 1: 10 mg base/kg (12.9 mg salt/kg) po Doses 2–4 (3 additional doses) at 6, 24, and 48 h: 5 mg base/kg (6.5 mg salt/kg) po per dose AND antirelapse treatment[g]: Primaquine phosphate[h]: 0.5 mg base/kg po daily × 14 d; or Tafenoquine[i]: 300 mg po × 1 dose, only for patients ≥16 years old
Chloroquine resistant (Papua New Guinea and Indonesia)	Acute treatment: A. Artemether-lumefantrine[a] (1 tablet: 20 mg of artemether and 120 mg of lumefantrine) 5 to <15 kg: 1 tablet po per dose 15 to <25 kg: 2 tablets po per dose 25 to <35 kg: 3 tablets po per dose ≥35 kg: 4 tablets po per dose 3-d course: day 1, initial dose and second dose 8 h later; days 2 and 3, 1 dose twice daily B. Atovaquone-proguanil[a] (adult tablet: 250 mg of atovaquone and 100 mg of proguanil; pediatric tablet: 62.5 mg of atovaquone and 25 mg of proguanil) 5 to <8 kg: 2 pediatric tablets po daily × 3 d 8 to <10 kg: 3 pediatric tablets po daily × 3 d 10 to <20 kg: 1 adult tablet po daily × 3 d 20 to <30 kg: 2 adult tablets po daily × 3 d 30 to <40 kg: 3 adult tablets po daily × 3 d ≥40 kg: 4 adult tablets po daily × 3 d C. Quinine sulfate[b] plus 1 of the following: doxycycline,[c] tetracycline, or clindamycin[d] Quinine sulfate: 8.3 mg base/kg (10 mg salt/kg) po 3 times daily × 3 or 7 d[c] Doxycycline: 2.2 mg/kg po twice daily × 7 d

Continued

Table 3. Treatment Recommendations for Uncomplicated Malaria Infection (Continued)

DRUG SUSCEPTIBILITY (BASED ON WHERE ACQUIRED)	RECOMMENDED PEDIATRIC REGIMENS
	Tetracycline: 25 mg/kg per day po divided 4 times daily × 7 d; clindamycin: 20 mg/kg per day po divided 3 times daily × 7 d D. Mefloquine[e] Dose 1: 13.7 mg base/kg (15 mg salt/kg) po Dose 2 at 6–12 h: 9.1 mg base/kg (10 mg salt/kg) po AND antirelapse treatment[g]: Primaquine phosphate[h]: 0.5 mg base/kg po daily × 14 d; or Tafenoquine[i]: 300 mg po × 1 dose, only for patients ≥16 years old

If an antimalarial is taken for chemoprophylaxis, a different drug should be used for treatment. Option A is preferred. Options B and C are adequate alternatives and should be used if more readily available than option A. Option D should be used only if other options are not available. po=by mouth.

[a]Administer with food to improve absorption.

[b]Quinine to be given for 3 days, except for infections acquired in Southeast Asia, where 7 days of treatment is required. Quinine available in the United States has 324 mg (salt) per capsule; therefore, 2 capsules for adult dosing. Pediatric dosing may need compounding pharmacies.

[c]Doxycycline or tetracycline combined with quinine is preferred due to more efficacy data, but not recommended during pregnancy or in children younger than 8 years unless no other options and benefits outweigh risks.

[d]Clindamycin with quinine is a preferred option for pregnant women and children younger than 8 years.

[e]Mefloquine is not recommended for infections acquired in Southeast Asia due to drug resistance. Not recommended if other options are available or in patients with neuropsychiatric history.

[f]Regimens used to treat chloroquine-resistant *P vivax* infections may be used if chloroquine and hydroxychloroquine are not available.

[g]Either option for antirelapse treatment recommended if chloroquine or hydroxychloroquine used for acute treatment. If regimens other than either chloroquine or hydroxychloroquine used for acute treatment, primaquine is the only option for antirelapse treatment.

[h]Primaquine and tafenoquine are associated with hemolytic anemia in those with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Before use, quantitative G6PD testing is needed to confirm normal activity. For those with intermediate G6PD deficiency, weekly primaquine may be used (45 mg per week) for 8 weeks with close monitoring for hemolysis. Those with G6PD deficiency may be given chloroquine 300 mg (base) po weekly for 1 year from acute infection to prevent relapses.

[i]Tafenoquine can be used only if chloroquine or hydroxychloroquine is administered for acute treatment due to limited data on efficacy when used in combination with other regimens.

Adapted with permission from the Centers for Disease Control and Prevention. CDC treatment recommendations. Available at: www.cdc.gov/malaria/diagnosis_treatment/clinicians1.html.

outlined in Table 3. Patients with severe malaria with parasitemia greater than 5% of red blood cell infection or signs of cerebral malaria or other end-organ disease require intensive care admission and parenteral treatment with intravenous artesunate. Primaquine is approved to prevent relapses of *P vivax* and *P ovale*. Screening for glucose-6-phosphate dehydrogenase deficiency must be performed before using primaquine because primaquine can cause hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency. (14)

There are effective measures to reduce the acquisition of malaria by travelers, including chemoprophylaxis (Table 4), and measures to prevent insect bites, including bed nets and mosquito repellents. The most current country-specific malaria prevention recommendations for travelers can be obtained on the CDC website (www.cdc.gov/malaria).

Prognosis

In 2020, malaria was estimated to cause 241 million illnesses and 627,000 deaths worldwide. (16) Severe malaria cases have a higher chance of death, and most deaths occur in young children (<5 years old). (14)

ROCKY MOUNTAIN SPOTTED FEVER

Epidemiology

The causative agent of Rocky Mountain spotted fever (RMSF) is *Rickettsia rickettsii*. The pathogen is transmitted to humans by the bite of *Dermacentor variabilis*, the American dog tick in the eastern and central states of the United States, and *Dermacentor andersoni*, the Rocky Mountain wood tick in the northern and western states. Most cases are reported in the southern states, specifically southeast and south central areas. The highest incidence of infection occurs in the months of April to September. During the past 20 years, there has been a rise in the number of cases reported to the CDC. (17)(18) The typical incubation period is approximately 1 week after the tick bite. The primary target of infection in hosts are endothelial cells lining small blood vessels of all major organs and tissues, leading to diffuse vasculitis (17).

Clinical Manifestations

Patients with RMSF typically present with high fever, myalgia, and headaches. Gastrointestinal signs and symptoms such as nausea, vomiting, diarrhea, and abdominal pain can also occur. The rash associated with RMSF typically begins within the first 4 days of symptoms. The

Table 4. Malaria Prophylaxis Regimens for Children

DRUG/LOCALE	DOSING	TIMING	ADVERSE EFFECTS AND CONTRAINDICATIONS
Chloroquine or hydroxychloroquine Only chloroquine-sensitive areas	Chloroquine: 5 mg/kg base (8.3 mg/kg salt), orally, once weekly, up to maximum 300 mg base Hydroxychloroquine: 5 mg/kg base (6.5 mg/kg salt), orally, once weekly, up to maximum 310 mg base	Begin 1–2 wk before travel, weekly during travel, and for 4 wk after leaving endemic area	Most common adverse effects: gastrointestinal tract disturbance, headache, dizziness, blurred vision, pruritus, insomnia Can exacerbate psoriasis
Mefloquine Only mefloquine-sensitive areas	≤9 kg: 4.6 mg/kg base (5 mg/kg salt), once weekly >9–19 kg: 1/4 tablet, once weekly >19–30 kg: 1/2 tablet, once weekly >30–45 kg: 3/4 tablet, once weekly >45 kg: 1 tablet, once weekly Each tablet contains 228 mg base (250 mg salt)	Begin 2–3 wk before travel, weekly during travel, and for 4 wk after leaving endemic area	Most common adverse effects: gastrointestinal tract disturbance, headache, insomnia, vivid dreams, visual disturbance, anxiety, dizziness Contraindicated in travelers with a known hypersensitivity to the drug and in those with an active or recent history of depression, anxiety disorder, psychosis, schizophrenia, other major psychiatric disorder, or seizures Do not use in those with cardiac conduction defects
Doxycycline All areas	2.2 mg/kg, up to maximum adult dose of 100 mg/d	Begin 1–2 d before travel, daily throughout travel, and for 4 wk after leaving endemic area	Most common adverse effects: photosensitivity, gastrointestinal disturbance Not recommended for pregnant women or for children <8 years old because duration of prophylaxis exceeds 21 d
Atovaquone-proguanil All areas	Pediatric tablets, 62.5 mg of atovaquone and 25 mg of proguanil hydrochloride 5–8 kg: 1/2 tablet >8–10 kg: 3/4 tablet >10–20 kg: 1 tablet >20–30 kg: 2 tablets >30–40 kg: 3 tablets >40 kg: 1 adult tablet (250 mg of atovaquone/100 mg of proguanil)	Begin 1–2 d before travel, daily throughout travel, and for 7 d after leaving endemic area	Most common adverse effects: abdominal pain, nausea, vomiting, headache Do not use in those with creatinine clearance <30 mL/min; not recommended for infants <5 kg, pregnant women, or women who are breastfeeding infants <5 kg

Adapted with permission from the Centers for Disease Control and Prevention. Table adapted from the CDC Prophylaxis Regimens for Traveler's. Available at: www.cdc.gov/malaria/travelers/drugs.html.

rash classically appears as a faint maculopapular rash that first appears on the ankles and wrists, and then spreads to the trunk. It can also involve the palms and soles (Fig 7). The rash may be subtle in early illness and may be absent in up to 10% of patients. As the rash progresses, it appears petechial, reflecting small-vessel vasculitis and severe disease. In severe cases, patients may develop meningismus, altered mental status, renal failure, disseminated intravascular coagulation and shock.

RMSF is a clinical diagnosis that should be considered when a patient presents with the classic triad of fever, headaches, and rash. Headaches are reported less commonly in young children. The classic laboratory abnormalities in patients with RMSF include elevated liver transaminase levels, thrombocytopenia in 33% of patients, and hyponatremia (serum sodium concentration <130 mg/dL [< 7.2 mmol/L]) in 20% of patients. Leukopenia and anemia can occur. The confirmatory test is indirect immunofluorescent antibody to the *R rickettsii* antigen. Both IgG and IgM antibodies start to rise 7 to 10 days after symptom onset, and confirmation of infection requires a 4-fold or greater increase in antigen-specific IgG between blood work obtained during 2 phases: acute (first 1–2 weeks of illness) and convalescent (2–4 weeks later). *R rickettsii* DNA PCR assays from whole blood, tissue, and serum specimens can also be performed. (17)

Management

Treatment should be initiated as soon as RMSF is suspected, and treatment is most effective within the first 5 days of symptom onset. Clinicians should not wait to start treatment while awaiting laboratory results. Doxycycline is the drug of choice in all ages. The typical duration of treatment is 5 to 7 days but may be longer in severe cases. Doxycycline should be continued until the patient

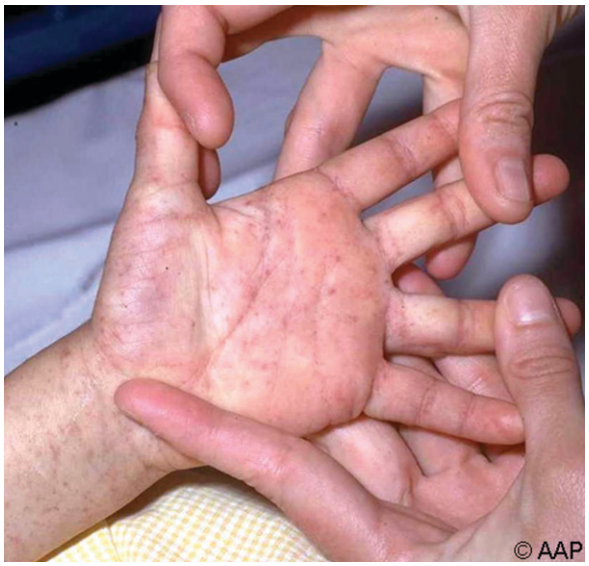

Figure 7. Rocky Mountain spotted fever. Sixth day of rash without treatment. (Reprinted with permission from the American Academy of Pediatrics.)

has defervesced for at least 3 days and demonstrates clinical improvement. Use of antibiotics other than doxycycline increases the mortality risk. (17)

Prognosis

RMSF can progress rapidly. Case-fatality rates of untreated RMSF range from 20% to 80%, with a median time to death of 8 days. In survivors, significant long-term neurologic and limb-related sequelae can occur. (17)

Summary

- The Intergovernmental Panel on Climate Change has reported that the prevalence of vector-borne diseases has increased in recent decades and that the prevalence rates of malaria, Lyme disease, dengue, and West Nile virus infection, in particular, are expected to increase further if control measures are not strengthened. (1)(2) (Based on high-quality evidence)
- Lyme disease is diagnosed using a 2-tiered testing serologic approach to increase diagnostic specificity. First, an enzyme-linked immunosorbent assay or an immunofluorescent antibody test is performed. If testing is negative, the patient is seronegative and no additional testing is indicated. If the enzyme-linked immunosorbent assay or immunofluorescent antibody is positive, a Western blot should be performed that examines IgM to 3 antigens and IgG to 10 antigens. A positive test requires identifying at least 2 IgM bands or 5 IgG bands. (8) (Strong recommendation, based on high-quality evidence)
- Doxycycline, amoxicillin, or cefuroxime may be used to treat erythema migrans in children of all ages. Doxycycline is the drug of choice for all facial palsies due to Lyme disease. Previously, doxycycline had not been recommended in children younger than 8 years due to risk of dental staining. However, more recent evidence demonstrates that doxycycline is safe to be used for short durations of therapy. (6)(8) (Strong recommendation, based on high-quality evidence)
- Patients with severe malaria with parasitemia greater than 5% of red blood cell infection or signs of cerebral malaria or other end-organ disease require intensive care admission and parenteral treatment with intravenous artesunate (Strong recommendation, based on high-quality evidence). (14)
- There are effective measures to reduce acquisition of malaria by travelers, including chemoprophylaxis, and measures to prevent insect bites, including use of bed nets and mosquito repellents. The most current country-specific malaria prevention recommendations for travelers can be obtained at the CDC website (www.cdc.gov/malaria) (Strong recommendation, based on high-quality evidence). (16)
- Treatment should be initiated as soon as Rocky Mountain spotted fever is suspected and is most effective within the first 5 days of symptom onset. Clinicians should not wait to start treatment while awaiting laboratory results. Doxycycline is the drug of choice in all ages (Strong recommendation, based on high-quality evidence). (17)

Take the quiz! Scan this QR code to take the quiz, access the references and teaching slides, and view and save images and tables (available on October 1, 2024).

PIR QUIZ

1. A 9-year-old girl is admitted to the pediatric inpatient service with a 3-day history of fever, fatigue, and worsening headache. She lives with her family in Arizona and 8 days ago returned from a 3-day camping trip in Arizona. A nonengorged tick was noted on her upper chest while on the trip, and the tick was removed without difficulty. She and other family members had multiple mosquito bites. She complains of pain with movement of her neck. On physical examination her vital signs are within normal limits. She is ill-appearing but answers questions. She has photophobia but no focal neurologic symptoms. She has a faint erythematous maculopapular rash on her trunk. There are no petechiae. A complete blood cell (CBC) count was normal. Electrolyte, aspartate aminotransferase, and alanine aminotransferase levels were normal. A lumbar puncture was performed. Cerebrospinal fluid (CSF) glucose level was normal and protein level was 72 g/dL (0.72 g/L). CSF cell count was 0 red blood cells and 81 white blood cells (65% lymphocytes, 10% monocytes, and 25% neutrophils). CSF Gram-stain showed no organisms. A multiplex polymerase chain reaction (PCR) assay was negative for bacterial pathogens, cytomegalovirus, enterovirus, parechovirus, herpes simplex virus, human herpesvirus 6, and varicella zoster virus. Which one of the following diagnostic tests is most likely to be positive?

   A. CSF and serum West Nile virus IgM antibodies.
   B. CSF dengue virus IgM and IgG antibodies.
   C. CSF *Rickettsia rickettsii* PCR.
   D. CSF West Nile virus RNA PCR.
   E. Serum *Anaplasma phagocytophilum* IgM and IgG antibodies.

2. A 4-year-girl with congenital asplenia who lives in upstate New York is diagnosed as having early localized Lyme disease. A CBC count and liver enzyme levels are normal. Testing for coinfection with which one of the following pathogens is most appropriate?

   A. *Babesia microti*.
   B. *Bartonella henselae*.
   C. *Ehrlichia canis*.
   D. *Ehrlichia chaffeensis*.
   E. *Rickettsia parkeri*.

3. A previously healthy 7-year-old boy presents to the office in July with a 3-day history of fever, fatigue, myalgia, and a rash on his abdomen at the belt line. The family lives on a farm in Wisconsin. An engorged tick from below his umbilicus was removed 13 days ago. On physical examination he is mildly ill-appearing. He answers questions appropriately. His temperature is 100.8°F (38.2°C) and his other vital signs are normal. He does not have meningismus. There is a 9-cm annular, macular erythematous lesion with some central clearing at the site of the tick bite. It is not painful or pruritic. The remainder of his physical examination findings are normal. Which one of the following is the most appropriate next step in management?

   A. Admit to the hospital and begin intravenous (IV) ceftriaxone.
   B. Admit to the hospital, obtain Lyme serology, and begin IV ampicillin.
   C. Begin oral cephalexin.
   D. Begin oral doxycycline.
   E. Send Lyme serology.

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4. A 12-year-old girl who emigrated from Tanzania 8 days ago presents to the emergency department (ED) with a 3-day history of fever and malaise. Her temperature in the ED is 103.6°F (39.8°C). A CBC count is performed, and the laboratory calls to say that there are numerous *Plasmodium* ring forms on the peripheral smear, but no gametocytes or schizonts are seen. The level of parasitemia is 15%. Her hemoglobin level is 6.9 g/dL (69 g/L) and platelet count is $120 \times 10^3/\mu L$ ($120 \times 10^9/L$). Her blood urea nitrogen and creatinine levels are normal. The patient is tired appearing and jaundiced but answers questions appropriately. There are no focal neurologic findings. A chest radiograph is normal. A blood sample is sent to a reference laboratory for *Plasmodium* speciation by PCR, but a result will take 2 to 3 days. Which one of the following is the most appropriate initial antibiotic treatment?

   A. IV artesunate.
   B. IV clindamycin.
   C. Oral chloroquine and primaquine.
   D. Oral hydroxychloroquine and tafenoquine.
   E. Oral hydroxychloroquine.

5. A previously healthy 7-year-old boy is admitted to the hospital in June with a 5-day history of fever. Within a day of the onset of fever he was noted to have an erythematous macular rash that started around his wrists and ankles and over the next day became generalized and involved the palms and soles. He was seen in an urgent care center on day 3 of illness and was thought to have a viral illness. He was then brought to the ED on the day of admission due to persistent and worsening fever, malaise, myalgia, fatigue, and headache. Parents also noted that he seemed to be "out of it" this morning. The family lives in a rural area of Oklahoma. They have noted ticks on their dogs but have not seen a tick on the patient. In the ED, in addition to the erythematous macular rash that blanched, he was noted to have petechiae predominantly on his hands, feet, arms, and legs. He was obtunded but had no focal neurologic deficits. His white blood cell count was 2,800/μL ($2.80 \times 10^9/L$), hemoglobin level was 10.3 g/dL (103 g/L), and platelet count was $88 \times 10^3/\mu L$ ($88 \times 10^9/L$). Alanine aminotransferase level was 85 U/L (1.42 μkat/L). He was given IV ceftriaxone and vancomycin in the ED and was admitted to the PICU. Lumbar puncture was performed, and CSF results are pending. Which one of the following is the most appropriate next step in management?

   A. Begin IV chloramphenicol.
   B. Begin IV doxycycline.
   C. Obtain an electroencephalogram.
   D. Obtain magnetic resonance images of the brain.
   E. Send serum for *R rickettsii* immunofluorescent antibody IgG and start doxycycline therapy if positive.