ZOONOSES

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Learning Objectives

1. Based on the vector, identify which regions of the country specific viral zoonoses occur.
2. Identify the manifestations of specific viral zoonoses.
3. Given a patient with viral encephalitis, evaluate his or her risk factors, symptoms, and manifestations of illness and design an appropriate management plan.
4. Given a patient's planned outdoor activities or living conditions based on the extent or risk of his or her likely exposure, recommend an appropriate prevention plan for mosquito bites.
5. Recommend appropriate prevention and management strategies for rabies.
6. Evaluate the presentation and management of specific bacterial and spirochetal zoonoses and provide management recommendations.
7. Distinguish the management of Rocky Mountain spotted fever (RMSF) from ehrlichiosis or tularemia.
8. Given a patient with RMSF, apply the principles of management outlined in the current practice guidelines.
9. Distinguish the differences in therapeutic options to treat specific bacterial and spirochetal zoonoses.
10. Evaluate the presentation and management of protozoal zoonoses.

Introduction

Zoonoses are a heterogenous group of infections caused by a wide array of pathogens that thrive and cause disease in animals. Zoonoses were defined by the World Health Organization in 1959 as "Those disease and infections (the agents of) which are naturally transmitted between (other) vertebrate animals and man." Recently, the concept has been expanded to "any detriment to the health and/or quality of human life deriving from relationships with (other) vertebrate or edible or toxic invertebrate animals." In general, zoonotic infections are transmitted from an infected nonhuman reservoir to humans either directly through contact with the nonhuman reservoir or by bites and licking or through ingestion of raw or improperly prepared animal products (e.g., meat, fish, organs, dairy products, and eggs) or vegetables contaminated by the nonhuman reservoir. Zoonotic infections also can be transmitted to humans indirectly through contact or inhalation of byproducts (e.g., secretions and excreta) of the infected nonhuman reservoirs, contact with intermediate arthropods or animal vector that had contact with an infected nonhuman reservoir, or residence in an environment contaminated by animals.

The risk of acquiring zoonotic infections depends on climate, cultural, and socioeconomic variables. Mosquitoes and ticks are important vectors for zoonotic infections; warm and damp climates are ideal for mosquitoes, whereas ticks thrive in cooler drier climates. Local or cultural practices also influence the risk of acquiring zoonoses. In certain countries, trading animals in open markets fuels the transmission of zoonoses because the animals are not properly handled, screened, or tested for diseases of infectious etiologies. Finally, socioeconomic variables such as poor sanitation or waste management, the intermingling of human and animal dwellings, and poverty can increase the risk of acquiring a zoonotic infection.

Zoonoses have existed worldwide throughout the ages and continue to do so. However, awareness of these infections peaks only when "new" zoonotic infections emerge in the United States. Although most known zoonotic infections are relatively uncommon in the United States, as a whole, they are common worldwide, and some cause significant morbidity and mortality. In this era of accessible travel and shipping and changing global climates, previously "rare" zoonotic infections can emerge and become established in the United States. The emergence of West Nile virus in the late 1990s is one of several examples of why health care professionals need a basic understanding

Abbreviations in this Chapter

AIDS	Acquired immune deficiency syndrome
CNS	Central nervous system
CSD	Cat-scratch disease
CSF	Cerebrospinal fluid
CTF	Colorado tick fever
DEET	N,N-diethyl-meta-toluamide
DV	Dengue virus
GI	Gastrointestinal
HGE	Human granulocytic ehrlichiosis
HPS	Hantavirus pulmonary syndrome
PCR	Polymerase chain reaction
RMSF	Rocky Mountain spotted fever
SLE	St. Louis encephalitis
TBRF	Tick-borne relapsing fever

of significant zoonotic infections in the United States and worldwide. A comprehensive review of all zoonotic infections is beyond the scope of this chapter. Rather, the purpose of this chapter is to review the history, epidemiology, clinical and laboratory manifestations, and treatment of key viral, bacterial, spirochetal, and protozoa zoonotic infections in the United States and worldwide (Table 1-1).

Viral Zoonoses

Countless viruses cause zoonoses, but many members of the family Flaviviridae, specifically in the genus *Flavivirus*, are medically important. Members of the *Flavivirus* genus are the most adept of all members of the family *Flaviviridae* in causing zoonoses. Viruses in this genus are transmitted by arthropods (mosquitoes or ticks), and are ecologically classified as "arboviruses" (arthropod-borne virus). Flaviviruses are adaptable to the hosts and insect vectors in a given region, which has helped them evolve and establish ecological niches in new geographical regions.

Hosts of flavivirus infection often have lifelong immunity to that virus. Therefore, animals with high reproductive rates are the ideal host for a flavivirus because the offspring are immunologically naïve and serve as future hosts. Humans acquire flavivirus infections by contact with the infected host. In humans, most flavivirus infections do not manifest as significant viremias, which makes subsequent transmission from a human unlikely. For this reason, humans are considered terminal hosts for flavivirus infections.

Currently, more than 70 species of *Flavivirus* have been isolated, only about 50% of which cause human infection. St. Louis encephalitis (SLE) virus and dengue virus (DV) are important flaviviruses. St. Louis encephalitis virus is closely related to other flaviviruses, such as West Nile, Japanese, and Murray Valley encephalitis viruses. St. Louis encephalitis virus also is distantly related to DV and yellow fever virus.

The family Bunyaviridae contains the five genera *Bunyavirus*, *Phlebovirus*, *Nairovirus*, *Hantavirus*, and the plant viruses *Tospovirus*. Viruses in the genera *Bunyavirus*, *Nairovirus*, and *Phlebovirus* can replicate in vertebrates and arthropods, whereas viruses in the genus *Hantavirus* are only known to replicate in vertebrates. These four genera are the only ones in the Bunyaviridae family that produce zoonotic infections. Viruses in genus *Tospovirus* can only be transmitted among plants, and is not discussed further.

Viruses in the genera *Bunyavirus*, *Nairovirus*, and *Phlebovirus* are transmitted by arthropod vectors, including mosquitoes, ticks, and phlebotomine (blood-seeking or bloodsucking) flies; viruses in the genus *Hantavirus* are transmitted through inhalation. The genus *Phlebovirus* is named after the phlebotomine vectors of its many species, including Rift Valley fever viruses. Rift Valley fever viruses afflict domestic animals and humans and primarily are found in the regions of Africa where sheep and cattle are raised. Human cases outside of Africa have been reported, which raises concerns in the United States. No cases have been reported in the United States, but compared to West Nile virus, Rift Valley fever virus is carried by more mosquitoes, can be transmitted by handling infected animal products, and is deadlier. Rift Valley fever is fatal in about 1% of human cases, with higher rates associated with severe disease. Rift Valley fever kills about 30% of infected animals; thus, given that livestock are commonly afflicted, the potential economic consequences of Rift Valley fever virus becoming established in the United States are significant. The genus *Bunyavirus*, named after Bunyamwera, a region in Uganda where this type of virus was isolated, contains many species, including the *California encephalitis* viruses. The genus *Nairovirus*, named from the first reported disease by a member virus (Nairobi sheep disease), contains many viruses, including the Crimean-Congo hemorrhagic fever virus. Members of the genus *Hantavirus* also cause a hemorrhagic fever and are discussed further in later sections of this chapter.

Mosquito-borne Viral Zoonoses

St. Louis Encephalitis

Background

St. Louis encephalitis was first described in 1933 during an outbreak of more than 3000 cases of encephalitis in the St. Louis, Missouri, area. One year earlier, a similar but smaller outbreak occurred in nearby Paris, Illinois. Eventually, SLE virus was isolated from a fatal case in the 1933 outbreak, and almost a decade later the mosquito was implicated as the principal vector for this disease.

Since then, SLE epidemics have occurred in almost every decade except the 1940s. To date, more than 4000 cases of SLE have been reported to the Centers for Disease Control and Prevention. The last large geographically widespread epidemic occurred in 1975. The reports extended from Canada to Texas, with 31 states confirming SLE cases. In the early 1990s, smaller SLE outbreaks occurred in Florida and Arkansas. Given the regularity with which SLE epidemics have occurred, many experts believe another one will occur soon.

Epidemiology and Microbiology

St. Louis encephalitis virus is a disease of the Americas because it has never been documented outside the Western hemisphere. St. Louis encephalitis cases have been reported from southern Canada to Argentina, but most have occurred in the United States. Mosquitoes are the primary vector of SLE virus transmission; however, the virus has been isolated from a tick *Dermacentor andersoni*. In the United States, SLE virus transmission occurs through the mosquito genus *Culex*. Members of the genus *Culex* are found in distinct geographical regions of the United States. The central and Atlantic states typically are inhabited by the *Culex pipiens* complex, which is comprised of *C. pipiens* and *Culex quinquefasciatus*. Specifically, *C. pipiens* are found mostly in the northern and eastern states, whereas *C. quinquefasciatus* are found primarily in midwestern and southern United States. *Culex quinquefasciatus* also are found in Arizona and California. The western United States is mostly inhabited by *Culex tarsalis*, although *C. quinquefasciatus* also inhabit areas of Arizona and California. The species *Culex nigripalpus* is located mainly in Florida, and is responsible for transmitting SLE virus in that state.

The SLE encephalitis virus is single-stranded ribonucleic acid viruses. Although SLE viruses are antigenically indistinguishable, they are biologically, genetically, and epidemiologically different. Individual SLE viruses differ by their ribonucleic acid oligonucleotide maps, which serve to divide SLE viruses into topotypes (i.e., geographically distinct viruses). Based on these topotypes, there are four genetically distinct viruses in the United States. The first and prototypical SLE virus is commonly found in the eastern central and Atlantic states, and it is transmitted by the *C. pipiens* complex. The second and third topotypes are found in Florida and are transmitted by the *C. nigripalpus*. The fourth topotype, found mainly in the western United States is transmitted by *C. tarsalis*.

The genetic differences among SLE virus are thought to be a result of a combination of genetic drift and introduction from other areas of the United States. In addition to their strong geographical correlation, SLE virus genotypes may differ in virulence and produce characteristic diseases in certain animal species. Accordingly, select SLE virus genotypes are believed to be more neuroinvasive, produce higher viremias, and are more prone to cause epidemics. Certain geographical locales can harbor a variety of distinct genotypes over a time period.

In the eastern United States, SLE outbreaks occur intermittently and usually are focused around one epicenter. The outbreaks tend to arise in urban or suburban areas, and are directly attributed to the breeding habits of the *C. pipiens* complex mosquitoes. *Culex pipiens* complex mosquitoes often are found in areas where stagnant water or sewage is present. They breed around ditches, leaky septic tanks, pools, and dormant or decaying organic materials that are common within cities. Mosquitoes also like to feed at dusk, making this an ideal time for exposure. In the southern and western United States, most SLE outbreaks are rural in nature and typically occur in farming communities. *Culex nigripalpus* mosquitoes have not been associated with a characteristic landscape, but epidemics have occurred mostly in major cities in Florida.

The primary reservoirs for SLE virus are nestling and pigeon-like adult and juvenile birds, in particular the sparrow. Bats and domestic birds such as robins, mocking birds, blue jays, cardinals, and other birds also can harbor SLE virus. These animals are capable of developing a transient viremia. Amplification is necessary to achieve mosquito infection rates needed to cause human epidemics. The amplification phase involves the rapid dissemination of SLE virus between mosquito vectors and various avian hosts. Most amplification occurs in juvenile birds because their immune systems are not fully developed, so the viremia is associated with a higher SLE virus titer and lasts longer. In addition, immature birds are sparsely feathered, have limited mobility, and rely on the adult birds for defense. These factors make them ideal feeding targets for mosquitoes. Once the bird becomes viremic, the SLE virus also can be transmitted to multiple vectors. After acquisition from a viremic bird, the virus travels to the mosquito gut barrier, where it may pass through the gut and reach the hemolymph system and the salivary glands. Once the virus reaches the salivary glands in sufficient quantity, the mosquito can transmit SLE virus when it next feeds. The virus is sustained in the mosquito for life; therefore, multiple transmissions can occur from a single mosquito. St. Louis encephalitis virus-naïve mosquitoes have a relatively short window of time to contract the virus because, within days of developing viremia, the virus may be cleared from the circulation of the reservoir.

Mosquitoes typically travel less than five city blocks during their lifespan; thus, there is little chance that a single mosquito could cause widespread disease. Consequently, SLE typically causes single or sporadic cases of febrile headaches or encephalitis in a small concentrated area. The occurrence of multiple cases from a condensed area often is the first harbinger of an impending SLE epidemic. For epidemics to develop, the climate must be dry (i.e., drought or unusually low precipitation) to confine and concentrate reservoir hosts (viremic birds) to water and food sources. Early season high temperatures and humidity also speed up the mosquito transmission cycles, viral incubation periods, and blood-seeking activity. Low socioeconomic conditions also can fuel the start of epidemics. Socioeconomically depressed locales tend to have areas of standing water, old buildings, no air conditioning, and poor or no screens in the windows. In 1991, an epidemic occurred in an Arkansas community with low socioeconomic conditions (lack of air-conditioned housing and poor window screens). A study of that epidemic revealed an independent risk factor for

Marfin AA, Bleed DM, Lofgren JP, et al. Epidemiologic aspects of a St. Louis encephalitis epidemic in Jefferson County Arkansas, 1991. Am J Trop Med Hyg 1993;49(1):30–7.

Savage HM, Smith GC, Moore CG, Mitchell CJ, Townsend M, Marfin AA. Entomologic investigations of an epidemic of St. Louis encephalitis in Pine Bluff, Arkansas, 1991. Am J Trop Med Hyg 1993;49(1):38–45.

Table 1-1. Overview of the Zoonotic Diseases

Disease	1º Vector	Reservoirs	1º Clinical Manifestations
St. Louis encephalitis virus	*Culex* mosquitoes	Nestling birds (i.e., sparrow, robin, and blue jays)	Prodrome with headache, fever, and CNS symptoms (e.g., confusion, photophobia, and meningismus)
Dengue fever virus	*Aedes aegypti*	Humans	Abrupt high fever, severe headache, significant bone/joint pain, nausea, vomiting, and rash
Colorado tick fever	*Dermacentor andersoni*, (Rocky Mountain wood tick)	Rodents, chipmunks, and ground squirrels	Abrupt fever, headache, myalgias, and "saddleback" and or intermittent fever
Hantavirus			
HFRS	*Murinae* rodents	Rodents, bats, cats, and shrews	Abrupt fever, "flu-like" symptoms, conjunctival hemorrhages, hypotension, oliguria, and renal failure
HPS	*Sigmodontinae* rodents	Rodents	Abrupt fever, and "flu-like" symptoms without respiratory complaints, progressing to cardiopulmonary collapse
Rabies virus		Bats, dogs, raccoons, skunks, and foxes	"Furious"—hydrophobia diaphragmatic contractions, pharyngeal spasms, sialorrhea, alternating hyperexcitability, coma, and death "Dumb"—limb weakness, sphincter paralysis, seizures, altered mental status coma, and death
Ehrlichiosis			
HME *(Ehrlichia chaffeensis)*	*Amblyomma americanum* (lone star tick)	White-tailed deer, small mammals, and avian hosts	High-grade fever, headache, rash thrombocytopenia, and increased AST/ALT
HGE *(Anaplasma phagocytophila)*	*Ixodes scapularis* (black-legged tick)	White-tailed deer, small mammals, and avian host	High-grade fever, headache, thrombocytopenia, and increased AST/ALT
	Ixodes pacificus (western black-legged tick)		
RMSF *(Rickettsia rickettsii)*	*Dermacentor andersoni* (Rocky Mountain wood tick)	Mice, wild rodents, deer, ground feeding birds, and dogs	Fever, headache, initial peripheral vasculitic rash, and thrombocytopenia
	Dermacentor variabilis (American dog tick)		

people developing SLE virus infection was sitting on a porch in the evening to escape the heat in their homes.

The SLE encephalitis virus is the leading cause of viral encephalitis in the United States, particularly in the southern United States where it is endemic. St. Louis encephalitis often occurs in late summer and fall, but cases have been reported in all months. Most SLE cases occur in Texas, but other regions such as southern California, the Mississippi River Valley, and Florida also have yearly occurrences of SLE. Typically, SLE is a relatively subtle disease that often is unrecognized, but it can become widespread in the presence of unusual climatic conditions.

Clinical Manifestations/Laboratory Findings

Normally, the incidence of SLE is low and unless there is an epidemic in the community, clinical disease is often unrecognized. In fact, less than 1% of all SLE virus infections lead to overt clinical manifestations. However, encephalitis ultimately develops in 75% of patients who become symptomatic. Although SLE virus infection often leads to encephalitis, it may only manifest as a febrile headache or aseptic meningitis, particularly among children. Disease severity is influenced by advancing age. The overall mortality rate for SLE is less than 8%; however, in people older than 60 years of age, the mortality is about 20%. Patients with hypertension and cerebrovascular disease also have increased mortality.

Neuroinvasive manifestations of SLE develop either abruptly or after a prodrome consisting of headache, fever, myalgias, and nonspecific gastrointestinal (GI) complaints. The prodrome evolves slowly over a week before the development of central nervous system (CNS) symptoms. After the prodrome, patients develop a stiff neck, nuchal rigidity, lethargy, confusion, photophobia, disorientation,

Table 1-1. Overview of the Zoonotic Diseases (continued)

Disease	1º Vector	Reservoirs	1º Clinical Manifestations
Tularemia *(Francisella tularemia)*	*Dermacentor andersoni* (Rocky Mountain wood tick) *Dermacentor variabilis* (American dog tick) *Amblyomma americanum* (Lone star tick) Less commonly *Culex, Aedes, and Anopheles* mosquitoes	Rodents, squirrels, voles, muskrats, beavers, deer, and ticks	Abrupt fever, chills, cough, headache, fatigue, abdominal pain, chest soreness, vomiting, and a pulse-temperature discrepancy
Lyme disease *(Borrelia burgdorferi)*	*Ixodes scapularis* (black-legged tick)	Rodents, white-footed mouse, chipmunks, and white-tailed deer	Fever, malaise, headache, fatigue, stiff neck, muscle, and joint pain with the characteristic "bull's eye" lesion: erythema migrans
Tick-borne relapsing fever	*Argasidae* family	Chipmunks, ground or tree squirrels, cattle, pigs, prairie dogs, gopher, tortoises, and snakes	Abrupt fever, headache, myalgias, chills, arthralgia, nausea, and vomiting
Leptospirosis	Rats and other rodents	Humans, and domestic and wild animals	Abrupt fever, myalgias headache, chills, conjunctival suffusion, anorexia, nausea, vomiting, prostration, and evidence of rhabdomyolysis
Cat-scratch disease *(Bartonella henselae)*	Cat flea	Domestic and wild cats	Fever, malaise, headache regional lymphadenopathy, and transient rash
Brucellosis		Cattle, goats, sheep, buffalo, camels, and yaks	Rolling fever, sweats, malaise, (*Brucella* species), anorexia, fatigue, weight loss, depression, lymphadenopathy, and hepatosplenomegaly
Q-fever (Query fever) *(Coxiella burnetii)*	*Dermacentor andersoni* (Rocky Mountain wood tick)	Goats, cattle, sheep, cats, and other domestic and wild animals	Q-fever pneumonia—abrupt fever, severe headaches, sweats, chills, myalgias, and pleuritic chest pain Q-fever hepatitis—some symptoms as above plus increased AST/ALT, and hepatomegaly
Babesiosis	*Ixodes scapularis* (black-legged tick)	White-footed mice, chipmunks, deer, rabbits, shrews, and voles	Fever, fatigue, chills, headache, hepatosplenomegaly, and jaundice
Cryptosporidiosis *(Cryptosporidium parvum)*		Wild and domestic animals, humans, and contaminated water or food products	Abdominal pain, weight loss, fever, and acute watery diarrhea without blood or leukocytes

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CNS = central nervous system; HFRS = hantavirus hemorrhagic fever renal syndrome; HGE = human granulocytic ehrlichiosis; HME = human monocytic ehrlichiosis; HPS = hantavirus pulmonary syndrome; RMSF = Rocky Mountain spotted fever.

and deterioration in mental status. Patients also may develop seizures, a tremor, focal weaknesses, cranial nerve palsies, and lose coordination. Eventually, the CNS symptoms worsen and patients develop delirium, drift into a stupor, or even become comatose. Urinary incontinence, urgency, frequency, and retention develop in 25% of patients with SLE.

Patients with SLE often do not seek medical attention until the onset of neurological disturbances. At this time, physical examination findings are consistent with meningitis and/or encephalitis. Almost 20% of patients present with cranial nerve palsy. Cranial nerves VII, IX, and X are most affected. Therefore, deficits in expression, taste sensations, tongue movement, pharynx and larynx movement, and the parasympathetic system also should be expected.

The laboratory findings in cerebrospinal fluid (CSF) usually are consistent with aseptic meningitis. Notable CSF findings often include a moderate lymphocytic pleocytosis, leukocytosis, and a normal protein. Patients with SLE often are hyponatremic, which often is associated with inappropriate secretion of antidiuretic hormone, although

the hypothalamic-pituitary-adrenal axis is normal.

About 30–50% of patients with neurological involvement who recover from SLE will have some residual impairment. Neurological deficits ranging from nervousness and somnolence to muscular incoordination, gait disturbances, and tremor can last for up to 3 years. However, in more severe cases, particularly among older patients, the impairments can persist.

Laboratory Diagnostic Methods

St. Louis encephalitis virus is rarely cultured from any body fluid site; therefore, the diagnosis is confirmed by positive serology. Most often, the immunoglobulin M capture enzyme-linked immunosorbent assay is used to diagnose SLE virus infection. The incubation period associated with SLE virus is 4–21 days, so the immunoglobulin M antibody is detected at the beginning of disease. However, once immunoglobulin M is detectable, it may remain for more than a year; therefore, presence of immunoglobulin M can indicate recent infection, but this test cannot distinguish acute infection from previous infection with SLE virus or other flaviviruses. Other serological tests that aid in diagnosing SLE virus infection are immunofluorescence antibody, neutralizing antibody, complement fixation, and hemagglutination antibody inhibition. Hemagglutination antibody inhibition is nonspecific; thus, its results should be interpreted with caution. Unfortunately, many times the diagnosis of SLE virus infection is confirmed on autopsy.

Treatment

Currently, there is no effective pharmacological therapy for SLE; in vitro studies and a pilot study have suggested that interferon-α2b may be effective for flavivirus infections, including SLE. Although interferon-α2b shows promise, until more data become available, its empiric and routine use is not recommended. Supportive management addressing fluid deficits, intracranial pressure, and symptoms are the cornerstones interventions. Prevention is the primary measure taken to reduce SLE virus infection. People in endemic areas of the Midwest should make sure their screens are properly maintained. Home installation of air conditioning will help limit mosquito exposure. *Culex* mosquitoes are highly active about 1 hour before sundown, throughout the night, and about 1 hour after sunrise; thus, avoiding outdoor activities around dusk and dawn may help to reduce and prevent contact with mosquitoes. They also breed in stagnant and freshwater areas and are prevalent after a rain; therefore, limiting exposure to these areas also will reduce a person's risk.

Most experts recommend that people engaging in outdoor activity wear long outer garments for maximum protection. However, such clothing may not be comfortable in hot climates; therefore, wearing mosquito repellent during outdoor activity also is recommended. Mosquito repellants that contain N,N-diethyl-meta-toluamide (DEET) are effective in protecting against *Culex* mosquito species. Pharmacists should understand that the percentage of concentration of DEET in a product determines how long it protects against mosquito exposure. In a recent study, products containing 23.8% or 20% DEET provided protection from mosquito bites for an average of 5 or about 4 hours, respectively. Products containing 6.65% DEET provide almost 2 hours of protection, whereas those that contained 4.75% DEET and 2% soybean oil were only protective for about 1.5 hours.

Although safety concerns surrounding DEET use on children have been raised, there are no definitive studies that specifically address what DEET concentration is safest for children. Furthermore, when DEET-containing repellents are used according the product recommendations, there have been no serious illnesses in children linked to DEET exposure. Recently, in response to concerns regarding West Nile virus transmission, the American Academy of Pediatrics Committee on Environmental Health updated its recommendation for use of DEET products on children, "Insect repellents containing DEET with a concentration of 10% appear to be as safe as products with a concentration of 30% when used according to the directions on the product labels." In addition, experts suggest that application of low concentrations of DEET on infants older than 2 months old is safe; other guidelines cite that the use of DEET-containing repellents on children older than 2 years of age also is acceptable.

Pharmacists should understand that repellents that do not contain DEET do not provide the same degree of protection against mosquito bites as DEET-containing repellents. When recommending a repellent for use on a child, the pharmacist should consider the ingredient (DEET vs. non-DEET-containing). If the pharmacist feels a DEET-containing product is needed, the choice of repellent should be based on the amount of time that a child will be outdoors and exposed to mosquitoes, as well as the risk of mosquito-transmitted disease in the area (see Table 1-2).

Dengue

Background

Dengue fever was first reported more than 200 years ago when outbreaks occurred on three continents, including North America. Dengue fever was long considered a benign, nonfatal disease centered in the tropics. Because it is a mosquito-borne infection, epidemics were slow to spread because of the limited ability of this vector to travel significant distances. However, epidemics have become more frequent, as populations have expanded and transportation has become more efficient. Consequently, DV and its mosquito vector have become more globally distributed.

Epidemiology and Microbiology

Dengue virus is perhaps the most significant arbovirus in the world with an estimated 2.5 billion people at risk for DV infection. Worldwide, the virus causes almost 100 million cases of dengue fever, 500,000 cases of dengue hemorrhagic fever, and kills about 25,000 patients annually. Dengue virus is a flavivirus with four recognized serogroups (DEN-1, DEN-2, DEN-3, and DEN-4). Infection with a particular serogroup confers lifelong immunity to only that

Fradin MS, Day JF. Comparative efficacy of insect repellents against mosquito bites. N Engl J Med 2002;347:13–18.

Table 1-2. Overview of Treatment Recommendations for Zoonotic Diseases

Disease	Primary Treatment	Secondary Treatment
St. Louis encephalitis virus	DEET, decrease mosquito habitats, and exposure	Supportive care (e.g., fluids and antipyretics)
Dengue fever virus	DEET, decrease mosquito habitats, and exposure	Symptomatic and supportive care
Colorado tick fever	Long-sleeve shirts, pants, and decreased open skin areas	Supportive care (e.g., fluids and antipyretics)
Hantavirus	Rodent-proofing homes, reducing rodent populations around homes, rodent trapping, and disposal	Early recognition, ICU admission, supportive care, mechanical ventilation, pressors as needed, and corticosteroids
Rabies virus	Prompt, and thorough wound care, receipt of human rabies immune globulin (20 IU/kg), and 1 ml of rabies cell culture vaccine on days 0, 3, 7, 14, and 28	Any questionable animal exposure (especially direct or indirect contact with bats) should require ED evaluation, and monitoring of the captive animal for up to 10 days
Ehrlichiosis	Doxycycline 100 mg orally/intravenously 2 times/day for 7–10 days	Tetracycline 500 mg orally 4 times/day for 7–14 days
RMSF	Doxycycline 100 mg orally/intravenously 2 times/day for 7–10 days	Chloramphenicol orally/intravenously 50–75 mg/kg in 4 days in divided dosages (typically reserved for pregnancy and children, and has resulted in fatal outcomes)
Tularemia	Gentamicin 3–5 mg/kg/day divided every 8 hours for 7–14 days	Ciprofloxacin 400 mg intravenously or 500 mg orally 2 times/day or Levofloxacin 500 mg/day orally/intravenously for 7–14 days
Lyme disease	Refer to Table 1-5	Refer to Table 1-5
Tick-borne relapsing fever	Doxycycline 100 mg orally 2 times/day for 7–14 days	Tetracycline 500 mg orally 4 times/day for 7–14 days
Leptospirosis	*Severe Disease*—Penicillin 1.5 MU intravenously every 6 hours for 7 days Ceftriaxone 1 g/day intravenously for 7 days	*Mild Disease*—Doxycycline 100 mg orally 2 times/day for 7 days Ampicillin 500–1000 mg intravenously every 6 hours for 7 days
Cat-scratch disease	Azithromycin 500 mg orally for 1 day, then 250 mg/day orally for 4 days	Doxycycline 100 mg orally/intravenously 2 times/day for 14 days
Brucellosis	Doxycycline 100 mg orally 2 times/day for 6 weeks plus gentamicin 3–5 mg/kg/day divided every 8 hours for 2–3 weeks	Doxycycline 100 mg orally 2 times/day plus rifampin 600–900 mg/day orally for 6 weeks
Q-fever		
Acute	Doxycycline 100 mg orally 2 times/day for 14 days	Ofloxacin 400 mg orally 2 times/day for 14–21 days
Chronic	Doxycycline 100 mg orally/intravenously 2 times/day plus hydroxychloroquine 200 mg 3 times/day for 18 months	Doxycycline 100 mg orally/intravenously 2 times/day plus ofloxacin 200 mg 3 times/day for 3 years
Babesiosis	Atovaquone 750 mg orally every 12 hours plus azithromycin 500 mg orally for 1 day, then 250 mg/day orally for 7 days	Clindamycin 1200 mg intravenously every 12 hours or (600 mg orally every 6 hours) plus quinine 650 mg orally every 8 hours
Cryptosporidiosis	Nitazoxanide 500 mg/day orally for 3 days	Paromomycin 1 g orally 2 times/day ± azithromycin 600 mg/day orally for 7–14 days

DEET = N,N-diethyl-meta-toluamide; ED = emergency department; ICU = intensive care unit.

serogroup, and does not provide cross-protective immunity to other serogroups. Therefore, individuals in endemic regions can be infected by all serogroups during their life.

The primary hosts for DV are mosquitoes and humans. Dengue virus infects *Aedes aegypti*, a domestic, day-biting mosquito, which then remains infected for the rest of its life. *Aedes aegypti* is the primary vector for DV and is ideally suited to transmit viral zoonoses. The mosquito is distributed worldwide, primarily in Central and South America, and Southeast Asia. *Aedes aegypti* also is found in South and Central Africa and in some parts of Australia. This mosquito prefers a meal of human blood; thus, it thrives near human dwellings. In addition, *A. aegypti* feeds in the daytime, which increases its ability to find a meal source. This mosquito also frequently uses several sources for a blood meal and can consume more than one blood meal before laying its eggs. Dengue virus is only known to cause disease in humans.

Since the 1940s, dengue fever and dengue hemorrhagic fever have become more common and more severe. During this period, significant increases in cases (about 3-fold per decade) were reported in Southeast Asia and the Americas. These trends are likely underestimated because DV infection is not a reportable disease in many countries. The reasons for the spread of DV are not fully understood, but population growth, poor water and waste management associated with rampant urbanization of the tropics, and advances in air travel have all likely contributed to the increasing globalization of this disease.

In the United States, there is a growing risk of dengue outbreaks. *Aedes aegypti* is found in the United States, primarily in southern Texas, southern regions of the Gulf Coast states, and throughout Florida. With the right conditions, data suggest that people in those areas of the United States are at risk for transmission and sporadic outbreaks of DV. During the past 25 years, transmission of DV has occurred in 3 separate years in south Texas with associated epidemics in northern Mexico. As with malaria, DV can be imported or introduced in the United States by travelers returning from DV endemic tropical areas.

Clinical Manifestations/Laboratory Findings

Dengue virus infection can manifest as five different diseases of variable severity. The mildest form is a nonspecific febrile viral illness (dengue fever). The other forms include "classic" dengue, dengue hemorrhagic fever, dengue hemorrhagic fever with dengue shock syndrome, and infection with more rare complications, including encephalitis and hepatic failure. Age, immune status, viral strain, serotype, and the genetic predisposition of the patient are all risk factors for DV infections, particularly dengue hemorrhagic fever.

Dengue fever typically afflicts young children and manifests as nonspecific rash. If patients are symptomatic, they often complain of mild upper respiratory symptoms. Classic dengue is more common among older children, adolescents, and young adults. These patients often are symptomatic and experience an abrupt-onset of high fever with severe headache, significant myalgias and arthralgias, nausea, vomiting, and a rash. The disease often is referred to as "breakbone fever" because the incapacitating pain associated with this form of infection is similar to that experienced with broken bones. Dengue hemorrhagic fever occurs primarily in children younger than 15 years of age who live in hyperendemic regions of the world. Dengue hemorrhagic fever is differentiated from dengue fever by increased capillary leakiness, not merely the presence of bleeding. Patients with dengue fever can have significant bleeding and do not meet criteria established by the World Health Organization to define dengue hemorrhagic fever. This form of the disease is characterized by increased vascular leakiness (more than 20% fluctuation in packed cell requirements, pleural effusions, and ascites), bleeding manifestations, and platelet counts less than 100,000 cells/mm^3 within 24 hours of fever resolution. In the absence of shock, mortality associated with this form of disease can reach 20%; but in the presence of shock, mortality rates can exceed 40%. A variety of rare cardiac, musculoskeletal, neurological, and hepatic manifestations also have been reported with DV infections.

Laboratory findings in DV infections are nonspecific and resemble those observed with other viral illnesses. Patients may experience neutropenia, lymphocytosis, elevations in liver function tests, and thrombocytopenia.

Laboratory Diagnostic Methods

Several serological methods are available to confirm the diagnosis of DV infection. However, the shared antigens of flaviviruses and DV serotypes make the serological diagnosis of DV infection difficult. Tests commonly used include the hemagglutination inhibition test, immunoglobulin G or immunoglobulin M enzyme-linked immunosorbent assay, and polymerase chain reaction (PCR). Serologically, diagnosis of DV infections is confirmed by at least a 4-fold rise in immunoglobulin G by hemagglutination inhibition test or an increase in immunoglobulin M antibody specific to DV by enzyme-linked immunosorbent assay. Using PCR, viral ribonucleic acid levels can be measured from acute phase sera in DV infection.

Treatment

No therapeutic drugs are specifically directed against DV. Thus, pharmacists should be aware that therapy is patient- and case-specific. Steroids, antivirals, and drugs that decrease capillary leakiness are all ineffective and therapy should be directed at providing symptomatic relief. In the absence of shock, oral hydration can be instituted as soon as possible. In patients with severe bleeding and shock, there is debate as to whether volume repletion should be performed using crystalloid or colloid expanders. However, if a crystalloid product is used, studies have shown no difference between normal saline and lactated Ringer's solution in producing volume repletion. Early recognition of symptoms is key to reducing mortality (see Table 1-2).

Halsted SB. Dengue. Curr Opin Infect Dis 2002;15:471–6.

Tick-borne Viral Zoonoses

Colorado Tick Fever

Background

Colorado tick fever (CTF) (also known as mountain tick fever or mountain fever) is common in the United States and Canadian Rockies, Sierra Nevada and Wasatch ranges, and the Black Hills region of North America.

Epidemiology and Microbiology

Colorado tick fever is caused by a double-stranded ribonucleic acid arbovirus belonging to the genus *Coltivirus* and family Reoviridae. About 22 strains of CTF virus have been identified, many of which cause disease in humans.

In North America, the primary tick vector for CTF virus is *D. andersoni* (Rocky Mountain wood tick). Cases of CTF are most commonly reported within regions that are inhabited by *D. andersoni*. On occasion, cases are reported in regions outside the geographical distribution of *D. andersoni*, where *Dermacentor variabilis* is suspected to be the vector. The CTF virus is maintained in a zoonotic cycle between immature stages of infected ticks and their mammalian hosts. Reservoirs for *D. andersoni* include wild rodents, and small and large mammals (e.g., chipmunks, ground squirrels, or porcupines). Ticks acquire the virus in their larval stage by feeding on infected hosts, and they remain infected for life. Adult ticks are responsible for infecting larger mammals, including deer and humans. Transmission also has occurred through blood transfusion.

Between 200 and 300 cases of CTF are reported yearly in the United States. Most cases occur in Colorado, Montana, Utah, and Wyoming, and involve people 20–30 years of age. The man-to-woman ratio is about 2:1. Case reports of CTF, like most tick-borne illnesses, are seasonally distributed. Most are reported between March and September, with a peak incidence between April and June.

Clinical Manifestations/Laboratory Findings

Colorado tick fever is characterized by an abrupt-onset of fever, headache, and myalgias 3–4 days (range 0 to 14 days) after tick exposure. The illness often manifests as a single febrile period or a "saddle back" fever curve. Patients demonstrating a "saddleback" fever curve typically experience a 2–3-day febrile period, followed by a 2–3-day afebrile period before recurrence of fever. Temperature may be higher during this second febrile period than in the initial episode. This biphasic temperature pattern is nonspecific and only occurs in 50% of cases. Photophobia, retro-orbital pain, and conjunctival infection can occur during febrile periods. Pharyngitis is reported in 20% of cases.

Physical findings in CTF also are nonspecific, but may include a rash and nuchal rigidity. Rash occurs in 15% of cases and can be macular, maculopapular, or petechial. Nuchal rigidity is reported in 18% of cases and is a sign of CNS involvement. In most patients, CTF is a self-limiting disease and symptoms resolve within 1 week. However, patients can experience extreme weakness and lethargy that persists for weeks or even months. Convalescence is age-dependent. In general, patients younger than 20 years of age return to normal health within a week or less, whereas the disease tends to persist in patients older than 20 years of age. In patients older than 30 years of age, about 70% will experience fatigue after 3 weeks.

Complications associated with CTF typically are rare, but may include aseptic meningitis, disseminated intravascular coagulation, encephalitis, epididymo-orchitis, GI hemorrhage, hepatitis, myocarditis, pneumonitis, and rheumatic fever-like syndrome. Some experts believe that coinfection with *Rickettsia rickettsiae* may cause several of these complications.

Leukopenia, the most common hematological abnormality in CTF, occurs in 66% of cases. The nadir typically occurs 5–6 days after disease onset, and reflects a decline in the absolute neutrophil count. Thrombocytopenia also may be reported. Persistent viremia results from intracellular, erythrocytic infection and can last up to 4 weeks in 50% of cases.

Laboratory Diagnostic Methods

Colorado tick fever can be confirmed by complement fixation, immunoperoxidase staining, or indirect fluorescent antibody test. However, these laboratory methods are not used for diagnosis in acute phases of the disease because of the delayed appearance of antibodies. Infection can be detected early in the disease (5 or fewer days) through reverse transcriptase-PCR, whereas immunoglobulin M capture assay may be diagnostic for convalescent samples (17 or more days).

Treatment

There is no pharmacological therapy for CTF, but viruses in this family have shown susceptibility to ribavirin. Thus, ribavirin 600 mg orally 2 times/day for 10 days may provide some limited benefit. The primary modality is supportive management, with fluids and antipyretic drugs given for symptomatic relief. Aspirin therapy is not recommended when treating CTF because it may aggravate or worsen the thrombocytopenia. Treatment is continued until the patient regains functional status and symptoms return to baseline.

As with mosquito-derived illnesses, exposure prevention is the key to limiting the risk of infections. Avoiding wide-open grassy or vegetative areas will decrease potential exposure to tick habitats. Proper protection (wearing long pants with overlapping socks and long sleeves) will minimize exposed areas of skin and prevent direct contact with tick vectors. Also, applying permethrin (i.e., Nix) to clothing and gear is toxic to biting arthropods, mosquitoes, and chiggers. Similarly, DEET applied to the skin may reduce tick exposure and bites. Thus, pharmacists should be knowledgeable about both agents as possible prevention strategies for tick exposures and bites, especially in rural areas or those areas with a large tick population (see Table 1-2).

Animal-borne Viral Zoonoses

Hantavirus

Background

Most significant viral zoonotic infections are transmitted by arthropod vectors. Members of the genus *Hantavirus* are unique in that they have established a unique ecological niche in vertebrate hosts, in particular, different primary rodent reservoir species or subspecies. These viruses are not

Table 1-3. Hantaviruses and Known Reservoirs Associated with Human Disease

Subfamily	Hantavirus	Reservoir Species	Geographical Region	Disease Type
Murinae				
	Hantaan	*Apodemus agrarius*	East Asia	HFRS
	Dobrava	*Apodemus flavicollis*	Baltic States, Slovenia	HFRS
	Seoul	*Rattus norvegicus*	East Asia	HFRS
Arvicolinae				
	Puumala	*Clethrionomys glareolus*	Europe	Mild HFRS
Sigmodontinae				
North America				
	Sin Nombre	*Peromyscus maniculatus*	Canada, United States	HPS
	New York	*Peromyscus leucopus*	Eastern United States	HPS
	Monongahela	*Peromyscus maniculatus nubiterrae*	Eastern United States	HPS
	Bayou	*Oryzomys palustris*	Southeastern United States	HPS
	Black Creek Canal	*Sigmodon hispidus*	Florida, United States	HPS
South America				
	Laguna Negra	*Calomys laucha*	Paraguay, Bolivia	HPS
	Andes	*Oligoryzomys longicaudatus*	Argentina, Chile, Uruguay	HPS
	Oran	*Oligoryzomys longicaudatus*	Northern Argentina	HPS
	Choclo	*Oligoryzomys fulvescens*	Panama	HPS
	Rio Mamore	*Neacomys spinosus*	Peru	HPS
	Lechiguanas	*Oligoryzomys flavescens*	Argentina	HPS

HFRS = hantavirus hemorrhagic fever renal syndrome; HPS = hantavirus pulmonary syndrome.

transmitted by arthropod vectors; rather, they are phylogenetic ribonucleic acid viruses hosted and transmitted by rodent species. The particular rodent vectors are derived from the Muridae family and the geographically exclusive subfamilies (Murinae [i.e., yellow-necked and striped field mice], Arvicolinae [i.e., red bank vole], and Sigmodontinae [i.e., deer mouse and white-footed mouse]) that are responsible for Hantavirus transmission (Table 1-3).

Hantaviral illness was first described during the Korean War, when about 3000 United Nations soldiers became infected with an acute hemorrhagic febrile illness and had associated renal failure. Later, a European scientist proposed that this disease was related to the Scandinavian disease called nephropathia epidemica caused by the Puumala Hantavirus. In 1983, the World Health Organization adopted the term hemorrhagic fever with renal syndrome to describe the Hantavirus infections identified in the Eastern hemisphere (Europe and Asia). A decade later, the first Hantavirus infection was recognized in the Western hemisphere when an acute outbreak of a fatal pulmonary illness occurred in the Four Corners region of the western United States. In contrast to the Eastern hemisphere form of infection, this disease primarily afflicted the lungs and only sparingly involved the kidneys. The disease was called the Hantavirus pulmonary syndrome (HPS) and the Hantavirus implicated in this outbreak was called the Sin Nombre virus. Since 1993, there have been more than 350 documented cases of HPS in North America.

Epidemiology and Microbiology

Hantaviruses are enveloped, segmented, ribonucleic acid viruses. Hantaviruses are unique in that their evolutionary process occurs through a complex quasispecies of closely related viruses that contain single point mutations. This complex population is thought to occur by a combination of natural selection and genetic drift. A second variation in the evolution of Hantaviruses is the ability to undergo recombination. Finally, as with other similar viruses, reassortment because of its segmented structure is possible; however, among Hantaviruses, this has only occurred between similar species and not between different species.

Hantaviruses are present in rodents, primarily of the Murinae family, but they also have been isolated from bats, cats, and shrews. Hantaviruses do not cause infections in their hosts and, thus, can be transmitted to the environment over the natural course of its life. Throughout the long history of Hantaviral infection, disease seems to stem from rodent-human contact, typically when humans encroach on the environmental space of the rodent. Most infections occur when humans inhale dried rat or mice excrement, urine, or other bodily secretions. On inhalation, the Hantavirus invades the human circulation and causes viremia.

Most Hantavirus infections result from occupational or recreational exposures (e.g., timber workers, parks personnel, trappers, and people opening abandoned rural dwellings). Most infections are because of indirect contact with rodents, but in rare cases, direct transmission from rat or mice bites has occurred. Historically, outbreaks of Hantavirus infection have been linked to indigenous rodent populations and the proximity and availability of water. Thus, Hantavirus infection depends on the number of rodents and their ability to populate and flourish.

Clinical Manifestations/Laboratory Findings

Hantaviruses produce two seemingly distinct diseases. Although the apparent complications are different between the Eastern and Western hemisphere Hantaviruses, the disease manifestations can overlap. Thus, for simplicity, the disease manifestations will be grouped by those producing

hemorrhagic fever with renal syndrome (Eastern hemisphere) and HPS (Western hemisphere).

When inhaled or ingested, Hantaviruses produce a significant capillary leak syndrome of the retroperitoneum and kidney (hemorrhagic fever with renal syndrome) or lungs (HPS). These syndromes result from excess production of inflammatory cytokines and cell-mediated immune responses. The inflammatory cytokines (tumor necrosis factor-α, interferon-γ, interleukin-2, interleukin-6, and interleukin-1) are produced in excess and cause a cascade of events that eventually lead to increased capillary permeability. Cell-mediated immune responses involved in this process likely involve $CD4^+$ and $CD8^+$ cytotoxic T-lymphocyte production in response to the nucleocapsid protein contained in the Hantavirus genome.

Hemorrhagic Fever and Renal Syndrome. The hemorrhagic fever with renal syndrome is caused by the Hantaan, Seoul, Dobrava, and Puumala Hantaviruses isolated from rodents in Europe and Asia. The Hantaan and Dobrava viruses typically cause severe disease, whereas Seoul virus causes a moderate disease. The Puumala virus produces the mildest form of the hemorrhagic fever with renal syndrome infection. In general, severe hemorrhagic fever with renal syndrome occurs in five distinct phases (febrile, hypotensive, oliguric, diuretic, and convalescent). The febrile phase occurs after the viral incubation period of 2–4 weeks. This phase consists of an abrupt "flu-like" illness that often manifests as fever, chills, malaise, headache, nausea, myalgias, abdominal pain, and GI symptoms. This phase lasts for about 3–7 days, and conjunctival hemorrhages and petechiae may begin to appear as it subsides. On about day 4 of the febrile phase, a characteristic and sudden albuminuria can occur. This albuminuria is followed by the hypotensive phase during which the acute drop in blood pressure may last for hours or days depending on the severity of the illness. In the 15% of the severe cases in which shock occurs, 33% result in death. Among survivors of the hypotensive phase, there is marked thrombocytopenia along with GI complaints and symptoms.

After the hypotensive phase, the oliguric phase begins, during which about 50% of patients die. In this phase, significant proteinuria and subsequent renal failure develop and often last 3–7 days. In addition, serum creatinine and blood urea nitrogen become markedly elevated and patients become normotensive or hypertensive. Survivors of this phase then progress to the diuretic phase, which is a positive prognostic sign. The diuretic phase may last for weeks to months. In this phase, patients may produce as much as 3–6 L of fluid, depending on the preceding clinical course. After the diuretic phase, patients progress to the convalescent phase where all laboratory markers return to normal and they begin to recover.

The overall mortality associated with severe hemorrhagic fever with renal syndrome is about 7%. The moderate hemorrhagic fever with renal syndrome produced by the Seoul virus results in death in about 2% of patients and the nephropathia epidemica that is characteristic of the Puumala virus is about 0.2%. The Hantaan and Dobrava viruses carry a larger mortality rate and, thus, make up the remainder of fatal outcomes.

Hantavirus Pulmonary Syndrome. In contrast to hemorrhagic fever with renal syndrome, HPS lacks significant renal involvement; it almost exclusively affects the pulmonary-thoracic cavity and is associated with minimal extrapulmonary complications. After a 2–3-week incubation period, Hantaviruses that cause HPS produce a prodrome similar to that seen in hemorrhagic fever with renal syndrome. This prodrome usually lasts 3–5 days and consists of myalgias, malaise, abrupt-onset fever nausea, vomiting, and abdominal pain. Notably, the prodrome lacks any evidence of pulmonary symptoms. Almost 50% of patients who experience this prodrome seek medical attention. However, unless their manifestations are severe, the diagnosis of HPS usually is not considered and the patients are symptomatically managed and often discharged before HPS fully develops. After the acute febrile phase, patients develop cardiopulmonary and GI symptoms. During this phase, patients typically have a cough, and will experience persistent tachycardia, tachypnea, and postural hypertension.

The first laboratory manifestation often is an abrupt thrombocytopenia. Subsequently, patients develop an elevated hematocrit, a marked left shift, and leukocytosis. In addition, the peripheral smears will contain immunoblasts, which often are interpreted as atypical lymphocytes. As the disease progresses, the cardiopulmonary manifestations become worse and more apparent. Patients progressively develop hypoxia and become hypocapnic. During the acute presentation, chest radiographs and examinations often are normal; however, within 24–48 hours, a frank interstitial edema is apparent. In addition, gross airspace disease and accompanying pleural effusion develop in more than 50% of patients. As the pulmonary status worsens, patients develop myocardial dysfunction, hypotension, and shock. Consequently, patients with advanced HPS often have a decreased systemic vascular resistance and develop metabolic acidosis. About 30–40% of patients die within 48 hours of HPS manifesting. Other abnormalities that occur as the syndrome progresses are decreased serum sodium, elevated aspartate aminotransferase, decreased protein, and a prolonged activated partial thromboplastin time. Proteinuria with concurrent elevations in serum creatinine develop in almost 25% of patients.

Laboratory Diagnostic Methods

Almost all patients with acute disease have circulating immunoglobulin M antibodies 1–2 days after infection; therefore, immunoglobulin M capture enzyme-linked immunosorbent assay is the primary serological test used to diagnose Hantavirus infection. This test is specific and sensitive for a broad class of Hantavirus reagents. The immunoglobulin G capture enzyme-linked immunosorbent assay is used less because of the seroprevalence of antibodies in endemic rural areas, and knowledge of the endemnicity of a particular region is crucial to interpreting its results. Reverse transcriptase-PCR also is used to detect Hantavirus infections and can be positive within the first 10 days of the illness. This test is useful because it can sequence and genotype the virus. The immunofluorescence antibody assay, which detects viral antigens from

Vero E6 cell cultures, is another widely used method to detect Hantavirus infections, but it cannot serotype Hantavirus species.

Treatment

Documented experience in treating Hantavirus infections is limited to small prospective studies and anecdotal reports. Two separate trials produced conflicting results on the efficacy of ribavirin in treating HPS. The initial prospective, double-blind, placebo-controlled trial showed a 7-fold reduction in mortality in the ribavirin arm compared to placebo; however, a subsequent open-label study showed no benefit. Both trials noted a high rate of drug-induced anemia. In the initial study, all patients in the ribavirin arm experienced a drug-related anemia and an increase in indirect bilirubin. On drug discontinuation, the anemia resolved in all but one patient. Similarly, in the open-label trial, 71% of patients experienced drug-induced anemia, 19% of which required transfusions. In addition, the incidence of hyperamylasemia and pancreatitis was greater in the active treatment arm. Currently, because of safety concerns and the questionable efficacy, ribavirin is not recommended for treatment of Hantavirus infections.

The use of corticosteroids has been advocated for managing Hantavirus infections because of their efficacy in treating similar syndromes, such as capillary leak syndrome, hemorrhagic fevers, and acute respiratory distress syndrome. Although corticosteroids may be useful in the supportive management of Hantavirus infections, their current proven benefit is limited to case reports. Therefore, the use of corticosteroids in Hantavirus infections requires further study before it routinely can be recommended.

In the absence of effective antiviral therapy, supportive care is the only treatment modality for Hantavirus infection. Early recognition of an exposure history and a clinically compatible illness is key to managing Hantavirus infections. Early admission to the intensive care unit, mechanical ventilation, and the concurrent use of inotropes (i.e., dobutamine) are recommended for patients exhibiting signs and symptoms consistent with hemorrhagic fever with renal syndrome and HPS. Close monitoring and early serological confirmation will help determine the phase of the illness and the disease prognosis. Treatment strategies should be continued until symptoms resolve and patients regain their functional status.

The Centers for Disease Control and Prevention has proposed recommendations for rodent-proofing homes, reducing rodent populations around homes, minimizing food available for attracting rodents, and rodent trapping and disposal (see Table 1-2).

Rabies

Background

Rabies, one of the oldest documented human diseases, was described more than 4000 years ago. In the early 1800s, saliva was recognized as a mode of transmission between different animal species. Pierre-Victor Galtier proved that intravenous injections of saliva immunized sheep blood; from this work, Louis Pasteur and colleagues began their landmark studies of rabies. They characterized rabies in the blood and demonstrated that serial passages could decrease the virus's virulence. In 1885, a boy was given this rabies emulsion derived from the spinal cord of an infected rabbit; after many inoculations, the infection was cured. This crude preparation heralded the start of the development and routine use of the rabies vaccine.

Today, more than 100 years after the first human vaccination, rabies is still a worldwide public health problem with more than 40,000 thousand cases of rabies annually. Most of these cases occur in Eastern Europe, Russia, Asia, Africa, and Central and South America. The principal vector of rabies in these regions is the dog. Cases of rabid dogs and cats occur in the United States as well, but they are considered overflow from infected wildlife in a particular locale. In the United States, because of the vaccination of domestic pets and the targeted mass vaccination of wildlife, rabies cases have dramatically declined since the 1920s. The routine vaccination of dogs started in the 1920s, when dogs were considered the primary vector, and then subsequently spread to encompass all domestic pets. Consequently, as the incidence of domestic pet-associated rabies declined, the incidence of wildlife-associated rabies increased in proportion. Skunks, raccoons, coyotes, foxes, and wild dogs still account for most of the wildlife rabies cases (about 4000 annually) in the United States today, but the incidence of wildlife-associated rabies has declined because of the mass oral vaccination of these animal populations. These oral vaccines are embedded into food sources and placed in areas these animals inhabit. This vaccination strategy has led to the virtual disappearance of fox rabies in Europe and the fox and raccoon rabies in the United States.

Epidemiology and Microbiology

Rabies is a single-stranded, negative-sense ribonucleic acid virus that belongs to the Rhabdoviridae family and the *Lyssavirus* genus. Within the *Lyssavirus* genus, there are seven genotypes (Table 1-4). The genotypes are referred to as rabies (genotype 1) or nonrabies lyssaviruses (genotypes 2–7). Genotypes 1 and 3–7 cause human disease. The majority of rabies cases have been from genotype 1, which is distributed throughout the world. Genotypes 4–7 cause an identical disease as genotype 1 (rabies). Genotype 3 (Mokola virus) is rare and causes a lethal encephalitis, with symptoms not typical of rabies. Genotype 2 has never been isolated in human cases of rabies.

Rabies viruses exhibit tropism for muscle and nerve tissue. These viruses may replicate in muscle tissue (which may account for long incubation periods) or attach directly to nerve tissue ends. Once attached, the virus travels in a retrograde direction toward the CNS. When the virus

Chapman LE, Ellis BA, Koster FT, et al. Discriminators between hantavirus-infected and -uninfected people enrolled in a trial of intravenous ribavirin for presumptive hantavirus pulmonary syndrome. Clin Infect Dis 2002;34:293–304.

Mills JN, Corneli A, Young JC, et al. Hantavirus pulmonary syndrome—United States: updated recommendations for risk reduction. Centers for Disease Control and Prevention. MMWR Recomm Rep 2002;51(RR-9):1–12.

Table 1-4. Lyssavirus Genotypes

Lyssavirus	Genotype	Region of the World	Predominant Hosts
Rabies Lyssavirus			
Rabies virus	1	Worldwide, except for Antarctica	Domestic and wild animals; insectivorous, and hematophagous bats
Nonrabies Lyssaviruses			
Lagos bat virus	2	Africa (rare)	Fruit bats and cats
Mokola virus	3	Africa	Shrews and cats
Duvenhage virus	4	Africa (rare)	Insectivorous bats
European bat lyssavirus 1	5	Europe	Insectivorous bats
European bat lyssavirus	6	Europe	Insectivorous bats
Australian bat lyssavirus	7	Australia	Frugivorous and insectivorous bats

invades the CNS, explosive replication occurs within the neurons and the virus is then transmitted cell to cell through synaptic junctions. Finally, the rabies virus moves from the CNS to somatic and autonomic nerves and then into accompanying tissues and organs. Viral invasion into these tissues coupled with neuronal apoptosis account for the large and varying amount of sequelae seen with rabies infections.

Worldwide, rabies kills more than 40,000 people yearly. If not treated immediately, the mortality of the disease is 100%; therefore, many people fear bite wounds from any animal, even humans. Consequently, annually more than 10 million people seek medical attention after a bite injury. Although untreated rabies is uniformly fatal, certain preventive and early treatment measures can prevent death.

The advent of vaccinations significantly reduced the incidence of human rabies in the United States, but the prevailing fear of rabies still lingers. In the United States, rabies has been documented in every state except Hawaii. In 2002, three cases of human rabies were reported in the United States, whereas more than 7000 animal cases were documented.

Many people incorrectly believe human rabies cases are associated with an obvious bite wound and animal contact; however, this has not been true in the United States during the past half century. From the late 1950s to 2000, 35 cases of human rabies were documented, 32 of which were consistent with exposure to bats; however, of those 32, 26 patients reported no history of a bite and only 12 patients had known physical contact with the bat. Thus, although bats seem to be the primary source of human rabies cases in the United States, a history or evidence of bat exposure may be lacking when patients seek medical attention.

Vampire bats of South America are well known for their transmitting rabies, but in the United States, the silver-haired (*Lasionycteris noctivagans*) and eastern pipistrelle (*Pipistrellis subflavus*) bats, which are largely insectivorous, are responsible for rabies transmission. The exact mode of rabies transmission from bat vectors is unknown, but two hypotheses exist. One hypothesis is that because silver-haired and eastern pipistrelle bats are small (less than 3 ounces), their bite wounds are unnoticed or unidentified. Several rabies cases are attributed to bat exposures that have involved people who awakened to find a bat in their bedroom without overt knowledge of an actual bite. The second hypothesis is that infections can arise from inhalational exposure to the virus. This stems from two cases of rabies in spelunkers who were exploring bat-infested caves, but denied any bite history. An accidental case of rabies documented in a rabies vaccine laboratory lent further credence to this hypothesis. Both hypotheses are plausible, but neither has been proven. Thus, any exposure to bats warrants immediate medical evaluation.

Recently, rabies virus transmission was attributed to an organ donor. The donor was apparently diagnosed with a subarachnoid hemorrhage that progressed to cerebral herniation and death. At the time of death, nothing specific in the donor's case led to the diagnosis of rabies infection and the organs were harvested and donated for transplantation. Subsequently, a liver and two kidney transplant patients received these organs. At hospital discharge, each of these transplant recipients quickly developed symptoms compatible with encephalitis (rabies). Unfortunately, each recipient died shortly after clinical-onset rabies. The diagnosis of rabies was discovered in each of these patients postmortem and the causal link was eventually established with the donor. The rabies infection likely occurred as a result of neuronal tissue contained in the transplanted organs because rabies virus is not spread hematologically. Although a history of animal exposure was absent, on further inspection of the donor's disease course, it was discovered that the donor presented to two local hospitals with severe mental status changes before his or her death. This was the first report of rabies transmission through solid organ transplantation; however, similar reports also have been documented after corneal transplants. Therefore, national donor screening practices may need to be reviewed in light of these cases.

Clinical Manifestations/Laboratory Findings

The clinical manifestations of rabies may proceed in two courses, both of which result in a fatal outcome. Only six patients have ever survived infection after the onset of clinical rabies. All but one of these survivors received some form of rabies vaccine. In 2004, the first unvaccinated survivor of clinical rabies was reported. This patient was a previously healthy 15-year-old girl, who picked up a bat 1 month before her illness, but had no history of a bite wound. Clinical management of the patient consisted of supportive and neuroprotective measures, including a drug-induced coma and mechanical ventilatory support. The patient was

maintained comatose for 1 week; during that period, results from lumbar puncture indicated that her antirabies immunoglobulin G (determined by immunofluorescent) increased 6-fold. The patient also received ribavirin intravenously. Eventually, she was tapered from her pharmacological-induced coma and became increasingly alert. About 1 month after the onset of illness, she was extubated, and within several days she was transferred to a rehabilitation unit; however, at that time, she was unable to speak because of her after prolonged intubation. Over time, her condition steadily improved while she was hospitalized. At the time of this writing, she had progressively improved her ability to walk with assistance, ride a stationary cycle, and feed herself. She also had regained some cognitive function, used sign language, and was regaining the ability to speak. The prognosis for her full recovery is unknown. The predominant form of rabies is the "furious" or encephalitic rabies, which represents up to 85% of all documented cases. This form produces the typical symptoms, including hydrophobia or aerophobia with accompanying diaphragmatic contractions, pharyngeal spasms, sialorrhea, alternating periods of hyperexcitability and coherence, autonomic dysfunctions, and eventual paralysis, coma, and death. The "dumb" or paralytic rabies is the less common form of disease and is heralded by limb weakness (most prominent early in the course) and sphincter paralysis as well as seizures and altered mental status. The disease progress rapidly into coma, and death ensues.

Clinical symptoms of rabies, once they occur, progress rapidly and are uniformly fatal within days to weeks. The progression of rabies follows five stages, but these stages vary depending on extent and location of the bite. The closer the bite is to the CNS, the faster the disease progresses. The first stage is the incubation period and it often ranges from 3 to 10 weeks, but may take as long as a year to manifest. The second stage is the viral prodrome, which can occur as early as 1 week after exposure and can last up to 2 weeks. The prodrome manifests as a low-grade fever, headache, malaise, irritability, nausea, and vomiting. Another initial symptom after the bite of a rabid animal is paresthesia or numbness surrounding the site. The next phase, the acute neurological syndrome, typically manifests within a week after the prodrome begins. This syndrome produces excessive salivation or frothing at the mouth, agitation, dysphagia, sporadic periods of hyperexcitability and lethargy, hallucinations, diplopia, and nystagmus. Patients also tend to fear water because of their painful, uncontrollable pharyngeal spasms. Symptoms of encephalitis also may be present. The fourth stage is a coma, which occurs about 1 week after the onset of the neurological symptoms. Symptoms of prolonged apnea, flaccid paralysis, and seizures result in impending respiratory failure and coma. The final stage is death, which occurs only days after the paralysis. Supportive medical care may delay this phase but severe neurological impairment and/or death is inevitable.

Early histopathological changes in brain tissue are absent during the initial presentation of rabies. Early in the disease course, magnetic resonance imaging of the brain usually is unremarkable. Later in the disease, intracytoplasmic inclusions called Negri bodies may be detected by histopathology. The presence of Negri bodies is not diagnostic, but may lead an astute clinician to suspect rabies. A second magnetic resonance imaging performed later in the disease course may detect diffuse edema and other significant changes, which occur as the patient is progressing into the paralysis and coma state.

The laboratory findings of rabies vary depending on the disease course. Cerebrospinal fluid pleocytosis is evident in more than 50% of encephalitic rabies cases, particularly early in the disease process. Other laboratory findings consistent with encephalitis are nonspecific to rabies. Laboratory findings consistent with multiorgan failure and paralysis develop as the disease progresses.

Laboratory Diagnostic Methods

The diagnosis of rabies typically is made from a thorough history and physical examination. Rabies may be considered in the differential diagnosis if there is a history of a wild animal bite or exposure. However, more commonly, a bite history or animal contact is unknown, and many diagnoses are considered. Unlike patients with other viral encephalitities, patients with rabies often are coherent and even manic when they seek medical attention.

Microbiological or serological studies aid in the diagnosis of rabies. The laboratory diagnosis of rabies depends on the identification of rabies virus antibodies in serum, CSF, saliva, corneal tissue, highly innervated hair follicles (e.g., neckline hair), skin biopsies, or mucosal sites. Antibodies typically are not present early in the disease course, so laboratory studies often are only positive in patients well into the disease course. Unfortunately, rabies often is diagnosed at autopsy by the direct fluorescent antibody test or enzyme-linked immunosorbent assay.

Reverse transcriptase-PCR tests to detect rabies virus ribonucleic acid in the saliva can be used early in the disease course, but its routine use has not been recommended or evaluated.

Treatment

Only six documented patients have ever survived a rabies infection after onset of clinical manifestations. All but one of these survivors received some form of rabies vaccination. Thus, vaccinations are recommended for all patients who are exposed, or potentially exposed to rabid animals or animals often known to carry rabies (see Table 1-2).

Postexposure Rabies Treatment. Current treatment for postexposure cases of rabies uses local wound cleansing, wound infiltration of rabies immune globulin, and cell-culture rabies vaccine administration. All these treatments must be done to ensure removal and neutralization of the rabies virus from the wound site. Local wound care involving thorough washing with soap and water or other antiviral drugs (e.g., iodine or isopropyl alcohol) is the first step in treating rabies. Second, rabies immune globulin should be infiltrated around the bite wounds. The total dose of the rabies immune globulin should be divided and placed around each wound site. If there are numerous bite wounds, the rabies immune globulin can be diluted with normal saline for injection to provide an adequate amount of drug for each wound. The dose of the human rabies immune globulin is 20 IU/kg. If human rabies immune globulin

cannot be obtained, equine rabies immune globulin may be used at twice the dose (40 IU/kg). Vaccination is the final step in the treatment process. The three marketed vaccines in the United States are the human diploid cell culture vaccine, the purified chick embryo cell vaccine, and the rabies vaccine adsorbed. Several vaccination schedules have been proven effective, but in the United States, the five-dose intramuscular vaccination series is the most commonly used schedule. This schedule consists of five 1-ml intramuscular injections given in the deltoid or thigh muscle on days 0, 3, 7, 14, and 28 postexposure. Injections should not be given in the buttocks or in the same place as the infiltrated rabies immune globulin. For patients with human immunodeficiency virus who are exposed to rabies and require postexposure prophylaxis, the regimen is doubled. Pharmacists can play a key role in obtaining, dosing, and clarifying the current immune globulin, its application, and type of rabies vaccine supplied by the pharmacy, thereby limiting dosing and administrations errors and preventing a potentially fatal outcome.

Preexposure Rabies Prevention. Preexposure rabies prevention is given to people at high risk for infection, including veterinarians, rabies research laboratory personnel, animal handlers, wildlife and game officers, travelers (especially children) to endemic rabies countries, spelunkers, and others who could commonly come into contact with the rabies virus. The preexposure intramuscular rabies vaccination regimen consists of three 1-ml intramuscular doses at days 0, 7, and 28. These doses should be given with cell culture vaccines of greater than 2.5 IU per dose. If possible, antibodies should be measured 1–3 weeks after the final vaccination dose and the titer should measure greater than 0.5 IU/ml. The preexposure intradermal regimen consists of three 0.1-ml doses of tissue culture vaccines, purified chick embryo cell vaccine, purified duck embryo cell vaccine, or purified vero cell vaccine given at days 0, 7, and 28. Antibody response can be measured 1–3 weeks after the final vaccination. Booster doses of people given preexposure vaccinations are recommended every 6 months to 1 year, provided there is continual exposure or risk of exposure to rabies. The booster dose is only required in those with a rabies antibody titer below 0.5 IU/ml.

Brain Tissue Vaccines. Brain tissue vaccines frequently are used in poor and underserved countries and, although their efficacy is questioned, they are considerably cheaper than tissue culture vaccines. Consequently, they are the most widely used rabies vaccines worldwide. Because brain tissue vaccines are grown in suckling animal brain tissue, they carry a risk of neurological complications. These vaccines contain animal myelin, which may cause autoimmune reactions of the CNS and other neurological complications. One in every 200 patients suffers a neurological complication from these vaccines. Another drawback to these vaccines is that they require more than 17 injections during the administration course. The World Health Organization does not endorse the use of these vaccines, but they are routinely used worldwide because of their reduced cost.

Other Therapies. There are no other pharmacological treatments for rabies. Ribavirin and interferon-α have been unsuccessful for treating rabies. Ketamine, a competitive *N*-methyl-D-aspartate antagonist, has demonstrated an inhibitory effect against rabies viral transcription in the brain, but concentrations required to inhibit rabies viral replication cannot be safely achieved in humans. Although corticosteroids have been used to decrease cerebral edema, they increased the incubation rate and the mortality of rabies in rodent models. Thus, corticosteroids are not recommended for treating rabies.

Bacterial Zoonoses

Because of their exotic names, lack of effective therapy, and devastating effects, many viral zoonoses (e.g., Hantavirus, West Nile virus, and rabies) often have garnered widespread notoriety. In contrast, before the terrorist attack on September 11, 2001, bacterial and spirochetal zoonoses, many of which are more common than their viral counterparts, were often taken for granted. The events of September 11 heightened awareness to the bioterrorism threat posed by infections, such as anthrax, plague, and tularemia. However, the more routine vector-borne transmission of these infections and other bacterial or spirochetal zoonoses are still somewhat underappreciated. These infections often do not have distinguishing clinical characteristics; rather, they are made up of a constellation of vague symptoms. Diagnostic laboratory studies typically are lacking and those that exist may not be very sensitive and/or specific. In addition, acute and convalescent titers often are required to properly interpret the test results. Therefore, the diagnosis of these infections is made on clinical findings. To recognize these infections, it often takes an astute physician with the wherewithal to elicit an appropriate history and tie it to the vague clinical manifestations and nonspecific physical findings. Consequently, these infections, especially milder cases, often go unrecognized.

The causative pathogens of bacterial and spirochetal zoonoses represent a diverse spectrum of genera and species. Historically, plague, caused by the gram-negative bacilli *Yersinia pestis*, is the most notorious bacterial zoonosis. The pandemic that afflicted Europe in the Middle Ages and killed 25% of the population and is well chronicled in art and literature. The disease is spread by exposure to environments inhabited by flea-infested rats. According to the World Health Organization, 1000–3000 cases occur worldwide each year. In the United States, an urban epidemic has not occurred in more than 75 years, but sporadic cases still occur, particularly in rural areas of California, northern areas of New Mexico and Arizona, southern regions of Colorado and Oregon, and

Tantawichien T, Jaijaroensup W, Khawplod P, Sitprija V. Failure of multiple-site intradermal postexposure rabies vaccination in patients with human immunodeficiency virus with low CD4+ T lymphocyte counts. Clin Infect Dis 2001;33:E122–4.

western Nevada. Other bacterial and spirochetal zoonoses are discussed in the following sections.

Tick-borne Bacterial Zoonoses

Ehrlichiosis

Background

Ehrlichiosis, first described in dogs from Algeria in the 1930s, was found to be transmitted by *Rhipicephalus sanguineus* ticks. The organism was called "rickettsia-like", but unlike *Rickettsia* species, it was found as inclusions within monocytes. The organism was placed in its own genus and named *Ehrlichia* species, after Paul Ehrlich, a German bacteriologist. In 1953, human ehrlichiosis was first described in a young Japanese man. The organism, found in the infected mononuclear cells of the patient's blood, was named *Ehrlichia sennetsu* (now called *Neorickettsia sennetsu*). This disease (Sennetsu fever) has remained only in countries of the Far East. Subsequently, the first documented human case of ehrlichiosis in the United States did not occur until 1986. The causative pathogen was eventually named *Ehrlichia chaffeensis* after a similar illness described in an army recruit from Fort Chafee, Arkansas. The diagnosis of both cases was established when intracytoplasmic inclusions were observed in the cells of a peripheral blood smear. The inclusions or morulae were definitive for *Ehrlichia* species. It was found later that the blood was highly reactive to the antigenically related *Ehrlichia canis* and produced a pronounced antibody titer. Similarly, two other *Ehrlichia* species cause human infections. These two species are *Anaplasma phagocytophila* (formerly an *Ehrlichia* species) and *Ehrlichia ewingii*.

Epidemiology and Microbiology

Ehrlichia species, are small (0.5 micron) intracellular gram-negative bacteria that have a preponderance for hematopoietic stem cell lines of their hosts. The organisms can be found in the vacuoles, where they form inclusions called morulae. The morulae can be seen in peripheral blood smears, but they are only present in 1–2% of cells so their absence does not exclude *Ehrlichia* infection.

Ehrlichia species cause two distinct diseases, one that primarily affects the monocytes (human monocytic ehrlichiosis) and one that affects granulocytes (human granulocytic ehrlichiosis [HGE]). Each disease has unique epidemiology and etiology, but they share a primary vector, ticks. Ticks responsible for causing human ehrlichiosis are from the genera *Amblyomma* and *Ixodes*. Ehrlichiosis is primarily transmitted through tick bites and indirect tick exposure. As with other tick-borne zoonoses, the spring and summer months (April to September), which coincide with the tick season, are the peak period for infections. Human monocytic ehrlichiosis and HGE share similar clinical manifestations; therefore, a thorough understanding of the etiology and epidemiology of each disease is key to the correct diagnosis.

Human Monocytic Ehrlichiosis. Human monocytic ehrlichiosis is caused by *E. chaffeensis*, which typically is harbored among *Amblyomma americanum* (lone star) ticks. Lone star ticks are predominantly found in the south central United States, but also inhabit the southeastern and Atlantic coastal states. Human monocytic ehrlichiosis has been reported in almost all 50 states, but the south central (Arkansas, Oklahoma, and Missouri) and southeastern states report the most cases, with the most reports coming from Arkansas.

The occurrence of infections beyond the distribution of lone star ticks may be due to the transmission of ehrlichiosis from other vectors, such as *D. variabilis* (American dog tick). *Dermacentor variabilis* is found in the Atlantic coastal states and its geographical distribution often overlaps with the lone star ticks. The primary reservoir for *A. americanum* is the white-tailed deer, but other mammals and avian hosts have been noted to carry *E. chaffeensis*.

Human Granulocytic Ehrlichiosis. Human granulocytic ehrlichiosis is caused primarily by *A. phagocytophila* and more recently *E. ewingii*. *Anaplasma phagocytophila* is transmitted by *Ixodes scapularis* (black-legged tick) or *Ixodes pacificus* (western black-legged tick). *Ixodes scapularis* predominantly is found in the upper Midwest and New England states, whereas *I. pacificus* is responsible for cases of granulocytic disease in the West Coast states (e.g., Washington, Oregon, and California). Human granulocytic ehrlichiosis has been reported from 13 states. The highest incidence is reported in Connecticut, but Wisconsin, Minnesota, and New York also report a high incidence of HGE infections.

In the New England and upper Midwest states, the occurrence of HGE significantly overlaps with other tick-borne zoonosis, such as Lyme disease and babesiosis, and dual infections with HGE and Lyme and/or babesiosis have occurred. Although ticks are the primary vector responsible for ehrlichiosis and HGE, other modes of disease transmission have occurred. Occupational acquisition and blood transmission of HGE has been reported in butchers and hunters. In these cases, there was blood exposure to known animal reservoirs harboring ehrlichiosis. The primary reservoir for *A. phagocytophila* is the white-tailed deer, but other mammals and birds have been documented as carrying *Ehrlichia* species.

Human Granulocytic Ehrlichiosis Caused by *Ehrlichia ewingii*. Recently, infections caused by *E. ewingii* have been reported in four humans. Before these reports, *E. ewingii* was only known to produce an HGE-like disease in dogs. The human infections occurred from 1996 to 1998 in Missouri during the summer months. Three of the four patients were immunocompromised, and all had a history of tick exposure. On testing, all sera reacted to *E. chaffeensis* and *Ehrlichia canis*, but the individual bacterial sequencing could only be matched to *E. ewingii*.

Clinical Manifestations/Laboratory Findings

Although *Ehrlichia* species and *Rickettsia* species have been distinctly differentiated from one another, they have been traced back to a common ancestor by the 16S ribosome. Therefore, they produce similar diseases that often are misdiagnosed or misnamed. Similarly, human monocytic ehrlichiosis and HGE often present in the same manner, but differences in the diseases do exist.

Buller RS, Arens M, Hmiel SP, et al. *Ehrlichia ewingii*, a newly recognized agent of human ehrlichiosis. N Engl J Med 1999;341:148–55.

Clinical manifestations of the *Ehrlichia* infections often arise after a known tick bite or tick exposure, but the absence of such history does not preclude the diagnosis. Each disease typically has a 7–14-day incubation period followed by a prodrome of nonspecific symptoms. The typical presentation is an abrupt high-grade fever, headache, and rash, which are present in about 33% of patients with human monocytic ehrlichiosis and in about 11% of patients with HGE. Thus, the presence or absence of a rash may not be diagnostic of either infection. Other common symptoms include myalgias, arthralgias, malaise, rigors, and GI complaints.

Typically, the rash, which may present as petechial, macular, or even erythematous, appears 5 days into the illness, manifests centrally, and extends to the arms and legs. However, the rash almost never affects the palms and soles of patients.

The laboratory findings of human monocytic ehrlichiosis and HGE also are similar. Thrombocytopenia and leukopenia occur in more than 70% of all patients with *Ehrlichia* infections. These cytopenias often are most pronounced during the first week of infection. A transient lymphopenia also occurs early in the disease process and results in a lymphocytosis as the disease progresses. Elevated liver enzymes (aspartate aminotransferase/alanine aminotransferase) are present in most *Ehrlichia* infections. Hyponatremia is another common abnormality seen, but it is more predominant in children. Other abnormalities that may occur are an elevated C-reactive protein, lactate dehydrogenase, and amylase, and coagulopathies, prolonged bleeding times, and electrolyte disturbances.

In about 20% of patients, human monocytic ehrlichiosis produces other complications such as respiratory and neurological complications. A spinal tap is required in cases of neurological impairment, and the CSF findings often include a lymphocytic pleocytosis and slightly elevated protein. Morulae typically are not found in the CSF. In severe cases, multiple organ failure can occur.

Human monocytic ehrlichiosis infections typically are more severe than HGE infections and require hospitalization in more than 50% of patients. The overall mortality of human monocytic ehrlichiosis infections is about 3%, whereas HGE infections are associated with 0.7% mortality. Although, human monocytic ehrlichiosis can be more devastating, both diseases have a predilection for elderly (older than 60 years of age), immunocompromised patients, and those with comorbid conditions.

Laboratory Diagnostic Methods

Ehrlichia infections can be diagnosed by the presence of morulae in the peripheral blood smears, but the yield is less than 5% for both diseases. Direct specimen culture also may be performed in cases of *Ehrlichia* infections, but their yield is low. Thus, other laboratory diagnostic methods are used. The immunofluorescence antibody test, which measures the immunoglobulin M and immunoglobulin G antibodies to each *Ehrlichia* species, is widely used. These antibodies may not be present early in the disease process and there is cross-reactivity among different *Ehrlichia* species, so false-negative and false-positive test results occur. To ensure proper interpretation, acute and convalescent titers should be drawn at least 4 weeks apart. A rise in antibody titers between acute and convalescent samples of more than 4-fold is diagnostic of infection. Polymerase chain reaction tests are becoming widely used as a complement to the immunofluorescence antibody test. Polymerase chain reaction may be positive before acute and convalescent titer interpretation. However, methods are not standardized and tests must be established and validated for each individual laboratory.

Treatment

The inability to culture the organisms and the relatively limited number of documented cases make it difficult to determine the "best" therapy for *Ehrlichia* infections. The only drug class to show both in vitro and in vivo activity is the tetracyclines. Rifampin has demonstrated in vitro activity and has been successfully used in pregnancy, but its clinical use remains unclear. Chloramphenicol also has shown in vitro activity, but its efficacy is variable even at maximal concentrations. Fluoroquinolones have demonstrated mixed in vitro results. Ofloxacin and ciprofloxacin demonstrate moderate activity against *Ehrlichia* species and levofloxacin demonstrated activity against *A. phagocytophila*. Thus, the fluoroquinolones may be a viable option in treating human ehrlichiosis, but more clinical data are needed before they can be recommended. Other drugs, including macrolides, penicillins, ceftriaxone, and imipenem, are ineffective against *Ehrlichia* strains in vitro, and are not used to treat ehrlichiosis.

Tetracyclines have been widely used and are the treatment of choice for *Ehrlichia* species. Doxycycline is the most convenient and well-tolerated tetracycline. The recommended dose of doxycycline for treating ehrlichiosis is 100 mg 2 times/day for 7–10 days. Doxycycline is contraindicated in children younger than 9 years of age. Nonetheless, the risk of doxycycline therapy (i.e., tooth discoloration and bone deformities) must outweigh its benefits to preclude its use. Several case reports have demonstrated the success of doxycycline in neonates and children without any detrimental side effects. Thus, doxycycline is recommended for treating ehrlichiosis in children as well as adults. The course should be limited to 7–10 days. The dosage of doxycycline in children often is disputed, but the Centers for Disease Control and Prevention recommends 4 mg/kg in two divided dosages for children who weigh less than 45 kg and the standard adult dose for those children who weight more than 45 kg. Other dosage regimens include have recommended using a loading dose of 4.4 mg/kg orally in two divided dosages on day 1, followed by 2.2 mg/kg/day orally (single dose) for the remaining treatment duration. Symptoms typically respond rapidly to doxycycline therapy. In general, the fever curve breaks within 24 hours and the headache resolves often with the first dose of therapy. Confirmation of disease and its response typically is made with follow-up visits (about 3–4 weeks after onset of disease), where convalescent titers are drawn to confirm the diagnosis and the patient's symptoms are monitored for improvement and return to baseline (see Table 1-2).

Rocky Mountain Spotted Fever

Background

The discovery of Rocky Mountain spotted fever (RMSF) is attributed to the work of Howard Ricketts who, during the early 1900s, demonstrated the transfer of disease from ticks to guinea pigs and later isolated the disease from the blood of infected patients. Ricketts also described the appearance and staining of the organism as "minute polar staining bacilli" and discovered that ticks were both a reservoir and a vector. In later years, the organism was again identified from infected patients' blood using a Giemsa stain. In 1919, S. Burt Wolbach determined the organism was an intracellular pathogen that caused vasculitic lesions in infected patients. The organism was later named *Rickettsia rickettsii* in honor of Ricketts' works. Before the discovery of effective therapy, the mortality rate associated with the disease was greater than 25%. Today, the disease is still the most fatal tick-borne infection in the United States, with 3–5% mortality.

Epidemiology and Microbiology

Rickettsia species are small intracellular gram-negative organisms. *Rickettsia rickettsii* is the organism responsible for causing RMSF, but is only one of many members of the spotted fever rickettsiae. In contrast to *Ehrlichia* species and other intracellular organisms, *Rickettsia* species, are not surrounded by host cell membranes and reside within the nucleoplasm of the cells. This is what causes the distinct vasculitic rash characteristic of RMSF.

Ticks are the reservoir and vector for *R. rickettsii* and RMSF, respectively. Early descriptions of RMSF identified *D. andersoni* (Rocky Mountain wood tick or wood tick) as the primary vector. This species inhabits the Rocky Mountain area and western states, but the term "RMSF" is a misnomer because the disease is more common in other regions of the United States and Canada. *Dermacentor variabilis* (American dog tick) transmits the disease in the Midwest and Atlantic coastal states. In addition to these regions, this tick also is found in the south central states. Another vector of RMSF is believed to be *A. americanum* (lone star tick), which is mainly found in the south central and midwestern states, but its role in RMSF is unknown.

Amblyomma maculatum is a recently identified tick vector that was first discovered in the Gulf Coast region. This tick species is responsible for carrying *Rickettsia parkeri*, which was thought to be nonpathogenic to humans. However, *R. parkeri* caused a RMSF-like illness in a patient from Virginia. The primary reservoirs for RMSF are ticks, but other reservoirs for *Dermacentor* ticks are mice, wild rodents, deer, ground-feeding birds, and dogs.

Ticks primarily transmit RMSF through transovarian passage to offspring. Transovarian is thought to be the main mechanism of *R. rickettsii* transmission. Ticks also can transmit RMSF by infecting a host that serves as a source of disease when other ticks feed on the now-infected animal. *R. rickettsii* is reported to infect less than one in every 1000 ticks; therefore, the presence of disease is attributed to the passage of disease to offspring.

For the past 50 years, 200–1000 cases of RMSF were reported to the Centers for Disease Control and Prevention annually. Only Maine, Vermont, Alaska, and Hawaii have been free of RMSF infections. Of the states that report infections, more than 50% of the cases come from the south Atlantic states. The states reporting the highest incidence of RMSF infection are North Carolina and Oklahoma. The peak time for infections is between April and September. This period account for about 90% of all RMSF infections, but infection has been documented in every month.

Rocky Mountain spotted fever mostly affects Caucasian men and children. The highest incidence of infection, with more than 2.5 cases per million people between 1993 and 1996, occured in children 5–9 years of age. In contrast, elderly patients older than 70 years of age have the lowest incidence of infection, but the highest mortality rate. Overall, adults between 40 and 49 years of age have the least attributed mortality.

Clinical Manifestations/Laboratory Findings

The incubation period for RMSF typically is 2–14 days. When patients seek medical attention, a history of a tick bite surprisingly will only be present in up to 18% of patients. Although the history of a tick bite may not always be apparent, a good history and physical examination typically will yield an exposure history and ultimately suspicion of RMSF.

Patients often manifest a symptom triad of fever, rash, and headache at their initial presentation. Fever and headache will be present in about 60–80% of patients during the first days of illness. A vasculitic lesion is characteristic for RMSF infections because of the predilection of *R. rickettsii* and other spotted fever *Rickettsia* for epithelial cells. These organisms invade the cell and replicate, and are immediately cytotoxic, which in turn causes the development of a rash. The rash may not be apparent during the initial visit, but appears in 85% of patients within the first 5 days. The rash first appears on the ankles and wrists and moves to the palms, soles, pubic, and torso areas. Initially, it appears as blanching macules and gradually becomes petechial. Younger patients tend to develop rash early in the disease course, but in older adults, the rash may be delayed, faint, or even spotless. In severe cases, the rash becomes ecchymotic and even necrotic, and the ensuing damaged and leaky vessels lead to other complications, including encephalitis, pulmonary edema, cardiac arrhythmias, and GI bleeding. Other manifestations of RMSF include myalgias, nausea, and vomiting.

The laboratory findings of RMSF are relatively nonspecific. About 30% of patients have anemia and more than 50% will have thrombocytopenia and hyponatremia. Prolonged bleeding times and increased liver enzymes also are common and markers of muscle and tissue breakdown such as elevated C-reactive protein, lactate dehydrogenase, and creatinine phosphokinase may be obvious.

If left untreated, the mortality rate can be as high as 25% but ranges between 3% and 5%. After symptoms manifest, the longer the initiation of therapy is delayed, the more

Paddock CD, Sumner JW, Comer JA, et al. *Rickettsia parkeri*: a newly recognized cause of spotted fever rickettsiosis in the United States. Clin Infect Dis 2004;38:805–11.

likely the disease will be fatal. Therefore, prompt recognition of the classic triad and early empiric antimicrobial therapy are crucial for patient survival.

Laboratory Diagnostic Methods

Rickettsia rickettsii is an intracellular pathogen; therefore, growing it in culture is difficult. A good history and physical examination combined with serological evidence of infection help secure the diagnosis of RMSF. The immunofluorescence antibody test, which detects immunoglobulin M and immunoglobulin G antibodies, is a widely used serological method. This test has greater than 94% sensitivity for *R. rickettsii*. As with other tests that measure antibody response, antibodies to *R. rickettsii* may not be present early in the disease process, so false-negative tests results can occur. Therefore, both acute and convalescent titers must be drawn to ensure proper interpretation of the test results. A rise in antibody titers between acute and convalescent samples of more than 4-fold is considered diagnostic for RMSF. A single titer of 64 or higher also is diagnostic for the presence of RMSF. Polymerase chain reactions have been applied to skin biopsies with good success because the test is able to amplify the *Rickettsia* species from biopsy specimens and the tick itself. Thus, PCR tests are particularly useful in cases of "spotless" RMSF infections.

Treatment

Early recognition and prompt initiation of therapy are crucial to successfully treat RMSF infection. Patients in whom antibiotic drugs are delayed more than 5 days have a worse prognosis than those who are treated earlier. As with other tick-borne illnesses (ehrlichiosis and Lyme), tetracyclines, particularly doxycycline, are the foundation of RMSF therapy. Although tetracyclines are contraindicated in both pregnant women and children younger than 9 years of age, the Centers for Disease Control and Prevention and the American Academy of Pediatrics endorse the use of doxycycline to treat RMSF in these populations. The adult dosage of doxycycline is 100 mg 2 times/day for 7–10 days. In pediatric patients, the dosages may vary, but two typically accepted regimens are 4 mg/kg orally divided 2 times/day or 4.4 mg/kg orally divided 2 times/day on day 1 followed by 2.2 mg/kg given in one daily dose. Therapy typically is administered for 7–10 days or for 2 days after the patient becomes afebrile.

An alternative to doxycycline is chloramphenicol. The use of chloramphenicol primarily is reserved for children and pregnant women, but has been used successfully in other patient populations as well. The recommended dosage for chloramphenicol is 50–75 mg/kg orally in four divided dosages for 14 days, but chloramphenicol therapy has been associated with fatal outcomes; therefore, its use must be applied with caution. Chloramphenicol is renowned for causing idiosyncratic aplastic anemia and concentration-dependent bone marrow suppression; therefore, the drug is not ideal for outpatient therapy and reticulocyte and red blood cell counts should be monitored. Moreover, chloramphenicol is not active against *Ehrlichia* species, which may present in a similar fashion to RMSF or be a concomitant infection; thus, chloramphenicol is inadequate as empiric treatment for a tick-borne infection.

Fluoroquinolones have demonstrated in vitro activity against *Rickettsia* species, but their use in humans has not been described. This fact coupled with their limited efficacy in *Ehrlichia* infections precludes their routine use in the treatment RMSF and ehrlichiosis.

Patients treated with doxycycline usually respond rapidly to therapy, but severe RMSF cases may require hemodynamic support and fluid resuscitation; thus, supportive management is critical. Corticosteroid therapy has no role in treating RMSF. Supportive care should be maintained until symptoms resolve and the patient becomes hemodynamically stable.

As with other tick-borne diseases, primary prevention is critical. Protective clothing is the optimal tool used to reduce tick exposure and contact, but in warm climate areas this modality is impractical. Thus, routine surveillance of the head, armpits, and groin area are important to discover and limit the time of tick attachment. Tick removal and disposal is an integral part in reducing exposure. Ticks should be grabbed close to the bite site using forceps and then carefully removed from the skin. Once removed, the affected area should be washed thoroughly with soap and water or other sterilizing materials (see Table 1-2).

Tularemia

Background

In the United States, tularemia was first described after a 1911 outbreak of a plague-like illness in ground squirrels. The causative organism was cultured and named *Bacterium tularense*, after the discovery of the disease in Tulare County, California. Human disease was later confirmed from an ocular infection in 1914; 10 years later, Edward Francis discovered that the same organism was responsible for causing deer fly fever. He also discovered that the organism came from mosquitoes in the Utah area. This organism was ultimately identified as *B. tularense*, and the term "tularemia" was born. Francis' work produced significant findings, including better cultivation and serological diagnostic methods, identification of the risk of laboratory transmission, and the role of other vectors and reservoirs, such as ticks. To recognize these works, the organism was later renamed *Francisella tularensis*.

Epidemiology and Microbiology

Francisella tularensis are small intra- or extracellular, pleomorphic, gram-negative coccobacilli. The classification of the *Francisella* genus is complex and often disputed; therefore, subspecies are used to identify the organisms. *Francisella tularensis*, the most virulent strain, comes from the biovar *tularensis*. This organism is highly pathogenic to humans and requires less than 10 colony-forming units to be lethal. This biovar primarily is found in North America, but also has been isolated in Europe. Compared to the biovar *tularensis*, the biovar *holarctica* (formerly *palearctica*) is less virulent. Biovar *holarctica* is found in North America, Europe, and Asia. Biovar *mediaasiatica* is found in Asia and parts of Russia. There is disagreement on whether biovar *Francisella novicida*, which also is found in North America, is actually a separate

species from *F. tularensis*. In humans, the organism produces a mild to moderate tularemia-like disease.

Tularemia is a disease of the northern hemisphere. Many arthropod vectors transmit *F. tularensis*, but in the United States, the primary vectors are ticks and mosquitoes. Tularemia associated with tick exposure occurs primarily east of the Rocky Mountains, whereas tularemia associated with mosquitoes occurs in and west of the Rocky Mountains. Tick vectors for tularemia include *D. andersoni* (Rocky Mountain wood tick or wood tick), *D. variabilis* (American dog tick), and possibly *A. americanum* (lone star tick). The mosquito vectors responsible for the transmission of tularemia are *Culex*, *Aedes*, and *Anopheles*. Most cases of tularemia arise from tick exposure; thus, mosquito-borne tularemia will not be discussed further.

Francisella tularensis is harbored in more than 250 vertebrate and nonvertebrate species; thus, this disease has many other names (e.g., deer fly fever, lemming fever, and hare fever). Rodents, squirrels, voles, muskrats, and beavers are the primary reservoirs in the United States. In addition to arthropod sources, *F. tularensis* may be transmitted by other means, including inhalation, ingestion, and indirect inoculation from blood. *Francisella tularensis* may be viable in the environment for more than 6 months; thus, it may be on fur or other products left in the surroundings by the source animal.

Tularemia has been documented in every state except Hawaii. The majority of tularemia infections occur in midwestern and south central states, mainly in Arkansas, Missouri, Oklahoma, and South Dakota. During the 1999–2000 reporting period, there were more than 1300 cases of tularemia. The incidence of tularemia was highest in adults older than 75 years of age and children 5–9 years of age. The incidence of tularemia has increased in recent years largely because of its reintroduction as a reportable disease.

As with other tick-borne diseases, peak incidence of tularemia is seasonally distributed, but unlike other tick-borne diseases, the pattern is bimodal. The first peak incidence occurs between April and September and primarily is because of tick exposure. The second peak incidence starts in late fall and is because of the hunting season and transmission from infected animals and carcasses.

Clinical Manifestations/Laboratory Findings

Francisella tularensis infections largely depend on the biovar, inoculum size, mode of entry, and host immune status. Subsequently, the disease may range from an asymptomatic illness to death. The incubation period for tularemia typically is 3–5 days, but may be as short as 1 day and as long as 21 days. The disease develops abruptly and usually is associated with fever, chills, cough, headache, fatigue, abdominal pain, chest soreness, and vomiting. A pulse-temperature discrepancy, characterized by the presence of a high fever without an accompanying increase in pulse rate, is a common finding. Left untreated, the fever may persist for more than a month.

Symptomatic patients who require medical attention for an infection for *F. tularensis* will present with one or a combination of six classic forms of tularemia: ulceroglandular, glandular, oculoglandular, pharyngeal, typhoidal, and pneumonic.

Ulceroglandular tularemia, the most common form of the disease, occurs in up to 85% of patients. This form is characterized by the presence of a regional lymphadenopathy and an accompanying skin lesion from the bite site. The lesion is commonly found adjacent to the swollen lymph node and typically progresses from a painful papule to a necrotic lesion (an inoculation eschar). The lesion may be present before, during, or after lymphadenopathy develops.

Glandular tularemia occurs in 3–20% of affected patients. This form also is characterized by a regional lymphadenopathy, but it is not associated with any noticeable skin lesion. With either ulceroglandular or glandular tularemia, if the lymph node is fluctuant, it should be drained or surgically removed.

Oculoglandular tularemia occurs in up to 5% of patients and usually is attributed to inoculation from contaminated fingers, splashes, or aerosolized bacteria. The disease manifests as a painful conjunctivitis, with associated eyelid edema and erythema, which usually results from adjacent lymph node involvement. The eye may contain yellowish ulcerations or papules.

Pharyngeal tularemia is seen in about 12% of patients and is acquired primarily through ingestion of contaminated water or food products. The disease is seen more often in children than in adults. The chief complaint is a severe sore throat and fever. On examination, there typically is pharyngeal ulcerations and evidence of exudative pharyngitis.

Typhoidal tularemia is the only form not associated with an obvious lymphadenopathy. In some regions of the world, more than 30% of patients experience this type of tularemia. The disease often occurs in patients with comorbid conditions or immunosuppression. The presentation consists of fever, chills, sore throat, cough, myalgias, nausea, vomiting, abdominal pain, and loose watery diarrhea. How this form is acquired is largely unknown; thus, any source is possible. Patients will have accompanying dehydration, hypotension that may lead to organ failure, and culture-negative septic shock. The disease may take on many forms and a good history and physical examination is crucial in making the diagnosis.

Pneumonic tularemia, the most lethal form of disease, may affect more than 20% of patients. Symptoms of this form predominantly involve the lungs. The mode of transmission may occur through inhalation or from the bloodstream supplying the lungs. Pneumonic tularemia often is acquired by occupational exposure (e.g., laboratory personnel, farmers, and herders). Pneumonic tularemia may occur with any of the prior forms discussed, but most often is associated with typhoidal disease. On examination, patients may have rales or evidence consolidation and may require oxygen or even mechanical ventilation. Excess pleural fluid may be removed and cultured, but the results often are nondiagnostic. Overall, mortality with pneumonic tularemia is about 7%.

Laboratory Diagnostic Methods

Francisella tularensis is highly contagious, and it grows poorly on standard culture media; thus, routine culturing is discouraged. Tularemia often is diagnosed based on clinical findings and confirmed with serology. The serological detection of *F. tularensis* can be done with agglutination techniques or by PCR tests. The agglutination techniques are latex and tube agglutination, and titers greater than 1:20, and 1:160, respectively, are suggestive of infection. However, a rise in antibody titer of more than 4-fold between acute and convalescent samples typically is diagnostic. This result can be seen in as few as 2 weeks, but may take as many as 4 weeks to become interpretive. Thus, weekly agglutination tests should be preformed to confirm any antibody response. Polymerase chain reaction tests are sensitive, but their specificity is based on the purity of the sample. Polymerase chain reaction tests often are used because they are less invasive and safer than culturing the organism.

Treatment

Literature describing the treatment of tularemia has been largely anecdotal. These reports indicate that streptomycin or gentamicin is highly effective. Streptomycin has been regarded as the primary drug for treating tularemia, with a clinical success rate that exceeds 95%. The recommended dose of streptomycin is 7.5–10 mg/kg intramuscularly 2 times/day for 7–14 days. An alternative adult regimen is 15 mg/kg intramuscularly every 12 hours for 3 days, followed by 7.5 mg/kg intramuscularly 2 times/day for the remaining treatment duration. The pediatric dose is 15–20 mg/kg intramuscularly 2 times/day. The main hindrances to streptomycin use is the increased risk of Jarisch-Herxheimer-like reaction, the need for 2 times/day intramuscular injections, and the limited availability of the drug. Therefore, gentamicin is considered the first alternative to streptomycin. Gentamicin had comparable efficacy (more than 85%) in limited published reports. The gentamicin dose is 3–5 mg/kg/day divided every 8 hours for 7–14 days. The desired peak gentamicin concentration should be greater than 5 mcg/ml, preferably between 8 mcg/ml and 10 mcg/ml. Neither drug has reliable penetration to the CSF; therefore, combination regimens should be used. Successful therapy for CNS tularemia used the combination of streptomycin (dosed as previously discussed) and chloramphenicol 50–200 mg/kg/day divided into four daily dosages for at least 14 days. Alternatively, gentamicin at maximal dosing every 8 hours and doxycycline 100 mg orally or intravenously 2 times/day were reported to be effective in tularemia meningitis.

Tetracyclines and chloramphenicol have been successfully used to treat tularemia. However, they are associated with a high frequency of relapses, perhaps because they are bacteriostatic against *F. tularensis*. Compared to chloramphenicol, the rate of relapse is less with tetracyclines; however, because there are other effective drugs, it is still unacceptably high.

The fluoroquinolones also have been successful in treating tularemia, with an 86% success rate in 79 reported cases. Ciprofloxacin use was associated with a 95% success in 22 patients. Similarly, levofloxacin 500 mg intravenously once daily, followed by oral levofloxacin 500 mg/day once was used successfully in two immunocompromised patients. The oral preparations of the fluoroquinolones make them suitable for outpatient therapy. Given the success rates of the fluoroquinolones and the paucity of data with other drugs, this class is an ideal alternative therapy for tularemia. Published dosing information is limited; therefore, standard treatment doses should be used. When considering fluoroquinolone therapy, ciprofloxacin 500 mg orally 2 times/day or levofloxacin 500 mg/day orally for 7–14 days are recommended. Therapy should be monitored based on resolution of clinical symptoms and reduction in lymph node size. Gentamicin must be given parenterally; therefore, therapy may require a percutaneously inserted central catheter to complete therapy. Percutaneously inserted central catheter line education and arrangements with home health need to be considered.

Macrolides have been used to treat tularemia with mixed success. Telithromycin, a ketolide, has demonstrated in vitro activity versus *F. tularensis* isolates, but its clinical use is unknown; therefore, it is cannot be recommended at this time. Likewise, many β-lactams have had conflicting reports of success and their use is not recommended either (see Table 1-2).

Similar to other arthropod-borne diseases, prevention is the primary mode to limit infection. As previously discussed, effective protective garments and proper repellents are vital to reducing tick exposure, attachment, and disease.

Spirochetal Zoonoses

Tick-borne Spirochetal Zoonoses

Lyme Disease

Background

Lyme disease or Lyme Borreliosis was first described in studies of a geographic clustering of "juvenile rheumatoid arthritis" in the Lyme, Connecticut, area in 1976. Soon after, it became apparent that Lyme arthritis was a late manifestation of a tick-borne illness. In 1981, Willy Burgdofer isolated a new spirochete from a tick (*I. scapularis*). This spirochete was then isolated in patients with Lyme disease, confirming the etiology of the infection.

Epidemiology and Microbiology

The agents of Lyme disease are thin, motile spirochetes of the genus *Borrelia* and are grouped in the *Borrelia burgdorferi* sensu lato complex. This complex includes the pathogenic species, *B. burgdorferi* sensu stricto, *Borrelia afzelii*, and *Borrelia garinii*, and eight closely related species that rarely cause human disease. *Borrelia afzelii* and *B. garinii* are responsible for most cases in Europe and Asia,

Perez-Castrillon JL, Bachiller-Luque P, Martin-Luquero M, Mena-Martin, FJ, Herreros V. Tularemia epidemic in northwestern Spain: clinical description and therapeutic response. Clin Infect Dis 2001;33:573–6.

and *B. burgdorferi* sensu stricto is the cause of Lyme disease in the United States.

Borrelia burgdorferi lives in an enzootic cycle involving ticks and their animal hosts. These cycles have evolved differently in separate geographic areas. In the northeastern and north central United States, infection is maintained through horizontal transmission of *B. burgdorferi* between larval and nymphal *I. scapularis* ticks and rodents, such as the white-footed mouse and chipmunks. White-tailed deer, the predominant host for adult *I. scapularis*, are not involved in the life cycle of the spirochete but appear to be critical for the survival of the tick. In human disease, nymphs cause the majority of cases. Their small size allows them to go unnoticed and remain attached for extended periods. Less than 50% of patients with Lyme disease recall having a tick bite.

On the West Coast, particularly in northern California, a bridge vector (*I. pacificus*) is needed to transmit the disease to humans. The primary reservoirs for Lyme vectors in this region are dusky-footed wood rat (also known as the pack rat, *Neotoma fuscipes*) and California kangaroo rats (*Dipodomys californicus*). Infection in these hosts is maintained by the nonhuman-feeding ticks *Ixodes neotomae* and *Ixodes spinipalpis*. About 15% of the *I. neotomae* are infected with *B. burgdorferi*, and they transmit the infection between hosts. In contrast, only about 5% of *Ixodes pacificus* are infected with *B. burgdorferi*. *I. pacificus* feeds on wood rats and humans; therefore, unlike *I. neotomae*, it is responsible for spreading the disease to humans. For human transmission to occur, the pack rat is first infected by *I. neotomae*, and then it is fed on by *I. pacificus*. After feeding on the infected rat, *I. pacificus* transmits the disease by biting a human. This inefficient transmission cycle is probably the reason the incidence of Lyme disease in the western United States is much lower than other regions. In the southeastern United States, the predominant hosts for nymphal *I. scapularis* are lizards, which are not susceptible to *B. burgdorferi* infection because of complement-mediated killing of the organism.

Lyme disease has been reported worldwide and is the most common tick-borne illness in the United States. The majority of cases occur in southern New England, eastern parts of the middle Atlantic states, and the upper Midwest. In addition, there is a smaller endemic area along the Pacific Coast. Lyme disease is rare in the south central and southeastern United States; however, a Lyme disease-like illness, southern tick-associated rash illness, has been reported. Southern tick-associated rash illness is associated with the bite of *A. americanum* (lone star tick) and is presumed to be caused by a novel spirochete, *Borrelia lonestari*. Lyme disease most commonly occurs from May through October, with the majority of cases occurring in June and July.

Clinical Manifestations/Laboratory Findings

The clinical manifestations of Lyme disease depend on the stage of the illness and are described in three categories of infection: localized, disseminated, and persistent. Early symptoms usually begin after an incubation period of 3–32 days. Erythema migrans, the most common manifestation of localized disease, starts as a red macule or papule rash near the site of the tick bite. As the rash slowly expands in size over a period of days or weeks, central clearing becomes apparent and gives the rash a classic "bull's-eye" appearance. Fever, malaise, headache, fatigue, stiff neck, and muscle and joint pain may accompany the skin lesion.

If left untreated, *B. burgdorferi* widely disseminates within a few weeks. Multiple erythema migrans are the most common manifestation in disseminated infection. These lesions are similar to the primary lesion but are smaller and are not associated with the site of the tick bite. Neurological involvement occurs in 15% of untreated patients and includes cranial nerve palsies, acute lymphocytic meningitis, and radiculoneuritis. Cardiac manifestations occur in 5% of untreated patients. The most commonly observed are fluctuating degrees of atrioventricular block. Arthralgia, myalgia, headache, and fatigue also occur in disseminated disease.

After weeks of disseminated disease, *B. burgdorferi* may survive in localized areas. Months after the onset of infection, 60% of untreated patients experience intermittent attacks of arthritis. The arthritis typically affects large joints, particularly the knee. A small number of patients develop inflammatory joint disease that does not respond to antimicrobial therapy. A rare, late neurological syndrome manifesting as Lyme encephalopathy has been described and includes subtle cognitive disturbances, spinal radicular pain, or distal paresthesias. In a small number patients' with Lyme disease, disabling musculoskeletal pain, neurocognitive symptoms, or fatigue develops. This persistent or chronic Lyme disease may last for months or years after antibiotic drug therapy.

Laboratory findings are nonspecific and primarily occur early in the illness. Commonly observed laboratory abnormalities include elevations in erythrocyte sedimentation rate, serum immunoglobulin M, or transaminase levels. Patients with elevated transaminase levels also often have increased lactate dehydrogenase levels that normalize within several weeks. Patients may have an elevated white blood cell count with a left shift and anemia may occur early in the disease. Antinuclear antibodies and rheumatoid factor usually are negative, and complement (C3 and C4) levels typically are normal or elevated. Urinalysis occasionally reveals microscopic hematuria and proteinuria.

Laboratory Diagnostic Methods

The diagnosis of Lyme disease is based primarily on clinical findings; however, serology may provide useful diagnostic information in patients with disseminated or chronic disease complications without a recent or current history of erythema migrans. When serological testing is indicated, the Centers for Disease Control and Prevention recommends initially testing with a sensitive test, such as an

James AM, Liveris D, Wormser GP, Schwartz I, Montecalvo MA, Johnson BJ. *Borrelia lonestari* infection after a bite by an *Amblyomma americanum* tick. J Infect Dis 2001;183:1810–4.

enzyme-linked immunosorbent assay, and then confirming with the more specific Western immunoblot.

Treatment

Practice guidelines for treating Lyme disease have been published by the Infectious Diseases Society of America. The choice of appropriate therapy depends on the signs and symptoms, as well as the age of the patient (See Table 1-5).

Tick-borne Relapsing Fever

Background

Tick-borne relapsing fever (TBRF) is a recurring febrile disease caused by *Borrelia* species that are transmitted to humans by soft-bodied ticks of the family Argasidae. Tick-borne relapsing fever is endemic in Africa, Central Asia, the Mediterranean, as well as North and South America.

Epidemiology and Microbiology

In the United States, TBRF is transmitted by soft-bodied ticks of the genus *Ornithodoros* (*Ornithodoros hermsi*, *Ornithodoros turicata*, and to a lesser extent *Ornithodoros parkeri*). Each tick species is responsible for transmitting a specific *Borrelia* species. In the western United States, *O. hermsi* and *O. parkeri* are found in coniferous forests at elevations of 1500–8000 feet. *Ornithodoros hermsi* primarily feed on chipmunks and ground or tree squirrels and are responsible for transmitting *Borrelia hermsii*. *Ornithodoros parkeri* is responsible for transmitting *Borrelia parkeri*, which causes few cases of TBRF. In contrast to *O. hermsi* and *O. parkeri*, *O. turicata* is found at lower elevations, in the drier habitats of the southern plains states. This species is commonly found in underground burrows and in caves. It feeds on many different mammals and reptiles, including cattle, pigs, ground squirrels, prairie dogs, gopher tortoises, and snakes. *Ornithodoros turicata* is responsible for transmitting *B. turicata*.

Endemic relapsing fever *Borrelia* species have been reported in most of the western United States. Cases of TBRF are sporadic and often are reported as common source outbreaks. Since 1977, most cases have been reported primarily from California, Colorado, and Washington. Individuals are exposed to *Ornithodoros* tick species while crawling under buildings and hiking. Therefore, cases in mountainous regions of the western and northwestern United States commonly occur after exposure to rustic cabins or rural dwellings, whereas cases in the semiarid plains most commonly are acquired after exposure to caves.

Tick-borne relapsing fever is a seasonal disease, with 71% of cases in the western and northwest occurring from June through September. In contrast, cases in Texas tend to peak later in the year, with 50% of cases occurring between November and January. About 52% of cases occur in men and the median age of the patient is 35 years old.

Clinical Manifestations/Laboratory Findings

Ornithodoros species feed rapidly, often at night and can transmit *Borrelia* within minutes. Consequently, most patients are unaware they have been bitten by a tick. A small pruritic eschar may develop at the site of attachment within a few days of exposure. Symptoms begin abruptly about 1 week after exposure (range 4 to 18 days). Fever (often higher than 40°C), headache, myalgia, chills, arthralgia, nausea, and vomiting are commonly reported during the febrile period. Abdominal pain, diarrhea, confusion, dry cough, eye pain, dizziness, photophobia, and neck pain are reported less frequently.

Relapsing fever *Borrelia* species cause disease manifestations through a process known as antigenic variation, which is responsible for the recurrent nature of the disease. During afebrile periods, the spirochetes are undetectable in the bloodstream and patients experience few symptoms, except perhaps malaise. During these asymptomatic periods, spirochetes become sequestered in internal organs, and under pressure from the host defenses, the *Borrelia* species alter their surface proteins and escape eradication by the host immune system. About 1 week after the afebrile period begins, the spirochetes reemerge from the internal organs with altered outer surface proteins. Because they escape recognition by host immunity, this process results in high levels of spirochetemia and produces the febrile periods. The primary febrile episode lasts about 3 days (range 12 hours to 17 days). Three to five relapses can be expected without appropriate treatment, but symptom intensity and duration tend to diminish with each relapse.

Physical findings include a petechial, macular, or papular rash, which is reported in 18% of cases. This rash typically heralds the beginning of the afebrile periods. Hepatomegaly and splenomegaly also can be found on physical examination. Neuroborreliosis is a potential complication of TBRF, particularly in cases caused by *B. turicata*. Between 27% and 80% of cases caused by *B. turicata* involve neurological manifestations compared to less than 5% of cases caused by *B. hermsii*. The most common forms of neuroborreliosis are cranial nerve palsies and meningismus. Cranial neuritis occurs primarily during the second or third febrile episode. Rare complications of TBRF include ocular disorders, myocarditis, and rupture of the spleen. Mortality rates for TBRF can be as high as 8%, and tend to be highest in small children and pregnancy.

In general, laboratory findings in TBRF cases are nonspecific. Thrombocytopenia is the most common hematological abnormality, whereas leukocyte counts typically remain in the normal range. Urinalysis may reveal proteinuria in 46% of cases and hematuria in 30% of cases.

Laboratory Diagnostic Methods

Because spirochetes are not usually present in the blood during afebrile periods, blood for serological testing and staining should be collected only during febrile periods. Hematogenous confirmation of TBRF is made by direct visual detection of borreliae in the peripheral blood. Although serological test methods exist, they are not commonly used to diagnose TBRF. More commonly, Giemsa or Wright stains are used to identify spirochetes in the blood of infected patients during periods of significant spirochetemia. Blood smears have a sensitivity of about 70%. In addition, borreliae may be visualized by direct or indirect immunofluorescent staining and examination with a fluorescence microscope.

Table 1-5. Recommended Therapy for Patients with Lyme Disease

Indication	Adults	Children
Tick Bite	None recommended; observe	None recommended; observe
Erythema migrans	**Preferred:**	**Preferred:**
Early or late	Doxycycline 100 mg orally 2 times/day for 14–21 days	Doxycycline 1–2 mg/kg 2 times/day for 14–21 days (not recommended if younger than 8 years old)
	Amoxicillin 500 mg orally 3 times/day for 14–21 days	Amoxicillin 50 mg/kg/day orally divided in three dosages for 14–21 days
	Alternative:	**Alternative:**
	Cefuroxime axetil 500 mg orally 2 times/day for 14–21 days	Cefuroxime axetil 30 mg/kg/day orally in divided dosages for 14–21 days
	Azithromycin 500 mg/day orally for 7–10 days	Azithromycin 10 mg/kg/day orally for 7–10 days (maximum 500 mg/day)
	Erythromycin 500 mg orally 4 times/day for 14–21 days	Erythromycin 12.5 mg/kg orally 4 times/day for 14–21 days (maximum 2000 mg/day)
	Clarithromycin 500 mg orally 2 times/day for 14–21 days	Clarithromycin 7.5 g/kg orally 2 times/day for 14–21 day (maximum 1000 mg/day)
Acute Neurological Disease		
Meningitis, radiculopathy, or cranial nerve palsy *with* CNS involvement	**Preferred:**	**Preferred**:
	Ceftriaxone 2 g/day intravenously for 14–28 days	Ceftriaxone 75–100 mg/kg/day for 14–28 days (maximum 2 g/day)
	Alternative:	**Alternative:**
	Cefotaxime 2 g intravenously 3 times/day for 14–28 days	Cefotaxime 150–200 mg/kg/day for 14–28 days (maximum 6 g/day)
	PCN G 18–24 MU/day intravenously in divided dosages every 4 hours	PCN G 200,000–400,000 units/kg/day in divided dosages every 4 hours (maximum 18–24 MU/day)
	Doxycycline 200–400 mg/day orally or intravenously in two divided dosages	
Cranial-nerve palsy *without* CNS involvement	**Oral therapy:**	**Oral therapy:**
	Same as treatment for erythema migrans	Same as treatment for erythema migrans
Cardiac Disease	**Oral therapy:**	**Oral therapy:**
First- or second-degree heart block	Same as treatment for erythema migrans	Same as treatment for erythema migrans
	Parenteral therapy:	**Parenteral therapy:**
Third-degree heart block	Same as treatment for meningitis for 14–21 days	Same as treatment for meningitis for 14–21 days
Late Disease		
Arthritis *without* neurological disease	Doxycycline 100 mg orally 2 times/day for 28 days	Doxycycline 1–2 mg/kg orally 2 times/day for 28 days (not recommended if younger than 8 years old)
	Amoxicillin 500 mg orally 3 times/day for 28 days	Amoxicillin 50 mg/kg/day orally in three divided dosages for 28 days
Recurrent arthritis after oral regimen	Repeat oral regimen for arthritis or intravenous ceftriaxone for 2–4 weeks	Repeat oral regimen for arthritis or intravenous ceftriaxone for 2–4 weeks
Persistent arthritis after two courses	Symptomatic therapy	Symptomatic therapy
CNS or peripheral nervous system disease	**Parenteral therapy:**	**Parenteral therapy:**
	Same as treatment of meningitis above	Same as treatment of meningitis above
Chronic or Persistent Lyme Disease		
	Antimicrobial drugs not recommended; symptomatic therapy	Antimicrobial drugs are not recommended; symptomatic therapy

CNS = central nervous system.

Adapted with permission from the University of Chicago Press. Wormier GP, Nadelman RB, Dattwyler RJ, et al. Practice guidelines for treatment of Lyme disease. Clin Infect Dis 2001;31(suppl 1):S1–S14.

Treatment

Currently, recommended antibiotic regimens for treating TBRF are based on anecdotal evidence. Nonetheless, tetracyclines are the preferred antibiotic drugs for treating TBRF. Doxycycline 100 mg orally 2 times/day or tetracycline 500 mg orally every 6 hours for 7–10 days are the recommended therapies. Alternative regimens include erythromycin and chloramphenicol, each given 500 mg orally every 6 hours for 7–10 days. Parenteral therapy should be used only when oral therapy cannot be tolerated or in patients with CNS involvement. Patients with meningitis should receive intravenous therapy with cefotaxime 1–2 g every 8 hours, ceftriaxone 1 g/day, or penicillin G 1.5 million units intravenously every 6 hours for at least 14 days. Penicillin, cephalosporins, or erythromycin should be used for pregnant women and children younger than 8 years old.

The Jarisch-Herxheimer reaction can be a serious consequence TBRF treatment and is reported in 39–54% of patients who receive treatment. This reaction is an acute exacerbation of the patient's symptoms that can occur with the initiation of antibiotic drugs. Manifestations include rigors, fever, and hypotension. The reaction has been attributed to transient increases in cytokines (e.g., tumor necrosis factor-α, interleukin-6, and interleukin-8). Anti-tumor necrosis factor-α antibodies prevent the Jarisch-Herxheimer reaction in louse-borne relapsing fever. Meptazinol, an opioid antagonist with agonist properties, also reduces the severity of symptoms, whereas naloxone is ineffective. In addition, pretreatment with acetaminophen or hydrocortisone is ineffective in preventing this reaction. Thus, pharmacists should tailor pharmacological therapy based on the severity of the disease and its clinical manifestations. Proper dosage regimens and adjustments as well as supportive management of treatment complications are an integral part to effective TBRF therapy (see Table 1-2).

Animal-borne Spirochetal Zoonoses

Leptospirosis

Background

Leptospirosis, a zoonotic disease caused by spirochetes of the genus *Leptospira*, is one of the most widespread zoonosis. Adolf Weil first described leptospirosis (Weil's disease) in 1886, but cases were commonly misdiagnosed as malaria or yellow fever, until spirochetes were identified as the cause in 1914. Then, until 1940, several diseases were attributed to *Leptospira* species, including canefield fever in Australia, swineherd's disease, swamp or mud fever in Europe, autumnal fever and 7-day fever in Japan, and Fort Bragg fever in the United States. Renewed interest in the disease arose in the late 1990s, when it was considered a reemerging infectious disease.

Epidemiology and Microbiology

Leptospires are highly motile, obligate aerobic spirochetes. *Leptospira* species are classified either on the basis of antigenic determinants or deoxyribonucleic acid sequencing. Based on antigenic determinants, there are 24 serogroups containing more than 250 serovars, 200 of which are pathogenic. Using deoxyribonucleic acid sequencing, *Leptospira* are divided into 17 genomospecies. This method provides useful taxonomic information, but it is not clinically useful.

The epidemiology of leptospirosis reflects the relationship between chronically infected mammalian hosts and humans. *Leptospira* species infect wild and domestic mammals, particularly rats and other rodents. Leptospirosis is maintained by persistent colonization of the proximal renal tubules in infected hosts that can shed infectious organisms in their urine for the remainder of their life. Humans and other animals become infected indirectly through contact with urine-contaminated soil or water, or directly through contact with infected hosts.

Human leptospirosis has been reported worldwide. The highest prevalence is found in tropical, developing areas with antibody prevalence rates exceeding 80% in some locations. Adult men tend to have the highest incidence of leptospirosis; however, data suggest that this is not because of greater exposure. Tropical areas such as the Caribbean islands, Central and South America, Southeast Asia, and the Pacific islands have the highest prevalence of leptospirosis. An estimated 100–200 cases are identified annually in the United States; Hawaii consistently had the highest incidence (1.29 cases per 100,000 people) between 1974 and 1998.

Leptospirosis is considered an occupational disease, particularly among abattoir (i.e., slaughter house) workers, animal trappers, hunters, dairy farmers, military personnel, miners, rice farmers, sewer workers, and veterinarians. Outbreaks also have been associated with flooding, tropical storms, and hurricanes in the Caribbean and Central and South America. Recently, newer routes of exposure have been identified, including recreational exposures (e.g., canoeing, kayaking, rafting, swimming, and wading) in contaminated lakes and rivers. Outbreaks in urban areas also have been documented, especially in areas that lack adequate sanitation.

Clinical Manifestations/Laboratory Findings

Leptospirosis manifests as a self-limiting, systemic disease (anicteric form) or fulminate disease (icterohemorrhagic form or Weil's disease). The anicteric form occurs in about 90% of infections. Although fulminate disease is not as common, it may result in renal failure, liver failure, and hemorrhagic pneumonitis. Both forms progress through an acute septicemic phase that is followed by an immune phase.

The incubation period usually is 5–14 days, but may last more than a month. The septicemic phase typically begins with an abrupt onset of high fever, headache, chills, conjunctival suffusion, anorexia, nausea, vomiting, and prostration. Almost all patients suffer severe myalgia during the septicemic phase, with most patients showing evidence of mild rhabdomyolysis. The most notable physical signs during the septicemic phase are conjunctival suffusion and

Dworkin MS, Anderson DE, Schwan TG, et al. Tick-borne relapsing fever in the northwestern United States and southwestern Canada. Clin Infect Dis 1998;26:122–31.

muscle tenderness. Hepatomegaly, lymphadenopathy, maculopapular skin rashes, pharyngeal infection, and splenomegaly also may occur. This acute phase of illness typically lasts for 3–7 days.

The resolution of septicemic symptoms may coincide with the immune phase of the disease. However, fever may recur after 3–4 days, producing a biphasic pattern. During the immune phase, prominent clinical findings include conjunctival suffusion with or without hemorrhage, photophobia, eye pain, muscle tenderness, and hepatosplenomegaly. Aseptic meningitis, a manifestation of the immune stage, is seen in up to 25% of all leptospirosis cases. Uveitis, iritis, iridocyclitis, and chorioretinitis also may occur during the immune phase.

Weil's disease, or the icterohemorrhagic form, is the most severe form of leptospirosis and is fatal in 5–15%. This disease may develop as either the second phase of biphasic illness or as a single progressive illness. Weil's disease is characterized by jaundice, renal failure, and hemorrhage; however, its clinical manifestations are highly variable. Jaundice in leptospirosis occurs in the absence of hepatocellular necrosis. Serum bilirubin levels may be quite high and may take weeks to normalize. Typically, hepatic transaminases and alkaline phosphatase are slightly elevated. Hepatic dysfunction usually resolves and is rarely the cause of death. Hypothrombinemia occurs in rare cases.

Renal involvement is common in leptospirosis. Acute renal failure, usually nonoliguric, occurs in 16–40% of patients. Oliguria, a significant predictor of death, and azotemia also may occur and usually develop in the second week of illness, but may develop within 4 days after the onset of illness.

Hemorrhagic pneumonitis and acute respiratory distress syndrome also can be prominent manifestations of leptospirosis and may develop in the absence of hepatic and renal failure. The incidence of pulmonary complications range from 20% to 70%. Pulmonary symptoms vary from cough, dyspnea, and hemoptysis to acute respiratory distress syndrome. Leptospirosis also may cause nonspecific electrocardiographic changes, but congestive heart failure is rare. Hypotension due to cardiovascular collapse can occur in icterohemorrhagic leptospirosis, with hemorrhage being observed in only the most severe cases.

Leptospirosis is associated with nonspecific laboratory findings. Urinalysis frequently reveals proteinuria, pyuria, and occasionally microscopic hematuria and hyaline or granular casts. In patients with aseptic meningitis, lymphocytic pleocytosis is common with cell counts typically below 50 cells/mm^3 . Cerebrospinal fluid protein levels are moderately elevated, whereas the CSF glucose concentration remains normal. About 50% of patients exhibit evidence of muscle involvement (i.e., elevations in creatine kinase). In cases with hepatic involvement, serum bilirubin and transaminases concentrations also may rise. In cases that involve the kidneys, blood urea nitrogen and serum creatinine will be significantly elevated. Other laboratory findings include anemia, thrombocytopenia, and leukocytosis with neutrophilia.

Laboratory Diagnostic Methods

Definitive laboratory diagnosis of leptospirosis is made through demonstration of *Leptospira* species by culture or immunohistochemical staining, or by identification of leptospiral deoxyribonucleic acid by PCR. *Leptospira* species are slow growing, which makes identification by culture difficult. Cultures must be maintained for a minimum of 6–8 weeks, preferably 4 months, before they can be reported as negative. In addition, sensitivity of culture for diagnosis is low and many clinical laboratories do not use the required specialized culture media. Polymerase chain reaction assays show considerable promise for a quick, accurate diagnosis, but they are not widely available. Thus, in the absence of PCR methods, diagnosis often is delayed or undetermined.

The standard serological test for diagnosing leptospires is the microscopic agglutination test. Unfortunately, this test requires considerable expertise, is difficult to standardize, and is only performed by a small number of reference and regional laboratories in the world. Other serological tests, such as an indirect hemagglutination and enzyme-linked immunosorbent assay, have been developed and can detect immunoglobulin M and immunoglobulin G antibodies that provide diagnostic information earlier than microscopic agglutination test.

Treatment

Because many patients present during the immune phase of the illness, treating leptospirosis with antibiotic drugs remains controversial. In a series of 153 cases, there was no significant difference in illness duration in patients who received antibiotic drugs versus patients who did not. However, initiating antibiotic drugs before the 7th day of symptoms was associated with a shortened illness duration, which is consistent with several studies that reported a decreased disease course when appropriate antibiotic drugs were administered within 2–4 days. Late administration of penicillin demonstrated decreased clinical efficacy and increased mortality rates in patients with severe disease. A Cochrane database review that assessed antibiotic drug effectiveness in leptospirosis concluded that because of the small number of randomized, clinical trials, the evidence was insufficient to provide clear guidelines for practice. However, the evidence from trials included in the review suggested penicillin or doxycycline could be beneficial in treating leptospirosis. Currently, recommended antibiotic drug regimens and dosages are based on disease severity. Doxycycline 100 mg orally 2 times/day and ampicillin 500–750 mg or amoxicillin 500 mg every 6 hours for 7 days is recommended for mild disease. Intravenous penicillin G 1.5 million units or ampicillin 0.5–1 g intravenously every 6 hours for 7 days are indicated in severe leptospirosis. Recently, a study demonstrated that intravenous ceftriaxone (1 g/day intravenously for 7 days) was equivalent to intravenous sodium penicillin G for treating acute severe leptospirosis. In this study, benefits of ceftriaxone included reduced frequency of administration and cost-effectiveness. In addition, it may be an alternative for patients with severe leptospirosis and penicillin allergies. As with other spirochete infections, a Jarisch-Herxheimer reaction can

develop after the initiation of antibiotic drug therapy. Thus, complications should be monitored closely during therapy (see Table 1-2).

Supportive therapy and close observation are important for detecting and treating complications of leptospirosis. Supportive care may require treatment of dehydration, hypotension, hemorrhage, and renal failure. Although renal manifestations spontaneously resolve in most cases, hemodialysis may be required. Vitamin K administration can be used to correct hypoprothrombinemia.

Prophylaxis with weekly oral doxycycline 200 mg is effective in preventing leptospirosis in people who have had significant short-term exposure in endemic areas, but not in preventing leptospiral infections in indigenous populations of a highly endemic area. In indigenous populations of highly endemic areas, oral doxycycline was effective in reducing clinical illness and mortality.

Cat-scratch Disease

Background

Cat-scratch disease (CSD) is a zoonotic bacterial infection caused by *Bartonella henselae*. Cat-scratch disease was initially described in 1950, but its infectious etiology was not appreciated until 1983 when small, pleomorphic organisms where isolated in the lymph nodes of afflicted patients. Initially, this disease was attributed to *Afipia felis*; however, serological and culture data have since identified *B. henselae* as the etiological agent in most cases of CSD.

Epidemiology and Microbiology

Bartonella species are small, weakly staining, gram-negative bacteria. The genus was expanded with the reclassification of organisms formerly of the genus *Rochalimaea*. Currently, 14 *Bartonella* species exist. *Bartonella henselae* (CSD), *Bartonella bacilliformis* (Carrion's disease), *Bartonella quintana* (Trench fever), *Bartonella elizabethae*, and *Bartonella clarridgeiae* currently are the known human pathogens. Cat-scratch disease is the most recognized manifestation of *Bartonella* infection in humans.

The domestic cat is the reservoir for *B. henselae* throughout the world. About 50% of cats show evidence of infection in some areas of North America. The organism is more often found in younger cats, especially males. The cat flea (*Ctenocephalides felis*) has been identified as a vector for cat-to-cat transmission; however, its role in human infection is unknown.

Cat-scratch disease occurs primarily in immunocompetent children and young adults, with the highest prevalence between 2 and 14 years of age. The occurrence of CSD is seasonal, with a peak distribution in fall and early winter. Cases are widely distributed throughout North America. In the United States, there are about 25,000 CSD cases annually, almost 10% of which result in hospitalizations each year. Risk factors for the disease include owning a cat, particularly one that is younger than a year old, and being scratched or bitten by a kitten that has fleas.

Clinical Manifestations/Laboratory Findings

Often, CSD manifests as a benign self-limited disease in about 90% of cases. Between 3 and 10 days after a scratch or bite, a 3–5-mm macule at the site of inoculation develops and may last for 1–3 weeks. All patients develop regional lymphadenopathy, typically within 2 weeks (range 1 to 7 weeks) that may persist for weeks to months. Fever (31–60%), malaise or fatigue (29–30%), headache (13–14%), and sore throat (10%) may accompany the lymphadenopathy. A transient rash may develop in about 5% of patients.

Although the typical manifestations in the vast majority of cases are benign, about 10% of patients experience atypical manifestations of CSD, which can be life-threatening. In these individuals, *B. henselae* disseminates, causing persistent systemic symptoms. The most common atypical manifestation of CSD is the Parinaud's oculoglandular syndrome. Other ocular complications include neuroretinitis, retinitis, macular exudates, and optic nerve swelling. Involvement of the CNS can include headache, encephalopathy, and seizures. Granulomatous hepatitis and osteolytic lesions also have been reported as atypical manifestations of CSD.

Cat-scratch disease may be acute or indolent in immunocompromised patients, with local or systemic complications. Atypical manifestations in immunocompromised patients may include the rare vasoproliferative disorders bacillary angiomatosis and bacillary peliosis.

Patients with CSD often develop transient leukocytosis, with increased neutrophil and eosinophils counts. Typically, the erythrocyte sedimentation rate is elevated in cases of CSD. However, laboratory findings are not particularly beneficial in patients with CSD encephalopathy. Elevations in CSF protein and leukocytes occur in only 33% of patients.

Laboratory Diagnostic Methods

The diagnosis of CSD is primarily based on clinical findings, and laboratory diagnostic tests are used to confirm the presence of infection. Serologic testing for *B. henselae* antibodies is the most widely used method to confirm the diagnosis of CSD. Immunofluorescence antibody assay and enzyme immunoassay are the two serological methods currently available. Histological examination may reveal *Bartonella* species with the use of the Warthin-Starry stain on tissue specimens. In addition, PCR assays are available in a few commercial laboratories.

Treatment

The role of antibiotic drug therapy depends on patients' immune status. In immunocompetent patients, CSD typically is self-limiting and not amenable to antibiotic drug therapy. However, in immunocompromised patients, CSD may be fatal if not treated. Most experience with antibiotic

Panaphut T, Domrongkitchaiporn S, Vibhagool A, Thinkamrop B, Susaengrat W. Ceftriaxone compared with sodium penicillin g for treatment of severe leptospirosis. Clin Infect Dis 2003;36:1507–13.

drug therapy in CSD is derived from case reports and retrospective analyses. Only one prospective, randomized, double-blind, placebo-controlled trial for treatment of typical CSD has been performed. In this small study, seven of 14 patients who received a 5-day course of azithromycin had an 80% or more decrease in lymph node size during the first 30 days after treatment compared with only one of 15 placebo recipients. However, after 30 days, there was no difference in adenopathy resolution between the two groups. Therefore, the recommended treatment of typical CSD is azithromycin orally 500 mg on day 1 and then 250 mg/day orally for 4 days (5 days total therapy) which may result in faster resolution of clinical manifestations for the first month. Whether longer treatment regimens would produce a more sustained effect is unclear.

Azithromycin, trimethoprim-sulfamethoxazole, rifampin, clarithromycin, doxycycline, ciprofloxacin, or gentamicin are reasonable choices for symptomatic patients who have acute or severe illness. Although in vitro data suggest β-lactam antibiotic drugs are active against *B. henselae*, clinical experience with these drugs has been disappointing.

There are no data regarding the benefit of specific antimicrobial drugs for treating immunocompetent patients with atypical CSD. Even with neurological complications, these patients should have a spontaneous resolution of symptoms, even without specific antibiotic drug therapy. In immunocompromised patients with atypical symptoms, most of the data regarding antibiotic drug therapy concern patients with bacillary angiomatosis and peliosis. These patients should receive erythromycin 500 mg orally 4 times/day or doxycycline 100 mg orally 2 times/day alone or in combination with rifampin 300 mg orally 2 times/day for at least 6–8 weeks. In the event of a relapse in an immunocompromised patient, therapy should be given for up to 6 months. Immunocompromised patients who experience multiple relapses should receive long-term suppressive therapy (see Table 1-2).

Brucellosis

Background

Brucellosis is a worldwide zoonosis caused by *Brucella* species. The first accurate description of the disease occurred during the Crimean War, but the causative pathogen was not identified until 1886 when *Brucella melitensis* was isolated from the spleens of patients with Malta fever. Since then, several different *Brucella* species have been identified, with four having moderate to significant human pathogenicity. Given its ease of aerosol transmission, *Brucella* species were studied as a possible biological weapon and became the first weaponized agent developed by the United States.

Epidemiology and Microbiology

Brucella species are small, nonmotile, aerobic, gram-negative coccobacilli. *Brucella* is divided into at least six species, with some species having several biovars. Four species are recognized as pathogens in humans. Of these, *B. melitensis* and *Brucella suis* are considered more virulent than *Brucella abortus* and *Brucella canis*.

Cases of brucellosis result from direct or indirect exposure to animals. *Brucella abortus* occurs primarily in cattle, but other hoofed animals indigenous to particular regions in the world may be important hosts. *Brucella melitensis* usually is found in goats and sheep, but also may arise from cattle or camels, particularly in the Middle East. The animal reservoir for *B. suis* varies across biovars. Most biovars are found in wild and domesticated swine, whereas one biovar has been found in reindeer and caribou. *Brucella canis*, the least common cause of human brucellosis, is found primarily in domesticated dogs. Once an animal develops brucellosis, it remain infected for life and sheds significant numbers of organisms in milk, urine, and placental fluid. Thus, human acquisition typically results from occupational exposure to animals or their infected fluids through a variety of modes (e.g., abrasions and cuts, inhalation, direct inoculation, and ingestion of unpasteurized dairy products).

Although brucellosis remains a major zoonosis worldwide, only about 100 cases are reported annually in the United States, largely because of the eradication or control of bovine brucellosis. Most cases involve *B. melitensis*, and are reported in California, Florida, Texas, and Virginia.

Clinical Manifestations/Laboratory Findings

The clinical manifestations of brucellosis are nonspecific. Unless treated, a characteristic rising and falling fever pattern occurs in all patients. Other prominent symptoms include sweats, malaise, anorexia, fatigue, weight loss, and depression. Symptoms may manifest abruptly or insidiously, but usually they develop over 2–4 weeks. Physical findings include a mild lymphadenopathy in up to 20% of cases and hepatosplenomegaly in about 33% of cases.

Brucellosis can affect any organ system of the body. Osteoarticular complications, especially sacroiliitis, are the most frequent problems and occur in up to 60% of cases. Other complications involving the bones and joints include arthritis, spondylitis, osteomyelitis, tenosynovitis, and bursitis. Brucellosis may occasionally involve the genitourinary system, in particular oorchitis is seen in about 20% of men. Neurobrucellosis, which usually presents as meningitis, is seen in less than 5% of cases. Less common neurological complications include encephalitis, myelitis-radiculoneuronitis, brain abscess, demyelinating syndromes, and meningovascular syndromes. Although *Brucella* species are a rare cause of endocarditis, this complication is responsible for the majority of brucellosis-related mortality. Pericarditis can manifest as the primary infection, or it can develop from endocarditis. Brucellosis commonly affects the liver, can cause abscesses and hepatitis, or can produce manifestations that mimic sarcoidosis. Neither cirrhosis of the liver nor significant alterations of liver function tests, typically occur with hepatic forms of brucellosis. Manifestations of pulmonary

Bass JW, Freitas BC, Freitas AD, et al. Prospective randomized double blind placebo-controlled evaluation of azithromycin for treatment of cat-scratch disease. Pediatr Infect Dis J 1998;17:447–52.

infections vary tremendously and symptoms may include bronchitis, bronchopneumonia, lung nodules, abscess, and pleural effusions. Routine laboratory studies are nonspecific and typically not helpful in recognizing the disease. The white blood cell count often is normal, but anemia, leucopenia, and thrombocytopenia are common.

Laboratory Diagnostic Methods

The diagnosis is made by isolation of the organism from cultures of blood, bone marrow, or other tissues. Several serological tests have been used to diagnose brucellosis. The serum agglutination test is the most widely applied. Other tests include complement fixation, Rose Bengal agglutination, antibrucella Coombs, and enzyme-linked immunosorbent assay. A PCR test also has been developed.

Treatment

Antibiotic drug therapy for *Brucella* infection relieves symptoms, shortens the illness duration, and reduces the incidence of infection. Tetracyclines are the most effective antibiotic drugs for treating brucellosis; however, combination therapy is recommended because relapse rates of single-drug regimens are unacceptably high. The recommended therapy for human brucellosis traditionally had been tetracycline 500 mg oral 4 times/day plus streptomycin 1 g/day intramuscularly for the first 3 weeks. Because doxycycline is equally active, dosed less frequently, and is associated with fewer GI side effects than tetracycline, it has become the preferred tetracycline antibiotic drug for treating brucellosis. Similarly, gentamicin has replaced streptomycin because of streptomycin's lack of availability. The preferred regimen consists of doxycycline 100 mg orally 2 times/day for 6 weeks with concurrent gentamicin 3–5 mg/kg/day divided every 8 hours for 2–3 weeks. An alternative regimen was recommended by the World Health Organization in 1986: doxycycline 100 mg orally 2 times/day plus rifampin 600–900 mg/day orally (15 mg/kg) for 6 weeks. A trial comparing regimens found them to be similarly efficacious in most patients with brucellosis; however, the doxycycline-rifampin combination was less effective in patients with spondylitis.

Treating *Brucella* infection during pregnancy requires alternative regimens. Rifampin 900 mg/day once for 6 weeks or the combination therapy with rifampin 900 mg/day once plus trimethoprim-sulfamethoxazole (5 mg/kg of the trimethoprim component 2 times/day) has been suggested to treat brucellosis during pregnancy.

To avoid the use of tetracyclines, oral trimethoprim-sulfamethoxazole (10–12 mg/kg/day of the trimethoprim component) plus rifampin (15–20 mg/kg/day of rifampin up to a maximum of 600 mg/day orally in two divided dosages) for 6 weeks has been suggested for use in children. An alternative regimen in children is the a combination of rifampin 15–20 mg/kg/day divided in two dosages for 6 weeks with gentamicin 5–6 mg/kg/day divided every 8 hours for the first 5 days.

Treating life-threatening complications of brucellosis, such as meningitis and endocarditis, requires prolonged therapy for 6–9 months, depending on response. In cases of endocarditis, valve replacement surgery often is required in addition to antibiotic drug therapy.

Therapy for brucellosis infections requires multidrug combinations and often aminoglycoside therapeutic drug monitoring; thus, pharmacists can play a role in dosing and adjusting the aminoglycosides. Therapeutic peak drug levels of 8–10 mcg/ml are needed for serious brucellosis infections while maintaining trough levels of less than 2 mcg/ml. The common use of rifampin in brucellosis therapy also provides a role for pharmacists. Adding rifampin to a patient's drug regimen requires surveillance for drug interactions and monitoring of low therapeutic index drugs (e.g., digoxin, theophylline, and warfarin) (see Table 1-2).

Q-fever

Background

The term Q-fever comes from a disease coined by Edward H. Derrick as query fever. This term was used to describe an outbreak of a febrile illness among abattoir workers in Australia in the mid-1930s. Derrick sent blood samples of these workers to F. Macfarlane Burnet and Mavis Freeman, who inoculated animals and first isolated the organism. Because the organism resembled a *Rickettsia* species they named it *Rickettsia burnetii*. Shortly thereafter, Harold Rae Cox and Gordon Davis discovered the "Nine Mile Agent" from ticks in Montana. They also described the agent as "rickettsia-like". Cox reproduced the disease in animals, but it was not characteristic of a typical RMSF, so he named it *Rickettsia diaporica*. However, on further study of both organisms, it was determined that the organisms were one in the same, and it was renamed *Coxiella burnetii* after the works of Cox and Burnet.

Epidemiology and Microbiology

Coxiella burnetii is a small pleomorphic intracellular gram-negative rod. The primary mode of entry into humans is through inhalation, but ingestion, contact with contaminated fluids, and even blood transfusions have been associated with infection. Once inside the body, *C. burnetii* enters monocytes and macrophages by passive diffusion. On entry into the cell, the organism resides in the acidic phagolysosome vacuoles where it proliferates. Two spore forms of *C. burnetii* exist, which are the small and large variants. The small variant resides extracellularly and is most likely responsible for the heartiness of the organism in the environment. The large variant is found intracellularly and is responsible for infections.

Q-fever is ubiquitous throughout all parts of the world, most likely because of the variety of reservoirs that carry the organisms. Q-fever reservoirs include arthropods, rodents, marsupials, cats, dogs, pigeons, ducks, turkey, deer, rabbits, and many other animals. Though there are many reservoirs, *C. burnetii* most often is found in goats, cattle, and sheep.

Ariza J, Gudiol F, Pallares R, et al. Treatment of human brucellosis with doxycycline plus rifampin or doxycycline plus streptomycin. A randomized, double-blind study. Ann Intern Med 1992;117:25–30.

Most animals are merely reservoirs for the organism, but humans are among the few animals that manifest symptoms after infection with *C. burnetii*. Female reservoirs are thought to carry the organism in their reproductive organs. Subsequently, *C. burnetii* infections are commonly associated with birthing animals and their offspring. Large amounts (10^9 organisms per gram of fluid) of *C. burnetii* have been detected in the amniotic fluid of birthing animals. Other hosts may shed the organism into their milk, urine, feces, and other excrement. The excretion of the organism coupled with its resistance to environmental stress make this organism an occupational hazard for those who come into contact with the infected (reservoir) animals.

Arthropod vectors are believed to be responsible for maintenance of the transmission cycle of *C. burnetii*. Although ticks can carry and transmit *C. burnetii* to humans, the role of the ticks in causing coxielliosis primarily is limited to infected ticks spreading *C. burnetii* among their animal hosts. Ticks become infected when a transient bacteremia occurs in the reservoir on which they are feeding. After ticks become infected, the organism proliferates in the midgut and may be shed by their urine or feces onto the skin of their reservoir or another previously uninfected host during their feeding process. Ticks also can pass *C. burnetii* transovarially to offspring. These modes allow *Coxiella* species to persist in the environment for long periods. Humans typically contact Q-fever from exposure to an infected reservoir. The first tick in which *C. burnetii* was isolated was *D. andersoni* (Rocky Mountain wood tick). Subsequently, in the United States, *C. burnetii* has been isolated form *Rhipicephalus sanguinesis*, *A. americanum*, *Ixodes dentatus*, and *Octobius magnini*.

Clinical Manifestations/Laboratory Findings

Q-fever often occurs in people who have continued contact with animals (e.g., farmers, veterinarians, and laboratory and slaughterhouse workers). Often, patients have an asymptomatic illness that does not require therapy or a self-limited febrile illness that can persist 1–3 weeks. Symptomatic infections are classified as either acute or chronic. Q-fever primarily is an acute disease that typically manifests as either pneumonia or hepatitis. Acute Q-fever pneumonia develops abruptly, with fevers, severe headaches, sweats, chills, myalgias, and pleuritic chest pain. This flu-like presentation occurs after 1–3 weeks of incubation. Q-fever pneumonia is an atypical pneumonia with a dry productive cough. The chest examination often is negative but may consist of crackles or even consolidation. The accompanying laboratory abnormalities are nonspecific and vary from case to case. The white blood cell count and liver functions tests may be elevated, and thrombocytopenia or thrombocytosis and hyponatremia can be present. About 50% of patients will have a microscopic hematuria. Another unusual finding of Q-fever pneumonia is the presence of autoantibodies (e.g., anticardiolipin and antimitochondrial antibodies). Patients also may develop pleural effusions and atelectasis, but chest radiographs often have variable findings. Acute Q-fever pneumonia is rarely fatal, but it can be in the presence of comorbid conditions.

Hepatitis accounts for more than 60% of the acute presentations of Q-fever. The disease manifests as an infectious hepatitis with elevated liver enzymes and hepatomegaly. The most common manifestation of the hepatitis is the presence of a nonspecific "doughnut granuloma" in the liver. The granuloma is made up of a dense fibrin ring within a lipid-filled vacuole. Q-fever hepatitis can develop in the presence of pneumonia and endocarditis, but in these cases the "doughnut granuloma" often is absent.

Chronic Q-fever typically manifests as endocarditis that primarily affects the aortic and mitral valves. Chronic Q-fever should be considered in cases of culture-negative endocarditis. The most common manifestations are clubbing, splenomegaly, hepatomegaly, elevated liver enzymes and erythrocyte sedimentation rate, and hypergammaglobulinemia. A vasculitic rash also occurs in about 20% of patients. The chronicity of the infection may produce an anemia. About 33% of patients with Q-fever endocarditis experience embolic events. Echocardiograms often are nonspecific, but may be helpful in a small number of patients. Q-fever carries an overall mortality rate of less than 10%, but relapses are quite common, especially in cases of endocarditis.

Because Q-fever infections commonly occur during pregnancy. Q-fever during pregnancy can result in premature births, abortions, and fatalities. Other complications of Q-fever include neurological impairments, aseptic meningitis, encephalitis, aneurysm infections, osteoarticular infections, and chronic fatigue syndrome.

Laboratory Diagnostic Methods

Q-fever can occur after exposure to only one organism; therefore, routine cultures are not recommended. Moreover, culturing of the organism requires a level III biosafety laboratory and special staining techniques; thus, the diagnosis of Q-fever is confirmed by serology. The two commercially available serological methods are compliment fixation and immunofluorescence antibody assay. Both methods detect the presence of immunoglobulin A, immunoglobulin G, and immunoglobulin M antibodies to *C. burnetii*. Patients typically seroconvert by week 3 of the disease; thus, presenting titers may be negative or inconclusive. Therefore, both acute and convalescent titers must be drawn. Because of the acute and chronic nature of Q-fever infections, phase II (acute) and phase I (chronic) antibodies may be present. The immunofluorescence antibody test is the preferred test because it only requires a small amount of antigen to be present. Acute anti-phase II antibody titers to greater than 1:200 for immunoglobulin G and greater than 1:50 for immunoglobulin M are considered diagnostic. Chronic anti-phase I antibodies also are measured. Titers of greater than 1:800 are diagnostic for

Langley JM, Marrie TJ, Covert A, Waag DM, Williams JC. Poker players' pneumonia. An urban outbreak of Q fever following exposure to a parturient cat. N Engl J Med 1988;319:354–6.

immunoglobulin G. Acute antibody titers gradually disappear over a couple of months, but the presence of persistent antibodies may be indicative of chronic infection. Therefore, follow-up serology is required to document that chronic Q-fever is not present.

Treatment

The primary treatment for acute Q-fever infections is doxycycline 100 mg orally 2 times/day for 14 days. Doxycycline reduces fever a half day faster than other antimicrobial drugs. Fluoroquinolones have been used with success for treating both acute and chronic Q-fever infections. Ofloxacin 400 mg orally 2 times/day for 14–21 days is effective in treating Q-fever. Levofloxacin and ciprofloxacin have in vitro activity, but there are few data describing their clinical use.

Macrolides also are effective for treating Q-fever. A study compared several macrolides to doxycycline, and although doxycycline reduced symptoms faster, there were no failures or relapses noted for either therapy. Clarithromycin demonstrated superior in vitro activity compared to erythromycin; thus, clarithromycin 500 mg orally 2 times/day may be an adequate alternative if doxycycline or the fluoroquinolones cannot be used. Trimethoprim-sulfamethoxazole has been used successfully to treat Q-fever in pregnancy and is a suitable option, especially during the first trimester. Although trimethoprim-sulfamethoxazole has successfully treated cases of Q-fever, doxycycline or a fluoroquinolone should still be considered first-line therapy for men and nonpregnant women.

Chronic Q-fever usually manifests as endocarditis. The fatality rate for untreated Q-fever endocarditis is more than 50%; therefore, adequate treatment is essential. Standard antimicrobial therapy for endocarditis is ineffective. Although monotherapy with doxycycline is an effective therapy for acute Q-fever, in chronic cases used alone, it is associated with more than 50% relapses. Thus, combination therapy with two drugs is recommended for treating Q-fever endocarditis. The preferred drugs are doxycycline in combination with hydroxychloroquine. This regimen was associated with a mortality rate of less than 5% and minimal relapses. The addition of hydroxychloroquine is thought to raise the environmental pH, which does not allow *C. burnetii* to proliferate. The regimen for this combination is doxycycline 100 mg orally 2 times/day and hydroxychloroquine 200 mg orally 3 times/day for 18 months. An alternative regimen is doxycycline 100 mg orally 2 times/day in combination with ofloxacin orally 200 mg 3 times/day for 3 years. This combination demonstrated similar efficacy to the doxycycline-hydroxychloroquine regimen, but the rate of relapse was more than 60%. Thus, it is considered a second-line therapy choice (see Table 1-2).

Symptoms usually decrease quickly once adequate therapy is initiated; however, relapses even with doxycycline and or combinations containing doxycycline can occur. Thus, careful monitoring of clinical response, longer treatment courses and even lifelong therapy could be considered in infections with Q-fever.

Parasitic Zoonoses

Parasitic zoonoses are a diverse group of infections that encompass several phyla, including Pentastomids, Nematodes, Trematodes, Cestodes, and Protozoa. Zoonotic parasites can cause disease directly in the host. In addition, they can be transmitted by animals, food and water sources, and arthropods. A complete discussion of parasitic zoonoses is beyond the scope of this chapter. Because infections due to pentastomids, nematodes, trematodes, and cestodes are somewhat rare in the United States, the remainder of the chapter is devoted to representative arthropod and animal-borne protozoan zoonosis.

Often, protozoa zoonoses are caused by gastrointestinal parasites, but because of their small size, unlike other parasites, they can infect a variety of host cells. Most protozoa require arthropod vectors, but *Giardia* and *Entamoeba histolytica* are two notable exceptions. These pathogens typically are acquired by the fecal-oral route. *Giardia* typically infect the brush border of intestinal epithelial cells, and are emerging as a significant cause of recurrent diarrhea. *Entamoeba histolytica* (Amebiasis) causes a variety of diseases ranging from chronic colitis with severe diarrhea to CNS, hepatic, or pulmonary abscesses.

Tick-borne Protozoal Zoonosis

Babesiosis

Background

Babesiosis, a malaria-like tick-borne illness is caused by an intraerythrocytic protozoa, is one of the most common infections worldwide among wild and domestic animals and is an emerging zoonosis in humans. Named for a Hungarian pathologist who first described the organism in 1888, human babesiosis is endemic in parts of the United States and Europe. The first human cases were reported in the former Yugoslavia in 1957 and in the United States almost 10 years later. Babesiosis also has been reported in subtropical areas, including the Canary Islands, China, Egypt, Mexico, South Africa, and Taiwan. Recently, in the 1990s, two previously unknown strains of *Babesia* species (WA-1 and MO-1) were identified in humans in Washington and Missouri.

Epidemiology and Microbiology

Babesia species are protozoa of the phylum *Apicomplexa*, class *Aconoidasida*, and order *Piroplasmida*. Morphologically, *Babesia* species can be oval, round, or pear-shaped, and vary in size between 1 micron and 5 micron. In vertebrate hosts, *Babesia* species enter erythrocytes and differentiate into trophozoites. These trophozoites reproduce asexually, forming 2–4 daughter cells known as merozoites that invade new erythrocytes and undergo additional asexual reproduction, subsequently

Raoult D, Houpikian P, Tissot HT, Riss JM, Arditi-Djiane J, Brouqui P. Treatment of Q fever endocarditis: comparison of 2 regimens containing doxycycline and ofloxacin or hydroxychloroquine. Arch Intern Med 1999;159:167–73.

leading to hemolysis. More than 100 *Babesia* species have been identified; however, only four have caused human disease.

Most cases in the United States are caused by *Babesia microti*. The recently discovered WA-1 and MO-1 strains have been reported much less frequently. *Babesia divergens* is not a common cause of babesiosis in the United States, but it is responsible for most reported cases in Europe. In the United States, most cases of human babesiosis are reported in the Northeast and Midwest. Reports in the Northeast occur in coastal areas and islands of Massachusetts, New York, Rhode Island, and in select areas of Connecticut. Reports of *B. microti* infection in the eastern United States have extended to Maryland, Virginia, Georgia, and New Jersey. In the Midwest, most *B. microti* infections have occurred in Minnesota and Wisconsin. The recent isolation of the MO-1 and WA-1 strains from humans may portend a new geographical distribution into the Central United States and West Coast. The isolation of MO-1 also is interesting in that it is closely related to *B. divergens*, which is not a common *Babesia* species in the United States.

Babesia species can use either vertebrate and nonvertebrate hosts, including mice, chipmunks, deer, rabbits, shrews, and voles to maintain their transmission cycles. In the United States, the white-footed mouse, *Peromyscus leucopus*, is the primary host, and in certain endemic regions, almost 70% may be infected with *B. microti*. *Ixodes scapularis* (black-legged tick) is the vector for *B. microti* in the northeastern United States. Ticks become infected during the larvae stage, and transmit *Babesia* species to each subsequent stage in their life cycle. Although all stages (larvae, nymph, and adults) of *I. scapularis* feed on humans, the nymphal stage primarily is responsible for human transmission of *B. microti*. An estimated 40% of *I. scapularis* nymphs are infected in endemic areas. The nymphs are only about 2 mm in length, so their bite often goes unnoticed.

Geographically, *I. scapularis* is widely distributed, and it is commonly found in the eastern, southeastern, and upper midwestern United States. Although *I. scapularis* is found in the southeastern United States, babesiosis is rarely reported in this region. The low incidence of babesiosis in this region has been attributed to *I. scapularis* primarily feeding on lizards, which are not suitable reservoirs for maintaining *B. microti* infection. The vectors and reservoirs for the newest strains of *Babesia*, WA-1 and MO-1, have not been identified.

Babesiosis occurs at any age, but patients older than 40 years of age have a higher risk for a more severe clinical disease. Men have a higher incidence of infection, accounting for 62% of cases. As with other tick-borne diseases, human babesiosis is reported mostly in summer months. Ninety percent of cases occur between June and August, with 43% of cases occurring in July.

Clinical Manifestations/Laboratory Findings

Similar to malaria, infection with *Babesia* species leads to hemolysis, which is responsible for the clinical manifestations of babesiosis. The severity of babesiosis is diverse and includes an asymptomatic disease, a mild flu-like illness, moderate illness, and a severe fulminating disease course that leads to prolonged illness or death. The severity of disease likely correlates with the level of parasitemia present. Studies have shown that most cases in the United States are asymptomatic. When symptoms occur, they typically begin gradually after an incubation period that can vary from 1 to 6 weeks. Common symptoms of babesiosis include fever (85%), fatigue (79%), chills (63%), and headache (39%). Rarely, other nonspecific symptoms (e.g., myalgia, anorexia, nausea, vomiting, cough, and sore throat) have been reported. In addition to a high fever, nonspecific physical findings include splenomegaly, hepatomegaly, and jaundice. Unlike other tick-borne illnesses, a rash is not usually seen in babesiosis.

Age and immune function appear to be important host determinants of disease severity. Patients older than 50, asplenic patients, those with human immunodeficiency virus infection or malignancy, or those taking immunosuppressive drugs are at greatest risk for severe babesiosis. Common complications in severe cases of babesiosis include acute respiratory failure (21%), disseminated intravascular coagulation (18%), congestive heart failure (12%), coma (9%), and renal failure (6%). In cases that require hospitalization, the mortality rate is between 5% and 9%.

Because symptoms are nonspecific, infection is difficult to recognize based solely on clinical findings. Therefore, laboratory findings also are important for diagnosing babesiosis. Because *Babesia* species are intraerythrocytic protozoans, laboratory findings of infection commonly include anemia, thrombocytopenia, and normal or slightly decreased white blood cell counts. Evidence of mild to severe hemolytic anemia may be present in addition to an elevated reticulocyte count, decreased serum haptoglobin, hyperbilirubinemia, and elevated lactate dehydrogenase. The erythrocyte sedimentation rate may be raised and the direct Coombs' test may be positive. Slight elevations in alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase also are common. Urinalysis may show proteinuria and hemoglobinuria.

Laboratory Diagnostic Methods

A definitive diagnosis of *babesiosis* is made by microscopic identification of *Babesia* species by Giemsa-stained blood films. To prevent false-negative results, multiple blood smears should be examined because few erythrocytes are infected in early stages of the disease. Polymerase chain reaction and serological testing for babesiosis also are available.

Treatment

Typically, cases of babesiosis are asymptomatic or associated with mild symptoms that resolve without pharmacological therapy. However, treatment is recommended for patients with significant symptoms or those who are elderly, splenectomized, or receiving immunosuppressive therapy. For many years, a combination of clindamycin and quinine for 7–10 days was recommended. The adult regimen was high-dose clindamycin (1200 mg intravenously every 12 hours or

600 mg orally every 6 hours) and quinine 650 mg orally every 8 hours. Children were given clindamycin 20 mg/kg/day in four divided dosages and quinine 25 mg/kg/day in three divided dosages. Although this regimen was effective, it produced significant drug-related toxicities, including diarrhea, hearing loss, tinnitus, and vertigo.

More recently, animal and human studies suggest that atovaquone plus azithromycin is an effective combination for treating babesiosis. This combination was compared to a combination of clindamycin and quinine in immunocompetent adults with nonlife-threatening babesiosis for 7 days. The resolution of parasitemia and symptoms was similar in both groups, but the atovaquone-azithromycin combination was safer and better tolerated. Compared to the clindamycin-quinine combination, the atovaquone-azithromycin regimen had fewer drug-related toxicities (15% vs. 72%). In addition, therapy had to be discontinued because of adverse drug reactions in significantly more patients receiving the clindamycin-quinine regimen. Thus, atovaquone 750 mg orally every 12 hours plus azithromycin 500 mg orally on day 1, followed by 250 mg/day orally for 6 days is the preferred regimen for treating babesiosis (see Table 1-2).

Exchange transfusions may be lifesaving procedures for patients with severe babesiosis. When used in conjunction with antibiotic drug therapy, exchange transfusions reduce parasitemia and remove babesial-, erythrocyte-, and macrophage-produced byproducts. Exchanges usually are reserved for cases involving profoundly ill patients with significant parasitemia (more than 5%) and either coma, hypotension, congestive heart failure, pulmonary edema, or renal failure.

Animal-borne Protozoal Zoonosis

Cryptosporidiosis

Background

Cryptosporidiosis is caused by *Cryptosporidium*, an intracellular protozoan parasite, and is associated with enteric infection in numerous birds, fish, reptiles, and mammals. This parasite is recognized as a primary cause of outbreaks, as well as sporadic cases of diarrhea in humans and animals. The first description of the disease occurred in 1907 when it was recognized in the stomachs of autopsied mice. The disease was thought to be insignificant for almost 50 years until it was linked to a GI disease in young turkeys in 1955. Interest in the disease was intensified in 1971 when it was identified as the cause of diarrhea in cattle. Several years later the first human cases occurred in an immunocompetent child and an immunosuppressed adult. Sporadic human cases were reported over the next few years until the early 1980s, when the number of human cases increased dramatically with the onset of the acquired immune deficiency syndrome (AIDS) epidemic. Cryptosporidiosis also has become a common cause of water-borne diarrhea. In 1993, about 400,000 residents of Milwaukee, Wisconsin, became infected from a faulty water treatment facility. This and other outbreaks have raised public health concerns for the disease.

Epidemiology and Microbiology

Cryptosporidium is in the phylum Apicomplexa, class Sporozoasida, subclass Coccidiasina, order Eucoccidiida, suborder Eimeriina, and family Cryptosporiidae. *Cryptosporidium parvum* is the most common species identified in humans and accounts for 97% of infections. *C. parvum* is divided into two major genotypes, each with unique transmission cycles and epidemiology. Genotype 1 appears to be transmitted from human to human, whereas genotype 2 has a wide zoonotic range which includes humans. Recently, newer species have been identified in humans. Humans become infected when as few as 10–100 oocysts are ingested. Oocysts undergo excystation in the GI tract and release infective sporozoites that attach to the epithelial cell wall. The sporozoites mature and undergo asexual reproduction into meronts, which release merozoites into the intestinal lumen. These can either reinvade host cells or mature into gametocytes. After fertilization occurs in the intestine, the life cycle is repeated. Newly formed oocytes can undergo excystation within the host GI tract (autoinfection) or can pass out into the environment.

Cryptosporidiosis is acquired through person-to-person contact, and environmental (i.e., contaminated food and water sources) and zoonotic transmission. Transmission between household and personal contacts, children and caretakers in day care centers, sexual partners, and patients and health care workers has been well established. Zoonotic transmission may occur from household pets, as well as laboratory and farm animals. More than 150 different mammalian species have been infected with *Cryptosporidium* species, with zoonotic transmission from cattle and sheep to humans having been well described. These animals currently are considered the most important reservoirs for *Cryptosporidium* species. Water-borne transmission is probably the most common mode of acquiring cryptosporidiosis. Drinking water usually becomes contaminated through contaminated surface waters. Human and cattle effluents are probably the most common source of surface water and environmental contamination. Outbreaks also have been associated with exposure to chlorinated pools and sprinkler systems. Person-to-person transmission usually occurs directly through the fecal-oral route or indirectly by fomites. In addition, several food outbreaks have been documented involving fresh-pressed cider, improperly pasteurized milk, chicken salad, uncooked green onions, and fresh vegetables.

Cryptosporidiosis has been reported in more than 40 countries on six continents in both immunocompetent and immunocompromised patients. *Cryptosporidium* infection is most common in developing countries with poor sanitation. About 6.1% of immunocompetent individuals with diarrhea in developing countries have *Cryptosporidium* infection compared with 2.2% of immunocompetent people in developed countries. Serological studies indicate that about 65% of children living in rural China experience cryptosporidial infection by 8–10 years of age, and as many as 90% of children in Northeast Brazil were seropositive by the end of their first year of life. Serology indicates that

Krause PJ, Lepore T, Sikand VK, et al. Atovaquone and azithromycin for the treatment of babesiosis. N Engl J Med 2000;343:1454–8.

20% of the United States population experiences cryptosporidial infection by young adulthood. Cryptosporidiosis is more common in immunosuppressed patients, especially patients with AIDS, than in immunocompetent individuals. In patients who are positive for human immunodeficiency virus and have diarrhea, the percentages of infected patients are 24% and 14% in developing and developed countries, respectively.

Cryptosporidiosis is seasonal, seen more commonly during wet seasons in tropical areas. People at the highest risk of cryptosporidiosis include travelers to highly endemic areas, household or family contacts of infected patients, health care employees, users of community swimming pools, sexual partners of infected patients, and immunosuppressed people.

Clinical Manifestations/Laboratory Findings

Cryptosporidiosis most commonly affects the intestinal tract. The length and severity of clinical symptoms depend primarily on patients' immune status. Immunocompetent patients typically have a milder disease course than immunocompromised patients. Immunocompetent individuals usually experience asymptomatic or self-limiting disease involving the intestine. The three major clinical presentations for immunocompetent individuals are asymptomatic carriage, acute diarrhea, and persistent diarrhea. The interval between ingestion of oocysts to the development of symptoms is 7–10 days (range of 5 to 28 days). Greater than 90% of patients present with acute watery diarrhea. Diarrhea may be transient, intermittent or continuous, and scant or voluminous (as much as 12–17 L/day). The diarrhea may contain mucus, but rarely blood or leukocytes. Abdominal pain (84%), weight loss (75%), and fever (57%) were the most commonly reported symptoms in the Milwaukee outbreak. Malaise, weakness, fatigue, loss of appetite, and nausea and vomiting also may accompany diarrhea. Symptomatic immunocompetent individuals usually experience full spontaneous recovery in about 2 weeks and clearing of parasites within a few months; however, cases of diarrhea persisting from 42 to 85 days have been reported in these patients. Evidence suggests that cryptosporidiosis in immunocompetent children in developing countries may have lasting effects on nutritional status and growth.

Immunocompromised patients are more likely to have a longer, more severe illness. In addition, they experience extraenteric manifestations more often. Patients with AIDS are the most common group of immunocompromised patients affected by cryptosporidiosis and may experience a wide spectrum of disease. There are four clinical patterns of cryptosporidiosis in patients with AIDS. Asymptomatic infection, where there is no change in bowel patterns and fewer than three stools a day, is seen in 4% of patients with AIDS. Transient disease, where diarrhea lasts less than 2 months and there is a complete remission of symptoms and loss of parasites in stool samples, is seen in 29% of patients with AIDS. Chronic diarrhea, defined as diarrhea lasting more than 2 months and persistence of parasites in stool or on biopsy, is seen in 69% of patients with AIDS. Finally, about 8% of patients with AIDS may experience fulminate infection, where they produce more than 2 L of watery stool a day. Patients with AIDS who have *Cryptosporidiosis* may lose as much as 10% of body weight and experience severe malabsorption. Most patients will never completely clear the infection.

Many extraenteric manifestations of cryptosporidiosis have been reported, including cholecystosis, cholangitis, hepatitis, pancreatitis, reactive arthritis, and respiratory tract involvement. Biliary tract involvement is the most common extraintestinal manifestation of infection and was seen in as many as 26% of patients with AIDS with intestinal cryptosporidiosis before the introduction of highly active antiretroviral therapy. Symptoms include right upper quadrant pain, nausea, vomiting, and fever. Alkaline phosphatase and bilirubin levels may be elevated. Pulmonary involvement is rare, but nonspecific respiratory symptoms including cough, dyspnea, fever, and thoracic pain may occur. There are no characteristic laboratory findings associated with cryptosporidiosis.

Laboratory Diagnostic Methods

The diagnosis of *Cryptosporidium* infection is most commonly established by the detection of organisms in stool specimens. In addition, the organisms also may be found in biopsies of the GI tract, respiratory secretions, and bile. The modified acid-fast staining of the organism is the simplest method of identifying oocysts. *Cryptosporidium* also can be seen using hematoxylin and eosin, Giemsa, or malachite green staining. Other diagnostic methods include direct or indirect immunofluorescence microscopy and enzyme-linked immunosorbent assay. Because many healthy people have cryptosporidium antibodies, serology is not particularly useful in identifying active infection.

Treatment

There is no dependable antimicrobial drug therapy for cryptosporidiosis. Because the clinical course depends primarily on the individual's immune status, treatment options vary. Immunocompetent patients usually experience spontaneous recovery within a few weeks and do not require specific therapy. Antidiarrheal drugs may provide temporary relief for infected individuals, whereas supportive care with fluid and electrolyte replacements helps correct dehydration and electrolyte abnormalities that accompany diarrhea. Although antidiarrheal drugs reduce the symptoms, they also prevent the excretion of the oocysts which may prolong or mask the disease process. Thus, the routine use of antidiarrheal drugs is not recommended and if the diarrhea persists despite antidiarrheal therapy, patients should be referred to their physician for further evaluation.

Cryptosporidium infection can be life-threatening in immunocompromised patients. Improvement of immune function with highly active antiretroviral therapy is the best therapy for patients with AIDS with cryptosporidiosis. Reduction in viral load with a concomitant rise in CD4 counts have resulted in rapid improvement in symptoms and a reduction of oocyst excretion. If highly active retroviral therapy is not effective or feasible, a combination of an antidiarrheal drug of limited duration and antimicrobial drug therapy should be initiated. Numerous drugs with activity against parasites have been tried with limited success. These drugs included atovaquone,

chloroquine, difluoromethylornithine, mefloquine metronidazole, quinine, pyrimethamine, and trimethoprim-sulfamethoxazole. The greatest experience is with paromomycin. This poorly absorbed aminoglycoside antibiotic drug is widely used as first-line therapy, although it only provides temporary improvement in symptoms and decreases in oocyst excretion. Paromomycin typically is difficult to obtain and must be specially ordered; thus, its use is limited. The dose of paromomycin is 1 g orally 2 times/day for 7–14 days. It may be used in combination with azithromycin 600 mg/day orally.

One of the newest chemotherapeutic drugs to be studied for treating cryptosporidiosis is nitazoxanide, an inhibitor of pyruvate ferredoxin oxidoreductase. A 3-day course significantly reduced the duration of diarrhea and the intensity of oocyst shedding in immunocompetent adults and children, and is indicated for treating cryptosporidiosis in immunocompetent children younger than12 years of age. The dose of nitazoxanide is 500 mg/day orally for 3 days. In addition, small studies has demonstrated efficacy of nitazoxanide in adults with human immunodeficiency virus, but longer treatment courses are recommended (i.e., 14 days). Furthermore, clinical trials with this drug as monotherapy and in combination with other drugs in immunocompetent and immunocompromised patients with *Cryptosporidium* infection are needed (see Table 1-2).

Conclusion

Zoonoses are distributed throughout the United States and the world; thus, they contribute a significant source of infection in humans. Pharmacists are accessible and often make up the front line of health care professionals who patients afflicted with these infections contact for advice on treatment remedies. Although, not all zoonoses are fatal, they can cause significant morbidity and mortality if left untreated. Therefore, pharmacists must have an understanding of the epidemiology and common manifestations associated with zoonoses, particularly those that are common in their locality. Having this understanding enables pharmacists to effectively counsel the patient and recommend appropriate preventive measures.

Many zoonoses are subtle in their presentation. When patients go to a medical facility, a recollection of tick, mosquito, or other environmental exposure may or may not be apparent, and manifestations and laboratory findings of the infection are nonspecific or even lacking. Most zoonoses are diagnosed based on clinical findings obtained from a thorough history and physical examination coupled with a high clinical suspicion. Because the manifestations of many zoonoses are so subtle and variable, if the infection is amenable to pharmacological therapy, early empiric treatment of these infections is critical and will significantly reduce any associated morbidity and mortality. For those zoonoses that are not amenable to therapy, an understanding of measures to limit or prevent exposure is critical.

Annotated Bibliography

Viral Encephalitities

1. Soloman T. Flavivirus encephalitis. N Engl J Med 2004;351:370–8.

   Because of the recent outbreaks of West Nile virus in the United States, arboviruses have made a resurgence into the medical literature. This article provides a concise review of arboviral causes of encephalitis. The author reviews the epidemiology, pathogenesis, clinical features, diagnosis, and treatment of West Nile virus and other medically important arboviruses. The author distinguishes the similarities and differences of each virus as well as how they interplay with one another. The review provides a clear, concise clinical picture of *Flavivirus encephalitis*. The article also supplies the reader with the most efficient laboratory techniques for diagnosis of arboviral encephalitis. The review concludes with the present and future of vaccine development and the current use of vaccine. Overall, this is a well-written summary of arboviral encephalitis that is easy to follow and not too cumbersome.

Rabies

2. World Health Organization. Rabies Web page. Geneva, Switzerland: World Health Organization, 2004. Available at *http://www.who.int/rabies/en/*. Accessed March 16, 2005.

   The World Health Organization rabies Web site provides a plethora of information on rabies, including links to other working documents and informational sources. The most helpful pages for pharmacists are under the subsection of "human rabies" (click on the "postexposure prophylaxis" link). This page provides information on the rabies vaccine, including administration instructions and guidelines for people who should be vaccinated. At the bottom of this page is a link to "guide for postexposure prophylaxis", which provides more in-depth information about each vaccine and its respective regimen, both intramuscular and intradermal. At the bottom of this page is a link to the "current World Health Organization guidelines for rabies pre- and postexposure treatment in humans." This document is a comprehensive resource for rabies treatment decisions, vaccination schedules, injection sites, use of immunoglobulin, and discussion on which schedule and vaccine to use. The document is cumbersome to retain on hardcopy, but is easily accessible through the Web site. The quick links help readers navigate this large document. The Web site is the most all-encompassing piece of literature available and is an excellent place to start a search for any topic pertaining to rabies and its treatment.

Tick-borne Bacterial Diseases

3. Donovan BJ, Weber DJ, Rublein JC, Raash RH. Treatment of tick-borne diseases. Ann Pharmacother 2002;36:1590–7.

   This review discusses several of the most prominent tick-borne bacterial infections (ehrlichia, Rocky Mountain

White AC Jr, Chappell CL, Hayat CS, Kimball KT, Flanigan TP, Goodgame RW. Paromomycin for cryptosporidiosis in AIDS: a prospective, double-blind trial. J Infect Dis 1994;170:419–24.

Rossignol JF, Ayoub A, Ayers MS. Treatment of diarrhea caused by *Cryptosporidium parvum*: a prospective randomized, double-blind, placebo-controlled study of Nitazoxanide. J Infect Dis 2001;184:103–6.

spotted fever [RMSF], and Lyme disease) in the United States. The article provides a concise overview, diagnosis, manifestations, prevention, and treatment for each infection. This review contains a useful table that summarizes the manifestations and treatment of pediatric and adult Lyme disease. In addition, there is a good table that differentiates the manifestations RMSF compared to human ehrlichiosis. Addressing all of the tick-borne bacterial diseases was beyond the scope of this manuscript, and the authors did well in reviewing the key infections. Nonetheless, the lack of discussion concerning tularemia is a significant omission to an otherwise outstanding review. The review was written by pharmacists and would be a valuable piece to have on hand.

Lyme Disease

4. Wormser GP, Nadelman RB, Dattwyler RJ, et al. Practice guidelines for the treatment of Lyme disease. Clin Infect Dis 2000;31(suppl 1):S1–S14.

These practice guidelines issued by the Infectious Diseases Society of America in 2000 represent the first evaluation of Lyme disease treatments using a disciplined, systematic, rules-of-evidence approach to the published literature and are meant to complement existing practice standards. A panel of 12 infectious diseases specialists participated in developing the recommendations. These guidelines cover a range of presentations, including tick bites and prophylaxis, early Lyme disease, Lyme arthritis, late Lyme disease, and chronic Lyme disease or post-Lyme disease syndrome, with evidence and treatment recommendations for each stage of illness. In addition to treatment recommendations, the expert panel concluded that there was insufficient evidence to regard "chronic Lyme disease" as a separate diagnostic entity. Thus, this is a comprehensive document that thoroughly covers Lyme disease in its entirety. The document is an advanced read for the generalist, but it is informative and will systematically lead the reader through the history and epidemiology to diagnosis and treatment of disease. The document is geared toward an infectious diseases physician, but it is a great comprehensive review.

Leptospirosis

5. Bharti AR, Nally JE, Ricaldi JN, et al. Leptospirosis: a zoonotic disease of global importance. Lancet Infect Dis 2003;3:757–71.

This is an excellent, comprehensive review of leptospirosis recently written on behalf of the Peru-United States Leptospirosis Consortium. The authors review the microbiology, taxonomy, epidemiology, pathogenesis, clinical features, diagnosis, treatment, and prophylaxis of leptospirosis. The treatment section, which is complete and thorough, includes a discussion of appropriate antibiotic drug therapy for treating both mild and severe leptospirosis. Descriptions of relevant clinical trials and a Cochrane review of antibiotic drug therapy for leptospirosis are discussed. The evidence for preventing leptospirosis with antibiotic drugs is reviewed, and the difficulties involved in vaccine development are discussed. The review is a great resource for a clinician to have on hand.

SELF-ASSESSMENT QUESTIONS

1. A 25-year-old man comes to your pharmacy complaining of fever, headaches, and a rash on his arms and the palms of his hands. His only pertinent history is a recent camping trip in the eastern Smoky Mountains. He denies any tick bites and is unaware of any tick exposures. Based on the preceding information, which one of the following is the most likely diagnosis?

   A. Human monocytic ehrlichiosis.
   B. Rocky Mountain spotted fever (RMSF).
   C. Lyme disease.
   D. Human granulocytic ehrlichiosis (HGE).

2. A 37-year-old plumber comes to your clinic with a flu-like illness. His only significant history was climbing through a crawl space under an abandoned building. He mentioned some exposure to rodents, cockroaches, and maggots, but no history of bites or any frank contact with these pests. He complains of high-grade fevers (higher than 39°C), myalgias, vomiting, and upset stomach. Laboratory values are normal and the patient is given a fluid bolus and sent home. Several days later, the patient goes to the emergency department with a productive cough, tachypnea, tachycardia, and worsening gastrointestinal complaints. The patient's condition rapidly declines, he becomes hypoxic, and is intubated. He is empirically started on piperacillin-tazobactam 3.375 mg every 4 hours, gatifloxacin 400 mg/day, and vancomycin 1 g every 12 hours. Laboratory values demonstrate an elevated white blood cell count of 26,000 cells/mm^3 with a marked left shift, severe thrombocytopenia, and an elevated hematocrit. The chest radiograph shows interstitial edema with pleural effusions. The patient becomes hypotensive, goes into shock, and later dies of multisystem organ failure. Which one of the following is the most likely viral zoonosis responsible for the clinical manifestations in this case?

   A. Rabies virus.
   B. Cryptosporidiosis.
   C. Hantavirus.
   D. Q-fever.

3. A 26-year-old Caucasian man returns from a summer camping trip in Glacier National Park in Montana. He reports sleeping in a tent that he carried with him. Three days after returning home, he experienced fever, headache, and back and leg pain, but no rash. He found an attached "brown tick", which was later identified as *Dermacentor andersoni* (Rocky Mountain wood tick). He was started on doxycycline for possible RMSF. Initially, his symptoms resolved but returned again 3 days later. Physical examination is unremarkable, except for a fever of 39°C. Laboratory analysis was only significant for leukopenia, with a white blood cell count of 2.2 cells/mm^3. Which one of the following tick-borne illnesses does this patient likely have?

   A. St. Louis encephalitis (SLE).
   B. Tick-borne relapsing fever (TBRF).
   C. Colorado tick fever (CTF).
   D. Lyme disease.

4. J.R. is a 39-year-old banker who is taking a vacation with his family (wife and two teenagers) and will be camping at a national park with a large lake. The campgrounds are situated on the shore of the lake. He states that he and his family will go on several of the park's world famous hiking trails for round-trip hikes lasting 4–6 hours. Which one of the following concentrations of N,N-diethyl-meta-toluamide

(DEET)-containing products should you recommend to provide the best protection from mosquitoes?

A. Products containing 23.8% or 20% DEET.
B. Products containing 6.65% DEET.
C. Products containing 4.75% DEET.
D. Products without DEET but with 2% soybean oil.

5. An 8-year-old girl is awakened by a noise in her room. She looks around to find a bat perched on the head of her bed. She screams for her father and he swats the bat with a tennis racket, knocking the bat against the wall and subsequently to the floor. He removes the bat from the room and they all go back to sleep. Based on this scenario, which one of the following statements is most correct?

A. The girl and the father should seek immediate medical attention for rabies.
B. Only the father should seek immediate medical attention for rabies.
C. Only the girl should seek immediate medical attention for rabies.
D. The girl, the father, and anyone else in the house at the time should seek immediate medical attention for rabies.

6. A 67-year-old woman was gardening at her home in North Carolina. Several days after gardening, she noticed several bites marks, but no attached ticks. She figured she was bitten by mosquitoes and continued about her day. A few days later, she awoke with a fever, severe headache, and a spotty rash near one of the bite sites. Her husband drives her to the emergency department and they give this history. Which one of the following best describes this woman's diagnosis?

A. Human granulocytic ehrlichiosis.
B. Tularemia.
C. Lyme disease.
D. Rocky Mountain spotted fever.

7. A 4-year-old boy arrives at the emergency department with vomiting, chills, and high-grade fevers (38.8°C). Vital signs include: pulse of 66 beats/minute, respiratory rate of 18 breaths/minute, blood pressure of 130/76 mm Hg, and current temperature of 39.2°C. Physical examination reveals an inflamed right inguinal lymph node that is nonfluctuant. After further investigation, you discover a red-purple lesion in the patient's scrotal area. Which one of the following is the most likely cause of this illness?

A. Rocky Mountain spotted fever.
B. Human ehrlichiosis.
C. Lyme disease.
D. Tularemia.

8. A 7-year-old girl from Arkansas is complaining of nausea, vomiting, high fever, and chills. Her history was remarkable for a tick bite on her right axilla several days ago. Physical examination was remarkable for a pulse temperature disparity, regional lymphadenopathy, and a small painful papule near the site of the tick bite. The physician suspects tularemia and decides to treat her. Which one of the following regimens should be recommended for this patient?

A. Doxycycline 4.4 mg/kg/day divided 2 times/day on day 1 and then 2.2 mg/kg/day for 7–14 days.
B. Ciprofloxacin 15 mg/kg orally 2 times/day for 7–14 days.
C. Gentamicin 3 mg/kg every 8 hours for 7–14 days.
D. Ceftriaxone 50 mg/kg/day for 7–14 days.

9. A 6-year-old boy from Connecticut is seen in the emergency department. His mother states that he was fine until about 5 days ago when he developed a subjective fever. Other complaints include a headache and stiff neck. He has no known drug allergies and his mother has been giving him acetaminophen for his fever. Currently, his temperature is 38.6°C. Physical examination is unremarkable except for a 6- by 10-cm erythematous lesion with central clearing located on his back. Which one of the following diagnoses is the most consistent with this patient's case?

A. Disseminated Lyme disease.
B. Persistent Lyme disease.
C. Q-fever.
D. Early localized Lyme disease.

10. A 4-year-old girl from Rhode Island is seen in the emergency department. Her father states she was fine until yesterday when she developed a fever, experienced fatigue, and complained of pain in her joints. Her history was remarkable for a tick bite on her left axilla a week ago. Physical examination revealed an otherwise healthy girl with 4- by 8-cm macular rash with a developing zone of clearing in the center. The physician suspects early localized Lyme disease and decides to treat her. Which one of the following regimens should be recommended for this patient?

A. Amoxicillin 50 mg/kg/day orally divided in three dosages for 14–21 days.
B. Azithromycin 10 mg/kg/day orally for 7–10 days.
C. Cefuroxime axetil 30 mg/kg/day orally in divided dosages for 14–21 days.
D. Doxycycline 1–2 mg/kg orally 2 times/day for 14–21 days.

11. A 36-year-old man from Wisconsin goes to the emergency department with pain and swelling of the right knee over the past week. He has no significant past medical history and no known drug allergies. On examination of his knee, a small effusion was noted without redness or warmth. Aspiration of the knee revealed a white blood cell count of 24,000 cells/mm^3 and elevated protein. Serology was positive for *Borrelia burgdorferi* in both synovial fluid and serum. Which one of the following is the most likely diagnosis and best treatment for this patient?

A. Lyme arthritis treated with amoxicillin 500 mg orally 3 times/day for 14 days.
B. Disseminated Lyme disease treated ceftriaxone 2 g/day intravenously for 14 days.

C. Localized Lyme disease treated clarithromycin 500 mg orally 2 times/day for 28 days.
D. Lyme arthritis treated doxycycline 100 mg orally 2 times/day for 28 days.

12. A 62-year-old man from California went to the emergency department with a fever and a 3-day history of headache, stiff neck, nausea, and new-onset left facial drop. He was seen by his primary care physician 3 weeks ago and found to have erythema migrans, but he refused treatment. He has no known drug allergies. Analysis of his spinal fluid reveals an elevation in total protein at 260 mg/dl and an elevated white blood cell count at 200 cells/mm^3 (90% lymphocytes). Serology was positive for B. burgdorferi in both the serum and the spinal fluid. Which one of the following is the patient's most likely diagnosis?

A. Early localized Lyme disease.
B. Early disseminated Lyme disease.
C. Persistent Lyme disease.
D. Late disseminated Lyme disease.

13. A 50-year-old woman from Connecticut goes to the emergency department with multiple rashes that evolved and now look like a bull's-eyes, and bilateral facial palsy. She stated that initially a single bull's-eye rash developed on her left leg where she had removed multiple ticks several weeks ago shortly after she went hiking in the woods. However, now she has noticed the development several other similar but smaller rashes on her other extremities and back. In addition, during the past week, she has had a persistent headache and a stiff neck and has felt fatigued. She states that until now she had not sought medical attention for her symptoms because she thought they would just go away. A lumbar puncture for cerebrospinal fluid (CSF) analysis revealed pleocytosis. The physician suspects early disseminated Lyme disease and decides to treat her. Which one of the following regimens should be recommended for this patient?

A. Amoxicillin 500 mg orally 3 times/day for 14 days.
B. Ceftriaxone 2 g/day intravenously for 14 days.
C. Cefuroxime axetil 500 mg orally 2 times/day for 14 days.
D. Doxycycline 100 mg intravenously 2 times/day for 14 days.

14. A 54-year-old man from Colorado was seen in the emergency department after a 3-day history of fever, headache, arthralgias, and myalgia. After developing a petechial rash, he decided to come to the hospital. He recently returned from a trip where he had been hiking and stayed in an old mountain cabin. No diagnosis was made in the emergency department, and he was sent home. After initially improving, his fever returned and he went back to the emergency department. Laboratory analysis was normal except for a mild thrombocytopenia. Microscopic analysis of the patient's blood demonstrated spirochetes. Given his clinical presentation, which one of the following is the best treatment at this time?

A. Ceftriaxone 2 g/day intravenously for 14 days.
B. Doxycycline 100 mg orally 2 times/day for 10 days.
C. Erythromycin 500 mg orally 4 times/day for 10 days.
D. Penicillin G 3 million units intravenously every 4 hours for 10 days.

15. A 26-year-old Caucasian man from Illinois was seen in the emergency department with abrupt onset of fever, headache, myalgias, anorexia, nausea, vomiting, and jaundice for 3 days. A week before he became ill, he reports he swam in a lake while training for a triathlon. The patient has no significant past medical history and is allergic to penicillin. His temperature was 38°C, his heart rate was 105 beats/minute, and his blood pressure was 90/62 mm Hg. On physical examination, he was jaundiced with a conjunctival suffusion. His liver was enlarged and his spleen was not palpable. Laboratory analysis reveals elevated aspartate aminotransferase (140 IU/L), alanine aminotransferase (100 IU/L), total bilirubin (23.8 mg/dl), creatine phosphokinase (1766 U/L), blood urea nitrogen (100 mg/dl), and serum creatinine (6.0 mg/dl). White blood cell count was elevated at 15,000 cells/mm^3. The patient was diagnosed with Weil's disease. Which one of the following regimens is the best treatment for this patient?

A. Amoxicillin 500 mg orally every 6 hours for 7 days.
B. Ceftriaxone 1 g/day intravenously for 7 days.
C. Doxycycline 100 mg orally 2 times/day for 7 days.
D. Penicillin G 1.5 million units intravenously every 6 hours for 7 days.

16. A 5-year-old boy from Arkansas was admitted to a hospital having fever for 10 days (up to 40°C). The child was scratched by a kitten 3 weeks before the onset of illness. His mother reports no significant medical problems and states that he has no known drug allergies. Physical examination was normal except for a 2- by 3-cm right inguinal lymph node. Laboratory analysis revealed only an elevated white blood cell count at 17,000 cells/mm^3. Immunofluorescence antibody assay immunoglobulin G titer for Bartonella henselae was 1:4000. Which one of the following is the patient's most likely diagnosis?

A. Q-fever.
B. Hantavirus.
C. Cat-scratch disease (CSD).
D. Rabies.

17. A 14-year-old previously healthy girl with normal immune function goes to her primary care physician in early December. She is afebrile, and complains of fatigue, a headache, and a sore throat. She also states that about 1 week ago, while playing with the family cat, she sustained several scratches on her left arm. Physical examination revealed swollen lymph nodes and several small (about 3 mm) macules on the left arm.

Blood samples for serological analysis were obtained and the physician suspects CSD and decided to treat her. Which one of the following regimens should be recommended for this previously healthy immunocompetent patient?

A. Azithromycin orally 10 mg/kg on day 1 and 5 mg/kg orally on the subsequent 4 days.
B. Ceftriaxone 1 g/day intravenously for 7 days.
C. Gentamicin 2 mg/kg/dose every 8 hours intravenously for 7 days.
D. Erythromycin 500 mg orally 4 times/day plus rifampin 300 mg orally 2 times/day for 6 weeks.

18. A 6-year-old girl was seen in the emergency department with a 2-week history of sore throat, fever, sweating, headache, and anorexia. Her mother reports that she has had a 5-pound weight loss in the past 2 weeks. The family had just moved to the United States in the past week from Kuwait. Her medical history is unremarkable and she has no known drug allergies. In Kuwait, she lived on a farm and consumed unpasteurized goat's milk. At admission, her temperature was 38.9°C, her heart rate was 108 beats/minute, and her blood pressure was normal. Physical examination revealed erythematous oropharynx, cervical adenopathy, right upper quadrant pain, hepatomegaly, and splenomegaly. Laboratory analysis revealed elevated aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase. Which one of the following regimens is the best treatment for this patient?

A. Doxycycline 100 mg orally 2 times/day plus rifampin 15 mg/kg/day orally for 6 weeks.
B. Doxycycline 100 mg orally 2 times/day for 6 weeks plus streptomycin 1 g/day intramuscularly for the first 14–21 days.
C. Rifampin 900 mg/day orally once for 6 weeks.
D. Trimethoprim-sulfamethoxazole (10–12 mg/kg/day of the trimethoprim component) plus rifampin (15–20 mg/kg/day) for 6 weeks.

19. A 46-year-old man is seen in the emergency department with a 6-day history of fever, sweats, and severe lumbar pain. In addition, he complains of a swollen and painful left testicle. The patient had recently moved to the United States from Peru. He has no significant past medical history and has no known drug allergies. Physical examination reveals a red, tender left testicle, hepatomegaly, and severe pain over both sacroiliac joints. His temperature was 39.4°C. Laboratory analysis revealed an elevation in white blood cell count at 18,000 cells/mm^3, aspartate aminotransferase at 100 IU/L, and alanine aminotransferase at 120 IU/L. Blood cultures were positive for *Brucella melitensis*. Which one of the following regimens is the best treatment for this patient?

A. Doxycycline 100 mg orally 2 times/day plus rifampin 15 mg/kg/day orally for 6 weeks.
B. Doxycycline 100 mg orally 2 times/day for 6 weeks plus streptomycin 1 g intramuscularly for first 14–21 days.
C. Rifampin 900 mg/day orally once for 6 weeks.
D. Trimethoprim-sulfamethoxazole (10–12 mg/kg/day of the trimethoprim component) plus rifampin (15–20 mg/kg/day) for 6 weeks.

20. A 40-year-old man from Massachusetts was seen in the emergency department with a 1-week history of fever, headache, chills, and fatigue. He reports going hiking in the woods 2 weeks before his illness, but did not recall a tick bite. He has a history of hypertension and splenectomy after trauma when he was 20 years old. He takes metoprolol and has no known drug allergies. His temperature was 37.7°C, pulse was 96 beats/minute, respiratory rate was 20 breaths/minute, and blood pressure was 109/54 mm Hg. Physical examination revealed jaundice and scleral icterus. He had minimal right upper quadrant pain but no hepatomegaly. Laboratory analysis showed a normal white blood cell count, with a mild anemia and thrombocytopenia. Total bilirubin was 14 mg/dl, aspartate aminotransferase was 45 IU/L, alkaline phosphatase 150 IU/L, and lactate dehydrogenase was 900 IU/L. Urinalysis showed the presence of hemoglobin. Peripheral blood smear revealed erythrocytes containing *Babesia*. The patient was diagnosed with babesiosis and started on a combination of clindamycin and quinine. Three days later, he says he can no longer take the regimen because of new-onset diarrhea and ringing in his ears. Which one of the following regimens represents an appropriate alternative therapy for this patient?

A. Atovaquone 750 mg orally 2 times/day plus azithromycin 500 mg orally on day 1 followed by 250 mg/day orally for 6 days.
B. Pentamidine 4 mg/kg/day intramuscularly.
C. Chloroquine 500 mg orally every 12 hours for 3 weeks.
D. Doxycycline 100 mg orally 2 times/day 7 days.

21. A 37-year-old man was seen in the emergency department with a 6-month history of chronic diarrhea, 16-pound weight loss, and new-onset right upper quadrant tenderness. He is positive for the human immunodeficiency virus with a CD4 count of fewer than 100 cells/mm^3 and viral load of more than 50,000 copies/ml. He currently is not on any therapy for his human immunodeficiency virus and reports no known drug allergies. Physical examination was unremarkable except for right upper quadrant pain. Laboratory analysis reveals an elevated total bilirubin (13 mg/dl) and alkaline phosphatase (300 IU/L). Biopsy from endoscopy is still pending. The physician suspects bilary cryptosporidiosis. Which one of the following is the best therapy for this patient?

A. Paromomycin 500 mg orally 4 times/day for 4 weeks.
B. Nitazoxanide 500 mg orally 2 times/day for 12 weeks.

C. Initiation of highly active antiretroviral therapy.
D. Loperamide as needed, with supportive fluid and electrolyte replacement.

Questions 22 and 23 pertain to the following case.
A 12-year-old boy was playing in the yard with some friends and was bitten by the neighbor's dog. The neighbor assures the boy's family that the dog was vaccinated despite not having any tags on the animal. The child goes to the emergency department and has the wound cleaned. He was treated with amoxicillin-clavulanate (80 mg/kg/day) for 7 days. Ten days later, the neighbor discloses that the dog was not current on his vaccinations, but the dog is otherwise healthy and normal per his veterinarian.

22. Which one of the following describes the best treatment option for this patient?
    A. The child should receive postexposure prophylaxis for rabies.
    B. The child should not receive postexposure prophylaxis for rabies.
    C. The child and friends should receive postexposure prophylaxis for rabies.
    D. The child should receive postexposure prophylaxis but his friends should not receive postexposure prophylaxis for rabies.

23. If the dog had exhibited signs and symptoms of rabies during the 10-day period, you would have had to treat the child. Which one of the following is the proper postexposure prophylaxis regimen?
    A. Local wound cleansing with soap and water; human rabies immune globulin 20 IU/kg; half of the dose should be infiltrated around the wound and the rest injected into the patient's buttock; and human diploid cell-culture vaccine 1 ml given intramuscularly on days 0, 1, 7, 21, and 28.
    B. Local wound cleansing with iodine; equine rabies immune globulin 20 IU/kg; the full dose should be infiltrated around the wound; and human diploid cell-culture vaccine 1 ml given intramuscularly on days 0, 3, 7, 14, and 28.
    C. Local wound cleansing with soap and water; human rabies immune globulin 20 IU/kg; half of the dose should be infiltrated around the wound and the rest injected into the patient's buttocks; and human diploid cell-culture vaccine 1 ml given intramuscularly on days 0, 3, 7, 14, and 28.
    D. Local wound cleansing with soap and water; equine rabies immune globulin 40 IU/kg; full dose should be infiltrated around the wound; and human diploid cell-culture vaccine 1 ml given intramuscularly on days 0, 3, 7, 14, and 28.

24. Which one of the following is the best statement concerning the agent and vector responsible for causing HGE?
    A. *Anaplasma phagocytophila* causes HGE and its vector is *Amblyomma americanum* (lone star tick).
    B. *Ehrlichia chaffeensis* causes HGE and its vector is *A. americanum* (lone star tick).
    C. *Ehrlichia chaffeensis* causes human monocytic ehrlichiosis and its vector is *Ixodes scapularis* (black-legged tick).
    D. *Anaplasma phagocytophila* causes HGE and its vector is *I. scapularis* (black-legged tick).

25. A 55-year-old cattle farmer from upstate New York goes to the emergency department with complaints of an abrupt fever and migraine-like headaches. Physical examination reveals clubbing of the extremities, hepatomegaly, and the presence a rash on the extremities and trunk. All other physical examination findings are normal. The patient's laboratory values demonstrate a mildly elevated white blood cell count, increased erythrocyte sedimentation rate, and anemia. All blood and urine cultures are negative. The patient is presumed to have endocarditis, but the transesophageal echocardiogram did not detect any vegetations. The patient was empirically started on vancomycin 1 g every 12 hours, gentamicin 80 mg every 8 hours, and fluconazole 400 mg/day. After 2 days of therapy, the patient spiked a fever and his white blood cell count increased to 21,000 cells/mm^3. The patient is diagnosed with a deep vein thrombosis and is placed on anticoagulation therapy. The infectious diseases team is consulted and they discover that the man had an abrupt-onset fever and headache several months ago, but it resolved spontaneously and no treatment was needed. The infectious diseases team suspects *Coxiella burnetii* and asks you how to treat this patient. Which one of the following is the recommended regimen and therapy duration?
    A. Doxycycline 100 mg 2 times/day plus rifampin 600 mg/day for 6 months.
    B. Doxycycline 100 mg 2 times/day plus tobramycin 80 mg every 8 hours for 6 weeks.
    C. Doxycycline 100 mg 2 times/day plus hydroxychloroquine 200 mg 3 times/day for 6 months.
    D. Doxycycline 100 mg 2 times/day plus hydroxychloroquine 200 mg 3 times/day for 18 months.

26. Which one of the following best characterizes the distribution of *Aedes aegypti*, the vector for dengue fever virus?
    A. Southern regions of Texas, Louisiana, Mississippi, and Alabama and throughout Florida.
    B. Southern Texas, Louisiana, Arkansas, Missouri, Iowa, and Minnesota.
    C. Only throughout Florida.
    D. Throughout Florida, the Atlantic coastal states, and New England states.

27. P.E. is a 16-year-old Hispanic boy who went to a clinic in Brownsville, Texas, complaining of an abrupt onset of high fever, muscle and joint aches, retro-orbital pain, photophobia, and lymphadenopathy. In addition, he

had a maculopapular rash. Laboratory tests were remarkable for leucopenia and thrombocytopenia. The clinic staff believe this boy may have an arboviral infection. Which one of the following organisms is the likely cause of P.E.'s manifestations?

A. Japanese encephalitis virus.
B. Murray Valley encephalitis virus.
C. St. Louis encephalitis virus.
D. Dengue virus.

28. J.J. is a 20-year-old Caucasian man who went to a clinic in south Florida and is subsequently diagnosed with dengue hemorrhagic fever with shock. Which one of the following represents the best plan for managing J.J.'s illness?

A. A 21-day course of ribavirin treatment.
B. Treat only with high-dose corticosteroids.
C. Supportive care, hydration, and aggressive fluid management.
D. Nothing, this form of dengue is self-limiting.